Abstracts of the 2nd Biennial Schizophrenia International Research Conference Florence, Italy
April 10–14, 2010

Special Session
GENE EXPRESSION IN SCHIZOPHRENIA - ANIMAL MODELS AND POSTMORTEM STUDIES
Chairperson: Amanda Law
Sunday, 11 April, 2010 - 1:30 pm - 3:30 pm

Overall Abstract: Variation in gene expression is a source of phenotypic differences in humans and an important mechanism underlying complex disease. This panel brings together international experts to present novel data on gene expression in schizophrenia. The topics addressed include; cell-type specific alterations in gene expression and function in the brain in schizophrenia, epigenetic regulation of susceptibility genes and its impact on neurodevelopment and disease, the development of novel animal models recapitulating disease related expression phenotypes and finally understanding how risk-associated DNA variation can impact gene expression and provide insight into the biological pathways involved in disease pathogenesis.

Prof. David Lewis: Circuit-Specific Alterations in Cortical GABA Neurotransmission in Schizophrenia. Dr Lewis, will present evidence and review recent findings indicating that pathological and compensatory changes in mediators of GABA neurotransmission are altered in cell type-, lamina- and circuit-specific fashions in the PFC of individuals with schizophrenia. The utility of these findings for the identification of novel drug targets to improve cognitive dysfunction in schizophrenia will be presented. Prof. Karoly Mirnics: Novel animal models for studying schizophrenia: BAC-driven miRNA-mediated in vivo silencing of gene expression. Dr Mirnics will present evidence that GAD1 disturbances are a core feature of schizophrenia, making it a leading candidate for developing transgenic animal models that mimic the disease phenotype. Specifically, neuropeptide Y (NPY), a phenotypic marker of a subpopulation of GAD1-containing interneurons, has shown reduced expression in the PFC in subjects with schizophrenia, suggesting that dysfunction of the NPY+ cortical interneuronal subpopulation might be a core feature of the disorder. Dr Mirnics will describe a novel technology and features of a transgenic mouse model in which GAD1 mRNA expression is down-regulated specifically in NPY+ neurons. Dr Schahram Akbarian. The Epigenetic Landscape of Prefrontal Neurons – Developmental Trajectories and Alterations in Schizophrenia. Dr Akbarian will speak about mapping histone and DNA modifications in prefrontal chromatin surrounding schizophrenia susceptibility genes, and the exploration of potential changes related to normal development, disease and psychotropic medication. Dr Amanda Law. ErbB4 and PI3KCD are Interacting Biological and Genetic Factors That Regulate NRG1-mediated PI3K Signaling and Risk for Schizophrenia. Dr Law will present data using a systems biology approach incorporating molecular, cellular and clinical genetics to interrogate interacting gene networks and biological pathways downstream of main effects of DNA variation in the ErbB4 gene. Dr Law will present evidence of identification of a specific downstream target of NRG1 activation in relation to ErbB4 genetic risk, the PI3-kinase gene-PI3KCD and show that in addition to alterations in ErbB4/ PI3KCD expression and function in human lymphoblastoid cell lines and the human brain, PI3KCD is linked with risk for schizophrenia. Prof. David Porteous DISC1 Pathway Expression in Mouse and Man. Dr Porteous will present data regarding the DISC1 interactome and how common variants and rare mutations in DISC1 directly and indirectly affect global patterns of gene expression, both in mouse and human. These DISC1 related transcriptional profiles may serve as useful central and peripheral biomarkers of disease and response to treatment. Prof. Paul Harrison. Will serve as the formal discussant.

doi:10.1016/j.schres.2010.02.005

CIRCUIT-SPECIFIC ALTERATIONS IN CORTICAL GABA NEUROTRANSMISSION IN SCHIZOPHRENIA

David Lewis
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Schizophrenia is characterized by dysfunction of the circuitry of the prefrontal cortex (PFC). This dysfunction is manifest as impairments in core cognitive processes, such as working memory, which are associated with disturbances in frontal lobe neural network oscillations at gamma band frequency (30-80 Hz). Because gamma oscillations depend on inhibitory activity in specific classes of GABA neurons, alterations in pre- and post-synaptic markers of GABA neurotransmission are thought to be a critical component of the pathology underlying impaired gamma oscillations and working memory dysfunction in the illness. This presentation will review recent findings indicating that pathological and compensatory...
changes in mediators of GABA neurotransmission are altered in cell type-, lamina- and circuit-specific fashions in the PFC of individuals with schizophrenia. The utility of these findings for the identification of novel drug targets to improve cognitive dysfunction in schizophrenia, and for the use of such drugs in both personalized and pre-emptive interventions, will be presented.

doi:10.1016/j.schres.2010.02.006

NOVEL ANIMAL MODELS FOR STUDYING SCHIZOPHRENIA: BAC-DRIVEN miRNA-MEDIATED IN VIVO SILENCING OF GENE EXPRESSION

Karoly Mirnics
Vanderbilt University, Nashville, TN, USA

In schizophrenia, GAD1 disturbances are robust, replicable and represent a core feature of the disease, making it a leading candidate for developing transgenic animal models that mimic the disease phenotype. However, GAD1 downregulation in the prefrontal cortex is not uniform across all the interneuronal subpopulations: parvalbumin- (PARV), somatostatin- (SST) and NPY-containing neurons appear to be preferentially affected in a complex pattern. Importantly, neuropeptide Y (NPY), a phenotypic marker of a subpopulation of GAD1-containing interneurons, has shown reduced expression in the PFC in subjects with schizophrenia, suggesting that dysfunction of the NPY+ cortical interneuronal subpopulation might be a core feature of this devastating disorder. To mimic these postmortem findings, we generated a transgenic mouse in which we down-regulated GAD1 mRNA expression specifically in NPY+ neurons. This novel, cell type-specific in vivo system for regulation of gene expression utilizes a bacterial artificial chromosome (BAC) containing the NPY promoter-enhancer elements, the reporter molecule (eGFP), and a modified intron containing a synthetic miRNA targeted to GAD1. Furthermore, due to incorporation of an eGFP coding sequence, the targeted cells are identifiable in both live and fixed tissue. The advantages of this in vivo gene silencing system are numerous, and include cell-type specific downregulation of transcripts, visualization of the targeted cells by eGFP, low cost and rapid generation and monoallelic inheritance. Finally, due to the small size of the silencing miRNAs, this method may allow targeting of specific splice-variants, generating splice-variant specific knockdown animals. Combined analysis of the NPY-, PV-, CCK-, and SST-BAC driven, GAD1 miRNA silenced mice (which are currently in production in our laboratory) will greatly contribute to our understanding the mechanisms by which different interneuronal subpopulations mediate cortical inhibition, working memory and cognition. Finally, this knowledge will help us understand the relationship between the cell-type specific GABAergic disturbances and the phenotypic manifestations of schizophrenia.

doi:10.1016/j.schres.2010.02.007

EPIGENOME MAPPING IN DEVELOPING AND DISEASED PREFRONTAL CORTEX

Schahram Akbarian
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Alterations in chromatin structure and function, including changes in levels or distribution of histone lysine methylation

markings and other epigenetic regulators of gene expression could affect neuronal signaling in schizophrenia and other major psychiatric disease. However, to date, nothing is known about the regulation of neuronal and other cell-type specific epigenomes in human or animal brain. Here, we provide first insights into the genome-wide distribution of trimethylated histone H3K4 (H3K4me3), a histone mark associated with actual or potential transcription, in neuronal nuclei collected postmortem from prefrontal cortex (PFC) across a wide age range (0.5-70 years). Massively parallel sequencing identified 16,000-22,000 H3K4me3 enriched regions (peaks), the majority located proximal to (within 2 kb of) the transcription start sites (TSS) of annotated genes. These included signatures specific to neurons as well as signatures specific to individual subjects. Preliminary findings reveal age correlated genome reorganization in the postnatal PFC, including a general increase in TSS-associated H3K4me3 peaks concomitant with loss of peaks at many developmentally regulated genes. In addition, H3K4me3 mappings in PFC neurons from subjects with schizophrenia and matched controls, and histone methyltransferase mutant mice, are in progress. We predict that epigenome mapping in defined cell populations of the human brain, in conjunction with RNA and transcriptome profiling in diseased tissue and preclinical model systems, will uncover novel mechanisms governing normal and diseased neurodevelopment. Schahram Akbarian, Iris Cheung, Hennady P. Shulha, Zhiping Weng Brudnick Neuropsychiatric Research Institute and Program in Bioinformatics and Integrative Biology, University of Massachusetts Medical School, Worcester, MA, USA Acknowledgments: Postmortem tissue was provided by BTB Dev. Dis., U.M. (Dr. R. Zielke), UC Irvine and Davis (Dr. W.E. Bunney Jr., Dr. E.G. Jones), MPRC (Dr. A. Lessard; Dr. R. Schwarcz), HBTRC (Dr. F.M. Benes) and Bronx VA (Dr .H. Haroutunian). Supported by the National Institute of Mental Health (5R01MH071476; S.A.), the National Science Foundation DBI 085006 (Z.W.), IMHRO and NARSAD.

doi:10.1016/j.schres.2010.02.008

ERBB4 AND PI3KCD AND ARE INTERACTING BIOLOGICAL AND GENETIC FACTORS THAT REGULATE NRG1-MEDIATED PI3K SIGNALING AND RISK FOR SCHIZOPHRENIA

Amanda Law
NIHM, Bethesda. MD, USA

Background: The identification of variations in DNA that increase susceptibility to disease is one of the central aims of human genetics. However, classical genetic approaches, whilst identifying susceptibility loci, provide little information as to how the genes relate to the disease. Here we provide a systems biology approach utilizing molecular, cellular and clinical genetic investigations to interrogate interacting gene networks and biological pathways downstream of main effects of DNA variation in the ErbB4 gene that associate with schizophrenia. Using cell and molecular biology we have uncovered a specific downstream target of NRG1 activation in relation to ErbB4 genetic risk, the PI3-kinase gene-PI3KCD. We show that in addition to alterations in PI3KCD expression and function of the PI3K system in human lymphoblastoid cell lines and the human brain, PI3KCD is linked with risk for schizophrenia in two independent family-based association studies and shows epistasis with ErbB4. We propose that altered NRG1/ErbB4 signaling represents an upstream effector of altered PI3K function in schizophrenia, mediated via PI3KCD.

Methods: PI3KCD expression, PI3K intracellular signaling and cell migration were measured in lymphoblasts from patients with schizophrenia and normal controls in relation to genetic risk

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variation in ErbB4 (Haplotype rs7598440, rs707284, rs839523). PI3KCD expression phenotypes were also examined in the human brain in the disease. Tag SNPs were selected in PI3KCD along with any coding variations in the NCBI database. 20 SNPs were genotyped in three independent clinical samples, two family based and one case-control. Main effects analyses of single SNPs and haplotypes were conducted using unconditional logistic regression in the case-control samples and using the family-based association test (FBAT) in families. Epistasis between DNA variants in ErbB4 and PI3KCD were tested in both the case-control and family samples using unconditional and conditional logistic regression. Results: Disease state and the ErbB4 risk haplotype were associated with differential expression of a PI3KCD/p55gamma complex in lymphocytes, downstream of changes in ErbB4 splice gene expression and upstream of altered NRG1-mediated intracellular PIP3 signaling and NRG1-induced cell migration. At the clinical genetic level, we report distorted transmission of SNP alleles in PI3KCD in two independent family-based samples and epistasis between ErbB4 and PI3KCD.

Discussion: Our results provide direct experimental and genetic evidence that complex diseases such as schizophrenia are emergent properties of interacting molecular networks modified by genetic loci. Variation in expression of the ErbB4 gene in relation to risk for schizophrenia has downstream functional consequences for the PI3K pathway at both the molecular and cellular phenotype level. A systems biology approach to elucidating the architecture of aberrant signaling networks in schizophrenia in relation to genetic risk has significant value for the identification of novel risk genes and for the development of new targeted therapeutics.

doi:10.1016/j.schres.2010.02.009

**DISC1 PATHWAY EXPRESSION IN MOUSE AND MAN**

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*University of Edinburgh, Edinburgh, UK*

**Background:** DISC1 is now well established as a genetic risk factor for a range of major mental illnesses, mediated through the role of DISC1 as a hub protein which interacts with multiple binding partners to regulate neurodevelopment and neurosignalling pathways. Methods Here, we describe the outcome of transcriptional profiling studies in the following experimental contexts: 1. Comparative analysis of fetal and adult brain expression profiles in the Q311 and L100P Disc1 mouse lines and the effect of behaviour modifying drug treatment in the L100P Disc1 line. 2. Transcriptional profiles of human lymphoblastoid cell lines with and without the t(1;11) translocation which disrupts DISC1. 3. The effect of common SNP variants of DISC1, PDE4 and NDE1 on transcriptional profiles of human lymphoblastoid cell lines. Results 1. GO Tree analysis of differentially expressed genes found over-representation of cell-cell signalling, transmission of nerve impulses, synaptic transmission, neurotransmitter secretion, vesicle docking during exocitosis and peripheral nervous system development, overlap with schizophrenia-associated CNV loci and independent DISC1 pathway analyses. 2. The effect of the t(1;11) is to dysregulate multiple signalling pathways. Genes showing significantly altered expression include candidate SZ/Autism genes and synaptic genes. 3. Disc1 pathway variants selectively modulate the expression of cytoskeletal, synaptogenetic, signalling and sensory perception genes. The Disc1 regulome is enriched for proteins that are current targets for psychiatric drug development. Conclusions In addition to the direct effects of DISC1 interaction with protein partners, the DISC1 interactome, common variants and rare mutations in DISC1 directly and indirectly affect global patterns of expression. These DISC1 related transcriptional profiles may serve as useful central and peripheral biomarkers of disease and response to treatment. Sarah Brown1, William Hennah1,2, Christoph Grunewald1, Xu Tang1, L. Miguel Camargo3, Steven Clapcote1,4, Kirsty Millar1 Pippa Thomson1, Kathy Evans1 & David Porteous1 1Medical Genetics Section, University of Edinburgh Molecular Medicine Centre and Institute of Genetics and Molecular Medicine, Edinburgh EH4 2XU, UK. 2Institute for Molecular Medicine Finland, National Institute for Health and Welfare, Biomedicum Helsinki, FI-00251, Finland 3Merck Research Laboratories Boston, 33 Avenue Louis Pasteur, Boston, MA 02115, USA. 4Institute of Membrane and Systems Biology, University of Leeds, Leeds LS2 9JT, UK.

doi:10.1016/j.schres.2010.02.011

**FIRST EPISODE PSYCHOSIS AND ASSERTIVE COMMUNITY TREATMENT**

Lisa Dixon  
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A variety of team-based approaches have proven to be effective for the care of persons with schizophrenia. Assertive Community Treatment (ACT) is an established evidence-based model. The most recent Schizophrenia Patient Outcomes Research Team (PORT) review recommended ACT on the basis that it reduces hospitalization and homelessness. When compared to standard community care, Cochrane reviews have found that those receiving ACT were more likely to remain in contact with services, were less likely to be admitted to hospital, and spent less time in hospital. Those receiving ACT also had more favorable accommodation status, employment and patient satisfaction. Recent attempts to focus on substance abuse and assisting forensic populations have yielded mixed results suggesting that more work is necessary to understand how to extend and focus ACT’s effectiveness. Multi-element team-based models analogous to ACT have also been tested in the care of individuals with recent onset of schizophrenia. Studies conducted in Europe and Australia have suggested a range of possible benefits of team based models including reduced symptoms, substance abuse, treatment retention, and social and occupational functioning. One of the US NIMH-funded Recovery After an Initial Schizophrenia Episode (RAISE) initiatives developed by The Research Foundation for Mental Health team (Lieberman, PI, Dixon, Co-PI) will employ a team-based approach that builds on principles of ACT, Critical Time Intervention (CTI) models, and previous
work conducted by first-episode teams. This presentation will provide an update on recent studies of team-based approaches for schizophrenia and outline the RFMH RAISE strategy.

doi:10.1016/j.schres.2010.02.012

COGNITIVE THERAPY FOR SCHIZOPHRENIA

David Kingdom¹, Douglas Turkington⁴, Marie Finn¹, Jesse Wright¹, Shanaya Rathod², Richard Gray³, Ron Siddle⁵
¹University of Southampton, Southampton, Australia United Kingdom; ⁴University Newcastle United Kingdom; ²Cumbira Partnership United Kingdom; ³Institute of Psychiatry, King's College London United Kingdom; ⁵Technische University, Munich, Germany

Evidence for the effectiveness of CT in schizophrenia is growing: there are now over 30 and a number of meta-analyses. This evidence will be briefly but critically reviewed. The techniques used will be described and their application to routine clinical practice outlined. These are based on a psychiatric formulation, which elicits vulnerabilities and strengths and examines possible precipitating events and circumstances in understanding current symptoms. It is then used for focused work, e.g. for compliance management and work on hallucinations, delusions, thought disorder and negative symptoms. Structured reasoning can assist in reattribution of ‘voices’, development of coping strategies and empowerment in managing critical content. Delusions may benefit from understanding perpetuating factors, e.g. low self-esteem and isolation, and systematically reorienting the patient towards dealing with these issues. Negative symptoms seem to have benefited from attention to pacing, timing and, paradoxically, reduction in perceived pressure. The audience will be encouraged to consider the applicability of these techniques to their own practice in working with people with severe mental illness.

doi:10.1016/j.schres.2010.02.013

COGNITIVE REMEDIATION

Susan McGurk
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A growing body of research supports the effects of cognitive remediation on cognitive functioning in schizophrenia. However, there continues to be ongoing debate about the impact of cognitive remediation on other outcomes, and the conditions necessary to make an impact on psychosocial functioning. This presentation will summarize recent controlled research on cognitive remediation for schizophrenia, with a particular focus on its impact on functional outcomes.

doi:10.1016/j.schres.2010.02.014

FAMILY PSYCHOEDUCATION

Gabriele Pitschel-Walz
Technische University, Munich, Germany

Meta-analyses have shown that family interventions are effective in reducing the rehospitalization rates in patients with schizophrenia. Besides medication, family interventions are considered an important part of the state-of-the-art treatment in modern treatment guidelines for schizophrenia. Most of the family intervention programmes studied can be classified as psychoeducational with cognitive behavioral therapy as background. Family psychoeducation should provide carers with information and therapeutic support to better cope with their relative’s mental illness and with their own illness-related problems. In a meta-analysis on the effectiveness of psychoeducation for schizophrenia Tania Lincoln found that only psychoeducational interventions that included families and were not focussed on the patients alone achieved significant results. On consideration of the evidence base for family psychoeducation in schizophrenia, there still exists an enormous gap between scientific findings and clinical reality. Fewer than 10% of family carers of patients with schizophrenia receive any support or family psychoeducation. Therefore psychiatric practitioners should put in a variety of efforts to provide these effective and much appreciated interventions. New studies investigate the challenges of dissemination, effects of various family intervention programmes in different cultural settings, peer-to-peer programmes or interventions for special target groups like families of patients with co-occurring substance abuse.

doi:10.1016/j.schres.2010.02.015

SUPPORTED EMPLOYMENT, SOCIAL SKILLS TRAINING, AND FIRST EPISODE PSYCHOSIS

Kim Mueser
Dartmouth University Medical School, Hanover, NH, USA

Supported employment is the most empirically validated approach to vocational rehabilitation for schizophrenia. Recent controlled studies of supported employment will be reviewed, including research on the model conducted outside the U.S. and with first episode psychosis. Next, the results of two recent meta-analyses of social skills training for schizophrenia will be summarized, followed by a brief discussion of research on skills training for special populations, such as patients with dual disorders or older patients. Finally, a brief description will be provided of the treatment model for first episode psychosis developed by the Zucker Hillside Hospital clinical research team in New York (PI: John Kane), and currently being evaluated as part of the NIMH-funded Recovery After an Initial Schizophrenia Episode (RAISE) initiative.

doi:10.1016/j.schres.2010.02.016

Symposium 1

MUTANT MODELS AND PSYCHOSIS AT THE CROSSROADS: A CRITICAL RE-EVALUATION OF TECHNIQUES AND TRANSLATION

Co-Chairpersons: Mikhail Pletnikov, John Waddington
Monday, 12 April, 2010 - 3:30 pm - 5:30 pm

Overall Abstract: Generating genetic animal models of human mutations sheds light on the pathogenesis of schizophrenia. Recent discoveries of susceptibility genes and copy number variants as important risk factors provide novel opportunities for producing promising animal models. The main goal of the symposium is to critically review current approaches to constructing animal models of the disease, with a particular focus on conditional mutants, mutants with spatial and temporal over-expression of the gene, CNV mutants and non-mouse genetic models. Four speakers of the symposium will
review new developments in genetic animal models of schizophrenia. Dr Mikhail Pletnikov (Johns Hopkins, USA) will discuss different approaches used to generate DISC1 mouse models and highlight the utility of his mouse model of inducible expression of mutant DISC1 for characterizing cell-specific, time-dependent and brain region-restricted effects of mutant DISC1 on neurodevelopment and schizophrenia-like phenotypic manifestations. Dr John Waddington (Royal College of Surgeons, Ireland) will overview novel methodologies for improving phenotypic assessment and will critically evaluate the data from Neuregulin 1 mutant models with a focus on positive and negative symptoms, cognitive and morphological phenotypes. Dr Maria Karayiorgou (Columbia University, USA) will present a new mouse model of copy number variants (CNVs) based on the 22q11.2 microdeletions. She will describe a mouse strain carrying a chromosomal deficiency, which spans a segment syntenic to the human 22q11.2 locus and provide evidence for cognitive impairments accompanied by specific neuronal abnormalities and dysregulation of synaptic genes. Our fourth speaker, Dr Bart Ellenbroek (Evotec Neurosciences, Germany), will present the development of a knockout rat model identified with an ENU mutagenesis screen. He will consider how a point mutation in the dopamine D1 receptor in rats may lead to a reduced expression of the receptor and resultant behavioural alterations relevant for the negative and cognitive symptoms of schizophrenia. Dr Jonathan Flint (Wellcome Trust Centre for Human Genetics, UK) will be our discussant to overview the highlights of each presentation in the context of the new challenges in the field and directions for further investigation. The symposium will provide an exciting, critical forum for discussing animal models of schizophrenia and will benefit a broad audience of both basic and clinical researchers interested in this rapidly developing field of translational neuroscience of schizophrenia.

doi:10.1016/j.schres.2010.02.017

NOVEL DEVELOPMENTS IN GENETIC MOUSE MODELS: A DISC1 STORY

Mikhail Pletnikov
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Mikhail Pletnikov1,2,5,6* and Christopher A. Ross1,2,3,4,5,6 Department of Psychiatry1, Neuroscience2, Neurology3 and Pharmacology4, Graduate Programs in Cellular and Molecular Medicine5 and Neurosciences6, Johns Hopkins University School of Medicine*. - Presenting author. Schizophrenia is a devastating disorder with worldwide prevalence. Despite the advances in research techniques during the last two decades, the pathogenesis of the disorder remains poorly understood. Several strategies have been taken to develop animal models. Early animal models were based on lesion methods, pharmacological challenges or environmental insults. Although these models have provided valuable insights into aspects of schizophrenia and have been useful for pre-clinical therapeutic studies, their etiological relevance has been uncertain. Recent progress in identification of candidate genetic risk factors has stimulated development of genetic models of schizophrenia. These have begun providing valuable data about the mechanisms whereby those genes, their mutations and protein products contribute to disease pathogenesis. Among strong candidate genes, Disrupted-In-Schizophrenia 1 (DISC1) has attracted a lot of attention because of its strong association with major mental diseases, including schizophrenia. Using DISC1 as a model, we will critically evaluate the strengths and weaknesses of the existing mouse lines with different genetic alterations of the gene. We will overview our own data for a mouse model of inducible expression of mutant human DISC1 to demonstrate how genetic manipulations in cell-specific, time-dependent and brain region-restricted manners can help to advance our knowledge of the complex pathogenic mechanisms of abnormal neurodevelopment relevant to schizophrenia and related mental conditions.

doi:10.1016/j.schres.2010.02.018

PSYCHOPATHOLOGICAL, COGNITIVE AND MORPHOLOGICAL PHENOTYPES IN SCHIZOPHRENIA RISK GENE MUTANTS: CHALLENGES AND THE EXAMPLE OF NEUREGULIN

John Waddington, Colm M.P. O’Tuathaigh
Royal College of Surgeons Dublin Ireland

Schizophrenia is thought to be a polygenic disorder that is associated with considerable phenotypic heterogeneity across patients, including variations in age at onset, diagnostic symptoms, functional deficits and subsequent course of illness. Consequently, the generation of incisive mutant models for this disorder faces substantial challenges. Furthermore, the majority of mutant models for schizophrenia relate to the functional roles of the increasingly large and diverse array of genes associated with risk for the disorder and to pathophysiological and pharmacological processes of as yet uncertain validity. Here, various technical approaches are considered and the diversity of methodologies adopted in phenotypic assessment is reviewed. Emphasis is placed on psychopathological [positive and negative symptoms], cognitive and morphological phenotypes, using neuregulin 1 mutants as a particular example. To further this goal, continually evolving mutant genomics is juxtaposed with emergent clinical genomic studies, and the potential value of genetic models for exploring gene-gene and gene-environment interactions relating to schizophrenia is considered. Finally, the principal challenges and opportunities faced by researchers engaging in the generation and evaluation of mutant models for schizophrenia are outlined, including issues of diagnostic specificity, the translational barrier associated with modelling schizophrenia and possible approaches to identifying improved models. The authors’ studies are supported by Science Foundation Ireland and the Health Research Board.

doi:10.1016/j.schres.2010.02.019

COPY NUMBER VARIATION IN SCHIZOPHRENIA: MODELING 22Q11

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Copy number variants (CNVs) are important genetic risk factor for schizophrenia. Over the last fifteen years, a strong and specific relationship has been established between one such CNV, the 22q11.2 microdeletion and psychosis in the diagnostic form of schizophrenia or schizoaffective disorder. Importantly, a number of studies have indicated that 22q11.2 microdeletions account for 1-2% of schizophrenia cases and represent to-date the only confirmed recurrent structural mutation responsible for introducing sporadic cases of schizophrenia into the population. We generated and analyzed an engineered mouse strain carrying a chromosomal deficiency, which spans a segment syntenic to the human 22q11.2 locus. We provided evidence for cognitive impairments accompanied by abnormalities in dendritic spine formation and dendritic complexity, as well as dysregulation of a number of neuronal and synaptic genes in hippocampal neurons. We
also uncovered a previously unknown alteration in the biogenesis of microRNAs (miRNAs) and identified a subset of brain miRNAs affected by the microdeletion, as well as potential targets. We showed that the abnormal miRNA biogenesis interacts with haploinsufficiency of other 22q11.2 genes to produce the behavioral, neuronal and molecular deficits associated with the 22q11.2 microdeletion.

doi:10.1016/j.schres.2010.02.020

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**THE Dopamine D1 MUTANT RAT: A NOVEL APPROACH TO MODELLING NEGATIVE AND COGNITIVE ASPECTS OF SCHIZOPHRENIA**

Bart Ellenbroek1, Ji Un Youn1, Judith R. Homberg1,2

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Schizophrenia is a devastating illness with patients suffering from a myriad of symptoms often clustered into positive, negative and cognitive symptoms. Although the current generation of antipsychotic drugs are effective in the treatment of positive symptoms, they have little influence on the negative or cognitive ones. Given the fact that these are highly relevant to overall outcome of the disease, there is a great unmet need for novel therapies. One receptor that has been implicated in negative and cognitive deficits in schizophrenia is the dopamine D1 receptor. However, so far it has been proven difficult to study the role of these receptors in detail, since the available pharmacological tools do not clearly differentiate between the D1 and the D5 receptors. Using an ENU mutagenesis screen we have recently identified a rat with a selective point mutation in the highly conserved third intracellular loop (I116S), resulting in a hydrophobic isoleucine by hydrophilic serine exchange. In these D1 mutant rats, as compared to wild type littermates binding of [3H]SCH23390 to brain slices was reduced by 50%. In COS cells expressing the mutant receptor as opposed to the wild-type receptor, we found a reduced number of D1 receptors in the cell membrane and an increased number of D1 receptors in the cytoplasm. Basal dopamine levels in the nucleus accumbens are not changed, but SKF81297-induced in vivo cAMP production tends to be decreased in the mutant rats. Behaviourally, body weight was modestly reduced in the mutant rats, and their behavioural responses to the D1,5 antagonist SCH23390, as well as to the dopamine enhancing drug cocaine, were decreased. With respect to schizophrenia, we found that mutant D1 rats have reduced prepulse inhibition. However, without any pharmacological data, it is difficult to link this to either the positive or the cognitive deficits. More specifically related to the positive symptoms of schizophrenia, we observed that the D1 mutant rats had a reduced response to dopamine enhancing drug cocaine, were decreased. With respect to schizophrenia, we found that mutant D1 rats have reduced prepulse inhibition. However, without any pharmacological data, it is difficult to link this to either the positive or the cognitive deficits. More specifically related to the positive symptoms of schizophrenia, we observed that the D1 mutant rats had a reduced response to dopamine enhancing drugs such as amphetamine, which is opposite of what has been reported for schizophrenia. However, in relation to the cognitive symptoms of schizophrenia, we found a significantly reduced performance in object recognition and Morris Water maze (especially in the so-called egocentric version, which relies heavily on the prefrontostriatal pathway). In addition, we found that succrose consumption is slightly reduced in D1 mutant rats, which may have relevance for the negative symptoms of schizophrenia (anhedonia), although more research is necessary here (including the analysis of social behaviour). In summary, we have found that a point mutation in the dopamine D1 receptor in rats leads to a reduced membrane expression and to a variety of symptoms that may be relevant for the negative and cognitive but probably less for the positive symptoms of schizophrenia, and might help to identify novel therapies in the future.

**SCHIZOPHRENIA GENETICS ON THE MATTER OF NEUROIMAGING IN THE CONTEXT OF SCHIZOPHRENIA GENETICS**

Co-Chairpersons: Rene Kahn, Celso Arango

Tuesday, 13 April, 2010 - 8:30 am - 12:00 pm

**ON THE MATTER OF NEUROIMAGING IN THE CONTEXT OF SCHIZOPHRENIA GENETICS**

Daniel Weinberger1, Panelists: Alessandro Bertolino2, Philip McGuire3, Eva Meisenzahl4, Andreas Meyer Lindenberg5, Steven Potkin6, Si Tianmee7, 8NIMH, Bethesda, MD, USA; 2University of Bar; 3Institute of Psychiatry, King's College; 4Ludwig Maximillian University; 5Central Institute of Mental Health; 6University of California, Irvine Brain Imaging Center; 7Peking University Institute of Mental Health

Have neuroimaging studies in schizophrenia been helpful in understanding the pathophysiology of the disease? Certainly, structural...
imaging studies have shown brain changes to occur during the course of the illness, but what do these changes mean? Similarly, functional imaging studies have found a range of functional abnormalities in schizophrenia patients, but the specificity and stability of these changes are questionable. Indeed, neuroimaging so far has failed to be helpful as a diagnostic or even prognostic tool. So what is next? Now it is claimed that neuroimaging may be helpful in dissecting the functions of genes relevant in psychiatric illness. And some studies using novel mathematical tools suggest that neuroimaging may, after all, be helpful in separating disorders. This panel will review the usefulness of neuroimaging in schizophrenia and review critically its role in future schizophrenia studies with an emphasis on relating brain function to genes. The following questions will be addressed: Will neuroimaging help identify genes relevant in schizophrenia? Will neuroimaging play a role in further defining schizophrenia?

doi:10.1016/j.schres.2010.02.023

PLENARY SESSION - ANTICIPATING DSM-V: NEW PARADIGMS
Co-Chairpersons: John Kane, Wolfgang Fleischhacker
Sunday, 11 April, 2010 - 8:30 am - 10:30 am

DSM-V: NEW PARADIGMS AND OTHER CONTROVERSIES

William Carpenter1, Panelists: Alex Hofer2, Richard Keefe1, Kim Mueser4, Dieter Naber2, Eric Chen6
1University of Maryland School of Medicine Baltimore, MD, USA; 2Medical University Innsbruck; 3Duke University Medical Center; 4Dartmouth Psychiatric Research Center; 5University Medical Center Hamburg; 6University of Hongkong

DSM-V is scheduled for release in 2013. There will be extensive efforts to harmonize with the next addition of ICD. The workgroup for Psychotic Disorders is considering modest changes in criteria for classification and major changes affecting the following: a) subtypes of schizophrenia; b) catatonia; and c) schizoaffective disorder. Two new paradigms may be added: a) the domains of pathology paradigm with dimensions representing critical aspects of psychopathology; and b) a risk syndrome chapter including a psychosis risk syndrome and mild cognitive impairment. The former is intended to address syndrome heterogeneity and focus assessment on pathologies requiring clinical attention. The latter is hotly debated [see also SIRS program for debate symposium]. The question of whether bipolar disorders should be grouped with psychotic disorders or mood disorders is being addressed and current status will be discussed. Field trials will begin in 2010. Plans affecting psychotic disorders will be presented. Response from the SIRS community will provide the workgroup with important feedback.

doi:10.1016/j.schres.2010.02.025

NEW DIRECTONS FOR ANIMAL MODELING IN SCHIZOPHRENIA

Bita Moghaddam1, Panelists: Inna Gaisler-Salomon2, Patriot O’Donnell2, Akira Sawa4, Pierre Sokoloff2, Peter Uhilhaas6
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Symposium 2
MAKING CONNECTIONS: ABNORMAL WHITE MATTER DEVELOPMENT IN THE EARLY STAGES OF SCHIZOPHRENIA
Chairperson: Marc L. Seal
Sunday, 11 April, 2010 - 3:30 pm - 5:30 pm

Overall Abstract: Neuropathological and neuroimaging studies have consistently identified white matter abnormalities in schizophrenia, however, the development of this neuropathology and the functional implications of abnormal white matter in schizophrenia remain unclear. Significantly, recent studies suggest that white matter abnormalities may be present in the early stages of the illness and even appear prior to illness onset. The aim of this symposium is to review the current research involving in vivo assessment of white matter integrity in the early stages of schizophrenia and to discuss these findings within the context of healthy neurodevelopment. The four presenters are international leaders in this field of research. Anthony James (Oxford) will present his work comparing shared and distinct white matter abnormalities between individuals with Early Onset Schizophrenia (EOS) and Early Onset Bipolar Disorder (EOB). Katie Karlsild (UCLA) will present an overview of her work on healthy white matter development in adolescence and white matter abnormalities in individuals at high risk of developing psychosis. Marek Kubicki (Harvard Medical School) will present his work identifying fronto-temporal abnormalities in first episode schizophrenia. Gary Price (Institute of Neurology, London) will present an overview of his first episode schizophrenia tractography studies. Finally, Sophia Frangou (Institute of Psychiatry, London), who has published a recent review on this topic, will act as the Discussant.

doi:10.1016/j.schres.2010.02.026

COMPARISON OF GREY AND WHITE MATTER AND NEUROPSYOMETRIC CHANGES IN EARLY-ONSET SCHIZOPHRENIA (EOS) AND EARLY-ONSET BIPOLAR DISORDER WITH PSYCHOSIS (EOBP) VERSUS CONTROLS

Anthony James
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Comparison of Grey and White Matter and Neuropsychometric Changes in Early-Onset Schizophrenia (EOS) and Early-Onset Bipolar Disorder with Psychosis (EOBP) versus Controls. Anthony James Recent genetic findings have called into question the dichotomy between schizophrenia and bipolar disorder with psychosis. To compare the neural networks underlying both disorders by examining white matter (WM), grey matter changes (GM) and cognitive function in an adolescent sample versus age-matched controls. A MRI and diffusion tensor imaging study of 43 subjects with EOS, 15 with EOBP, and 36 controls. DTI. In EOS cases widespread WM changes were found in the major cortical, subcortical and cerebellar tracts with associated reduced GM density in the frontal and temporal lobes. By contrast, in EOBP WM changes were confined to the corpus callosum and GM changes to the bilateral cuneus/prefrontal —visual processing areas, and the right crus of the cerebellum. Similar levels of cognitive impairment were evident in EOS and EOBP, however, the pattern of correlation with WM and GM changes differed. The pattern of WM and GM changes are suggestive of differing neural network abnormalities with an overlap in the corpus callosum. This adds some support for a distinction between EOS and EOBP in the early stages of the neurodevelopment. 1. Craddock N. et al, Schizophrenia Research 2009, 35: 482-490.

doi:10.1016/j.schres.2010.02.027
DIFFUSION TENSOR IMAGING INVESTIGATIONS OF WHITE MATTER DEVELOPMENT IN SCHIZOPHRENIA

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Diffusion Tensor Imaging Investigations of White Matter Development in Schizophrenia. Katherine H. Karlsgodt. Several lines of evidence indicate that schizophrenia has a strong developmental component, with some periods of special vulnerability throughout the lifespan. One such period is in late adolescence, proximal to the period when disease onset often occurs. During this time, the brain is undergoing developmental changes even in healthy controls: there is the well known pruning of the grey matter, however there is also a simultaneous increase in white matter volume as the brain reaches its adult levels of myelination. That this phenomenon occurs so close to disease onset is of particular interest for schizophrenia, as it is often hypothesized to be a disorder of disrupted or reduced connectivity. Our group has previously shown that there are deficits in white matter integrity as measured by diffusion tensor imaging (DTI) even in the early stages of schizophrenia. Using tract-based spatial statistics (TBSS), deficits in frontal-parietal connections were shown in a sample of first-episode patients (within two years of onset). Furthermore the degree of impairment correlated with verbal working memory performance, a cognitive deficit commonly observed in schizophrenia that is known to be associated with frontal-parietal circuitry. However, though there is a growing body of work showing deficits in recent-onset patients, it has been less clear whether white matter deficits exist prior to disease onset or in high-risk individuals. Moreover, whether the deficits emerge as a result of an abnormal developmental process, or from a normal process exerted on an already impaired system, has been unknown. Our recent work has assessed this using DTI in patients clinically defined as being at ultra-high risk for schizophrenia, recruited through the Center for Assessment and Prevention of Prodromal States (CAPPs) at UCLA. Investigations, again using TBSS, in a sample spanning adolescence and early adulthood (age 12-26), indicate that there are changes in white matter integrity even before the onset of the illness. Moreover, cross-sectional analyses showed different patterns of age-related change in patients and healthy controls, with patients failing to show a normal increase of white matter integrity across adolescence in the temporal lobes. This suggests that there is a different developmental trajectory in the period just prior to disease onset, which may result in the lowered measures of white matter integrity in adult subjects and inform our understanding of how onset occurs. The same temporal lobe regions (medial temporal white matter and inferior longitudinal fasciculus) that showed a difference across age were also predictive of later social and role functioning as measured by the Global Function: Social scales. Patients with lower white matter integrity at baseline were likely to have worse functional outcome at 15 months follow up. Taken together, these findings indicate that white matter changes are present very early in the disorder and possibly pre-date the illness, that these changes may arise through a disrupted developmental process, and that they have a significant impact on subsequent levels of functioning.

doi:10.1016/j.schres.2010.02.028

CHANGES IN WHITE MATTER IN THE EARLY STAGES OF SCHIZOPHRENIA

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Recent longitudinal magnetic resonance imaging studies demonstrate progressive changes in gray matter in both temporal and frontal cortices following illness onset. In contrast, far less is known about the evolution and progression of white matter abnormalities, in particular the integrity of white matter tracts that connect the frontal and the temporal lobes, tracts that have long been thought to be abnormal in schizophrenia. We here report recent findings of fronto-temporal abnormalities in first episode schizophrenia, including the uncinate fasciculus, fornix, cingulum bundle and superior longitudinal fasciculus. We also present findings in first episode patients diagnosed with schizophrenia (FESZ) and compare them to previously reported findings in patients with chronic schizophrenia. We discuss these findings in the context of white matter development, degeneration and schizophrenia related medication.

doi:10.1016/j.schres.2010.02.029

DIFFUSION-TENSOR-TRACTOGRAPHY IN FIRST-EPISODE SCHIZOPHRENIA

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Abnormalities in white matter integrity may be relevant in the pathophysiology of schizophrenia. Diffusion-tensor imaging tractography has allowed white matter pathways to be studied in detail and in vivo. In this talk we will, for the most part, present our studies of the corpus callosum (CC) and uncinate fasciculus (UF) in patients with first-episode psychosis (schizophrenia and schizoaffective disorder) using a probabilistic tractography algorithm (Pic). In the study of the CC, white matter tracts crossing the splenium and genu were studied using a multi-threshold approach and multiple linear regressions were used to explore group differences. Fractional anisotropy (FA) was reduced in patients compared to controls in tracts crossing the genu, and to a lesser degree in the splenium. The study of the UF used two seed points to isolate each tract. FA and probability of connection were obtained for every voxel in both tracts. Although there were no patient-control differences in mean tract FA values, the FA distribution, as measured by the squared coefficient of variance was reduced in the left UF in the patient group: the number of voxels with high FA values in the left UF was reduced in patients. These results suggest that there are subtle structural connectivity abnormalities in white matter tracts in patients in their first-episode of psychosis that may involve aberrant connectivity in the core of these tracts.

doi:10.1016/j.schres.2010.02.030

Symposium 3
BRAIN ABNORMALITIES IN EMERGING PSYCHOSIS: ARE NEUROIMAGING-BASED ENDOPHENOTYPES VALID AND RELIABLE MARKERS FOR BASIC SCIENCE RESEARCH, EARLY RECOGNITION AND DISEASE PREDICTION?
Co-Chairpersons: Christos Pantelis, Phillip McGuire
Sunday, 11 April, 2010 - 3:30 pm - 5:30 pm

Overall Abstract: The at-risk mental state for psychosis and the early phase of the disorder probably constitute the most active
The rise of interest in endophenotypes appears related to frustration with the pace of progress in understanding schizophrenia and related disorders. We tend to think of endophenotypes, following Gottesman, as genetically mediated “hidden phenotypes” which are closely related to genetic risk factors but also raise the risk of clinical “exophenotypes”. In this presentation, I will challenge these views. I will demonstrate that (a) some endophenotypes are genetically mediated but are not on the causal pathways to psychosis (i.e., intermediate phenotypes), (b) other endophenotypes are not necessarily genetic but may still be intermediate phenotypes and (c) existing technologies can actually distinguish between schizophrenia and bipolar disorder, and between the relatives of patients with these disorders. I will conclude that endophenotypes are a useful concept in psychosis research, particularly in terms of helping to specify mechanisms but that researchers need to be careful about the use of these terms and the implications of these uses.

doi:10.1016/j.schres.2010.02.032

PROGRESSIVE BRAIN CHANGES ACROSS THE TRANSITION TO PSYCHOSIS: WHERE TO FROM HERE?

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Although the underlying neurobiology of emerging psychotic disorders is not well understood, there is a growing conviction that there are progressive brain changes in patients at clinical high risk for the illness. These changes are likely to begin well before the frank onset of the disorder and may continue for a number of years. In this talk, I will summarize the extant neuroimaging studies of people at clinical high risk for psychosis, both cross-sectional and longitudinal. By and large, there are few definitive markers that distinguish those who go on to develop the illness from those who do not. The two most consistently abnormal brain regions in schizophrenia research, the hippocampi and the lateral ventricles, do not show volumes significantly different to those of healthy controls prior to psychosis onset. However, frontal lobe measures (eg. cortical thickness in the anterior cingulate) do show promise, as do functional imaging measures sensitive to prefrontal cortex dysfunction. Further, longitudinal magnetic resonance imaging findings in individuals at clinical high risk show that there are excessive neuroanatomical changes in those who convert to psychosis. These aberrant changes are observed most prominently in medial temporal and prefrontal cortical regions. While the pathological processes underlying such changes remain unclear, speculatively they may reflect anomalies in genetic and/or other endogenous mechanisms responsible for brain maturation, the adverse effects of intense or prolonged stress, or other environmental factors. Active changes during transition to illness may present the potential to intervene and ameliorate these changes with potential benefit clinically.

doi:10.1016/j.schres.2010.02.033

STRUCTURAL AND NEUROFUNCTIONAL ABNORMALITIES IN THE AT-RISK MENTAL STATE (ARMS) OF PSYCHOSIS

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Over the past decade there has been an exponential growing of neuroimaging research in the early phases of psychosis. Despite the complexity of techniques worldwide engaged and the number of published papers, the clinical significance of anatomical or functional abnormalities is still mostly unknown. Thus, recent research
The aim of the study was to investigate brain structure and function in individuals with an at-risk mental state (ARMS) relative to patients with first-episode psychosis (FE) and healthy volunteers (HC). The subjects were recruited within the Basel Early Detection of Psychosis Clinic (FEPsy) which has been established at the Psychiatric Outpatient Department, University Hospital Basel. Cross-sectional and longitudinal structural and functional magnetic resonance imaging (MRI) data were acquired using a 3.0 T scanner from individuals with an ARMS, similar to the PACE criteria, FE and HC. Images were processed and analysed using voxel based morphometry (VBM) and region-of-interest methods. Volumetric and neurofunctional abnormalities in areas that are also altered in schizophrenia were associated with specific abnormalities in people with an ARMS. However, results indicate that treatment with typical as well as atypical antipsychotics may also contribute to structural alterations. To conclude, some structural and neurofunctional abnormalities were specific to individuals with an ARMS and may be a correlate of their increased vulnerability to psychosis. Further changes within the ARMS appear to be associated with the subsequent onset of psychosis.

Reliable biological markers of the at-risk mental state for psychosis (ARMS) are crucial for early recognition and therapeutic intervention in ultra-high risk individuals. In this regard, previous studies showed that the ARMS is associated with subtle neuroanatomical abnormalities found in similar brain regions as in the established disorder. We employed multivariate analysis techniques in order to investigate whether different ARMS for psychosis and their clinical outcomes could be reliably diagnosed on the individual level based on structural brain alterations both at the cross-sectional and longitudinal level. Multivariate machine learning algorithms were applied on the structural magnetic resonance imaging (MRI) data of individuals in “early” (n = 24) and “late” (n = 27) ARMS of psychosis and healthy controls (HC, n = 25). The method’s ability in predicting a subsequent transition to psychosis based on the baseline MRI data was evaluated in a subgroup of the ARMS population with available clinical follow-up information (transitions: n = 16, non-transitions: n = 18) compared to HC (n = 17). The specificity, sensitivity, accuracy, significance and generalizability of the methodology were evaluated by means of permutation analysis and five-fold cross-validation. Furthermore, we analyzed in a subgroup of 25 ARMS versus 28 HC individuals the significance and stability of whole-brain covariance patterns between brain volume changes and clinical changes over a follow-up period of 4 years and used these patterns to predict the clinical outcome in the ARMS group at the individual level. In the cross-sectional classification analysis of the baseline data, high cross-validated classification accuracies (>85%) were observed, (a) when we delineated the different at-risk mental states versus each other and versus HC and (b) when we tried to predict a subsequent transition or non-transition to psychosis. The longitudinal multivariate analysis revealed highly significant and stable patterns of differential volumetric changes that were most pronounced in the converter group but that were also detectable to a lesser degree in the non-converters versus HC. Correlations between morphometric changes and clinical changes did not only consist of a pattern of accumulating volume losses in those that deteriorated clinically over time, but included also regions of brain volume expansion in those ARMS individuals who showed clinical improvement between baseline and follow-up. The individualized prediction of clinical change based on these patterns of longitudinal volumetric alteration achieved accuracies similar to baseline analysis (>80%). These findings suggest that different ARMS and their clinical outcomes may be reliably identified on an individual basis by assessing patterns of whole-brain neuroanatomical abnormalities. Furthermore, repeated MRI scanning may provide useful information regarding the neurobiological activity of the disease process but also possibly with respect to factors associated with resilience to the disease. Thus, both cross-sectional and longitudinal neuroanatomical classification systems may play an important role in the clinical management of the at-risk mental state and the early phases of psychosis.

doi:10.1016/j.schres.2010.02.034

**MRI-BASED BIOMARKERS FOR INDIVIDUALIZED NEURODIAGNOSTICS IN THE AT- RISK MENTAL STATE AND THE EARLY PHASE OF PSYCHOSIS**

Nikolaos Koutsouris
Ludwig-Maximillian-University, Munich, Bavaria, Germany

Reliable biological markers of the at-risk mental state for psychosis (ARMS) are crucial for early recognition and therapeutic intervention in ultra-high risk individuals. In this regard, previous studies showed that the ARMS is associated with subtle neuroanatomical abnormalities found in similar brain regions as in the established disorder. We employed multivariate analysis techniques in order to investigate whether different ARMS for psychosis and their clinical outcomes could be reliably diagnosed on the individual level based on structural brain alterations both at the cross-sectional and longitudinal level. Multivariate machine learning algorithms were applied on the structural magnetic resonance imaging (MRI) data of individuals in “early” (n = 24) and “late” (n = 27) ARMS of psychosis and healthy controls (HC, n = 25). The method’s ability in predicting a subsequent transition to psychosis based on the baseline MRI data was evaluated in a subgroup of the ARMS population with available clinical follow-up information (transitions: n = 16, non-transitions: n = 18) compared to HC (n = 17). The specificity, sensitivity, accuracy, significance and generalizability of the methodology were evaluated by means of permutation analysis and five-fold cross-validation. Furthermore, we analyzed in a subgroup of 25 ARMS versus 28 HC individuals the significance and stability of whole-brain covariance patterns between brain volume changes and clinical changes over a follow-up period of 4 years and used these patterns to predict the clinical outcome in the ARMS group at the individual level. In the cross-sectional classification analysis of the baseline data, high cross-validated classification accuracies (>85%) were observed, (a) when we delineated the different at-risk mental states versus each other and versus HC and (b) when we tried to predict a subsequent transition or non-transition to psychosis. The longitudinal multivariate analysis revealed highly significant and stable patterns of differential volumetric changes that were most pronounced in the converter group but that were also detectable to a lesser degree in the non-converters versus HC. Correlations between morphometric changes and clinical changes did not only consist of a pattern of accumulating volume losses in those that deteriorated clinically over time, but included also regions of brain volume expansion in those ARMS individuals who showed clinical improvement between baseline and follow-up. The individualized prediction of clinical change based on these patterns of longitudinal volumetric alteration achieved accuracies similar to baseline analysis (>80%). These findings suggest that different ARMS and their clinical outcomes may be reliably identified on an individual basis by assessing patterns of whole-brain neuroanatomical abnormalities. Furthermore, repeated MRI scanning may provide useful information regarding the neurobiological activity of the disease process but also possibly with respect to factors associated with resilience to the disease. Thus, both cross-sectional and longitudinal neuroanatomical classification systems may play an important role in the clinical management of the at-risk mental state and the early phases of psychosis.

Symposium 4
AN UPDATE ON THE NEXT WAVE OF SCHIZOPHRENIA THERAPEUTICS
Co-Chairpersons: Nicholas J. Brandon, Christopher J. Schmidt Sunday, 11 April, 2010 - 3:30 pm - 5:30 pm

**Overall Abstract:** Current treatment of schizophrenia is dominated by atypical antipsychotics with mixed pharmacologies at the dopamine D2, serotonin 5HT2A and other receptors. A number of mechanisms are now entering clinical trials do not directly target the D2 or 5HT2A receptors but either directly or indirectly modulate glutamate receptor function. The glutamate hypothesis of schizophrenia suggests that N-Methyl-D-Aspartic acid (NMDA) receptor function is compromised in schizophrenia and may be responsible for the positive, negative and cognitive symptoms found in the disorder. We will provide an update on four novel mechanisms with an emphasis placed on their biology and pre-clinical efficacy profile. Kjell A. Svensson will discuss the Group II mGlu receptors (mGlu2 and mGlu3) as novel targets for schizophrenia. These receptors are located in forebrain and limbic brain regions and function as presynaptic autoreceptors to limit excessive glutamatergic neurotransmission. As excessive glutamatergic neurotransmission has been implicated in the pathophysiology of schizophrenia, stimulation of group II mGlu receptors may represent a potential target for the treatment of the disorders. In pre-clinical animal models, agonists of mGlu2/3 receptors and now more recently allosteric potentiators (PAM's) of mGlu2 receptors block many of the behavioral effects of NMDA receptor antagonists. Critically preliminary clinical data supports antipsychotic efficacy of an mGlu2/3 agonist prodrug in schizophrenic patients and an update on this clinical plan will be presented. Christopher J. Schmidt will discuss for the first time the type 1 glycine transporter (GlyT1) program at Pfizer. GlyT1 maintains synaptic concentrations of the NMDA receptor co-agonist glycine with inhibition predicted to increase synaptic glycine concentrations and thereby augment NMDA receptor mediated neurotransmission. He will introduce the GlyT1 inhibitor, PF-3463275, which has shown efficacy in cognition models in rodent and non-human primates and also been shown to potentiate the effects of risperidone in a pre-pulse inhibition model. This molecule has now entered Phase 1 studies in healthy volunteers where it was shown to be safe and well-tolerated at doses producing 2-3 fold elevations in CSF glycine. Pete Hutson will show how activation of mGlu5 receptors enhances NMDA receptor function provide another approach to treating schizophrenia.
mGlu5 positive allosteric modulators enhance the potency of glutamate for the orthosteric site in the mGlu5 receptor subtype and are active in animal models of positive and negative symptoms. Moreover these molecules increase the cortical and hippocampal expression of proteins related to synaptic plasticity and reverse cognitive deficits induced by NMDA receptor antagonists. The final talk will have Nick Brandon discuss new data with the striatal enriched phosphodiesterase PDE10A. PDE10A is a dual cAMP and cGMP PDE. Theoretically inhibition of PDE10A has the potential to treat all symptoms of schizophrenia and he will provide data backing up these claims from a range of preclinical models utilizing the compounds MP-10, which has entered clinical development, papavenerine and a novel compound known as WEB-3. Furthermore he will discuss how PDE10A regulates AMPAR and other synaptic proteins and how its own regulation by post-translational mechanisms could be important for drug effects. Discussion: The session will be concluded with an open discussion led by Tony Grace on the four talks with the hope of rationalizing the different approaches in the context of circuitry and etiology of the disease process.

doi:10.1016/j.schres.2010.02.036

THE MGLU2 RECEPTOR AS A NOVEL DRUG TARGET FOR SCHIZOPHRENIA

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This presentation will review the metabotropic glutamate (mGlu2 receptor as a novel target for schizophrenia. The focus is on preclinical studies with orthosteric mGlu2/3 agonists, but data on positive allosteric modulators (PAM's) for mGlu2 will also be discussed. The acute administration of non-competitive N-methyl-D-aspartate (NMDA) receptor antagonists (phencyclidine, ketamine and MK-801) is a commonly used experimental model of schizophrenia because in humans these drugs induce symptoms common to schizophrenia (Javitt and Zukin, 1991). In rodents, the effects of NMDA receptor antagonists manifest as increases in locomotor activity, stereotypies impaired cognition and attentional deficits. Evidence suggest that the behavioral effects of NMDA receptor antagonists may be mediated by increased limbic forebrain release of glutamate dopamine, norepinephrine, and serotonin and inhibition of GABAergic neurotransmission. Group II mGlu receptors (mGlu2 and mGlu3) are located in forebrain and limbic brain regions and function as presynaptic autoreceptors to limit excessive glutamatergic neurotransmission (Scheppe, 2001). As excessive glutamatergic neurotransmission has been implicated in the pathophysiology of schizophrenia, stimulation of group II mGlu receptors may represent a potential target for the treatment of the disorder (Schoepf and Marek, 2002). In pre-clinical animal models, agonists of mGlu2/3 receptors (eg LY379268) block many of the behavioral effects of NMDA receptor antagonists. Moreover, mGlu2/3 receptor agonists have been shown to normalize increased glutamate and catecholamine efflux in limbic brain regions after NMDA receptor antagonism (Lorrain et al., 2003, Schoepf and Swanson 2005). Preclinical studies using transgenic knock-out mice for mGlu2, and mGlu3 receptors and also double mGlu2/3 knock-outs, support a role of mGlu2 in the antipsychotic like properties of mGlu2/3 agonists (Fell et al., 2003). In addition, both in vitro and in vivo data exclude direct interactions of LY379268 with the dopamine D2 receptor (Nelson et al., 2008 and Fell et al., 2009, but see Seeman et al, 2009) pointing towards a novel mechanism of antipsychotic action. Preliminary clinical data supports antipsychotic efficacy of an mGlu2/3 agonist produg in schizophrenic patients (Patil et al., 2007). Several allosteric potentiators (PAM's) of mGlu2 receptors have been described (Fraley et al., 2009). These PAM's act at a site within the seven transmembrane domain and induce a leftward shift in the glutamate concentration-response curve. PAM's are selective for mGluR2 and do not potentiate responses to the activation of mGluR3 or other mGlu receptor subtypes. Compounds such as BINA blocks PCP (but not amphetamine) induced hyperlocomotor activity and disruptions in PPI in mice (Galici et al., 2006). A recently study also suggests that BINA can reverse the increase in BOLD fMRI signal in the rat brain induced by PCP (Jones et al., 2008). Together these data suggests that like orthosteric agonists of mGlu2/3 receptors, selective mGlu2 PAM's have efficacy in animal models of psychosis and could offer utility as a novel approach for the treatment of schizophrenia. In addition, the mechanism of allosteric modulation could potentially offer advantages in terms of improved tolerability and without the development of tolerance when compared to classical orthosteric agonists.

doi:10.1016/j.schres.2010.02.037

DEVELOPMENT OF GLYT1 INHIBITORS FOR THE TREATMENT OF SCHIZOPHRENIA

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The type 1 glycine transporter (GlyT1) maintains synaptic concentrations of the NMDA receptor co-agonist glycine at subsaturating levels. Inhibition of GlyT1 is predicted to increase synaptic glycine concentrations and thereby augment NMDA receptor mediated neurotransmission. Based upon the hypothesis that deficits in NMDA receptor function contribute to many of the symptoms of schizophrenia, GlyT1 inhibition has been proposed as a potential therapeutic approach to this devastating disorder. The GlyT1 inhibitor, PF-3463275, potently binds to and inhibits the function of the human GlyT1c transporter expressed in HEK293 cells as well as endogenously expressed GlyT1a in human SK-N-MC neuroblastoma cells. Studies in rodents confirm that PF-3463275 and its analogs increase extracellular concentrations of glycine as measured in CSF or in forebrain regions by microdialysis and that this increase is associated with enhanced signaling at the NMDA receptor. Although inactive alone, PF-3463275 was shown to augment the improvement in PPI produced by a subthreshold dose of risperidone in poor gating C57BL/6j mice. The improvement in sensorimotor gating occurred at doses of PF-3463275 below those required to produce increases in CSF glycine. In the rat, PF-3463275 and its analogs were shown to prevent or reverse the disruption of auditory gating produced by amphetamine in the CA3 hippocampus and to prevent MK-801 induced deficits in working memory assessed in a radial arm maze task (RAM). Again, these effects were observed at doses that did not elevate CSF glycine concentrations. In contrast, high doses of glycine were also effective in PPI and RAM but only at doses producing significant increases in CSF glycine. Finally, at exposures found to be effective in PPI and RAM, PF-3463275 prevented the disruptive effects of ketamine in a spatial delayed response test in nonhuman primates. Phase 1 studies in healthy volunteers indicate that PF-3463275 is safe and well-tolerated at doses producing 2-3 fold elevations in CSF glycine. Based on the conclusion that inhibition of GlyT1 preferentially elevates glycine at the synaptic level, PF-3463275 appears to be an acceptable tool for testing the hypothesis that GlyT1 inhibitors will be useful in the treatment of schizophrenia.

doi:10.1016/j.schres.2010.02.038
MGLU5 RECEPTOR POSITIVE ALLOSTERIC MODULATORS AS PUTATIVE ANTIPSYCHOTIC AGENTS

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The glutamate hypothesis of schizophrenia suggests that N-Methyl-D-Aspartic acid (NMDA) receptor function is dysfunctional in schizophrenia and may be responsible for the positive, negative and cognitive symptoms found in the disorder. One approach to modulate glutamate function is via activation of mGlu5 receptors which enhances NMDA receptor function. mGlu5 positive allosteric modulators enhance the potency of glutamate for the orthosteric site in the mGlu5 receptor subtype and are active in animal models of positive and negative symptoms. Moreover these molecules increase the cortical and hippocampal expression of proteins related to synaptic plasticity and reverse cognitive deficits induced by NMDA receptor antagonists. This overall preclinical profile suggests that mGlu5 positive allosteric modulators may be beneficial across all symptom domains in schizophrenia.

doi:10.1016/j.schres.2010.02.039

EVALUATION OF PDE10A INHIBITORS IN MODELS OF THE POSITIVE, NEGATIVE AND COGNITIVE DOMAINS OF SCHIZOPHRENIA AND ADVANCES IN THE UNDERSTANDING OF THE MECHANISM AND BIOLOGY OF THIS APPROACH

Nicholas Brandon
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Phosphodiesterase 10A (PDE10A) is a dual specificity PDE, degrading both cAMP and cGMP and is remarkable for a highly enriched striatal expression pattern within so-called ‘Medium Spiny Neurons’ (MSNs). This expression pattern stimulated immediate interest in a potential role for this enzyme in treating the positive symptoms of schizophrenia. Utilizing PDE10a KO mice and an increasing repertoire of specific inhibitors it has been shown that PDE10a inhibition has a strong anti-psychotic profile in preclinical models. We will present new data showing that this mechanism also shows promising efficacy in models of cognition, and the negative symptoms of schizophrenia, two disease domains that are underserved by current treatments. To this end we will present data with the compounds MP-10, which has entered clinical development, papaverine and a novel compound known as WEB-3. Specifically these compounds show an ability to increase sociality in BALB/cj mice in the Social Approach/Social Avoidance assay, reverse the effects of chronic MK-1801 treatment in a forced swim test, enhance social odor recognition in mice, and improve novel object recognition in rats. We will also present data confirming their anti-psychotic profile and exploring the neurochemical correlates of these effects. In addition we have been very interested in understanding the cellular effects of these compounds in the brain. In particular we have seen that they regulate the phosphorylation status of a panel of glutamate receptor subunits in the striatum. Strikingly PDE10A inhibition increased the phosphorylation of the AMPAR GluR1 subunit at residue serine 845 at the cell surface. In addition we have investigated the cell biology of this enzyme and will show that phosphorylation and palmitoylation of PDE10A are critical to determine the subcellular localization of the enzyme. The relationship of small molecule inhibition to such dynamic processes will be discussed. Together, our results will suggest that PDE10A inhibitors show broad spectrum efficacy in pre-clinical models and will provide insight into mechanisms of action of these compounds.

doi:10.1016/j.schres.2010.02.040

Symposium 5
EARLY INTERVENTION SERVICES FOR FIVE YEARS?
Co-Chairpersons: Merete Nordentoft, Ashok Malla
Sunday, 11 April, 2010 - 3:30 pm - 5:30 pm

Overall Abstract: A critical period up to five years after onset of illness has been hypothesized to represent a window of opportunity for influencing long-term outcome. Extending specialized early-intervention service up to five years may allow the beneficial effects of the specialized service to continue beyond this high-risk period, through consolidation of improved social and functional outcome. Specialized Early Intervention services are characterized by comprehensive, multi-modal and phase-specific treatment of first-episode psychosis, modified to suit the needs of this patient population (including intensive/assertive case management and family involvement). In this symposium we will present results from five-year follow-up of the Danish OPUS trial (RCT), suggesting a loss of the short-term (two years) gains on multiple dimensions (adherence, relapse, substance abuse, negative symptoms, functional outcomes, use of inpatient services, and user satisfaction) made by patients treated in a Specialized Early Intervention service compared to patients treated in standard treatment, and we will present the design and preliminary results a Canadian and a Danish RCT comparing extension of Specialized Early Intervention service to five years in comparison to routine care after initial two years of Specialized Early Intervention. These results will be discussed in the context of the critical period hypothesis.

A RANDOMIZED CONTROLLED EVALUATION OF “EXTENDED SPECIALIZED EARLY INTERVENTION SERVICE” VS. “REGULAR CARE” FOR LONG-TERM MANAGEMENT OF EARLY PSYCHOSIS: A PILOT STUDY

Ashok Malla1,2, S. Abadi1,2, R. Joober1,2, E. Latimer1,2, N. Schmitz1,2, T. Brown1,2, A. Abdel-Baki3,4, R. Norman5,6, M. Nordentoft7, S. Iyer1,2
1Prevention and Early Intervention Program for Psychoses, Douglas Mental Health University Institute, Montreal, Quebec, Canada; 2McGill University, Montreal, Quebec, Canada; 3Centre Hospitalier de l’Université de Montréal, Montreal, Quebec, Canada; 4Université de Montréal, Montreal, Quebec, Canada; 5Prevention and Early Intervention Program for Psychoses, LHSC, London, Ontario, Canada; 6University of Western Ontario, London, Ontario, Canada; 7University of Copenhagen, Copenhagen, Denmark

Introduction: Short term benefits (2 years) of Specialized Early Intervention (SEI) services for treatment of a first episode of psychosis (FEP) are not sustained when patients are transferred to regular care. Optimum length of SEI services remains to be determined.

Objective: To carry out a randomized controlled trial (RCT) of extending SEI service for an additional three years compared to “regular” care after both groups have received two years of SEI treatment.

Hypothesis: The experimental group (extended SEI) will have better clinical and functional outcomes and be cost effective compared to the control group (regular care).
METHODS: With the aim of randomizing a total of 200 patients following two years of SEI service for their FEP, 90 patients were randomized either to extended SEI or to regular care. Outcome evaluations to assess symptoms, functioning and service utilization are carried out at entry and every three months. In this report we will report only the method and preliminary results on the sample recruited thus far.

RESULTS: Thirty-nine (81.2%) of the 48 patients approached agreed to be randomized. Patients were young (mean age 25), mostly male (n = 26) with a diagnosis of Schizophrenia Spectrum Psychosis (71%). The average length of follow up to date is 52 weeks (s.d. = 35.9; range 1.0 to 98.1 weeks). Treatment discontinuation in the experimental and control conditions were 0 and 15%, respectively.

CONCLUSION: The preliminary results show the feasibility for carrying out such a study. The challenges of conducting a long termRCT will be discussed.

doi:10.1016/j.schres.2010.02.042

THE OPUS – TRIAL; A RANDOMISED SINGLE-BLINDED TRIAL OF INTEGRATED VERSUS STANDARD TREATMENT FOR PATIENTS WITH A FIRST EPISODE OF PSYCHOTIC ILLNESS – RESULTS OF FIVE-YEARS FOLLOW-UP AND PRESENTATION OF A NEW TRIAL

Merete Nordentoft, Marianne Melau, Pia Jeppesen, Lone Petersen, Anne Thorup, Johan Øhlenschlager, Phuoc Le Quach, Torben Østergaard Christensen, Gertrud Krapur, Per Jørgensen, Mette Bertelsen
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Context: Intensive early treatment for first episode psychosis has shown to be effective. It is unknown if the positive effects are sustainable over time.

Objective: To determine long term effects of specialized assertive early intervention programme (OPUS) for first episode psychotic patients.

Design: Single-blinded randomised controlled trial of two years of specialized assertive early intervention programme versus standard treatment. Follow-up at two and five years.

Patients: 547 first-episode psychotic patients. 369 patients were interviewed after two years, 301 after five years. All patients were followed for five years in the registers.

Interventions: Two years of OPUS treatment versus standard treatment. OPUS treatment consisted of ACT with family involvement and social skills training. Standard treatment offered treatment as usual.

Results: At five-year follow-up, the effect of the treatment seen after two years (psychotic dimension: $-0.32$ 95% CI $-0.55$ to $-0.06$, P = 0.02, negative dimension: $-0.45$ 95% CI $-0.67$ to $-0.22$, P = 0.001) had equalized between treatment groups. A significantly smaller percentage of patients from the experimental group were living in supported housing (4% versus 10%, OR 2.3, 95% CI 1.1 to 4.8, P = 0.02) and were hospitalized fewer days (mean days 149 versus 193, mean difference 44, 95% CI 0.15 to 88, 12 P = 0.05) during the five-year period.

Conclusions: The OPUS treatment improved clinical outcome after two years, but the effects were not sustainable up to five years after. A difference on supported housing and use of bed days was found after five years in favour of the OPUS treatment. In a new trial we will randomize 400 patients to two years versus five years of specialized assertive treatment. Researchers will be kept blind to treatment allocation, randomization will be centralized and computerized with concealed randomization sequence. Primary outcome measure will be negative symptoms. The results will guide the implementation of specialized early intervention services both in Denmark and in other countries.


doi:10.1016/j.schres.2010.02.043

HOW LONG SHOULD EARLY INTERVENTION LAST IN THE FIRST EPISODE PSYCHOSIS?: INSIGHTS FROM THE DISCONTINUATION PROTOCOL OF THE CANTABRIA’S FIRST EPISODE CLINICAL PROGRAMMES (PAFIP CLINICAL PROGRAMME)

Jose’ Vazquez-Barquero1,2, Rocío Perez-Iglesias1,2, Benedicto Crespi-Facorro1,2, Ignacio Mata2, Jackeline van Don2
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Introduction: In today’s treatment guidelines of schizophrenia, neuroleptic maintenance is the recommended strategy for both multiple and first episode patients, however, it is well known that there are risks associated to long term neuroleptic maintenance. Given this concern and the resistance to maintenance antipsychotic treatment by first-episode patients, it has repeatedly been suggested that prescribed discontinuation of antipsychotics should be contemplated in remitted first episode psychosis. However despite its relevance there are not many studies exploring prospectively the consequences of guided discontinuation in remitted first episode psychosis.

Objective: The objective of this presentation is to describe, using data from the Cantabria’s First Episode Psychosis Clinical Program (PAFIP), the long term outcome of patients undergoing guided discontinuation of antipsychotic treatment.

Methods: For this 46 remitted first episode patients were incorporated into a guided antipsychotic discontinuation protocol. A follow-up of 18 months was conducted. The main outcome measure was clinical relapse. Clinical and social reductors of relapse were also explored.

Results: The study demonstrated, among other things, high rates of relapse after guided discontinuation of antipsychotic treatment (58.7% in the first 18 months), been the risk significantly higher for patients with a diagnosis of schizophrenia or schizophreniform disorder (66.7%) than in those affected by a brief psychotic disorder. While the Early Signs Scale did not predict the risk of relapse, certain clinical factors such as severity of symptoms or the need of hospitalization in the first episode or the use of certain substances (cannabis and cocaine) appear to confer a higher risk for relapse. Further research is needed to elaborate more efficient discontinuation protocols and to find predictors of successful discontinuation for the appropriate selection of first episode patients to be included in these protocols.

doi:10.1016/j.schres.2010.02.044

IT TAKES TWO TO TANGO: RESEARCH ON ACT IN EARLY PSYCHOSIS AND IMPLICATIONS FOR DAILY PRACTICE

Giel Verhaegh
Mental Health Care Eindhoven, University of Tilburg

Results from scientific research often don’t find an enthusiastic feeding ground. Both dissemination and implementation of research findings do not occur automatically. On the other side research processes do not take account of practice based evidences, practical impossibilities and deviating priorities. In
this presentation we address the necessity of a two sided cooperation between research and daily practice to achieve successful improvement and implementation of the quality of mental healthcare. We present study results as examples and demonstrate experiences during the research process of a recently accomplished PhD-study on the effectiveness of Assertive Community Treatment in early psychosis. The study was carried out in two mental health organizations in the south of Holland (mental healthcare Midden Brabant and mental healthcare Eindhoven). We address the following topics: How to integrate research tasks in daily practice? How to improve the treatment program based on research results during the study? How to organize an active client feedback system in regard to research input? What explanations we found for not benefiting from research findings? What pitfalls we encountered and what practical solutions we found for obstructions?

doi:10.1016/j.schres.2010.02.045

Symposium 6
MULTIPLE MECHANISMS FOR THE GENETIC BASIS FOR SCHIZOPHRENIA
Co-Chairpersons: Lynn DeLisi, Pablo Gejman
Sunday, 11 April, 2010 - 3:30 pm - 5:30 pm

Overall Abstract: Over the past two decades tremendous advances have occurred in the field of molecular genetics, providing new technology each year that has been able to be applied toward understanding particularly the many complex medical disorders that do not follow usual Mendelian patterns of inheritance within families. Schizophrenia is one of these illnesses for which a genetic cause has remained a puzzle to all involved in its search. The following symposium is organized to cover all major new genetic approaches that are now available to uncover genetic risk factors for schizophrenia and the speakers are those investigators who have specifically contributed new findings in pursuit of specific genetic hypotheses. Dr. Sibylle Schwab will discuss the latest knowledge about the candidate genes that were thought to be established as risk genes for schizophrenia, at least up to a few years ago (e.g., Dysbindin, Neuregulin). Pablo Gejman will discuss findings from the new large Genome-wide association studies (GWAS). Mary-Claire King will discuss her hypothesis focused on findings from the new large Genome-wide association studies (GWAS) of large cohorts have identified several disease loci (including single nucleotide polymorphisms and copy number variants), and strongly suggest a polygenic background. Furthermore, the new molecular data is redefining the phenotypic boundaries of the disorder as pleiotropy with bipolar disorder, autism, and epilepsy has been observed. On the other hand, none of the classical candidate genes has been strongly supported in European samples. Two fundamental problems for the field are: 1- how to follow-up GWAS results and, 2- the characterization of missing heritability. The first question pertains to additional exploratory analyses of GWAS data, the prioritization of genomic regions for re-sequencing to find the genetic variant underlying associations, the selection of a set of functional studies (e.g., genome-wide expression analysis), and the integration of sequence and functional data. These approaches, if successful, will lead to physiological explanations and to the testing of new hypotheses in epidemiological designs. The second question is a subject of controversy among competing research programs.

doi:10.1016/j.schres.2010.02.047

MULTIPLE COMMON GENE VARIANTS IN SZ: THE GWAS DATA
Pablo Gejman
Northshore University Health Systems, Evanston, IL, USA

Schizophrenia is a psychotic disorder with peak incidence in young males and is associated with lower fertility. Although epidemiological studies have demonstrated a strong genetic component, its pathophysiology remains largely unknown. Genome-wide association studies (GWAS) of large cohorts have identified several disease loci (including single nucleotide polymorphisms and copy number variants), and strongly suggest a polygenic background. Furthermore, the new molecular data is redefining the phenotypic boundaries of the disorder as pleiotropy with bipolar disorder, autism, and epilepsy has been observed. On the other hand, none of the classical candidate genes has been strongly supported in European samples. Two fundamental problems for the field are: 1- how to follow-up GWAS results and, 2- the characterization of missing heritability. The first question pertains to additional exploratory analyses of GWAS data, the prioritization of genomic regions for re-sequencing to find the genetic variant underlying associations, the selection of a set of functional studies (e.g., genome-wide expression analysis), and the integration of sequence and functional data. These approaches, if successful, will lead to physiological explanations and to the testing of new hypotheses in epidemiological designs. The second question is a subject of controversy among competing research programs.

CANDIDATE GENES FROM LINKED CHROMOSOMAL REGIONS: WHAT HAPPENED TO NEUREGULIN AND DYSBINDIN?
Sibylle Schwab1, Dieter Wildenauer2
1University of Western Australia Centre for Medical Research, Nedlands, Australia; 2University of Western Australia, Graylands Hospital, Mt. Claremont, Australia

With respect to the topic of this symposium – multiple mechanisms for the genetic basis for schizophrenia – the two candidate genes dysbindin and neuregulin seem to be the dinosaurs under the currently discussed candidate genes for schizophrenia. Some time ago these genes dominated the research until the new aera of whole genome wide association studies and
copy number variation came onto the scene. Both of these genes seem to play a minor role in discussions since. It would be worthwhile to discuss what made them once the most attractive candidate genes and how good the evidence is for their involvement in deregulating pathways which might play key roles in the development of the disorder. Using well characterized family samples with schizophrenia, both genes have been identified about eight years ago after systematic screening of the genome. No obvious disease causing changes in the DNA sequence has been identified so far. In this regard, we do not know more or less than for any of the more recently identified candidate genes. We will discuss in more detail the current knowledge related to these two genes.

doi:10.1016/j.schres.2010.02.048

AN EVOLUTIONARY PERSPECTIVE ON THE GENETICS OF SCHIZOPHRENIA

Ezra Susser
Columbia University Medical Center, New York, NY, USA

This presentation will comprise three parts. First I will describe evolutionary perspectives on medicine which are being elaborated but are not familiar to most schizophrenia researchers. Second I will synthesize the most recent evidence on the distribution of schizophrenia by time and place, selectively, in order to provide grounding for evolutionary questions. Third I will present theories on evolution and schizophrenia that are found in the current literature. Finally I will consider the match between these theories and the genetic and epidemiologic evidence now available.

doi:10.1016/j.schres.2010.02.049

Symposium 7
IMPROVING NEUROCOGNITION IN SCHIZOPHRENIA: REPORTS FROM NIMH TURNS AND MATRICS-CT
Co-Chairpersons: Stephen R Marder, Robert W Buchanan
Monday, 12 April, 2010 - 1:30 pm - 3:30 pm

Overall Abstract: Improving Signal Detection in Schizophrenia Clinical Trials by Multiple MethodsChair & Discussant: Wolfgang FleischhackerPresenters: David Daniel, Michael Detke, John Harrison, Nina SchoolerClinical trials of approved medications for schizophrenia fail more frequently than their powering indicates they should (A. Khan, 2005). Furthermore, the drug-placebo separation on new drug applications for schizophrenia has been worsening over the last decades (N. Khin, 2009). This may be the result of at least two fundamental problems: firstly, some patients enrolled into clinical trials may be insufficiently ill and/or inaccurately diagnosed to benefit from the therapies being tested; and secondly, assessment methods for detecting efficacy may be inadequate and/or inconsistent. In this symposium, each speaker will present data on a different approach to improving signal detection in schizophrenia clinical trials, focusing on empirical evidence for the effectiveness of these methods. Dr. David Daniel will present data on the effectiveness of rater training that utilizes ongoing instruction, monitoring and feedback to address scoring ability, inter-rater reliability, interviewing competency and diagnostic skills on clinician-rated scales. Dr. Michael Detke will present data on the effectiveness of centralized raters and centralized review/monitoring, in patient ascertainment and outcomes assessments, again on subjective clinician-assessed scales. The last two presenters will focus on other kinds of outcomes: Dr. John Harrison will present data from trials that have employed the measures that comprise the MATRICS Consensus Cognitive Battery, as well as test data collected using both paper-and-pencil assessments and computerized cognitive outcome measures. Dr. Nina Schooler will address the peculiar challenges of functional outcome measures and in defining appropriate long-term outcome measures beyond just symptom remission, as well as strategies for their accurate assessment. She will also focus on the role of informants.

doi:10.1016/j.schres.2010.02.050

SEARCHING FOR COGNITIVE ENHANCERS IN SCHIZOPHRENIA: THE TURNS PROGRAM STRATEGY

Donald C. Goff
Massachusetts General Hospital Boston, MA, USA

Ever since Kraepelin first characterized the disorder now called schizophrenia as dementia praecox, cognitive deficits have been considered a hallmark of its pathology. Despite this there is no treatment with proven efficacy that has been developed. Recent results from the NIMH CATIE study, as well as other studies, have shown that the second generation antipsychotic drugs have no direct or primary effect that enhances cognition beyond the reduction of psychotic symptoms. Thus cognitive enhancing agents will most likely need to be administered as adjuncts to APDs. The NIMH TURNS program was established to identify compounds with the potential to enhance cognition in patients with schizophrenia. To do so, agents with affinities for biologic targets involved in cognitive pathology and enhancement were sought to evaluate their efficacy in the context of clinical trials. Thusfar, the TURNS program has evaluated close to 100 compounds nominated by the pharmaceutical and biotechnology industry and selected several for clinical testing. This presentation will describe this process, the compounds reviewed and selected and the issues and factors that have influenced this process. It will also present results with work done compounds selected illustrated by the D-1 agonist DAR100-A that is currently being studied.

doi:10.1016/j.schres.2010.02.051

EFFECTS OF INTRANASAL AL-108 (DAVUNETIDE) ON NEUROCOGNITION AND FUNCTIONAL OUTCOME IN SCHIZOPHRENIA

Daniel C. Javitt
Nathan Kline Institute Orangeburg, NY, USA

Background: Persistent neurocognitive dysfunction is a primary predictor of impaired long-term outcome in schizophrenia. AL-108 (Davunetide) is an intranasal drug product containing NAP, an 8 amino-acid peptide (Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln; NAP/SIPQ, MW = 824.9)
fragment of the much larger Activity-Dependent Neuroprotective Protein (ADNP), which participates in neurodegeneration and neuro-protection. AL-108 acts, in part, by stabilization of microtubular structure. AL-108 is active in rodent models of neurodegeneration and was originally developed for treatment of neurocognitive dysfunction in Alzheimer disease and mild cognitive impairment.

Methods: 69 subjects (54 completers) were randomized in a 12-week, parallel group randomized controlled clinical trial of 2 doses of AL-108 (5 and 30 mg/d intranasally) vs. placebo. Subjects were 18–60 yr old male and female patients with DSM-IV diagnosis of schizophrenia being treated with oral second generation antipsychotics or first generation injectables with controlled positive and negative symptoms. The primary pre-designated outcome measure consisted of the composite score of the MATRICS Consensus Cognitive Battery (MCCB). Secondary outcome measures included the UCSD Performance-based Skills Assessment (UPSA) total score and measures of positive (BPRS) and negative (SANS) symptoms.

Results: No significant beneficial effects of AL-108 were observed on cognition as assessed using the MCCB. Absolute magnitude of change was 4.6 ± 7.2 (p = .4) and 3.9 ± 4.6 (p = .6) MCCB units for the 5 and 30 mg doses, respectively, vs. 3.2 ± 4.9 for placebo. 6/19 patients receiving 5 mg AL-108 and 3/19 receiving 30 mg showed > 9 point change on MCCB vs. 1/19 receiving placebo. Despite lack of significant effect on MCCB, a significant improvement in UPSA performance was observed for AL-108 vs. placebo (p = .048), with significant change in the 5 mg group vs. placebo (p = .015). Differences may have been driven in part by lower baseline UPSA scores in the 5 mg (83.7 ± 7.6) vs. placebo (91.9 ± 19.0) group, but nevertheless survived co-variation for baseline score. No significant beneficial effects were observed on either positive or negative symptoms for either treatment dose. Both doses of AL-108 were well-tolerated without serious adverse events.

Discussion: AL-108 is a novel peptide under development for treatment of cognitive dysfunction associated with dendritic pathology. Although no significant treatment-related effects were observed on cognition, greater change was observed for the experimental, compared with placebo, groups. Significant pro-therapeutic effects of AL-108 were observed on the UPSA, a proposed co-primary measure for use in clinical studies of neurocognition in a pre-planned analysis. However, given baseline differences, these findings should be interpreted with caution. Overall, AL-108 appeared safe and well-tolerated. Further studies with this compound in schizophrenia appear warranted.

doi:10.1016/j.schres.2010.02.052

VALIDATION OF INTERMEDIATE (CO-PRIMARY) MEASURES FOR CLINICAL TRIALS OF COGNITION-ENHANCING DRUGS FOR SCHIZOPHRENIA

Michael F. Green, Nina R. Schooler, Robert S. Kern, Larry Seidman, John Sonnenberg, William Stone, David Walling
Semel Institute at UCLA Los Angeles, CA, USA

Background: One key obstacle for drug development of cognition-enhancing drugs in schizophrenia is the lack of a consensus regarding functionally meaningful intermediate or co-primary measures that can be used in relatively short-term clinical trials of cognition enhancing drugs. In such trials, change in community functional outcomes such as work and independent living is unlikely. The Food and Drug Administration has taken the position that improvement on cognitive performance tests would be necessary, but not sufficient, for approval of a drug for cognitive impairment in schizophrenia. Also needed would be improvement on a functionally meaningful measure. MATRICS-CT (co-primary and translation) is an NIMH Initiative. It is an industry – government – academic consortium that was formed to facilitate the development of pharmacological agents for cognitive impairment in schizophrenia. MATRICS-CT is currently conducting the Validation of Intermediate
Measures (VIM) study to assess possible intermediate measures on their psychometric properties, validity, and practicality/tolerability. The measures in this study were selected based on rigorous review by a RAND panel convened in February 2008.

**Methods:** A total of 166 patients with a diagnosis of schizophrenia and who were clinically stable outpatients were assessed at baseline and again at four weeks at four sites. Participants received two types of intermediate measures: performance-based measures of functional capacity and interview-based measures of cognition. Three measures from each category were selected through the RAND Panel process for inclusion in the VIM study. Criteria for evaluation were: 1) psychometrics, including: test-retest and inter-rater reliability; and utility as a repeated measure, 2) validity, including: correlation with measures of cognitive performance; and correlations with measures of real-life functioning; and 3) practicality and tolerability, including: ease of set-up, scoring, and administration of the measures; ratings of participant satisfaction with the measures; and length of administration.

**Results:** Data collection was completed in July 2009 and the project is currently in a data analysis phase. Valid assessments were conducted on 163 participants at baseline, and 144 of these individuals were retested at 4 weeks. The mean age of the sample is 43.7 (10.1) years, the mean education is 12.3 (2.0) years, the mean duration of illness is 20.3 (10.6) years, and the sample is 36% female. The range in level of independent living is suitably broad: mean of 4.1 (2.1) on a 7-point rating scale.

**Discussion:** The data will be presented for each of the intermediate measures being evaluated (3 performance-based and 3 interview-based) according to each of the criteria (psychometrics, validity, and practicality/tolerability). Recommendations for measures will be made based on these criteria. Strengths and weakness of each measure will be discussed in terms of their expected performance in a short-term psychopharmacology clinical trial.

doi:10.1016/j.schres.2010.02.054

**Symposium 8**
**NEW DEVELOPMENTS IN FAMILY PSYCHOEDUCATION**
**Co-Chairpersons:** Gabriele Pitschel-Walz, Lisa Dixon
**Monday, 12 April, 2010 - 1:30 pm - 3:30 pm**

**Overall Abstract:** Family psychoeducation should provide relatives with information and therapeutic support to better cope with their relative’s mental illness and with their own illness-related problems. It is well documented that family psychoeducation decreases relapse rates of individuals with schizophrenia. New studies investigate the effective elements of psychoeducational interventions, challenges of its dissemination, and effects of various family intervention programmes in different cultural settings or for special target groups like families of patients with co-occurring substance abuse. Tania Lincoln will present her meta-analytic data on the effectiveness of psychoeducation for schizophrenia and will show that only psychoeducational interventions that included families and were not focussed on the patients alone achieved significant results. Isabel Montero will describe the dissemination and effects of family interventions in Spain. She found a lack of family interventions in routine care, but when they are applied the results are comparable to those of study interventions. Some strategies to overcome the obstacles for the implementation will be suggested. Guiseppe Carrà will report on a randomised study that tested two unifocal family intervention programmes with different intensity in Milano, Italy. After 12 months the more intensive family intervention showed some advantages, but the benefits declined at 24 months. He will advocate “third generation” family interventions that deal with the long-term needs of the families. Kim Mueser will summarize the results of a randomised study on the comparative effects of two family intervention programmes for patients with co-occurring substance abuse: the new developed programme Family Interventionfor Dual Disorder (FIDD) vs. a general brief family psychoeducation programme. In the discussion section of the symposium we will work out the implications of the findings for routine care and for research.

doi:10.1016/j.schres.2010.02.055

**EFFECTIVENESS OF PSYCHOEDUCATION FOR SCHIZOPHRENIA IS FAMILY INCLUSION NECESSARY?**

**Tania Lincoln**
**Philips-Universität Marburg Marburg, Hessen, Germany**

**Background:** Psychoeducation (PE) for schizophrenia is a widely adopted but insufficiently evaluated intervention for patients with schizophrenia. So far, meta-analytic data has demonstrated efficacy for PE as part of a broader family intervention and for PE-focused interventions that include family members. Whether PE directed solely at patients is also effective remains unclear.

**Methods:** We conducted a meta-analysis to evaluate short- and long-term efficacy of PE-focused interventions with and without inclusion of families with regard to relapse, symptom-reduction, knowledge, medication adherence, and functioning. We included randomized controlled trials comparing PE to standard care or non-specific interventions. Among the 2952 publications identified by a keyword procedure in relevant scientific data-bases, 18 studies met our inclusion criteria. These studies were coded with regard to methodology, participants, interventions and validity. Effect sizes were integrated using the fixed effects model for homogeneous effects and the random effects model for heterogeneous effects.

**Results:** Independent of treatment modality, PE produced a medium effect at post-treatment for relapse and a small effect size for knowledge. PE had no effect on symptoms, functioning and medication adherence. Effect sizes for relapse and rehospitalization remained significant for 12 months after treatment but failed significance for longer follow-up periods. Interventions that included families were more effective in reducing symptoms by the end of treatment and in preventing relapse at 7-12 month follow-up. Effects achieved for PE directed at patients alone were not significant.

**Conclusions:** It is concluded that the additional effort of integrating families in PE is worthwhile and the potential mechanisms by which treatment benefits from family-inclusion are discussed.

doi:10.1016/j.schres.2010.02.056

**TRAINING AND DISSEMINATION OF FAMILY INTERVENTION IN SPAIN**

**Isabel Montero**
**University of Valencia Valencia Spain**

**Background:** The transfer of benefits detected in experimental studies to clinical medicine implies a challenge for our psychiatric health services. Implementation in our field is currently low, there are few opportunities for specific training in therapy strategies and the risk of introducing low-cost products with their resulting poor efficiency are some of the reasons that have lead us to develop our project.
Methods: To promote in a real setting therapy strategies that have been empirically demonstrated through the provision of regulated and quality training followed by their supervised application to clinical practice, and ascertaining limits, establishing indicators, evaluating the quality of their application and their effects, thereby obtaining essential information for their future dissemination in clinical practice.

Results: the preliminary results from the mental health services of the Murcia Region are presented. The low application in clinical practice is confirmed, particularly in mental health centres, with therapy/family per year ratios ranging between 0-8. The benefits obtained where strategies have been applied are similar to experimental studies. The greatest shortcomings identified were connecting with the family and the absence of re-call sessions. The current organisation of services and overburdened staff and the need for changes on the part of professionals towards a therapy model that takes setting into account, are underlined as the greatest obstacles for their implementation.

Conclusions: Additional measures are necessary, such as specific funding and professional incentives.

doi:10.1016/j.schres.2010.02.057

MULTIPLE GROUP FAMILY TREATMENT FOR SCHIZOPHRENIA IN ITALY

Guiseppe Carra
Royal Free and University College London United Kingdom

Background: Family psychoeducation has been widely tested in a range of Anglo-Saxon settings (Bustillo et al., 2001) and a few from China (Xiong et al., 1994; Ram et al., 2003; Chien and Chan, 2004). However some evidence from Spanish-speaking immigrants (Telles et al., 1995) and Dutch (Linszen et al., 1996) samples suggest that cultural differences may be an impediment to successfully applying existing family therapy interventions to diverse cultural groups. This study should evaluate the effectiveness of multiple group family treatment for schizophrenia in Italy.

Methods: Relatives were randomly provided with an informative programme (n = 50), or allocated to receive an additional support programme (n = 26). Patients did not attend the programme to overcome cultural and organizational implementation barriers. The 12 and 24 months clinical and family outcomes were assessed.

Results: Patients’ compliance with standard care was greater at 12 months in the more intensive behavioural management group over a control group receiving treatment as usual (TAU) (n = 25). A reduction in levels of expressed emotion (EE), significantly more frequent in those receiving the additional support programme than just the informative, occurred after treatment completion. Other clinical and family outcomes did not differ. However, treatment benefits declined at 24 months, when baseline high EE was again predictive of patient’s admission and relatives were more vulnerable to objective burden. Baseline illness severity variables predicted a number of medium and long-term poor clinical outcomes.

Conclusions: Although family psychoeducation has been tested in a wide range of Anglo-Saxon settings, there remains need to assess outcomes more internationally. Effective family interventions for people with schizophrenia probably require continued administration of key-elements or ongoing informal support to deal with the vicissitudes of illnesses.

doi:10.1016/j.schres.2010.02.058

FAMILY PSYCHOEDUCATION WITH PATIENTS WHO HAVE CO-OCCURRING SUBSTANCE USE DISORDERS AND SEVERE MENTAL ILLNESS

Kim Mueser, Shirley M. Glynn, Haiyi Xie, Roberto Zarate, Corinne Cather, Lindy Fox, Rosemarie Wolfe, Robin E. Clark, James Feldman
Dartmouth Medical School Hanover, New Hampshire, USA

Background: Substance abuse has a negative impact on the course of schizophrenia and bipolar disorder, including precipitating relapses and hospitalizations and worsening social and global functioning. Substance abuse also takes a heavy toll on the family members of persons with these co-occurring disorders, such as increased family stress, burden, and conflict, often culminating in the loss of family support and episodes of homelessness. Despite the development and empirical validation of different family intervention programs for schizophrenia, bipolar disorder, and addictive disorders, little attention has been paid to the development of such programs that target the integrated treatment of severe psychiatric and addictive disorders together. To address this need, we developed and evaluated a family program to treat these comorbid disorders.

Methods: The Family Intervention for Dual Disorder (FIDD) program was developed for persons with schizophrenia, schizoaffective disorder, or bipolar disorder and co-occurring substance abuse, and pilot tested to establish feasibility. The FIDD program includes a combination of psychoeducation about dual disorders, motivational interviewing, communication skills training, and problem solving training, delivered initially in weekly sessions that taper to monthly sessions over 12-18 months. The patient is included in all family sessions. To evaluate the impact of the FIDD program, a randomized controlled trial was conducted at two sites (in Boston and Los Angeles) comparing families randomized to the FIDD program or a brief (6-8 sessions) family psychoeducation program. A comprehensive battery of assessments was conducted at baseline and every six months for three years.

Results: A total of 108 persons with dual disorders and a key family member were recruited into the study and randomized to receive either the FIDD program or the brief family psychoeducation program. Rates of engagement in both family programs were high, 88% and 84% for FIDD and brief family psychoeducation, respectively, but rates of longer term retention and exposure to the core elements in each model were lower, 61% and 55%, respectively. The comparative effects of the two family intervention programs over the three year study period are currently being analyzed. This presentation will summarize those outcomes, with a focus on substance abuse, psychopathology, family knowledge about mental illness, family burden and quality of relationships, and social problem-solving.

Conclusions: The implications of the findings for the role of the family in the treatment of persons with co-occurring severe mental illness and substance use disorders will be discussed.

doi:10.1016/j.schres.2010.02.059

Symposium 9
GENE-BRAIN INTERACTION IN THE PATHOPHYSIOLOGY OF PSYCHOSIS
Co-Chairpersons: Tilo Kircher, Ruben Gur
Monday, 12 April, 2010 - 1:30 pm - 3:30 pm

Overall Abstract: A number of susceptibility genes for psychosis, such as DTNBP1, NRG1, DISC1, G72 and others have been identified. However their pathophysiological mechanisms are not yet fully understood. Traditionally, schizophrenia is being diagnosed according to psycho-
pathological criteria. Yet, there is little data on the interaction between etiological factors, psychopathology and brain function/structure. On the behavioral level, psychopathological symptoms can hardly separate the potential variety of pathophysiological subgroups. Contrary to nosological entities, biologically based phenotypes - referred to as intermediate phenotypes - consisting of neuropsychological, electrophysiological, functional and structural brain imaging parameters, could represent etiological basis more directly. In this symposium, we will try to bridge the gap between brain structure and function, cognition, and their relation to susceptibility genes in schizophrenia, most recently identified through GWAS. The literature will be reviewed and newest findings presented.

doi:10.1016/j.schres.2010.02.060

EMOTIONS, GENES AND THE BRAIN

Ruben Gur, Monica E. Calkins, Amy Pinkham, Raquel E. Gur
University of Pennsylvania Philadelphia, Pennsylvania, USA

There is increased evidence that while schizophrenia is highly heritable, and several candidate genes are implicated by genomewide association studies with some replicated findings, this alone would not be sufficient to harness the power of genomics in the service of improved diagnosis and treatment. Needed are data on intermediate quantitative phenotypes that likely play a role in the cascade leading to the manifestations of schizophrenia and that can point to targets for treatment in specific subgroups of patients. Prior work has focused on cognitive deficits, especially executive functions and memory, which contribute to the devastating effects of schizophrenia on adjustment and employability of patients. We present more recent efforts focusing on emotion processing and social cognition. We will describe a series of studies that have established individual differences in the ability to recognize and express facial and vocal cues of emotion and examine the deficits in schizophrenia. Large scale family studies have demonstrated that these abilities are dysfunctional in patients and are highlyheritable. The deficits appear both for facial affect and for vocal affect (prosody), and indicate deficits in very early processing of the sensory signals. Structural and functional neuroimaging studies offer some clues on the neural substrates of these deficits, and suggest avenues for developing treatment targets. These novel treatments can be applied to specific sub-population of patients and families who suffer from flat or inappropriate affect and would combine pharmacological and behavioral approaches.

doi:10.1016/j.schres.2010.02.061

GENETIC CONTRIBUTIONS OF THE DOPAMINE SYSTEM TO SCHIZOPHRENIA

Alessandro Bertolino
University of Bari Bari Italy

Risk for schizophrenia is largely explained for by genetic variation. Involvement of dopamine in the pathophysiology of schizophrenia has long been hypothesized. The main conceptual basis for this hypothesis is that there is no antipsychotic on the market that does not block the dopamine D2 receptor. However, even though association of the gene for D2 receptors (DRD2) with schizophrenia has been reported in several studies, the specific functional variant has not been firmly established yet. D2 receptors exist in two alternatively spliced isoforms, the D2 long (D2L) located primarily postsynaptically, and the D2 short (D2S) functioning as presynaptic autoreceptor (Usiello et al., Nature 2000). In a recent study we determined that the G allele within an intronic SNP rs1076560 (G/T) is associated with D2S/D2L ratio of splice variants both in human prefrontal and striatal tissue as well as with more efficient activity of prefronto striatal circuits during working memory (Zhang et al., PNAS 2007). In a subsequent study, we have also determined the effects of this functional SNP on mRNA, cognitive, and imaging phenotypes in patients with schizophrenia demonstrating similar effects to those seen in healthy subjects (Bertolino et al., Brain 2009). Moreover, in an effort to establish epistasis with other dopamine genetic variants and because activity of the dopamine transporter is also determined by D2 signaling, we have evaluated the interaction of rs1076560 within DRD2 with the 3’VNTR functional polymorphism of the Dopamine Transporter gene (DAT). Consistent with the known inverted-U like relationship between dopamine signaling and prefrontal neuronal activity, these two genetic variants interact epistatically describing a non-linear profile of activity in prefrontal cortex and in striatum during working memory (Bertolino et al., J Neurosci 2009). Since, D2 signaling within the cortico-striato-thalamic-cortical pathway is denser in striatum, we hypothesized that the effects in prefrontal activity and cognition may also have been associated with genetically determined dopamine D2 signaling in striatum. To test this further hypothesis, we have performed another DRD2 genotype-based study with multimodal imaging in 37 healthy subjects undergoing BOLD fMRI during working memory and SPET with [123I]FP-CIT (for DAT binding) and [123I]IBZM (for D2 binding) and [123I]JPF-CIT (for DAT binding). The G allele of rs1076560 is associated with greater striatal binding of both radio-tracers. Moreover, the G allele is associated with a direct relationship between dopamine signaling in the striatum (as measured with factor analysis) and prefrontal activity during working memory, whereas this relationship is negative in subjects carrying the T allele. These results together suggest that DRD2 rs1076560 may be associated with risk for schizophrenia by virtue of these effects on dopamine signaling within specific brain circuits.

doi:10.1016/j.schres.2010.02.062

SINGLE GENETIC VARIANTS FOR SCHIZOPHRENIA AND THE EFFECT ON BRAIN STRUCTURE, FUNCTION AND CONNECTIVITY

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The prevalent model of the aetiology of schizophrenia implicates interactions of genetic variants and environmental factors. In a series of own studies with a large number of subjects, the influence of single genetic variants on behaviour (n = 523 subjects) and brain structure and function (n = 101 controls, n = 24 patients with Sz) was investigated. Among the variants tested were SNPs in NRG1, DTNBP1, NRCN, G72 and CACNA1C. For the genotype variants, an influence on cognitive variables such as verbal fluency and executive functioning could be detected. In addition, several variants e.g. in NRG1, G72 and DTNBP1 showed an influence on neuroticism and schizotypal personality traits. During IMRI scanning, subjects performed several cognitive tasks tapping into domains of working memory, verbal fluency, episodic memory encoding and retrieval as well as attention. During these tasks, carriers of the minor alleles in a number of susceptibility genes exhibited differential activations in prefrontal, temporal and parietal regions that were also found to be differentially activated in patients with schizophrenia. Voxel based morphometry (VBM) analyses revealed differences in brain structures such as the amygdala in carriers of minor alleles in NRG1. Diffusion tensor
imaging (DTI) demonstrated an overlay of middle temporal hyperactivations found during a semantic fluency task in minor allele carriers of DTNBP1 that was accompanied by reduced fractional anisotropy in the same region, among others. The data show that single susceptibility variants for schizophrenia exert an influence on behaviour and neural systems on a structural and functional basis that can already be detected in healthy subjects. These influences were found in regions that are also implied in schizophrenia. These results shed more light on the pathogenetic mechanisms underlying the aetiology of psychiatric disorders and could result ultimately in novel insights into diagnosis, classification and therapeutic strategies of schizophrenia.

doi:10.1016/j.schres.2010.02.063

IMAGING GENETICS IN PSYCHIATRY: DISEASE PATH OR GARDEN PATH?

Michael Owen
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Over the past few years there has been great interest in the use of endophenotypes, especially those based upon neuroimaging, both for risk gene discovery and for studying the function of established risk genes. This approach has been embraced enthusiastically but uncritically. In particular there are concerns about the two major assumptions underlying the use of endophenotypes: that the genetic architecture will be simpler than for disease and that endophenotypes necessarily lie upon the pathway between gene and clinical phenotype. With regard to the latter there have been few if any studies addressing the question of whether imaging endophenotypes mediate the effect of risk genes rather than indexing common risk mechanisms. Given the evidence for pleiotropy in psychiatric genetics this is of particular concern. These issues will be discussed in relation to research on schizophrenia and recommendations for future studies presented.

doi:10.1016/j.schres.2010.02.064

SYMPOSIUM 10
NEURAL SUBSTRATES OF THE ASSOCIATION BETWEEN CANNABIS AND SCHIZOPHRENIA
Co-Chairpersons: Nadia Solowij, F. Markus Leweke
Monday, 12 April, 2010 - 1:30 pm - 3:30 pm

Overall Abstract: Evidence for an association between cannabis use and schizophrenia has grown from large scale epidemiological studies as well as from clinical observation and laboratory studies. Cannabis use can trigger psychotic symptoms or overt schizophrenia in vulnerable individuals and significant recent research has aimed to understand the mechanisms by which this can occur and the inherent vulnerabilities. For example, there is some evidence that individuals with a specific polymorphism of the COMT gene are at risk of developing schizophrenia if they use cannabis during adolescence, a critical neurodevelopmental period. This symposium brings together researchers at the forefront of investigating the interactions between cannabis use or the endogenous cannabinoid system and schizophrenia to present new developments in understanding this interaction. Cecile Henquet will present data from epidemiological and observational studies that inform the gene-environment interactions and raise the question of whether imaging endophenotypes mediate the effect of risk genes rather than indexing common risk mechanisms. Given the evidence for pleiotropy in psychiatric genetics this is of particular concern. These issues will be discussed in relation to research on schizophrenia and recommendations for future studies presented.

CROSS-SENSITISATION BETWEEN CANNABIS AND STRESS: GENE-ENVIRONMENT INTERACTIONS UNDERLYING PSYCHOSIS

Cecile Henquet
Maastricht University, Maastricht, Netherlands

Gene-environment interactions are likely to underlie the association between cannabis and psychosis. Epidemiological data and observational studies in daily life will be presented to further examine these underlying mechanisms of gene-environment interaction, as well as possible self-medication effects. In addition to the use of cannabis, the urban environment and traumatic experiences during childhood have been found to increase the risk for psychotic illness. It is unknown, however, whether these environmental factors may interact with cannabis use as well in increasing psychosis risk. Prospective data from the German EDSP study, the Greek National Perinatal survey and the Dutch NEMESIS study will be presented to show that the effects of cannabis may be particularly detrimental for those who are growing up in an urban environment or for individuals who have experienced childhood trauma.

CANNABIS, COGNITION AND SCHIZOPHRENIA: STRUCTURAL BRAIN ALTERATIONS AND SYMPTOMATOLOGY

Nadia Solowij
University of Wollongong, Wollongong, Australia; Schizophrenia Research Institute, Sydney, Australia

Chronic cannabis use has been found to result in cognitive deficits that resemble the cognitive endophenotypes of schizophrenia. We have conducted a number of studies in adult and adolescent cannabis users aimed at better understanding these cognitive deficits and their neural substrates. Deficits in verbal learning and memory are prominent and associated with the duration, frequency, dose and age of onset of cannabis use. The adolescent brain appears to be more vulnerable to the deleterious effects of cannabis. Our neuroimaging studies of chronic cannabis users have found significant dose-related reduction of the hippocampus, of a magnitude similar to that seen in schizophrenia, and this was associated with the development of subclinical positive psychotic symptoms. Negative symptoms and depressive symptoms were also elevated. Changes to the amygdala and cerebellum were...
observed and suggest alterations in the functional circuitry of the brain in association with cannabis use and symptoms. Data examining cognition and brain structural alterations in people with first-episode psychosis or established schizophrenia and comorbid cannabis use will also be presented and discussed.

doi:10.1016/j.schres.2010.02.067

ACUTE NEURAL EFFECTS OF THE MAIN INGREDIENTS OF CANNABIS: IMPLICATIONS FOR PSYCHOSIS

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Background: Delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD), the two main ingredients of the cannabis sativa plant have distinct symptomatic and behavioural effects. THC can induce psychotic symptoms and anxiety, impair memory and psychomotor control in healthy individuals, exacerbate existing psychotic symptoms, anxiety and memory impairments in patients with schizophrenia and is thought to be the ingredient responsible for the increased risk of developing schizophrenia following regular cannabis use. In contrast, CBD has anxiolytic and possibly antipsychotic properties and does not impair memory or other cognitive functions. The neural basis for these distinct effects of THC and CBD on psychiatric symptoms and cognitive function is unclear. We combined functional magnetic resonance imaging (fMRI) in healthy volunteers and pharmacological challenge with oral THC and CBD to examine the neural correlates of the various symptomatic and cognitive effects of cannabis. We also examined whether THC and CBD had opposite effects on regional brain function.

Methods: Fifteen healthy men with minimal previous exposure to cannabis were scanned while performing an oddball novelty processing task, a verbal learning task, a response inhibition task, during the oddball novelty processing task, a verbal learning task, a response inhibition task, a sensory processing task and when viewing fearful faces. Subjects were scanned on three occasions, each preceded by oral administration of 10 mg of THC, 600 mg of CBD or placebo. BOLD responses were measured using fMRI.

Results: During the oddball novelty processing task, while responding to emotionally neutral target stimuli that were salient because of their deviance/frequency, participants found the ‘baseline’ stimuli inappropriately salient compared to the ‘oddball’ stimuli while under the influence of THC. This was accompanied by attenuation of activation in the striatum and hippocampus by THC, while CBD augmented activation in these regions relative to placebo. The effect of THC on striatum was inversely correlated with the psychotic symptoms it concurrently induced. During the verbal learning task, THC augmented activation in the parahippocampal gyrus during the encoding condition such that the normal linear decrement in activation across repeated encoding blocks was no longer evident. THC also attenuated the normal time-dependent change in ventromedial and striatal activation during the retrieval condition, which was directly correlated with concomitantly induced psychotic symptoms. THC and CBD also had opposite effects on activation relative to placebo in the striatum during verbal recall, in the hippocampus during the response inhibition task, in the amygdala when subjects viewed fearful faces, in the superior temporal cortex when subjects listened to speech, and in the occipital cortex during visual processing.

Discussion: The modulation of medial temporal and striatal function by THC may underlie the effects of cannabis on verbal learning, stimulus salience and psychotic symptoms. Evidence that THC influences function in these regions, particularly in the context of altered processing of salience, provides a plausible mechanism for the increased risk of schizophrenia in regular cannabis users. THC and CBD can have opposite effects on regional brain function, which may underlie their different symptomatic and behavioural effects, and is consistent with a potential therapeutic role for CBD in various neuropsychiatric conditions.

doi:10.1016/j.schres.2010.02.068

TRANSLATIONAL STUDIES ON (ENDO-)CANNABINOIDS IN SCHIZOPHRENIA: BENCH TO BEDSIDE

F. Markus Leweke
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Introduction: In the search of new mechanisms for antipsychotic drugs, translational approaches are of increasing relevance. These approaches include animal studies, mechanistic studies and clinical trials in healthy volunteers as well as innovatively designed phase IIa clinical trials.

Methods: We report on an approach targeting the endogenous cannabinoid system for the treatment of acute schizophrenia. Endocannabinoids were measured by HPLC/MS in brain tissue of rats prior to and after administration of psychotomimetics and in cerebrospinal fluid and serum from clinically well characterized healthy volunteers and acute psychiatric patients. In addition, a randomized, double-blind, active controlled clinical trial of phase IIa was performed investigating cannabidiol, a phytocannabinoid, in acute schizophrenia.

Results: In animal studies anandamide, a major endogenous agonist to the cannabinoid CB1-receptor, is significantly elevated in brain tissue under the influence of psychotomimetics. This is associated with respective behavioral data. In parallel, anandamide is markedly elevated in cerebrospinal fluid of acute first-episode antipsychotic-naive schizophrenic patients and inversely correlated with psychotic symptoms. In our phase IIa clinical trial, cannabidiol showed significant antipsychotic properties associated with a mild side-effect profile and a characteristic mechanism of action.

Discussion: Based on our findings, we suggest that the endocannabinoid system plays a significant pathophysiological role in schizophrenia and that modulation of its functioning may yield antipsychotic effects in this devastating disease. Thus, modulation of endocannabinoid functioning represents a promising new approach to the treatment of acute schizophrenia.
phrenia suggesting that ubiquitination of TrkB may underlie downregulation of BDNF signaling in schizophrenia. Vincent Calhoun will discuss brain imaging and genetic analyses that may lead to diagnostic capabilities. The results of fMRI and a SNP array were combined in a hierarchical machine learning method in order to classify schizophrenia when compared to controls. The combination of SNP-fMRI led to a higher classification accuracy than either alone. Charles Schulz will describe a multimodal imaging study assessing early and persistently ill schizophrenic patients and controls. The purpose of the study was to utilize different brain measures in the same sequence in order to examine the relationship of chemistry, connectivity, blood flow and structure to one another. Further, by including subjects who were recently diagnosed to those who were persistently ill, the impact of the course of illness will be addressed. At the conclusion of the four presentations, Carol Tamminga will provide a discussion and synthesis of the symposium.

doi:10.1016/j.schres.2010.02.070

THE EXPRESSION OF POSITIVE AND NEGATIVE SYMPTOMS IN THE REALM OF DAILY LIFE

Inez Myin-Germeys
University of Maastricht, Maastricht, Netherlands

Inez Myin-Germeys, Viviane Thewissen, Dina Collip, Margreet Oorschot, Jim van Os, Philippe Delespaul Maastricht University.

Background: A growing body of research suggests that there is meaningful and widespread variation of psychotic symptoms over time. Understanding this variation and the determinants thereof, both internal and situational, is thus crucially important for the diagnosis and treatment of these symptoms. This paper investigates the expression of positive and negative symptoms in the realm of daily life.

Method: The Experience Sampling Method, a momentary assessment technique, was used to investigate anhedonia and paranoia in the context of daily life. 173 patients with psychotic spectrum disorders (divided in low vs high negative symptoms on the PANSS) and 163 controls were included to study anhedonia. For the paranoia study, a sample of individuals (n = 154) ranging across the continuum in level of paranoia was included.

Results: In the anhedonia study, patients reported lower levels of positive and higher levels of negative emotions compared to controls. However, whereas patients with negative symptoms did not differ from controls in emotional variability and capacity to generate pleasure, low negative symptom patients reported increased levels on both. The paranoia study showed that paranoia intensity is variable over time and both a decrease in self-esteem and an increase in anxiety is predictive of the onset of a paranoid episode. Subjects with medium levels of trait paranoia reported more momentary paranoia in less familiar company whereas the high paranoia group reported no difference in momentary paranoia between familiar and unfamiliar contacts.

Conclusion: This study revealed no evidence for a generalized deficit in emotional experience nor a hedonic deficit in patients with psychosis spectrum disorders. Rather than the high negative symptom group, the low negative symptom group showed a deviant pattern in emotional processing, reporting increased reactivity to the environment. Paranoia was context-dependent at lower levels of trait paranoia, probably reflecting adaptive processes, whereas at high levels of trait paranoia, momentary paranoia seems to become autonomous and independent of the social reality. These results show that capturing the film rather than a snapshot of daily life reality may challenge our current concepts of symptoms.

doi:10.1016/j.schres.2010.02.071

DEFICITS IN BRAIN DERIVED NEUROTROPHIC FACTORS: POTENTIAL AS AN EARLY-PHASE BIOMARKER FOR SCHIZOPHRENIA?

Peter Buckley1, A. Pillai2
1Medical College of Georgia, Augusta, GA Augusta, GA, USA; 2Medical Research Service, Charlie Norwood VA Medical Center Augusta, GA, USA

There is much interest-derived from current neurochemical, genetic, and therapeutic research in the role of brain neurotrophins in schizophrenia. Neurotrophins play key roles in neuronal development and differentiation (i.e., promoting dendritogenesis and synaptogenesis), and in orchestrating the neuronal response to stress/noxious stimuli. Previous findings suggest that neurotrophins are low at the onset of psychosis and that core deficits in neurotrophins may be a neurobiological marker for vulnerability to psychosis. In a study of BDNF levels in patients with first-episode psychosis in comparison with normal, healthy subjects, patients showed significant reduction (N = 16; 135 ± 21.77 pg/ml; P = 0.001; f = 12.873) in plasma BDNF compared to normal controls (N = 14; 290.3 ± 38.91 pg/ml). In another preclinical study, we explored the role of Brain derived neurotrophic factor (BDNF) through its receptor, TrkB signaling in schizophrenia. We identified an E3 ubiquitin ligase, C-Cbl that associates with TrkB in the postmortem brain samples from schizophrenia and bipolar disorder subjects. C-Cbl gene expression was analyzed in dorsolateral prefrontal cortex samples from 100 individuals (35 with schizophrenia; 31 with bipolar disorder, and 34 psychiatrically normal controls) and we found significantly increased expression of c-Cbl in both schizophrenia and bipolar disorder suggesting that ubiquitination of TrkB maybe involved in the down-regulation of BDNF signaling in schizophrenia (and bipolar disorder). We are also examining the role of plasma BDNF levels as a biomarker in studies of first-episode psychosis and in chronic schizophrenia patient populations. This presentation will describe our work thus far, as well as the substantial challenge in defining ecologically – valid biomarkers towards characterizing the phenotypic expression of schizophrenia.

doi:10.1016/j.schres.2010.02.072

CLASSIFICATION OF SCHIZOPHRENIA USING FMRI AND GENETIC DATA

Vince Calhoun1,2, Jingyu Liu1,2, Jing Sui1,2, Godfrey Pearlson3, Honghui Yang1,2
1Mind Research Network (MRN) Albuquerque, NM, USA; 2University of New Mexico Albuquerque, NM, USA; 3Yale University Medical School New Haven, CT, USA

Background: Schizophrenia is a complex mental disorder with many subcategories, contributed to by both genetic and environmental factors. The complexity of the disorder makes accurate diagnosis of schizophrenia extremely hard using only clinical assessments and no objective metrics. The goal of this study is to understand how genetic information and neuroimaging data can aid in classifying schizophrenia patients from healthy subjects, and therefore potentially be able to help characterize schizophrenia in future.

Methods: Data comprise fMRI collected during an auditory oddball task, and a 367 single nucleotide polymorphism (SNP) array genotyped via an Illumina microarray. We developed a hierarchical machine learning
MULTIMODAL IMAGING STUDIES OF EARLY STAGES AND PERISTANT SCHIZOPHRENIA

Charles Schulz1,2, Juan Bustillo3, John Lauriello3, Oliver Freudenreich4, Donald Goff4, Jeremy Bockholt2, Kelvin Lim1

1University of Minnesota, Minneapolis, MN; 2University of New Mexico and Mind Research Network, Albuquerque, NM; 3MGH and Harvard University; 4Mind Research Network (MRN)

OVERALL PANEL PROPOSAL: The Many Faces of Psychosis Co-Chairs: S. Charles Schulz Carol A. Tamminga Participants: Inez Myin-Germeys Peter Buckley Vincent Calhoun S. Charles Schulz Discussant: Carol A. Tamminga The perplexing, but interesting, aspect of psychotic disorders is their complexity. Psychotic illnesses at times seem archetypical and at other times to present as a combination of disorders. To address the complexity of the study of psychosis the following presentations will be made: Inez Myin-Germeys will present the impact of moments of negative emotional change on psychotic symptoms such as paranoia. The findings illustrate a mechanism for the co-occurrence of depressive and psychotic symptoms. Dr. Buckley will describe both preclinical and clinical research examining whether neurotrophins, specifically Brain Derived Neurotrophic Factor (BDNF), may be a neurobiological marker for vulnerability to psychosis. In a study of BDNF levels in patients with first-episode psychosis in comparison with normal, healthy subjects, patients showed significant reduction (N= 16; 135±21.77 pg/ml; P=0.001; f =12.873) in plasma BDNF compared to normal controls (N= 14; 290.5±38.81 pg/ml). In another preclinical study, we explored the role of Brain derived neurotrophic factor (BDNF) through its receptor, TrkB signaling in schizophrenia. We identified an E3 ubiquitin ligase, c-
Cbl that associates with TrkB in the postmortem brain samples from schizophrenia and bipolar disorder subjects. C-Cbl gene expression was analyzed in dorsolateral prefrontal cortex samples from 100 individuals (35 with schizophrenia, 31 with bipolar disorder, and 34 psychiatrically normal controls). We found significantly increased expression of C-Cbl in both schizophrenia and bipolar disorder suggesting that ubiquitination of TrkB maybe involved in the downregulation of BDNF signaling in schizophrenia (and bipolar disorder). We are also examining the role of plasma BDNF levels as a biomarker in studies of first-episode psychosis and in chronic schizophrenia patient populations. This presentation will describe our work thus far, as well as the substantial challenge in defining ecologically – valid biomarkers towards characterizing the phenotypic expression of schizophrenia.

**SPEAKER 3 ABSTRACT: Classification of Schizophrenia Using fMRI and Genetic Data**

Vince Calhoun, Jingyu Liu, Honghui Chen
1Mind Research Network (MRN) 2University of New Mexico

**Background:** Schizophrenia is a complex mental disorder with many subcategories, contributed to by both genetic and environmental factors. The complexity of the disorder makes accurate diagnosis of schizophrenia extremely hard using only clinical assessments and no objective metrics. The goal of this study is to understand how genetic information and neuroimaging data can aid in classifying schizophrenia patients from healthy subjects, and therefore potentially be able to help characterize schizophrenia in future.

**Methods:** Data comprise fMRI collected during an auditory oddball task, and a 367 single nucleotide polymorphism (SNP) array genotyped via an Illumina microarray. We developed a hierarchical machine learning method to classify schizophrenia and healthy individuals and applied to 40 subjects. The method consists of four stages: (1) a support vector machine (SVM) based classifier ensemble for SNPs, (2) a SVM classifier ensemble for voxels in fMRI, (3) an SVM classifier for independent factors of fMRI activation, and (4) an integrated SNP-fMRI classifier.

**Results:** The classification accuracy obtained was: 0.74 for the SNP only classifier; 0.82 for the fMRI voxel only classifier; 0.85 for the fMRI factor classifier and 0.90 for the combined SNP-fMRI classifier. The most discriminating SNP loci identified by classification were in genes of SELP, COMT, GAD2, HTR3B, DISC1, CYP2C19, and etc. The brain regions contributing most to classification consist of inferior, middle and medial frontal gyrus, cingulate gyrus, superior temporal gyrus and precuneus.

**Discussion:** Some SNPs selected in the study have previously been shown to be schizophrenia related, such as COMT, DISC1, and HTR3B. The brain regions identified including large portions of frontal lobe and superior temporal lobe, are also consistent with previous literature showing functional differences between schizophrenia and healthy subjects. In summary, experimental results show that the proposed method achieves better classification accuracy by combining genetic data and fMRI data than using either of them. Results suggest an effective way in identifying schizophrenic individuals from healthy control groups which may prove useful for assisting in the diagnosis and treatment of schizophrenia.

**SPEAKER 4 ABSTRACT: Multimodal Imaging Studies of Early Stages and Persistent Schizophrenia**

S. Charles Schulz1,4, Juan Bustillo2, John Lauriello2, Oliver Freudenreich3, Donald Goff2, Jeremy Bockholt1, Kelvin Lim1
1University of Minnesota; 2University of New Mexico; 3MGH and Harvard University; 4Mind Research Network (MRN)

**Introduction:** Brain imaging’s original impact on knowledge of brain structure has now been extended to methodologies to assess connectivity (DTI), chemistry (spectroscopy), and function (fMRI). Many brain imaging studies to date have reported on a single measure. Recent work has begun to report on the relationship of structure and function. In order to address the relationship of structure, function and chemistry, a multimodal imaging sequence was designed and administered to first-episode and persistently ill schizophrenic research subjects. A secondary aim was to explore possible differences over the course of the illness.

**Methods:** Subjects with a diagnosis of schizophrenia, schizophréniform, or schizoaffective disorder were eligible for the study. Those who had received less than 12 weeks of treatment were assigned to the First Episode group and those with longer treatment were designated to the persistently ill group. Research subjects were matched to controls. Three sites in the clinical consortium of the Mind Research Network (MRN) all equipped with a 3T Siemens scanner entered subjects in an MRI sequence that included a structural assessment, proton echo planar spectroscopic imaging (PEPSI), DTI, and a resting fMRI measure. Analyses will include assessment of potential differences between groups as well as comparisons of different measures.

**Results:** The enrollment for the study has been completed and 60 subjects have undergone scanning. Of the total group, 12 were first episode with 15 controls, and 19 were persistently ill with 16 controls. The first episode subjects were an average age of 21 years old as were the controls. The persistently ill subjects were an average age of 41 years old and the controls had an average age of 40 years old. MRI scanning results of the multimodal sequence will be presented examining the differences between each patient group and controls, differences between the two patient groups and then comparisons of measures.

**Conclusions:** Substantial progress in brain imaging has been made over the last three decades. However, the relationship of different methods over the course of the illness is now emerging. Results of this study may shed light on brain measures over the course of the illness and the relationship of different approaches.

**doi:** 10.1016/j.schres.2010.02.074

**Symposium 12**

**EINHEITSPSYCHOSE? COMPARISON OF SCHIZOPHRENIA AND BIPOLAR DISORDER ACROSS GENES, BRAIN, AND BEHAVIOUR**

**Co-Chairpersons:** Melissa J Green, Jim van Os

**Monday, 12 April, 2010 - 3:30 pm - 5:30 pm**

**Overall Abstract:** Science is catching up with century-old diagnostic traditions in psychiatry, as emerging evidence across a range of disciplines fails to provide unequivocal support for the distinction between schizophrenia and bipolar disorder as discrete pathological entities. Despite their classic demarcation, schizophrenia and bipolar disorder share transient episodes of psychosis alongside disturbances in cognition, motivation, and affect, culminating in a lifetime of social and occupational dysfunction. Moreover, the clinical reality is one of mixed psychotic and affective symptoms in many individual cases. With mounting evidence for common susceptibility genes for these conditions, the question of shared neuropathology has been raised with timeliness as we approach the DSM-V. Einheitpsychose? It is time to take stock. This symposium brings together recent evidence across the domains of epidemiology, genetics, neurobiology and cognition, to address controversial issues relevant to both the classification and search for underlying neuropathology of schizophrenia and bipolar disorder. The speakers will address issues such as: Whether the strict separation of affective and non-affective psychotic disorder imposed by current classification systems has led to missed opportunities to study the
NEUROANATOMICAL CHANGES ACROSS THE COURSE OF SCHIZOPHRENIA AND BIPOLAR DISORDER

Alex Fornito
University of Melbourne Melbourne, VIC, Australia

A large volume of structural magnetic resonance imaging (sMRI) research has been published examining the neuroanatomical abnormalities associated with schizophrenia and bipolar disorder. This talk will focus on how these abnormalities emerge and develop over the course of the disorders, and how they relate to neuropathological findings. In general, the available evidence indicates that schizophrenia is associated with volumetric reductions in a network of frontal, temporal, limbic, striatal and thalamic regions. Some of these abnormalities are apparent prior to psychosis onset and may progress with ongoing illness. Findings in bipolar disorder have been more variable with both volumetric increases and decreases being reported across several brain regions and at different illness stages. There is preliminary evidence however, to suggest that the trajectory of volumetric changes in certain brain regions differs between the two illnesses, suggesting developmental considerations may be important for distinguishing between the two illness phenotypes. Neuropathological studies of both patient groups suggest the cellular changes associated with these volumetric differences affect diverse tissue compartments and brain regions in different ways. Such findings underscore the need to better characterize both regionally and diagnostically specific pathophysiological mechanisms, a goal that would be facilitated by greater integration of neuroimaging and neuropathological research.

doi:10.1016/j.schres.2010.02.076
memory, and executive functioning presenting in a trait-like manner (persisting during periods of euthymia). Data derived from family studies have clearly demonstrated heritability of cognitive impairment in families with a history of SZ and early evidence suggests a similar genetic influence in BPD. Thus, efforts to understand the underlying pathophysiology of neurocognitive impairment in BPD and SZ have necessarily begun to address the potential contributions of genetic variation to this trait across diagnostic categories. Recent data from candidate gene studies along with evidence from large-scale genome-wide investigations have led to the conclusion that there are likely to be some genes that impart a more generalized effect on susceptibility to psychopathology regardless of diagnosis (shared) and other genes with more illness-specific effects (unique). Likewise, inasmuch as neurocognitive deficits reflect biomarkers related to risk for the illness, it follows that impairments common to both disorders are likely to be associated with shared genetic factors, while others may be more specific to either schizophrenia or bipolar disorder, based on phenotypic profiles. This presentation will first briefly describe the pattern and extent of cognitive impairment in BPD in contrast with SZ, with a focus on the influence of the overlapping feature of psychosis. Next, the neurocognitive deficits that appear to be most closely associated with genetic predisposition will be discussed, reviewing evidence of cosegregation in SZ families and providing new data derived from an ongoing discordant sibling pair study in BPD. Finally, several examples of candidate genes will be presented (e.g. DTNBP1; COMT) that have been consistently shown to influence neurocognition both within psychiatric samples and across the normal cognitive range. Concluding remarks will focus on the importance of utilizing intermediate phenotypes related to brain function to better understand the etiology of these complex diseases.

The usefulness of genetic testing for schizophrenia (SZ) is controversial. Proponents state that there is little else, besides family history, that provides any prediction of risk for schizophrenia, and some prediction is better than none. Furthermore, individuals should have the personal autonomy to choose whether to have the tests or not. The critics state that tests are not yet informative enough and may lead to premature / incorrect conclusions, and the educational tasks for clinicians and consumers to understand test results may be formidable. In the case of antipsychotic drug response, and in particular for side effects, there is likely a much clearer case to incorporate genetic testing into clinical practice.

**Methods:** We surveyed 900 undergraduate and medical students with a 40 item questionnaire regarding opinions toward psychiatric genetic testing. Secondly, we genotyped 32 SZ patients and 43 OCD patients from our CAMH hospital and retrospectively assessed medication response and side effects. Thirdly, we have introduced CYP450 gene testing as a prospective tool for choice of medication type and dosage, primarily directed at patients who are having difficulties with antipsychotic treatment.

**Results:** In the student survey, there was strong support for the usefulness of pharmacogenetic tests, with 92% endorsement. In the scenario of testing for Huntington’s Disease, only 47% stated that they would have the test done on themselves if they were at risk, and 43% would refuse to have the test. For a genetic test for depression that would denote ‘higher’ vs ‘lower’ risk, 34% of respondents would agree to have such a test, and 54% would not. In the retrospective study of CYP2D6 genotype, we found significant correlation between poor or rapid metabolizer status and poor outcome in medication treatment. Our effort in prospective pharmacogenetic testing has yielded interesting case studies revealing a potential role for CYP450 gene tests in general clinical practice.

**Conclusions:** Genetic testing for the diagnosis of SZ does not appear useful at the present time. The risks of providing pharmacogenetic tests to physicians for their patients appear to be relatively low, and the early indications are that these kind of tests would be widely accepted. Limitations in terms of ethics, funding, and education will be discussed.

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**Symposium 13**

**PHARMACOGENOMICS IN SCHIZOPHRENIA:**

**HOW FAR TO THE CLINIC?**

**Co-Chairpersons:** Anil K. Malhotra, Alessandro Bertolino

**Monday, 12 April, 2010 - 3:30 pm - 5:30 pm**

**Overall Abstract:** Recent research indicates that pharmacogenomic studies of antipsychotic drug response may be informative and there are now commercially available products to test specific genetic markers putatively associated with drug response. Nevertheless, the heterogeneity of drug response provides unique challenges for pharmacogenetics that may require novel approaches to fully realize the prospects for this area of inquiry. In this symposium, we will assess the status of pharmacogenomic testing in schizophrenia, with a focus on the acceptance and development of new approaches towards pharmacogenomic testing. Todd Lencz (New York, USA) will first discuss methodological issues in pharmacogenetics research including new developments in the assessment of complex phenotypes such as homoygosity mapping, rare variant detection, and the use of alternative in vitro and in vivo methods to identify candidate genes and candidate variants for examination. Alessandro Serretti (Bologna, Italy) will present data from an ongoing study of antipsychotic drug response, in which multiple genes underwent a detailed pharmacogenetic analysis with the aim of developing a complex predictive model to be used in everyday clinical practice. Alessandro Bertolino (Bari, Italy) will expand the discussion to incorporate the use of alternative endpoints, or endophenotypes, in pharmacogenomic studies. He will review data from his lab utilizing functional brain imaging and neurocognitive measures as response parameters in an olanzapine treatment study, as these phenotypes may more closely reflect the subtle effects of genetic variation on the brain. Anil Malhotra (New York, USA) will review data on the use of adverse events as a phenotype in pharmacogenomic studies, as side effects may be a more readily quantifiable dependent measure and perhaps be more critical to establishing treatment success than simple efficacy in schizophrenia. He will also discuss the development of commercial tests on the pharmacogenomics of adverse events, and address the strengths and weaknesses of this development. Finally, James Kennedy (Toronto, Canada) will serve as discussant and highlight areas of confluence and discrepancy from the various perspectives presented during the symposium, in order to fully synthesize the wealth of data in this rapidly emerging field.

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**Issues Regarding Genetic Testing for Schizophrenia Risk and for Antipsychotic Drug Effects**

**James Kennedy. Matthew Lanktree, Gwyneth Zai, Jessica Sturgess, Daniel J. Mueller**

Centre for Addiction and Mental Health Toronto, ON, Canada

The usefulness of genetic testing for schizophrenia (SZ) is controversial. Proponents state that there is little else, besides family history, that provides any prediction of risk for schizophrenia, and some prediction is better than none. Furthermore, individuals should have the personal autonomy to choose whether to have the tests or not. The critics state that tests are not yet informative enough and may lead to premature / incorrect conclusions, and the educational tasks for clinicians and consumers to understand test results may be formidable. In the case of antipsychotic drug response, and in particular for side effects, there is likely a much clearer case to incorporate genetic testing into clinical practice.

**Methods:** We surveyed 900 undergraduate and medical students with a 40 item questionnaire regarding opinions toward psychiatric genetic testing. Secondly, we genotyped 32 SZ patients and 43 OCD patients from our CAMH hospital and retrospectively assessed medication response and side effects. Thirdly, we have introduced CYP450 gene testing as a prospective tool for choice of medication type and dosage, primarily directed at patients who are having difficulties with antipsychotic treatment.

**Results:** In the student survey, there was strong support for the usefulness of pharmacogenetic tests, with 92% endorsement. In the scenario of testing for Huntington’s Disease, only 47% stated that they would have the test done on themselves if they were at risk, and 43% would refuse to have the test. For a genetic test for depression that would denote ‘higher’ vs ‘lower’ risk, 34% of respondents would agree to have such a test, and 54% would not. In the retrospective study of CYP2D6 genotype, we found significant correlation between poor or rapid metabolizer status and poor outcome in medication treatment. Our effort in prospective pharmacogenetic testing has yielded interesting case studies revealing a potential role for CYP450 gene tests in general clinical practice.

**Conclusions:** Genetic testing for the diagnosis of SZ does not appear useful at the present time. The risks of providing pharmacogenetic tests to physicians for their patients appear to be relatively low, and the early indications are that these kind of tests would be widely accepted. Limitations in terms of ethics, funding, and education will be discussed.
METHODS FOR OBTAINING CLINICALLY USEFUL PHARMACOGENETIC PREDICTORS; AN EXAMPLE OF A DETAILED INVESTIGATION IN AN HALOPERIDOL TREATED SAMPLE

Alessandro Serretti1, Antonio Drago1, Ina Giegling1, Annette M. Hartmann1, SchaferMartin Schäfer1, MöllerHans-Jürgen Möller1, Diana De Ronchi2, Dan Rujescu1

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Pharmacogenetic studies are hampered by the complexity of the drug response phenomenon. Therefore the optimal methodology for investigations should include a detailed clinical and sociodemographic data collection, plasma level of drugs, frequent measurements on various dimensions of the phenomenon with appropriate genetic and statistical tools including pathway and gene coverage and epistatic events. As an example we report new data investigating a set of 50 SNPs located in 11 genes coding for subunits of glutamategic receptors, as modulators of the efficacy of haloperidol in a sample of 101 schizophrenic patients. Furthermore, we investigated the possible impact on the motor side effect profile associated with haloperidol treatment. Patients were administered the PANSS and ETRS tests at baseline and at day 3, 7, 14, 21 and 28. MANCOVA analysis for repeated measures was applied along with the FDR correction for multiple tests. T/T genotype at rs477292 (GRIA1) was found to be associated with a better response to haloperidol treatment than G/T at PANSS positive at week 2 (f=6.18, \( p=0.001 \)) after covaring for haloperidol plasma levels and influencing clinical variables. C/C genotype at rs1461231 (GRIA1) was found to be associated with a better response to treatment compared to G/G genotype at PANSS positive scores at week 1 (f=7.32, \( p=0.00032 \)). Despite limitations linked to the small sample size, those findings provide an example of a detailed pharmacogenetic analysis in antipsychotic response possibly allowing a complex predictive model to be used in everyday clinical practice.

doi:10.1016/j.schres.2010.02.082

USE OF INTERMEDIATE PHENOTYPES IN PHARMACOGENETICS

Alessandro Bertolino
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Recent important advancements in genomic research have opened the way to new strategies for public health management. One of these questions pertains to how individual genetic variation may be associated with individual variability in response to drug treatment. The field of pharmacogenetics may have a profound impact on treatment of complex psychiatric disorders like schizophrenia. However, pharmacogenetic studies in schizophrenia have produced conflicting results. The first studies examined potential associations between clinical response and drug receptor genes. Conflict results may be at least in part explained by variability and choice of the phenotype, by choice of candidate genes or genetic variants of unknown functional significance, or by the relatively little knowledge about the neurobiology of this disorder. Single-nucleotide polymorphisms (SNPs) are assuming specific relevance, particularly if they have functional consequences for the proteins that they code for. Functional SNPs modify the structure and/or function of the protein so that its activity varies as a function of the allelic variant present in each individual. Along with these, intronic SNPs with a role in mRNA processing are increasingly being recognized as potentially having a profound impact. All these variations might differentially impact on brain physiology, behavior, and pathophysiology, thus contributing to susceptibility for schizophrenia and to modulate individual responses to pharmacological treatment with antipsychotics. More recent studies have sought the association between genetic variants and endo-phenotypes (or intermediate phenotypes). Intermediate phenotypes are represented by any measurable and reproducible cognitive or neurobiological phenomenon with relatively lower levels of complexity, possibly explained by the effect of one or few genes. We propose that choosing intermediate phenotypes that allow in vivo measurement of specific neuronal functions may be of great help in reducing several of the potential confounds intrinsic to clinical measurements. Functional neuroimaging is ideally suited to address several of these potential confounds, and it may represent a powerful strategy to investigate the relationship between behavior, brain function, genes, and individual variability in the response to treatment with antipsychotic drugs in schizophrenia. Following the logic just detailed, we have been investigating response to treatment in a group including 70 patients with schizophrenia treated with olanzapine as monotherapy. All patients had been drug-free or drug-naïve before entering the study and were followed-up for eight weeks. During this time period, patients underwent several clinical assessments with PANSS, neuropsychological assessment with several working memory and attention tests, BOLD fMRI at two time points during performance of working memory and attention tests. Using these measures, we have investigated differential responses to treatment based on functional SNPs within COMT, DRD2, and AKT1 demonstrating that these genetic variants have an impact on clinical and endo-phenotype measures.

doi:10.1016/j.schres.2010.02.083

PHARMACOGENOMIC APPROACHES TO RARE AND COMMON SIDE EFFECTS ASSOCIATED WITH ANTIPSYCHOTIC DRUG TREATMENT

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Although the second generation antipsychotic drugs may confer advantages over first generation agents, they are still notable for association with a number of rare and common side effects. To date, there are no apriori methods to identify which patients are at greatest risk for the development of these adverse effects, and therefore treatment is almost entirely based upon an empirical “trial and error” approach. Recent pharmacogonomics data, however, suggests that individualization of treatment may be possible through the identification of the key molecular variants that predispose to development of drug-induced side effects. In this presentation, we will focus on candidate gene and genome-wide association (GWAS) pharmacogenetic studies focused on 1) a rare side effect; clozapine-induced agranulocytosis (CIA), and 2) a common side effect; antipsychotic drug-induced weight gain. For CIA, we will present data on a two-stage candidate gene study including two cohorts of subjects characterized for CIA. In this study, an initial candidate gene screening study revealed suggestive evidence for association of five genes with development of CIA. Follow-up work in a second independent cohort revealed that one gene, HLA-DQB1, significantly influenced risk for CIA in both cohorts, with an odds ratio of over 16. We will also present GWAS data from this study, and compare these results with a second independent GWAS study of CIA currently being conducted. For drug-induced weight gain, we will focus on candidate gene studies conducted in first episode schizophrenia patients that implicate genes in the dopamine (DRD2) and serotonin (5-HT2C) receptor systems, as well as discuss a drug induced weight gain GWAS from a cohort of pediatric patients receiving antipsychotic drug treatment for the first time. Taken together, these data suggest that the
molecular variants that predispose to both rare and common side effects of antipsychotic drug treatment can be identified through candidate gene and GWAS pharmacogenomic studies, and may provide further impetus for the development of personalized medicine in the clinical setting.

doi:10.1016/j.schres.2010.02.084

Symposium 14
NEW RESEARCH IN THE EARLY PREDICTION OF ANTIPSYCHOTIC RESPONSE IN SCHIZOPHRENIA
Co-Chairpersons: Christoph U Correll, John Kane
Monday, 12 April, 2010 - 3:30 pm - 5:30 pm

Overall Abstract: A currently unanswered question is how long to wait for antipsychotic response in patients with schizophrenia. None of the available guidelines are data driven and recommendations differ. Recent studies suggest that the majority of antipsychotic response occurs early, and that early response/non-response can help to identify patients who are unlikely to respond to a longer trial. These data have enormous clinical and research implications for elucidating the underpinnings of the heterogeneity of treatment response. This symposium will discuss novel data on this topic, including previously unstudied populations, designs and data analytic techniques. Stefan Leucht will review the available data in chronically ill patients with schizophrenia that have helped establish the early antipsychotic response paradigm and refute the previously proposed late response idea. He will also review recent data from prospective studies and in first episode patients that further support the utility of early non-response as a clinical marker for later/ultimate non-response. Study designs and methodology will be examined critically to establish a standard in the field that can help generate useful and comparable data sets regarding intra-individual response prediction for the treatment with antipsychotics. Christoph Correll, MD, will present early antipsychotic response data from a naturalistic, real-world study in 127 adolescents with schizophrenia spectrum disorders, and a post-hoc analysis of a randomized, placebo controlled trial of 293 adolescents with schizophrenia. The predictive value of CGI, PANSS total score reductions and of extrapyramidal side effects and weight gain at week 2 for response at study endpoint are examined. Bruce Kinon, MD, will report on the first prospective evaluation of early antipsychotic response in a randomized, controlled 12-week study of 628 acutely ill patients with multi-episode schizophrenia. Patients were first assigned to risperidone (2–6 mg/day). Early responders continued on risperidone, while early non-responders were randomized to continue risperidone or switch to olanzapine for 10 additional weeks. Symptomatic as well as functional outcomes are presented. He will further present path analyses on the individual symptom item response as predictors of ultimate response that provide novel, and more refined ways to assess early antipsychotic response predictors. Shitij Kapur, MD, will report on novel statistical approaches to the analysis of early antipsychotic response and its predictive power for later outcomes. Data will be presented from studies using growth-mixture modeling, showing that while, at a group level, antipsychotics work early, at an individual level patients show multiple trajectories. Placebo and antipsychotic trajectories are compared, indentifying four distinct pathways, which can be distinguished across individuals, rather than treatment conditions.

doi:10.1016/j.schres.2010.02.085

CURRENT STATUS IN THE TIME COURSE OF ANTIPSYCHOTIC DRUG EFFECT, EARLY RESPONSE PREDICTION, EARLY SWITCH STUDIES AND RESEARCH ON TRAJECTORIES OF RESPONSE TO ANTIPSYCHOTICS

Stefan Leucht
Technische Universität München, Bavaria, Germany

A crucial question in clinical routine is the duration of an appropriate antipsychotic drug trial. Generally, the response to medication varies considerably from patient to patient. In some patients a significant improvement already appears after several hours; for other patients it can take weeks. Recent evidence refuted the long-held textbook statements that the effect of antipsychotic drugs only shows up with a delay of several weeks. In a meta-analysis of 53 studies with 8177 patients, Agid et al. found that the greatest symptom reduction occurs in the first weeks and continuously declines at later stages. This finding was expanded to one year in an analysis of more than 700 individual patient data (Leucht et al. 2005) and other studies found that the effects of antipsychotics can be disentangled from those of placebo within 24 hours. The new “early onset of antipsychotic drug action hypothesis” has stimulated hope that it may be possible to predict response early after initiation of treatment. A series of studies since the 1980’s have shown that a degree of initial response correlates well with the degree of response after 4–6 weeks. The main limitation of these studies was that they were all of a correlative nature and but did not provide cut-offs of a degree of initial non-response which predicts future response or remission. Important recent evidence from post-hoc analyses of completed studies were conducted to develop more clinically useful models, which allow to predict response early on in treatment. Although the individual results differed, analyses from retrospective and one recently completed prospective study suggest that no to little reduction of symptoms (~< 20%-25% BPRS/PANSS total score reduction) predicts later non-response with sufficient specificity. Data will be shown from recent first-episode schizophrenia studies to explore that generalizability of these findings to the initial illness phase. Prospective studies are trying to establish whether switching at two weeks in case of little early improvement is an effective strategy. Furthermore, researchers are trying to identify different patterns or trajectories of response to antipsychotic drugs to resolve some of the heterogeneity associated with drug response. Study methodologies will be compared and critiqued attempting to identify a standard for future trials in this area.

doi:10.1016/j.schres.2010.02.086

TIME COURSE AND RELEVANCE OF EARLY TREATMENT RESPONSE IN ADOLESCENTS WITH SCHIZOPHRENIA-SPECTRUM DISORDERS

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Background: In acutely ill adults with schizophrenia, the majority of symptomatic response occurs early on and early response/non-response predicts later response/non-response. It is unknown whether these findings extend to adolescents with schizophrenia.

Methods: We examined time course and predictive power of early response in 1) a 3-month cohort study of atypical antipsychotics; and 2) an industry sponsored, 6-week, placebo-controlled trial (RCT) of aripiprazole. In the “real-world” sample, we assessed time course of CGI-S and CGAS scores, and the prediction of presence/absence of a CGI-I score of at least minimally improved at 4 weeks (early response = ER) for ultimate response (UR) at endpoint (at least much improved on the
DIFFERENCES BETWEEN EARLY RESPONDERS AND EARLY NON-RESPONDERS TO ATYPICAL ANTIPSYCHOTICS ON SYMPTOM AND FUNCTIONAL OUTCOMES IN THE TREATMENT OF SCHIZOPHRENIA

Bruce Kinon1, Lei Chen1, Virginia Stauffer1, Haya Ascher-Svanum1, Wei Zhou1, Sara Kollack-Walker1, John Kane3, Shitij Kapur1
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Objectives: In this study, we extend the findings from a prospective clinical trial (Study HGMN) assessing the effects of early response to an atypical antipsychotic across multiple functional outcome measures. In addition, we applied a data-driven decision tree to the data in order to assess the value of using specific predictors to differentiate responders from non-responders.

Methods: This was a randomized, double-blind, flexible-dose, 12-week study that enrolled chronically-ill patients (n = 628) diagnosed with schizophrenia or schizoaffective disorder who were experiencing an acute symptom exacerbation. Patients were initially assigned to risperidone drug therapy (2-6 mg/day), and their response status at 2 weeks determined. Early responders continued with risperidone therapy, whereas early non-responders were randomized (1:1) in a double-blind manner to either continue on risperidone or switch another atypical antipsychotic for 10 additional weeks of therapy. Subsequent improvement in functioning was measured by the Schizophrenia Objective Functioning Instrument (SOFI), Quality of Life Scale (QLS), and Subjective Wellbeing under Neuroleptics (SWN) scale. A decision tree constructed using classification and regression tree (CART) analysis with pooled data from six randomized, double-blind trials (N = 1494) was applied to HGMN data. Response was defined as a 30% reduction in Positive and Negative Syndrome Scale (PANSS) Total score by Week 8 of treatment. Analyzed UX predictors were change in individual PANSS items at Weeks 1 and 2.

Results: Early response to risperidone was observed in 27.6% of patients. Compared to early non-responders, early responders to risperidone showed significantly more improvement from baseline to endpoint on the SOFI total score and 4 subdomains (p < 0.001), the QLS total score and 4 subdomains (p < 0.01), and the SWN total score and 5 subdomains (p < 0.05). Most of these differences in functioning were already evident and significantly different between the early response and early non-response groups by 2 weeks of treatment. From the pooled data set, a 2-step, 6-PANSS item decision tree was created which utilized a 2-point decrease in at least two of five positive PANSS items at Week 2 (Step 1) followed by a 2-point decrease in the PANSS excitement item at Week 2 (Step 2). Using this approach with HGMN data, response could be predicted in most patients (93%) with a high positive predictive value (70%) and negative predictive value (77%).

Conclusion: Patients who show an early response to antipsychotic treatment as measured by improvement in psychiatric symptom severity show early and consistent improvement across multiple domains of functioning, a finding that was consistent between both physician- and patient-rated quality of life scales. Additional analyses are ongoing to explore specific symptoms and/or functional domains whose early response may predict subsequent clinically relevant global outcomes.

doi:10.1016/j.schres.2010.02.087

EARLY RESPONSE TO ANTIPSYCHOTICS – WHAT CHANGES EARLY AND HOW?

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Background: While the ‘early onset’ of antipsychotic response is now relatively well established – two subsequent questions emerge: what symptoms change early and do they have different trajectories of response? While the majority of the PANSS items and all ‘factors’ (whether one uses three subscales or five factors) show some degree of improvement – it raises the interesting question of whether all these factors and subscales show a similar trajectory of improvement.

Methods: To resolve this issue we examined it in a large dataset of 420 individuals treated with olanzapine, haloperidol and placebo – the presence of a large number of placebo-treated patients gives one the possibility of testing whether drugs and placebo have similar trajectories. The data were modelled as a Growth Mixture Model in M-Plus.

Results: The trajectory of response of the psychotic symptoms rejected a single-trajectory model, and instead best-fit a four-trajectory model. The most common trajectory showed modest change (about 20% improvement over six weeks) – at the margin of what is clinically detectable. A small subset of patients showed significant (50%) or dramatic (70%) response in symptoms. The latter were significantly over-represented in the drug-treated dataset.

doi:10.1016/j.schres.2010.02.088
Conclusions: The results capture what clinicians have intuitively known – that individual patients follow different trajectories. They go beyond intuition in showing that this inter-individual variation is not just a random dispersion about a mean response, but, follow discernable trajectories. We are now attempting to see if this can be confirmed in other large datasets, and whether these trajectories as observed for the psychosis factor are also observed for the other subscales and factors measured in schizophrenia.

doi:10.1016/j.schres.2010.02.089

Symposium 15
VOCATIONAL RECOVERY IN FIRST EPISODE PSYCHOSIS: INTERNATIONAL EVIDENCE FOR EARLY INTERVENTION
Chairperson: Eoin Killackey
Monday, 12 April, 2010 - 3:30 pm - 5:30 pm

Overall Abstract: Increasingly considerations of recovery in schizophrenia are extending beyond the symptomatic domain to include other areas of psychosocial functioning. Oftentimes, where good symptomatic remission is achieved, it is actually deficits in these other areas of functioning that are chiefly responsible for the disability and social isolation experienced by those with psychotic illness. A key area of functioning that has received considerable attention in populations with chronic illness has been vocational recovery. Not only is returning to work a consistently highly ranked goal of people with schizophrenia, but in returning to work they obtain for themselves a meaningful role, the economic means to participate in society and a normalised way of contributing to their communities. The approach with the most empirical evidence of efficacy is Supported Employment, the most defined form of which is Individual Placement and Support (IPS). However, until the last few years all of the IPS research had been conducted in people with chronic illness. The most common onset age for psychotic illness is between 15 and 25. This phase of life is one in which all kinds of important developmental tasks are occurring, one of which is vocational development. This involves the completion of education and the beginning of employment, which for most people will lead to career development. A psychotic illness has the potential to seriously derail this process. Therefore, it would make sense to intervene to minimise damage to vocational development at the earliest opportunity. Early intervention has the potential to lead to career recovery rather than just job recovery. Early intervention in psychotic illness is a paradigm that has been developed over the last 20 years. It seeks to identify and treat psychotic illness as early as possible with the goal of better resolution of symptoms and preventing or reducing the development of disability. While the initial focus of these early interventions tended to be primarily on symptoms, introducing interventions targeting functional recovery into this paradigm broadens the opportunities to have an impact on the course of schizophrenia. This symposium will consist of four presentations from the only centres to have examined, in samples in an early phase of psychosis, that individual patients follow different trajectories. They go beyond intuition in showing that this inter-individual variation is not just a random dispersion about a mean response, but, follow discernable trajectories. We are now attempting to see if this can be confirmed in other large datasets, and whether these trajectories as observed for the psychosis factor are also observed for the other subscales and factors measured in schizophrenia.

doi:10.1016/j.schres.2010.02.089

SUCCESSFUL RETURN TO WORK OR SCHOOL IN RECENT-ONSET SCHIZOPHRENIA: THE UCLA RANDOMIZED CONTROLLED TRIAL OF INDIVIDUAL PLACEMENT AND SUPPORT
Keith Nuechterlein
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At the UCLA Aftercare Program for young persons with a recent onset of schizophrenia, a randomized controlled trial of Individual Placement and Support (IPS) focused on returning patients as quickly as possible to competitive work or regular schooling following their clinical stabilization. IPS was adapted to meet the personally-relevant goals of each individual, whether those goals involved competitive employment or schooling or both. The UCLA trial combined IPS and a Workplace Fundamentals Module (WFM) for enhanced outpatient work rehabilitation. The enhanced rehabilitation program (N = 46) was contrasted with the provision of clinical treatment and conventional vocational rehabilitation by separate agencies (N = 23). An IPS worker integrated with the clinical team provided educational and employment services, facilitated a rapid search for work or schooling, used assertive outreach to employers, schools, patients, and family members, and gave ongoing work/school support. WFM included group skills training in nine workplace skill areas, using motivational interviewing, video-assisted social learning, role-play practice and problem-solving methods. All 69 patients in the 18-month study were provided weekly case management and psychiatric services by the same clinical team. All patients received atypical antipsychotic medication, starting with oral risperidone at baseline. The IPS-WFM combination showed a striking advantage for helping patients to return to competitive work or regular schooling, compared to conventional rehabilitation. During the initial six months of intensive treatment, 83% of patients in this intervention returned to competitive work or school, compared to 41% in the comparison group (p = .005). The IPS-WFM intervention continued to show advantages at the end of the 18-month trial (72% vs. 42%), after the intensity of treatment had been decreased. The IPS-WFM intervention also led to a longer total duration of time in a job or in school (p = .005). The results clearly support the efficacy of an innovative, active intervention focused on recovery of patient’s participation in normative work and school settings in the initial phase of schizophrenia. The adaptation of the IPS worker’s role for young patients in the initial period of schizophrenia and the coordination of IPS with U.S. policies for individuals with psychiatric disabilities will be elucidated with case examples.

doi:10.1016/j.schres.2010.02.091

MODIFYING INDIVIDUAL PLACEMENT & SUPPORT FOR AN EARLY INTERVENTION IN PSYCHOSIS COHORT: RESULTS OF A NATURALISTIC UK STUDY
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Background: Vocational recovery is being increasingly recognised as an important outcome in mental health care. There is now robust evidence that individual placement & support (IPS) is the vocational intervention of choice in people with established schizophrenia. However, due to the typical age of onset in first episode psychosis cohorts it is necessary to modify this model in order to take account of developmental needs and to include...
edical outcomes. How best to do this, and the potential benefits of doing so, remain relatively untested.

**Design:** VIBE is an occupational-therapy led vocational intervention service embedded within an early intervention team serving two of London’s inner city boroughs. The intervention is a locally-derived modification of IPS and due to a difference in funding was only available to one of the two boroughs served by the early intervention team. Using a naturalistic, prospective cohort study design we set out to evaluate the effectiveness of VIBE in aiding vocational recovery following first episode psychosis. 114 first episode psychosis patients being case managed between 2003 and 2006 were followed up for 12 months; 44 lived in the borough with access to the vocational intervention, compared to 70 who did not.

**Results:** in a multivariate analysis three variables were found to be statistically significant predictors of vocational recovery during 12 months of follow up; having access to the vocational intervention, being educated beyond secondary level and being occupied at baseline. Patients who had access to VIBE had a significantly greater odds of achieving vocational recovery than those who did not (odds ratio = 3.53, 95% confidence interval = 1.25, 10.00).

**Conclusion:** our results support the conclusion that IPS is effective if modified for use in first episode psychosis cohorts in the UK. This is consistent with emerging international evidence and is an important outcome of interest to patients, clinicians and commissioners alike.

doii:10.1016/j.schres.2010.02.092

**LIGHTING FIRES NOT FILLING BUCKETS: MEANINGFUL VOCATIONAL RECOVERY IN FIRST EPISODE PSYCHOSIS**

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**Background:** Despite the existence in Australia of government funded employment services for people with disabilities as well as general job seekers, the employment outcomes of those with psychotic illness are among the worse of any socially excluded group. Reasons for this include the gaps in both knowledge and geography that exist between mental health and employment services, as well as perverse incentive systems which actually increase the value of placing a person when they have been unemployed for a longer period. Clearly there is a need for a better approach to the vocational recovery of people with mental illness, and specifically psychotic illnesses. As is well recognised, the onset of psychotic illness is potentially devastating to a number of developmental tasks which typically occur in the same life phase. Among these is vocational development, the completion of education and initiation of career. Failure to undergo this development, even in the absence of mental illness, would predispose to future social disability. In conjunction with mental illness, it has the potential to exacerbate disability and lead to complete social marginalisation. However, a method to address this has been developed called Individual Placement and Support (IPS). This intervention has significant supporting evidence in helping those with chronic illness return to work. However there is only developing evidence in the early phases of the illness. Additionally most of the work in chronic populations has been carried out in the context of the USA. This presentation will report on a study of IPS in first episode psychosis conducted in Melbourne Australia.

**Method:** 41 people with first-episode psychosis wanting to find work were randomized to IPS (n = 20) or treatment-as-usual (TAU, n = 21). The IPS group worked with an employment consultant collocated with the clinical team for a six month period. Those in TAU could access all normal clinical services and external vocational agencies. Assessments were at baseline and six months.

**Results:** More of those in the IPS group became employed or enrolled in courses than those in TAU (17 vs 6, p = 0.000). For employment only there was still a significant difference (IPS 13 vs TAU 2, p = 0.000). Those in the IPS had a higher median income ($2432 vs $0, p = 0.012) and worked more hours per week (median 38 vs 22.5 p = 0.006) and more weeks (median 5.0 vs 0, p = 0.021) than those in the TAU group. The IPS group also significantly reduced use of welfare benefits.

**Conclusion:** The presentation will demonstrate that IPS is effective in young people with first episode psychosis. It will also discuss some of the local considerations that needed to be made to the model. It will point out that while the answers may be unique to setting, the questions that need to be addressed often are not and need consideration when establishing similar programs elsewhere. Finally, the importance of evidence based functional recovery being integrated into treatment for psychotic illness will be highlighted by reference to some case examples.

doii:10.1016/j.schres.2010.02.093

**EVIDENCE BASED SUPPORTED EMPLOYMENT IN EARLY PSYCHOTIC ILLNESS: IMPLEMENTATION IN THE REAL WORLD**

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There has been an increasing amount of interest in vocational rehabilitation for people with mental illness, particularly those early in the course of their illness, where there is potential for significant long term functional gain. There has also been evidence from randomised controlled trials showing supported employment approaches (of which Individual Placement and Support (IPS) is the most defined) to be a significantly better approach to this area than other employment strategies. However, there is less evidence as to the implementation of supported employment approaches into ‘real-life’ clinical services. At the South West London and St Georges Mental Health Trust in England a project has been conducted in which IPS was integrated into routine clinical practice. There were two elements to the implementation: whether IPS could be integrated into a clinical team and maintain fidelity with the model, and; if IPS was implemented in such a fashion would it produce good employment outcomes for those people whom it sought to assist. Demographic, clinical and vocational data were collected over a 12-month period to evaluate the effect on vocational outcomes at 6 months and 12 months of the employment of a vocational specialist in the clinical team, and to assess model fidelity. All clients of the service (n = 40) received vocational support for 6 months and 22 clients received the intervention for 12 months. Following vocational profiling and input from the vocational specialist and the team, there were significant increases in the proportion of clients engaged in work or educational activity over the first 6 months of the intervention, and in a subsample over a second 6-month period. At baseline 65% of the sample was unoccupied (not employed or studying). At 6 months this had reduced to 7% and to 5% at 12 months. Importantly, of those who were occupationally engaged at the point of referral, all were supported in their occupation throughout the study. The evidence-based Supported Employment Fidelity Scale was used to measure the degree of implementation, which scored 71, signifying ‘good implementation’. The results suggest that implementing evidence-based supported employment within an early intervention service increases employment and education opportunities for patients within the service. Importantly, as well as addressing employment and education involvement for those without it, this
study showed that this intervention can maintain those in work or study and thus contribute to a key goal of early intervention which is the prevention of the accumulation of disability.

doi:10.1016/j.schres.2010.02.094

Symposium 16
BRAIN PROGRESSION IN SCHIZOPHRENIA: WHO, WHERE, WHEN, WHY
Chairperson: Robert W. McCarley
Tuesday, 13 April, 2010 - 3:30 pm - 5:30 pm

**Overall Abstract:** One of the most striking changes in schizophrenia research has been the increasing evidence for progression of brain changes in the time before clinical onset (prodrome) and in the time immediately after onset. This symposium brings together new data presented by leaders of research teams who have been at the forefront of this dramatic change in our perception of schizophrenia. There is a striking concurrence of data from Europe (Kahn), USA (McCarley), Japan (Kasai) and Australia (Pantelis) that underscores the validity of the findings. This symposium will offer the SIRS attendees a state-of-the-art window into the latest results and research methods on the individuals at risk (the "who" in the title), where in the brain changes occur, when they occur, and indicate the "why" is not due to medication effects. The discussant (DeLisi), a pioneer in the study of progression, will lead the discussion of these findings. SPEAKER 1 ABSTRACT: Pantelis and colleagues used MRI to examine gray matter (GM) volume of the insular before psychosis onset in 97 individuals at risk for psychosis (UHR; 31 later developed psychosis [UHR-P]) and 55 matched controls. 31 UHR (11 UHR-P) and 20 controls examined longitudinally. Cross-sectionally: UHR-P had significantly smaller insular bilaterally compared with UHR-NP (non-psychotic UHR) and on left compared with controls. Longitudinally: UHR-P showed greater GM reduction (-5%/year) compared with controls (-0.4%/year) or UHR-NP (-0.6%/year). Results will be compared with findings at later stages of psychosis. SPEAKER 2 ABSTRACT: McCarley and colleagues analyzed longitudinal data from 21 first episode schizophrenics (FESZ) & 23 matched healthy controls using a new algorithm (DARTEL) providing improved VBM morphological resolution. Gray Matter (GM) loss over 1.5 years was observed in frontal, temporal and parietal gyri. Progressive GM loss in different regions showed distinct clinical correlations, the more loss, the worse the symptoms. Examples: Heschl gyrus/STG loss & Thinking disturbance/hallucinations; Inferior Frontal gyrus/insula and negative symptoms. VBM findings were validated by cingulate & STG longitudinal ROI analyses. Concurrent electrophysiological changes (mismatch and gamma band) further indicate the functional relevance of the MRI changes. SPEAKER 3 ABSTRACT: Kasai and coworkers have conducted longitudinal, integrative neuroimaging assessments in people at ultra-high risk for developing psychosis and at first-episode of psychosis. The integrative neuroimaging assessments include structural and functional MRI, MR spectroscopy, diffusion tensor imaging, near-infrared spectroscopy (NIRS), and event-related potentials (ERPs). In their preliminary analysis on cross-sectional samples of at risk mental state (ARMS), first-episode, and chronic patients, they found that fMRI and NIRS may be useful in tracking functional brain abnormalities and its progression through the clinical stages in schizophrenia. SPEAKER 4 ABSTRACT: Kahn and coworkers examined cortical thickness in patients with schizophrenia over time. Measures of functional outcome, and cumulative intake of antipsychotic medication were also assessed. Two MRI scans were obtained over a 5-year interval of 96 schizophrenia patients and 113 healthy subjects between 16 and 56 years. Excessive cortical thinning was found in widespread areas on the cortical mantle, most pronounced bilaterally in the temporal and in the left frontal cortex. Poorer outcome was associated with more pronounced cortical thinning. Thus, the cortex shows excessive thinning over time, most pronounced in the frontal and temporal areas and progresses across the entire course of the illness.

doi:10.1016/j.schres.2010.02.095

INSULAR CORTEX GREY MATTER CHANGES BEFORE AND DURING TRANSITION TO PSYCHOSIS. FURTHER EVIDENCE FOR DYNAMIC BRAIN CHANGES AT ILLNESS ONSET

Christos Pantelis
Univ. Melbourne Melbourne, Victoria, Australia

Pantelis and colleagues used MRI to examine gray matter (GM) volume of the insular before psychosis onset in 97 individuals at risk for psychosis (UHR; 31 later developed psychosis [UHR-P]) and 55 matched controls. 31 UHR (11 UHR-P) and 20 controls examined longitudinally. Cross-sectionally: UHR-P had significantly smaller insular bilaterally compared with UHR-NP (non-psychotic UHR) and on left compared with controls. Longitudinally: UHR-P showed greater GM reduction (-5%/year) compared with controls (-0.4%/year) or UHR-NP (-0.6%/year). Results will be compared with findings at later stages of psychosis.

doi:10.1016/j.schres.2010.02.096

PROGRESSION OF GRAY MATTER LOSS AND ITS CLINICAL CORRELATES IN FIRST EPISODE SCHIZOPHRENIA

Robert W. McCarley
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McCarley and colleagues analyzed longitudinal data from 21 first episode schizophrenics (FESZ) & 23 matched healthy controls using a new algorithm (DARTEL) providing improved VBM morphological resolution. Gray Matter (GM) loss over 1.5 years was observed in frontal, temporal and parietal gyri. Progressive GM loss in different regions showed distinct clinical correlations, the more loss, the worse the symptoms. Examples: Heschl gyrus/STG loss & Thinking disturbance/hallucinations; Inferior Frontal gyrus/insula and negative symptoms. VBM findings were validated by cingulate & STG longitudinal ROI analyses. Concurrent electrophysiological changes (mismatch and gamma band) further indicate the functional relevance of the MRI changes.

doi:10.1016/j.schres.2010.02.097

INTEGRATIVE NEUROIMAGING ASSESSMENT THROUGH CLINICAL STAGES IN SCHIZOPHRENIA

Kiyoto Kasai
Univ. Tokyo Tokyo Japan

Kasai and coworkers have conducted longitudinal, integrative neuroimaging assessments in people at ultra-high risk for developing psychosis and at first-episode of psychosis. The integrative neuroimaging assessments include structural and functional MRI,
MR spectroscopy, diffusion tensor imaging, near-infrared spectroscopy (NIRS), and event-related potentials (ERPs). In their preliminary analysis on cross-sectional samples of at-risk mental state (ARMs), first-episode, and chronic patients, they found that fMRI and NIRS may be useful in tracking functional brain abnormalities and its progression through the clinical stages in schizophrenia.

doi:10.1016/j.schres.2010.02.098

PROGRESSIVE BRAIN CHANGES IN HEALTH AND DISEASE: UNDERSTANDING ITS FUNCTIONAL SIGNIFICANCE

Rene Kahn
Univ.Utrecht, Rudolph Magnus Inst. Utrecht Netherlands

Kahn and coworkers examined cortical thickness in patients with schizophrenia over time. Measures of functional outcome, and cumulative intake of antipsychotic medication were also assessed. Two MRI scans were obtained over a 5-year interval of 96 schizophrenia patients and 113 healthy subjects between 16 and 56 years. Excessive cortical thinning was found in widespread areas on the cortical mantle, most pronounced bilaterally in the temporal and in the left frontal cortex. Poorer outcome was associated with more pronounced cortical thinning. Thus, the cortex shows excessive thinning over time, most pronounced in the frontal and temporal areas and progresses across the entire course of the illness.

doi:10.1016/j.schres.2010.02.099

Symposium 17

DYSREGULATION OF THE DOPAMINE SYSTEM: THE FINAL COMMON PATHWAY TO SCHIZOPHRENIA?

Co-Chairpersons: Jim Van Os, Oliver Howes
Tuesday, 13 April, 2010 - 3:30 pm - 5:30 pm

Overall Abstract: In recent years several streams of new evidence have substantially refined understanding of dopamine’s role in the pathophysiology of schizophrenia. This evidence derives from in vivo neurochemical imaging studies, findings on the impact of environmental risk factors, as well as research into at risk populations and animal models. This symposium brings together international experts to present the latest findings in each of these areas and provides a forum to consider how they may interact in the development of schizophrenia. SPEAKER 1 ABSTRACT: The neurodevelopmental perspective: Dopamine system overdrive by the hippocampus in an animal model of schizophrenia and reversal by antipsychotic drugs. There is substantial evidence for hyperactivity within the hippocampus in schizophrenia patients. Using a developmental disruption rat model, Dr. Grace’s lab found a hyperactivity within the hippocampus that correlates with a loss of parvalbumin interneuron staining and disruption of evoked gamma activity. This hyperactivity was found to increase dopamine neuron population activity, leading to hyper-responsivity to phasic inputs. Acute administration of first- and second-generation antipsychotic drugs attenuated population activity in the schizophrenia model rats but not in controls. In contrast, restoration of hippocampal activity using a novel GABAergic alpha-5 benzodiazepine was found to reverse the increase in dopamine neuron population activity and the behavioral hyper-responsivity to amphetamine.

doi:10.1016/j.schres.2010.02.100

THE NEURODEVELOPMENTAL PERSPECTIVE:
DOPAMINE SYSTEM OVERDRIVE BY THE HIPPOCAMPUS
IN AN ANIMAL MODEL OF SCHIZOPHRENIA AND REVERSAL
BY ANTIPSYCHOTIC DRUGS

Anthony Grace
University of Pittsburgh Pittsburgh, PA, USA

There is substantial evidence for hyperactivity within the hippocampus in schizophrenia patients. Using a developmental disruption rat model, Dr. Grace’s lab found a hyperactivity within the hippocampus that correlates with a loss of parvalbumin interneuron staining and disruption of evoked gamma activity. This hyperactivity was found to increase dopamine neuron population activity, leading to hyper-responsivity to phasic inputs. Acute administration of first- and second-generation antipsychotic drugs attenuated population activity in the schizophrenia model rats but not in controls. In contrast, restoration of hippocampal activity using a novel GABAergic alpha-5 benzodiazepine was found to reverse the increase in dopamine neuron population activity and the behavioral hyper-responsivity to amphetamine.

doi:10.1016/j.schres.2010.02.101

THE ROLE OF ENVIRONMENTAL FACTORS

Alain Dagher
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Human and animal research suggests that the magnitude of the dopamine response to drugs, natural rewards, and stressors may be a marker of vulnerability to certain diseases. Patients with schizophrenia have an enhanced dopaminergic response to stimulant drugs and stress. Stress can trigger a psychotic episode in at-risk individuals. It is therefore possible that hyper-dopaminergia represents a risk factor for schizophrenia. We will review evidence that individuals at risk for schizophrenia demonstrate enhanced dopamine release in response to psycho-social stress. Also, while this enhanced dopamine response may be partly genetic, environmental factors may also play a role.

doi:10.1016/j.schres.2010.02.102

DOPAMINE DYSREGULATION: PATHOPHYSIOLOGY OR ENDOGENOTYPE?

Oliver Howes
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Studies of people at high risk of psychosis provide evidence that structural and functional brain alterations predate the onset of schizophrenia. People with prodromal symptoms of schizophrenia show presynaptic dopamine excess that is linked to greater symptom severity, worse neurocognitive function, and frontal cortical dysfunction. These data and data on dopaminergic function in relatives of people with schizophrenia is presented and discussed.

doi:10.1016/j.schres.2010.02.103
LINKING Dopamine Dysregulation To Symptoms And Clinical Phase Brain Imaging Studies
Anissa Abi-Dargham
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Brain imaging studies assessing indices of dopamine (DA) transmission have shown that striatal dopamine excess relates to positive symptoms and their response to treatment, while alterations in cortical DA transmission relate to cognitive deficits and negative symptoms. More recently evidence emerged for differences across the striatal substructures subserving different symptoms and varying also with comorbid substance use. DA dysregulation is also present, although to a milder degree, in spectrum disorder patients, like schizotypal personality disorders, and varies in magnitude across different phases of the illness. We will discuss these alterations, the role they may play in the pathogenesis of the disorder and their implications for treatment.

doi:10.1016/j.schres.2010.02.104

Symposium 18
Improving Signal Detection in Schizophrenia Clinical Trials by Multiple Methods
Chairperson: Wolfgang Fleischhacker
Tuesday, 13 April, 2010 - 3:30 pm - 5:30 pm

Overall Abstract: Improving Signal Detection in Schizophrenia Clinical Trials by Multiple MethodsChair & Discussant: Wolfgang FleischhackerPresenters: David Daniel, Michael Detke, John Harrison, Nina SchoolerClinical trials of approved medications for schizophrenia fail more frequently than their powering indicates they should (A. Khan, 2005). Furthermore, the drug-placebo separation on new drug applications for schizophrenia has been worsening over the last decades (N. Khin, 2009). This may be the result of at least two fundamental problems: firstly, some patients enrolled into clinical trials may be insufficiently ill and/or inaccurately diagnosed to benefit from the therapies being tested; and secondly, assessment methods for detecting efficacy may be inadequate and/or inconsistent. In this symposium, each speaker will present data on a different approach to improving signal detection in schizophrenia clinical trials, focusing on empirical evidence for the effectiveness of these methods. Dr. David Daniel will present data on the effectiveness of rater training that utilizes ongoing instruction, monitoring and feedback to address scoring ability, inter-rater reliability, interviewing competency and diagnostic skills on clinician-rated scales. Dr. Michael Detke will present data on the effectiveness of centralized raters and centralized review/monitoring, in patient ascertainment and outcomes assessments, again on subjective clinician-assessed scales. The last two presenters will focus on other kinds of outcomes: Dr. John Harrison will present data from trials that have employed the measures that comprise the MATRICS Consensus Cognitive Battery, as well as test data collected using both paper-and-pencil assessments and computerized cognitive outcome measures. Dr. Nina Schooler will address the particular challenges of functional outcome measures and in defining appropriate long-term outcome measures beyond just symptom remission, as well as strategies for their accurate assessment. She will also focus on the role of informants.

doi:10.1016/j.schres.2010.02.105

MULTIFACTORIAL APPROACH TO TRAINING AND SURVEILLANCE OF RATERS IN CNS CLINICAL TRIALS
David Daniel
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Multifactorial Approach to Training and Surveillance of Raters in CNS Clinical Trials.

Background: In multi-site, international clinical trials, signal detection may be undermined by multiple factors, such as variation in rater credentials, language and culture, as well as measurement error, drift in ratings technique over time and baseline inflation. We hypothesized that each of these risk factors to data quality could be usefully addressed within a comprehensive rater training, certification and monitoring approach.

Method: To assess the ability of training to synchronize rating of culturally sensitive psychopathology, we compared levels of agreement among US and non-US raters from multiple languages and countries in rating negative symptoms of schizophrenia. To assess variation in rater credentials, we compared use of doctorate vs. non-doctorate raters in 66 industry-sponsored multi center trials by region. In a subgroup trained we examined the relationship between educational level and competency to conduct an interview as measured by the Research Interview Assessment Scale (RIASA).

To evaluate the effectiveness of a rater monitoring program we assessed whether post-training surveillance of patient ratings data coupled with very rapid rater feedback and remediation could reduce rater errors early in the course of a complex multi-center clinical trial using multiple rating scales (MADRS, QIDS-SR, HAM = A, CGI-S and CGI-I).

To determine if rater drift could be controlled by periodic remote refresher training and assessment we retrospectively compared measures of agreement in ratings of videotaped patient interviews at initial training and mid-study in 18 CNS clinical trials. Results: For raters participating in two large international trials, there was no significant difference between US and non-US raters (90.9% vs. 95.9%) in meeting criteria for agreement in using a novel measure of negative symptoms (NSA-16). The levels of agreement were at least as good with the more familiar PANSS.

The differences among the five regions in the use of doctorate vs. non-doctorate raters was statistically significant (chi-square=1581, p<0.0000001, df=4) primarily due to lower use of doctorate level raters in North America (54.6%) compared to Europe (94%) and Asia (66.8%). In a subset of US PANSS raters the difference between mean total RISA scores for doctorate (278) vs. non-doctorate (259) raters approached but did not reach statistical significance (t=1.95, p<0.06). In a complex multi-center clinical trial, the rater error index scores were reduced at day 7 (t=6.19, p<0.00001) and at day 14 (t=8.78, p<0.00001) compared to baseline suggesting that rater surveillance followed by rapid individualized remediation may reduce ratings errors very early in the course of a clinical trial. At mid-study, 89% of raters met a priori criteria for acceptable agreement in rating a videotaped interview compared to 83.2% at study initiation (chi-square=22.14, p<0.0000005), suggesting that rater drift could be modulated by a simple mid-study refresher training procedure.

Discussion: Successful facilitation of signal detection is likely to result from a multifactorial approach involving careful assessment of rater credentials, systematic and thorough training of interview and ratings technique, attention to cultural variation in symptom perception, mid-study refresher training, and ongoing quality assurance surveillance and remediation based on actual patient ratings. The analyses described above support the feasibility of each of these interventions.

doi:10.1016/j.schres.2010.02.106
IMPROVING SIGNAL DETECTION IN SCHIZOPHRENIA CLINICAL TRIALS

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Improving Signal Detection in Schizophrenia Clinical Trials – Centralized Ratings / Centralized Review.

Clinical trials in schizophrenia fail more frequently than they should and the drug-placebo separation has been worsening. This presentation will focus on two possible root causes: first, some patients enrolled into clinical trials may be inaccurately diagnosed and/or insufficiently ill to benefit from the treatments being tested; and second, assessment methods for detecting efficacy may be inadequate and/or inconsistent.

The first potential root cause is patient ascertainment. Previous studies in MDD & GAD have shown that 1/3 to 1/2 of the patients enrolled in trials by site raters would be excluded based on the patient’s self-rating or remote blinded clinicians’ ratings of initial severity. New data from ongoing schizophrenia studies shows that 5-56% of patients enrolled in trials by site raters would be excluded based on remote blinded clinicians’ ratings of initial severity. New data on diagnosis at study entry in ongoing psychiatric trials show that an additional cohort of patients would be excluded with remote blinded clinicians performing the diagnostic evaluations. The second potential root cause is inadequate or inconsistent assessments. Data will be reviewed showing that >50% of assessments of primary efficacy scales were inadequately performed in one study, and that assessment quality decayed over the life of another trial.

One potential solution to both of these possible root causes is to employ remote blinded clinicians to do assessments of key inclusion/exclusion criteria, such as diagnosis and initial severity, as well as to assess key outcomes. Data will be reviewed showing that this methodology improved signal detection in a recent schizophrenia clinical trial. An alternative to centralized assessments by videoconference is to videotape assessments performed at clinical trial sites, for review by a continuously calibrated group of centralized clinicians, much as a single cardiologist reviews EKGs from multiple sites. Initial data from this approach will be presented, with trends showing improvement in diagnostic and outcomes assessments from clinical trials in various psychiatric indications.

doi:10.1016/j.schres.2010.02.108

FUNCTIONAL OUTCOME AS A LONG-TERM TREATMENT GOAL: DEFINITION AND ASSESSMENT IN CLINICAL TRIALS

Nina Schoeller
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Functional outcome as a long-term treatment goal: definition and assessment in clinical trials.

As clinical trials in schizophrenia become longer and targets for treatment become more specific, the concern with outcomes has developed beyond domains that are readily assessed by clinical observers and direct trial participant report. In particular, the current focus on cognitive deficits in schizophrenia has led to increased interest in functional outcomes that are mediated in part by cognitive deficits. This presentation will review the current state of functional outcome assessment from a number of critical perspectives: burden, opportunity to observe, availability of assessor and validity of assessment. Most prior consideration of instruments has involved scale or instrument level comparisons. The focus here will be on the examination of domains of functional outcome such as work, family relationships, social relationships, living situation and life orientation/satisfaction to identify optimal strategies for assessment that are domain specific. Consideration of domain specificity may be advantageous in encouraging development of instruments that will facilitate evaluation of new treatments.

doi:10.1016/j.schres.2010.02.109

Symposium 19
AUTISTIC AND COGNITIVE TRAITS IN THE GENETIC UNDERSTANDING OF THE CONTINUUM IN NEURODEVELOPMENTAL DISORDERS AND FUNCTIONAL PSYCHOSIS
Co-Chairpersons: Lourdes Fañanás, Marie-Odile Krebs
Tuesday, 13 April, 2010 - 3:30 pm - 5:30 pm

Overall Abstract: The assumption that neuropsychiatric disorders are phenotypically heterogeneous with overlapping findings suggests the participation of more than one etiological factor and pathophysiological process, some of them being partly shared across the traditional classification categories. Autistic Spectrum Disorders and Psychotic Disorders are complex neuropsychiatric syndromes affecting between 0.3 and 0.6% of the children and 3% of the adult world population (1, 2). Although their separation is clear since DSM-
Ill publication, the emergence of some common cognitive, family, genetic and imaging findings has pointed out the interest of core neurobiological processes common for subsets of these two heterogeneous clinical groups (3). There is no wonder that this remarkable heterogeneity is intimately related to the complexity of the genetic control of brain development and function. In this sense, there are numerous direct and indirect genetic data linking both disorders (4-6). Specifically, various candidate gene and linkage studies (based on genes implicated in brain development and functioning pathways such as DISC1, NRXN1, RELN or GAD1), highlighting the emerging evidence for biological links between both disorders (3). Moreover, more recently, genomic microduplications and deletions or copy number variants (CNVs) have been reported in both Autism and Psychosis (7-10). Accordingly, it is likely that genetic studies will increasingly implicare patterns of brain developmental disturbance, leading to define disorders in novel ways.


doi:10.1016/j.schres.2010.02.110

DE NOVO MUTATIONS IN SYNAPTIC GENES IN SCHIZOPHRENIA AND RELATED NEURODEVELOPMENTAL DISORDERS

Guy Rouleau
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Schizophrenia (SCZ), autism spectrum disorders (ASD) and mental retardation (MR) are common, devastating and poorly treated brain disorders. Converging evidence suggests that genetically disrupted synaptogenesis and plasticity during development may underlie the pathogenesis of such brain disorders. In 2006 we have initiated the project Synapse to Disease (STD) aiming at the identification of genes that cause or predispose an individual to neurodevelopmental diseases. We hypothesize that a significant fraction of SCZ, ASD and non-syndromic MR cases are a result of novel mutations in many different genes involved in synapse formation and function. To identify genetic factors predisposing to these diseases we have adopted an innovative two-step strategy: direct re-sequencing of all genes encoding proteins acting at the synapse, followed by functional validation of variants in zebrafish, drosophila or mouse hippocampal cell models. We established a list of 5,079 synaptic and potentially synaptic genes based on published studies and databases and prioritized them using a ranking system. In the initial phase of this study, we designed and optimized PCR amplimers to amplify all coding exons and their intronic junction of a prioritized subset of these genes chosen from our synaptic list based on their involved in synapse formation and or structure. Fragments are then amplified from DNA samples isolated from 143 SCZ, 142 ASD and 95 non-syndromic MR unrelated probands, and sequenced on one strand. Sequence traces were aligned and variants identified and genotyped in all samples using a number of SNP automatic discovery methods such as PolyPhred. To date we have screened 488 genes and have identified >8000 variants, of which >6000 are novel and not found in public SNP databases. We have identified a total of 22 de novo variants in 16 different genes. In addition, we have identified a further 14 protein-truncating variants in 12 genes that are transmitted from either the unaffected mother or father. We tested whether some of the interesting identified de novo variants have a functional effect on protein function using several animal models. For instance, we knock-down expression of the candidate gene in zebrafish embryos using morpholino oligonucleotides, and
check for a phenotype. Then we try to rescue the morpholino-induced phenotype by co-injecting the wildtype (WT) human cDNA of the test gene. Finally, we test whether co-injection of morpholino and mutated human cDNA can rescue the phenotype in the fish embryos. Using these approaches, we have identified several new genes associated with these diseases (such as SHANK3, IL1RAPL1, SYNGAP1, STXBP1, and others). Interestingly, some of the identified genes show deleterious de novo mutations in patients from the 3 disease cohorts, suggesting close biological overlap in these three. A combination of high-throughput sequencing, automated SNP discovery, genetic and biological validation strategies can be used to identify SCZ and AUT genes. This approach can also be used to identify genes involved in other common diseases, especially as next-generation sequencing technologies become available to screen a larger number of candidate genes in more patient samples. However the challenge remains in robustly linking a DNA variant to a clinical phenotype. Acknowledgements: Genome Canada and Génome Québec, Université de Montréal and Canadian Foundation for Innovation & CHIR.

doi:10.1016/j.schres.2010.02.112

RARE PATHOGENIC COPY NUMBER MUTATIONS IN MENTAL DISORDERS

David Collier
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Rare structural variants may account for a larger fraction of the overall genetic risk than previously assumed. In contrast to rare single nucleotide mutations, rare copy number variations (CNVs) can be detected using genome-wide single nucleotide polymorphism arrays. This has led to the identification of CNVs associated with mental retardation and autism. In a genome-wide search for CNVs associated with schizophrenia, we used a population-based sample to identify de novo CNVs by analysing 9,878 transmissions from parents to offspring. The 66 de novo CNVs identified were tested for association in a sample of 1,433 schizophrenia cases and 33,250 controls. Three deletions at 1q21.1, 15q11.2 and 15q13.3 showing nominal association with schizophrenia in the first sample (phase I) were followed up in a second sample of 3,285 cases and 7,951 controls (phase II). All three deletions significantly associate with schizophrenia and related psychoses in the combined sample. The identification of these rare, recurrent risk variants, having occurred independently in multiple founders and being subject to negative selection, is important in itself. CNV analysis may also point the way to the identification of additional and more prevalent risk variants in genes and pathways involved in schizophrenia.

doi:10.1016/j.schres.2010.02.114

FUTURE DIRECTIONS FOR THE NEUROPATHOLOGY OF SCHIZOPHRENIA

Co-Chairpersons: David Cotter, Paul Harrison
Tuesday, 13 April, 2010 - 3:30 pm - 5:30 pm

Overall Abstract: This symposium will summarise the value of post-mortem brain research in schizophrenia and to discuss the possible future directions of work in this area. Common themes
include an awareness of a need to use integrative approaches and an acknowledgement that there is a continued need for detailed neuropathology using newer technologies and studying multiple cortical regions and assessing different developmental time periods. Dr Kleinman in his role of discussant will integrate the conclusions of these talks and provide a summary regarding future work in this area.

doi:10.1016/j.schres.2010.02.115

ABNORMAL N-GLYCOSYLATION OF PROTEINS OF THE GLUTAMATE SYNAPSE IN SCHIZOPHRENIA

James Meador Woodruff
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Recent data suggest abnormalities of glutamate transmission in schizophrenia. While many findings of abnormal glutamate receptor expression in schizophrenia have been published, findings are subtle or even contradictory. These conflicting studies on the expression of these receptors leads to a reconsideration of the "glutamate hypothesis of schizophrenia" as not "too many" or "too few" receptors, but rather one of alterations in the cell biological processes that manage the total pool of receptors. Recent data point to abnormalities of glutamate receptor trafficking, delivery, densritic localization, recycling, and degradation in the brain in schizophrenia. In this study, we extend our findings of abnormalities of intracellular trafficking of the AMPA subtype of glutamate receptor in schizophrenia. AMPA receptor trafficking starts in the endoplasmic reticulum (ER), in which AMPA receptor subunits are posttranslationally N-glycosylated. N-linked high mannose containing sugars added to AMPA subunits, which are trimmed and replaced by more elaborate sugars in the Golgi, after which AMPA subunits are trafficked for insertion into the plasma membrane. We assayed N-glycosylation status of AMPA subunits in prefrontal cortex in schizophrenia. N-glycosylation was assessed following digestion with endoglycosidase H (Endo H), which removes immature high mannose containing sugars, or with peptide-N-glycosidase F (PNGase F), which removes all N-linked sugars. We found that both GluR2 and GluR4 were sensitive to Endo H and PNGase F treatment, indicating that they are N-glycosylated; neither GluR1 nor GluR3 are N-glycosylated in human brain. GluR2 was found to have less N-linked high mannose and/or hybrid sugars in schizophrenia. This was confirmed by immunoprecipitation of GluR2 and probing with Concanaval A, a mannose-specific lectin. GluR2 immunoprecipitated from schizophrenia cortex was significantly less reactive to Con A comparing to the comparison group. These results indicate that GluR2 is abnormally glycosylated in schizophrenia, consistent with abnormal assembly or trafficking of the AMPA receptor. Abnormalities of glycosylation in schizophrenia may be more extensive, as we also have preliminary results suggesting abnormalities of N-glycosylation of NMDA subunits and two of the glutamate transporters. These results suggest that there are changes in glutamate receptors in schizophrenia that involve abnormalities of intracellular processes that effectively reduce receptor function even though total cellular levels of these receptors may be normal. Such findings are important because they point to the complexity of molecular and intracellular abnormalities in schizophrenia, and highlight novel sites that may be profitably targeted for drug.

doi:10.1016/j.schres.2010.02.116

WHAT PROTEOMICS WILL ADD TO OUR UNDERSTANDING OF THE NEUROPATHOLOGY OF SCHIZOPHRENIA

David Cotter
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Proteomic studies of the post-mortem brain offer direct insights into the pathogenesis of schizophrenia at the level of protein expression. Until recently, the methods have been hampered by technological difficulties, not least the lack of a high though-put protein confirmation method. Fortunately, mass spectrometry methods have advanced greatly and these will have an impact on the field in the short term. We have reviewed the proteomic studies of post mortem brain studies of schizophrenia and will summarises the major protein pathways implicated in the disease pathology. The findings generally point towards prominent cellular assembly and organisation abnormalities, diminished cytoskeletal integrity, synaptic pruning and plasticity, and metabolic dysfunction. In our own data we have observed changes in several pathways which have the potential for providing novel insights into schizophrenia. For example, we have observed differential protein expression of a number of proteins involved in clathrin-mediated endocytosis and NMDA receptor recycling. We have also observed changes iron-homeostasis proteins, which are responsible for oligodendroglial function, in schizophrenia. Together these finding have the potential to provide novel insights into our understanding of the proposed NMDA hypofunction and, myelin changes in schizophrenia. Considering the complexity of the proteome it should be appreciated that we have only begun to explore the proteomic 'iceberg' that has relevance to schizophrenia. Future studies will be able to focus on previously inaccessible proteins by enriching for various membrane, synaptic, and cytoskeletal sub-proteomes. This will be an improvement on previous studies which have been based largely on relatively crude whole tissue preparations. Large scale validation of the various protein pathways will also need to be done. The advent of the mass spectrometry multiple reaction monitoring method (MRM) for absolute quantification may be the answer in this regard. However, integrating the findings from various "omic" fields should provide answers that will not be apparent from the study of one field alone. Thus, there is an argument for future work in schizophrenia to apply more integrative approaches that incorporate the findings relating to envirome, genome, transcriptome in addition to the proteome.

doi:10.1016/j.schres.2010.02.117

THE FUTURE OF POST-MORTEM RESEARCH - 1

Maree Webster
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Much emphasis has been placed on investigating the genetic susceptibility of the major mental disorders. However, the recent identification of a brain-specific isoform as a risk gene for schizophrenia and the identification of polymorphisms with clear tissue-specific effects on both gene expression and splicing indicate that the genetics of gene expression will need to be studied in cells that represent, and are most relevant to, the disease state. Thus, it is becoming apparent that in order to identify and understand the susceptibility genes and the most relevant associated biological pathways, post-mortem brain tissue will need to be utilized. To facilitate this effort future studies may need to integrate genomic and genome-wide expression data as well as neuropathological, proteomic, and neurochemical data from the same set of brains in
THE FUTURE OF POSTMORTEM RESEARCH

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Postmortem brain collections are an incredibly valuable resource, as none of the disease models can adequately mimic the pathophysiological processes that occur in the diseased human brain. Thanks to the postmortem research, we identified critical processes and molecular mechanisms that are critically involved in schizophrenia, and there is an emerging consensus about some of the most critical findings. However, there are many additional lines of postmortem research that should be explored over the next decade. In future postmortem studies the complexity of the anatomical brain structures will represent a significant challenge. The cellular phenotypes making up the brain are different, and the disease process will affect them differently. Thus, we must find the way to respect the microanatomy in our postmortem experiments. Harvesting single cells with laser-capture techniques and various other micro-harvesting methods can provide critical staring material for analyses that will focus on cell-type specific assessment of splice variants, epigenetic modifications and various emerging technologies. We can also anticipate that methods of extracting RNA from fixed tissue are likely to improve markedly, though some limitations of postmortem tissue will undoubtedly remain. However, recent studies suggest that archival, previously fixed tissue may become a valuable source of RNA in the near future. Most of the postmortem analyses to date have been performed on a limited number of brain areas. Yet, one should not assume that only a few brain areas are important to study in schizophrenia and bipolar disorder. Schizophrenia appears to be the disease of multiple brain regions, and we must expand our experiments beyond the prefrontal cortex, temporal cortex, anterior cingulate and hippocampus. Finally, investigating the same samples with many different tools (e.g. expression arrays, SNP chips, epigenetic modifications, etc) may be a very powerful strategy, especially if all those data are properly integrated into an easy to use database. These combined approaches may hold the key to understanding the heterogeneity within the disease spectrum, and may help us subgroup patients into biological subphenotypes of the disease.

doi:10.1016/j.schres.2010.02.118

COMPENSATORY COGNITIVE TRAINING FOR PATIENTS WITH PSYCHOSIS

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Individuals with primary psychotic disorders experience numerous neuropsychological and functional impairments. Compensatory Cog-
nitive Training (CT) is a manualized, 12-week, group-based intervention to improve prospective memory, attention, learning and memory, and executive functioning. Each session emphasizes strategy learning, development of new cognitive habits, and transfer of new skills into community settings. 51 outpatients with schizophrenia or related psychotic disorders participated in a 6-month randomized controlled trial comparing CT plus standard pharmacotherapy to standard pharmacotherapy alone (SP). Participants were mainly men (69%), Caucasian (78%), and high school educated, with a mean age of 47 and a mean illness duration of 24 years. Measures, administered at baseline, 3 months, and 6 months, included assessments of neuropsychological performance (forward digit span; Hopkins Verbal Learning Test; Wisconsin Card Sorting Test; Memory for Intentions Screening Test), psychotic symptom severity (PANSS; HAM-D), everyday functioning capacity (UCSD Performance-Based Skills Assessment), and quality of life (Quality of Life Interview). Repeated measures ANOVA and Pearson correlations were used to analyze the data. CT participants improved differentially in verbal delayed memory ($F = 4.25$, $p = .045$) and negative symptom severity ($F = 8.79$, $p = .005$), and there were trends toward improvement in functional capacity and quality of life. Neither age nor global neuropsychological performance at baseline was associated with any change measure. These results indicate that compensatory CT may lead to improvements not only in cognition, but also in more distal outcomes, such as clinical symptomatology.

doi:10.1016/j.schres.2010.02.121

Efficacy of a multisite group based cognitive remediation program in Malaysia

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Introduction: A cognitive remediation therapy (CRT) programme was introduced in Malaysia in 2006. The project, which was named the Cognitive Remediation Project for Schizophrenia (CREPS), was based on the principles of Neuropsychological Educational Approach to Remediation (NEAR) but modified to suit local resources and needs. The modifications include the use of a web-based assessment for neurocognition to accommodate the lack of neuropsychologists to do cognitive assessments and simplification of the treatment programme so that it could be run by paramedics with minimal training in psychology. These modifications were necessary to accommodate for lack of resources in a developing country. In addition, CREPS includes a computer orientation programme at the beginning of CRT and there is a significant focus on software targeting speed of processing to enhance overall improvement in cognitive functions. The rationale for the latter was that, there is substantial evidence that speed of processing might be a mediating factor to other cognitive disturbances. Hence, a plausible approach is to focus a significant part of CRT at improving speed of processing to enhance improvement in other areas of cognition such as attention, memory and problem solving.

Aims: A randomised controlled trial was conducted to study the effectiveness of this group based CRT involving five treatment centres throughout Malaysia. There was also an additional phase to ascertain whether adding booster sessions after completion of treatment would give additional benefit to the outcome of CRT.

Methodology: In Phase I, 85 subjects were recruited and randomised into CRT ($N = 57$) and Waitlist ($N = 28$). Thirty-two and 25 subjects from each group respectively completed the study. Assessments of cognitive functioning, psychosocial functioning and psychopathology were done at baseline and post-treatment. In Phase II, subjects were randomised into standard CRT (SCRT; $N = 19$) and CRT with additional 4 booster sessions (BCRT; $N = 18$). Fourteen subjects from SCRT and 15 from BCRT completed the study and similar tests were conducted at 5 week follow-up.

Results: Patients receiving CRT showed improvement in all cognitive domains studied compared to WL, as well as in psychopathology and psychosocial functioning. These findings were maintained at 5 weeks follow up. However, addition of booster sessions did not give any additional benefit to the outcome of CRT.

Conclusions: The outcome of this study was comparable to other studies. It is postulated that this may be the result of some local modifications to the programme which included inclusion of computer orientation, simplification of the training programme to suit local needs and focus on processing speed. Nevertheless, results from this study were at best exploratory in nature because of small sample size, the lack of active comparator as the control group and all the limitations due to the lack of resources in the local setting.

doi:10.1016/j.schres.2010.02.122

Groups to improve awareness about cognitive dysfunction in schizophrenia

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Individuals diagnosed with schizophrenia spectrum disorders have significant cognitive deficits that have been linked to poor functional outcome, yet many people with schizophrenia who score in the impaired range on cognitive tests are not aware that their illness may negatively affect skills like memory, attention, organization and problem solving. This lack of awareness can contribute to noncompliance with cognitive remediation, and with the pharmacologic treatments that eventually will be available to treat cognition. If people do not perceive that a treatment has any value for them, they may be less likely to comply with it. This talk will review the need for psycho-education about cognition and the group based approaches that have been used. For example, one brief group based psycho-educational program to improve awareness about cognitive dysfunction in schizophrenia is called Braincheck, and it has been implemented successfully at several community based programs in the USA. Braincheck is a low cost, easily implemented verbal group that engages participants in a discussion about cognition and a brief exercise to evaluate their own cognition. The effectiveness of this program was studied in a randomized controlled trial with 70 subjects and a positive impact on awareness was found. Results of this trial suggest that awareness of cognitive impairment is a potentially responsive target for treatment and that improving awareness of cognitive deficit can be done in a group format using low budget techniques that can easily be disseminated in different languages.

doi:10.1016/j.schres.2010.02.123

Integrated neurocognitive therapy: a group based approach to improve neuro- and social cognition

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Objectives: Impairments in cognitive functioning in schizophrenia patients are regarded as important treatment targets. The basis of such treatment approaches are integrative models postulating a strong connection between neuro- and social cognitive deficits,
negative symptoms and functional outcome. We recently developed a combined treatment approach, Integrated Neurocognitive Therapy (INT), which we are currently evaluating. INT aims at improving both neuro- and social cognitive functioning by targeting the cognitive dimensions defined by the MATRICS initiative. This “bottom up” and “top down” approach puts a strong focus on the patients’ daily life context to promote transfer and generalization and facilitates intrinsic motivation, resources and group processes.

Methods: INT is currently evaluated in an ongoing international randomized multi-site study in Switzerland, Germany and Austria, which is supported for 5 years by the Swiss National Science Foundation. INT is being compared with treatment as usual (TAU) in a sample of younger outpatients with schizophrenia. Patients receive 30 therapy sessions, two per week, lasting 90 minutes each. Assessments comprise proximal and distal measures. They are administered before and after therapy and at a 1-year follow-up. 161 outpatients have participated in the study.

Results: INT patients obtain significant improvements in objective cognitive test performance (speed, attention/vigilance, verbal memory, problem solving, affect recognition) and self-ratings of cognitive functioning during therapy compared to TAU. Additionally, superior effects for INT patients could be found in the distal outcome areas of negative symptoms and social functioning. These favourable effects were maintained or improved during follow-up. Structural equation modeling (SEM) revealed evidence in the INT group that social cognition and negative symptoms function as mediators of the link between neurocognition and functional outcome. Finally, the low drop-out rate of the INT patients during the study represents a high acceptance by the patients.

Conclusion: The favourable outcome effects as well as the SEM analysis provide empirical evidence for INT as a significant group therapeutic intervention to improve functioning in younger outpatients. Moreover, the inclusion of treating negative symptoms directly could be a promising goal to optimize treatment efficacy.

doi:10.1016/j.schres.2010.02.124

PANDOPAMINERGIC D2 SUPERSENSITIVITY RELATED TO MOVEMENT DISORDERS AND SCHIZOPHRENIA

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Although dyskinesia is regarded by most psychiatrists as Tardive Dyskinesia, a side effect of antipsychotic medication, one could argue that this is too narrow a view and therefore presents an interesting area for further investigation. The facts that: i) schizophrenia is the only psychiatric disorder in which antipsychotic naïve patients display far more signs of dyskinesia, and ii) first degree relatives of patients with schizophrenia can display signs of dyskinesia (Koning, Tenback et al. 2008), suggest that dyskinesia is a marker for schizophrenia susceptibility. Besides this, dyskinesia and also spontaneous parkinsonism can be considered a marker for disease severity, as it is related to a poor outcome with regard to the course of the illness (Chatterjee, Chakos et al. 1995; Schroder, Silvestri et al. 1998; Tenback, van Harten et al. 2007). As a marker for schizophrenia as well as a predictive marker for potential disease severity, dyskinesia and spontaneous parkinsonism in schizophrenia are fascinating phenomena in the context of the pathophysiological basis of schizophrenia. Since imaging studies show D2 dopamine up-regulation in the nigrostriatal pathways (Silvestri, Seeman et al. 2000; Hirvonen, van Erp et al. 2005), especially in patients with a poor prognosis (Schroder, Silvestri et al. 1998), we hypothesized that a D2 supersensitivity might not be restricted to the nigrostriatal pathway alone, but that the pan-dopaminergic system could be involved in the pathophysiological basis of dyskinesia and spontaneous parkinsonism, and probably of schizophrenia. Several proxy measures representing the different dopamine tracts as predictors for the emergence of dyskinesia in schizophrenia were examined in a large cohort (n = 10,000) of patients with schizophrenia: i) Extra Pyramidal Syndromes as a proxy for the nigrostriatal dopamine tract; ii) sexual adverse events as a proxy for the tuberoinfundibular dopamine tract; iii) worsening of psychosis represented by a worsening of the Clinical Global Impression (CGI) as a proxy for the mesolimbic and mesocortical dopamine tract (Tenback, van
Harten et al. 2007). The sample was not suitable for other, more detailed, proxy measures for the mesocortical and mesolimbic dopamine tracts such as cognitive and positive symptoms, as the CGI schizophrenia, which measured all schizophrenia symptom clusters, did not differentiate in a factor analysis. We will discuss the pan-dopaminergic involvement in emergent dyskinesia together with antipsychotic medication as a differential exogenous risk factor for the pan-dopaminergic tract for emergence of dyskinesia. When TD emerges under FGA, TD has a higher rate of reversibility than when emerging under SGA. Combining the findings of the different chapters into a coherent hypothesis, a framework is proposed of pan-dopaminergic involvement in emergent dyskinesia together with antipsychotic medication as a differential exogenous risk factor for the pan-dopaminergic tract for emergence of dyskinesia.

### MOVEMENT DISORDERS ARE SPECTRUM CONDITIONS IN SCHIZOPHRENIA

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Many movement disorders and schizophrenia are complex diseases caused by multiple genetic and environmental factors, which are probably partly shared. A recent meta-analysis reported spontaneous dyskinesia and parkinsonism in antipsychotic naïve patients with schizophrenia, and a higher prevalence of tardive dyskinesia in healthy family members of patients with schizophrenia than matched controls (Koning, Tenback et al. 2008). Various combinations of susceptibility genes may converge on synaptic processing in microcircuits, affecting a final common pathway of dysfunction and related symptoms, and secondary morphological alterations (Coyle J et al. 2006, Ross CA et al. 2006). It is noteworthy that movement disorders fulfill the criteria for classifying a trait as a spectrum condition of a disorder, in this case schizophrenia: heritability, familial link, co segregation, and biological and clinical plausibility (Faraone S 1999). Spectrum conditions refer to mild psychopathology of little clinical significance among relatives without the full disorder. The advantage of spectrum conditions in contrast to a full disorder may be their fewer risk factors and therefore less complex chain of mechanisms involved leading to their onset, which makes research easier to perform. (Pharmacogenetic studies may help elucidate these common pathways in the development of both spectrum conditions, and the full disorder. As a result, meta-analyses found significant genetic association between tardive dyskinesia and some genes coding for schizophrenia, e.g. dopamine 3 receptor (DRD3) (Bakker PR et al. 2006), dopamine 2 receptor (DRD2) and catechol-O-methyltransferase gene (COMT) (Bakker PR et al. 2008). An important development in human (pharmaco)genetics is the possibility of genome-wide association studies (GWASs) since 2005 (Psychiatric GWAS Consortium, 2009), with the advantage of ‘hypothesis free’. Hence, unbiased approach revealing new DNA variants influencing genetic susceptibility of many common diseases, and elucidating new pathological mechanisms. Until now, two GWASs of movement disorders were performed: i) the study of Inada e.a. (Inada et al. 2008) suggesting involvement of the GABA receptor signaling pathway in the development of therapy-resistant tardive dyskinesia, and ii) the study of Akelai e.a (Akelai A et al. 2009) specifying EPF1, NOVA1, and FGN as promising genes related to antipsychotic induced parkinsonism. In the near future, larger GWAS samples will detect more common susceptibility variants with smaller effect sizes, and, stronger evidence will be found in meta-analyses of GWAS, as proposed by the Psychiatric GWAS Consortium (PGC). The genetic relationship between movement disorders as spectrum disorders and schizophrenia will be discussed.

### INSTRUMENTAL ASSESSMENT OF MOVEMENT DISORDERS IS MORE SENSITIVE THAN TRADITIONAL RATING SCALES IN SCHIZOPHRENIA RESEARCH

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Movement disorders such as dyskinesia and parkinsonism have been reported in antipsychotic naïve patients with schizophrenia and may be regarded as core features of the illness. In addition, first degree relatives of patients also appear to have more dyskinesia and parkinsonism compared to controls, suggesting that these movement disorders constitute (genetic) markers of vulnerability. However, most individual studies on patients and first degree-relatives failed to find this association, possibly due to insufficient sensitivity of the applied clinical rating scales. Quantitative instrumental measurements are thought to be more sensitive to detect movement disorders. We therefore compared the degree of dyskinesia and parkinsonism in medicated patients with schizophrenia, healthy siblings and matched controls using clinical and quantitative instrumental assessments. Clinical assessment of dyskinesia and parkinsonism using the Abnormal Involuntary Movement Scale (AIMS) and the Unified Parkinson Disease Rating Scale (UPDRS) was compared with instrumental assessments using force variability to quantify dyskinesia and tremor and instrumental assessment of velocity scaling to quantify bradykinesia. Both assessments were carried out in 45 medicated patients with schizophrenia, 49 non-affected siblings of patients with a non-affective psychosis and 32 healthy controls. Siblings and controls were matched for all socio-demographic characteristics. Patients could be differentiated from controls on both clinical ratings scales and instrumental assessment. There were no significant differences between siblings and controls in the clinical rating scales scores. However, instrumental assessment of dyskinesia and parkinsonism (bradykinesia) revealed significant different scores for siblings compared to controls. The presence of subclinical dyskinesia and parkinsonism in non-affected siblings suggests that movement disorders are related to the (genetic) risk of developing schizophrenia and that instrumental assessment is more sensitive to detect subtle movement disorders compared to traditional rating scales.

### THE THEORETICAL, CLINICAL, AND GENETIC BASIS TO ADD MOVEMENT DISORDERS AS AN A-CRITERION IN DSM-V

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Movement disorders are common in schizophrenia and the relationship between psychosis and spontaneous movement disorders such as dyskinesia and parkinsonian symptoms was established more than a century ago. With the introduction of the antipsychotics the attention shifted to medication-induced movement disorders and new diagnostic categories in DSM-IV TR appeared such as tardive dyskinesia and drug induced parkinsonism. However, the awareness of spontaneous movement disorders recurred and several recently published meta-analyses report about movement disorders in antipsychotic naïve patients with schizophrenia and also in first degree family members that display more dyskinesia and parkinsonian signs than the healthy control group. These findings strongly suggest that movement disorders are pathogenetically related to psychosis and schizophrenia. Criteria for psychiatric illnesses are usually selected on the basis of an
adequate prevalence base rate, sufficient inter-rater reliability and consistency. Although there is no specific DSM agreed-upon minimum base rate for inclusion as a criterion, a minimum prevalence rate of around 10% is suggested; more than 30 to 40% is ideal. Instrumental measurements in antipsychotic-naive patients with schizophrenia report prevalence rates of 13 to 20% for dyskinesia and 18-28% for parkinsonian signs respectively, rates which approach the ideal base rate. If instrumental measurement is used, inter-rater reliability is excellent without the necessity of extensive training. Furthermore, meta-analyses show that the relationship between schizophrenia and movement disorder is consistent. Other than an adequate base rate, aspects such as i) predictive value, ii) a biological basis, or iii) the specificity of the symptom add to the value of a criterion. With regard to the predictive value, only (or at least predominantly) in schizophrenia and possibly schizotypal personality disorder do antipsychotic-naive patients exhibit movement disorders. The biological origin of schizophrenia and movement disorders is likely to reside in a shared dysfunction in the dopamine system. Despite the fact that schizophrenia exhibits a wide clinical variability and heterogeneous genetic architecture, dysfunction in the dopamine system seems to be the final common pathway. The specificity of movement disorders in antipsychotic-naive patients with schizophrenia supports the inclusion as an A criterion for schizophrenia. All other DSM criteria of schizophrenia are non-specific and non-pathognomonic, i.e. many symptoms are also prevalent in affective disorders. Additionally, movement disorders can be assessed easily and objectively as no interview or extensive testing is required, merely a short instrumental examination. In conclusion, movement disorders should be an A criterion for schizophrenia.

doi:10.1016/j.schres.2010.02.129

Symposium 23
BRAIN MATURATION DURING ADOLESCENCE AND THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA: RELEVANCE FOR UNDERSTANDING PSYCHOSIS, COGNITIVE DYSFUNCTIONS AND IMPLICATIONS FOR TREATMENT
Co-Chairpersons: Peter J. Uhlhaas, David A. Lewis
Wednesday, 14 April, 2010 - 8:30 am - 10:30 am

Overall Abstract: Schizophrenia is a neurodevelopmental disorder that characteristically emerges during the transition from adolescence to adulthood. However, the mechanisms that underlie the expression of psychotic symptoms during this developmental period are still unclear. Cortical development during adolescence involves substantial refinements in the neurotransmitter systems, network physiological properties and cognitive abilities that are critically impaired in schizophrenia. Thus, knowledge of the nature and determinants of adolescent cortical maturation may be critical for both understanding the disease process of schizophrenia and for developing new means of secondary prevention and treatment. In this symposium, we will review the findings from complementary approaches on adolescent cortical development with the goal of informing hypothesis generation and testing in schizophrenia. Gogtay (Bethesda) will present structural magnetic resonance data on the development of gray matter (GM) in control subjects and in patients with childhood-onset schizophrenia (COS). These findings indicate cortical GM loss during adolescence in COS, which appears to be an exaggeration of the normal developmental pattern. GM loss is also shared by healthy siblings of COS probands, suggesting a genetic influence on abnormal brain development. Changes in gene expression of several interneuron markers in human prefrontal cortex (PFC) during development will be presented by Weickert (Sydney). Expression of RNAs and protein levels were examined in healthy controls and patients with schizophrenia at different developmental stages. The results revealed prolonged development of interneuron markers that extended into adolescence, suggesting continued maturation of the inhibitory system. Interestingly, patients with schizophrenia were also characterized by deficits in the expression of interneuron markers, except for calbindin, suggesting that the development of interneurons is dysregulated. The implications of brain development during late adolescence for the functional properties of cortical circuits in PFC will be examined by Lewis (Pittsburgh). He will present anatomical, molecular and electrophysiological findings from monkey PFC indicating that certain pre- and post-synaptic markers of GABA neurotransmission are strikingly remodeled during adolescence and that these same markers are selectively impaired in schizophrenia. Maturation of GABAergic neurotransmission is compatible with marked changes in neural synchrony during adolescence in human electro- and magnetoencephalography (EEG/MEG) -data. Uhlhaas (Frankfurt) will present findings from a face perception task and a working memory paradigm in children, adolescence and adults that show that high-frequency oscillations and their synchronisation emerge only during the late adolescent period during normal development. Furthermore, recent EEG/MEG data from his laboratory suggest that high-frequency oscillations are strongly decreased in patients with schizophrenia.

doi:10.1016/j.schres.2010.02.130

DEVELOPMENTAL REFINEMENTS IN SYNAPTIC MARKERS OF CORTICAL GABA TRANSMISSION
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In schizophrenia, working memory dysfunction is associated with alterations in both pre- and post-synaptic markers of GABA neurotransmission in the dorsolateral prefrontal cortex (DLPFC). These alterations include lower expression of GABA\textsubscript{A} receptor \(\alpha\textsubscript{1}\) subunits and higher expression of GABA\textsubscript{A} receptor \(\alpha\textsubscript{2}\) subunits that are predominantly found post-synaptic to specific classes of GABA neurons. In rodents, cortical \(\alpha\textsubscript{1}\) subunit expression shifts from low \(\alpha\textsubscript{1}\) and high \(\alpha\textsubscript{2}\) to high \(\alpha\textsubscript{1}\) and low \(\alpha\textsubscript{2}\) during early postnatal development. Because these two \(\alpha\) subunits confer different functional properties to the GABA\textsubscript{A} receptors containing them, we determined whether this shift in \(\alpha\textsubscript{1}\) and \(\alpha\textsubscript{2}\) subunit expression continues through adolescence in macaque monkey DLPFC, potentially contributing to the maturation of working memory during this developmental period. We found that the mRNA and protein levels of \(\alpha\textsubscript{1}\) and \(\alpha\textsubscript{2}\) subunits, progressively increased and decreased, respectively, throughout postnatal development including adolescence. We also performed whole-cell patch clamp recording of miniature inhibitory post-synaptic potentials (mIPSPs) in DLPFC slices prepared from pre- and post-pubertal monkeys. As predicted by the different functional properties of \(\alpha\textsubscript{1}\)-containing versus \(\alpha\textsubscript{2}\)-containing GABA\textsubscript{A} receptors, the mIPSP duration was significantly shorter in post-pubertal than in pre-pubertal animals. These findings demonstrate that, in contrast to rodents, the developmental shift in GABA\textsubscript{A} receptor \(\alpha\) subunit expression continues through adolescence in primate DLPFC, inducing a marked change in the kinetics of GABA neurotransmission. Thus, an arrest or disruption of these refinements during adolescence could give rise to the alterations in GABA\textsubscript{A} receptor \(\alpha\) subunits in schizophrenia and thus contribute to impaired working memory in the illness.

doi:10.1016/j.schres.2010.02.131
PROTRACTED DEVELOPMENT OF CORTICAL INHIBITION AND ITS RELATIONSHIP TO SCHIZOPHRENIA

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The onset of schizophrenia symptoms in late adolescence implies a neurodevelopmental trajectory for the disease. Indeed, the GABAergic inhibitory system shows protracted development and GABAergic deficits are widely replicated in post-mortem schizophrenia studies. We examined expression of several interneuron markers across postnatal human development and in schizophrenia to determine whether protracted development of certain interneuron subpopulations may make them particularly vulnerable in schizophrenia.

**Method:** RNA was extracted from the dorsolateral prefrontal cortex of individuals (n = 68) at developmental ages from 6 weeks to 49 years, and from a cohort consisting of controls and schizophrenia subjects (n = 37 pairs). Expression levels of parvalbumin, cholecystokinin, somatostatin, neuropeptide Y, calretinin, calbindin, and vasoactive intestinal peptide were measured by quantitative reverse transcriptase-polymerase chain reaction. Western blots were used to examine changes in parvalbumin and calretinin protein levels.

**Results:** Interneuron marker genes followed one of three general expression profiles, either increasing (parvalbumin, cholecystokinin) or decreasing (somatostatin, calretinin, neuropeptide Y) in expression over postnatal life with the most dramatic changes seen within the first decade of life before reaching a plateau; or a dynamic pattern increasing to peak expression at toddler age, then decreasing (calbindin, vasoactive intestinal peptide). Expression of all interneuron marker genes, with the exception of calbindin (which increased), showed a significant reduction (between 8 - 31%) in schizophrenia. Somatostatin showed the most dramatic reduction (31%) in schizophrenia.

**Conclusions:** Developmental changes in interneuron marker mRNAs extends well into school age suggesting that the inhibitory system takes years to mature in humans. It appears that a neurodevelopmental trajectory for the disease. Indeed, the GABAergic inhibitory system shows protracted development and GABAergic deficits are widely replicated in post-mortem schizophrenia studies.

**Acknowledgments:** The authors acknowledge the generous support of the National Institute of Mental Health (MH072905 and MH072905). The views expressed in this article are those of the authors and do not reflect the official policy of the Department of the Army.

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ADVANCES IN NEUROIMAGING ALLOW PROSPECTIVE STUDY OF HUMAN BRAIN DEVELOPMENT

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Advances in neuroimaging allow prospective study of human brain development. Studies on pediatric populations are particularly informative, as they explore the pathophysiological processes that are tied to important periods of brain development. Furthermore, childhood-onset counterparts of adult-onset illnesses usually show a more severe phenotype, one that is less likely to be influenced by environmental factors and more likely to show genetic influences. With the overarching hypothesis that major neuropsychiatric disorders arise from abnormal brain development, we have mapped brain development in healthy and psychiatrically ill children from early childhood through early adulthood using longitudinally acquired anatomic brain MRI scans. Using novel cortical pattern matching algorithms, we created the first dynamic map (movies) of healthy brain development from early childhood through late adolescence, which established that structural cortical maturation follows functionally relevant milestones. Comparison of these maturational patterns with similarly created time-lapse sequences for various neuropsychiatric conditions allows us to gain insights into the pathophysiological mechanisms for these illnesses. More specifically, brain development for childhood-onset schizophrenia (COS) shows a ‘back to front wave’ of profound GM loss during adolescence evolving into the adult pattern by age 25. On the other hand, cortical development in pediatric bipolar illness (mapped before and after the onset of bipolar illness) has a distinct, yet subtle pattern of GM gain in left temporal cortex and GM loss in cingulate areas, which also overlaps with that seen in atypical psychosis. Further, GM maps of developmental trajectories in healthy COS siblings suggest that the cortical GM changes in schizophrenia may be intermediate phenotypes. These observations have led to another studies evaluating the effects of the risk alleles on quantitative measures of brain morphometry. For example, initial analyses show that both COS probands (n = 75, 176 scans) and their healthy siblings (n = 44, 92 scans) with val COMT polymorphism show steeper slopes of frontal GM loss in prefrontal and temporal cortices compared to healthy controls (n = 166,402 scans) suggesting the importance of familial/genetic factors on brain development.

**References:**

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doi:10.1016/j.schres.2010.02.133

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DEVELOPMENT OF TASK-RELATED NEURAL SYNCHRONY AND THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

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Schizophrenia is associated with an onset of symptoms during late adolescence and early adulthood, suggesting that aberrant brain maturation during this period may be involved in the expression of psychosis. In the current study, we examined task-related neural synchrony during human development as well as its impairment in patients with schizophrenia with electro- and magnetoencephalography (EEG, MEG) to examine the developmental role of synchronized, oscillatory activity in the pathophysiology of schizophrenia. Development of neuronal synchrony was investigated during perceptual integration and working memory in healthy children, adolescents and adult participants (N = 80) between 6-25 years. We found marked changes during development in the amplitude of high-frequency oscillations and synchrony in both EEG- and MEG-data that were particularly pronounced during the transition from adolescence to adulthood. In EEG-recordings, the development of neural synchrony occurred in two distinct phases the transition being characterized by a marked reorganization of network topology and reduction of neural synchrony during adolescence. Following late adolescence, we observed significant increases in theta- and gamma-spectral power as well as in phase-synchronization in the theta- and beta-band during early adulthood. EEG/MEG experiments using the same perceptual integration paradigm showed that unmedicated, first-episode and chronic patients with schizophrenia are specifically impaired in indexes of neural synchrony that undergo important changes during adolescence. Thus, patients with schizophrenia show reduced high-frequency gamma-band activity and decreased long-range synchronization in the theta- and beta-band during perceptual organisation. These data suggest close relations between the expression and the increase of temporal precision of synchronous oscillatory activity, the reorganization and maturation of functional networks and the developmental changes of cognitive functions. Specifically, we propose that the pronounced changes in neural synchrony during adolescence reflect a critical developmental period that is associated with a major rearrangement of functional networks that are selectively impaired in...
Psychotic Symptoms in the Community: Where Are We Today?
Chairperson: Michael Davidson
Wednesday, 14 April, 2010 - 8:30 am - 10:30 am

Overall Abstract: Population-based surveys from all over the world indicate that psychotic-like experiences manifest in up to 30% of apparently healthy individuals in the general community. Understanding the relationship (or lack of it) between these experiences and mental illness (which is much less prevalent), is crucial to the understanding of mental illness. For example, it is important to determine what are (if any) the intervening factors which modulate understanding of mental illness. For example, is important to mental illness (which is much less prevalent), is crucial to the standing the relationship (or lack of it) between these experiences and apparently healthy individuals in the general community. Understanding the relationship between these experiences and mental illness is a dynamic process with different manifestations of psychosis in the prodromal risk paradigm is about 35% over 2.5 years. Psychotic symptoms in the general population are now the focus of considerable research interest as they appear to index an increased risk for psychotic outcomes. As yet the relationship between these psychotic symptoms and the 'prodrome' has been clarified. The prodrome or 'At Risk Mental State' is a syndrome expressing as correlated dimensions in the general population. In this sample also met criteria for a prodromal syndrome. These findings indicate that prodromal risk syndromes may be diagnosed in non-help-seeking adolescents in the community. Further work is needed to characterize these 'non-help-seeking' prodromal subjects in the community and to determine how they differ from the more traditional 'help-seeking' prodromal risk group. Dr. Weiser will present longitudinal data on a population-based birth cohort of 5000 adults ages 24-34 follow over 25 years, showing that psychotic experiences increased the risk of later hospitalization for non-affective psychotic disorder (OR=3.04, 95% CI: 1.19-7.76) and non-psychotic disorders (OR=2.49, 95% CI: 1.33-4.66), with evidence for a dose-response relationship. Risk of non-affective psychotic disorder was highest in those with evidence of social dysfunction at baseline. Dr. McGrath will present data on a population-based birth cohort of 5000 persons showing that having either a lifetime diagnosis of major depressive disorder or an anxiety disorder was associated with significantly higher Peters Delusional Inventory (PDI) total scores (highest versus lowest quartile adjusted Odd Ratio and 95% confidence intervals = 4.43, 3.09-6.36; 3.08, 2.26-4.20 respectively). The odds of having hallucinations or delusions was increased in those with a major depressive or anxiety disorder, and the presence of current anxiety disorder symptoms was significantly associated with PDI score (OR 5.81, 95% CI 3.68-9.16). This finding shows again that manifestation of mental illness is a dynamic process with different manifestations at different stages of development. In summary, the data which will be presented will constitute the background on which an interactive exchange of views will emerge on the role of circumscribed psychotic experiences towards development of psychotic illness.

doi:10.1016/j.schres.2010.02.136

Prevalence of Prodromal Risk Syndromes Among a Community Sample of Adolescents

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Psychotic symptoms in the general population are now the focus of considerable research interest as they appear to index an increased risk for psychotic outcomes. As yet the relationship between these psychotic symptoms and the 'prodrome' has been clarified. The prodrome or 'At Risk Mental State' is a syndrome characterised by evolving attenuated positive symptoms, 1and functional impairment, and is mainly diagnosed among help-seeking youth with a mean age of 18 years. The risk of progression to psychosis in the prodromal risk paradigm is about 35% over 2.5 years. In this study we wished to investigate the relationship between psychotic symptoms diagnosed on clinical interview and the prodromal risk syndrome in a young adolescent population.

Methods: 334 school children aged 11-13 were screened using a 7-item psychosis screener. All adolescents who scored 2 or more were invited to attend for interview along with a random sample of those who scored less than 2. There was no significant difference in

doi:10.1016/j.schres.2010.02.135

Affective Dysregulation and Reality Distortion

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Evidence from clinical patient populations indicates that affective dysregulation is strongly associated with reality distortion, suggesting that a process of misassignment of emotional salience may underlie this connection. To examine this in more detail without clinical confounds, affective regulation–reality distortion relationships, and their clinical relevance, were examined in a German prospective cohort community study. A cohort of 2524 adolescents and young adults aged 14-24 years at baseline, drawn from the Early Developmental Stages of Psychopathology (EDSP) study, was examined by experienced psychologists. Presence of psychotic experiences and (hypo)manic and depressive symptoms was assessed at two time points (3.5 and up to 10 years after baseline) using the Munich-Composite International Diagnostic Interview. Associations were tested between level of affective dysregulation on the one hand and incidence of psychotic experiences, persistence of these experiences and psychotic impairment on the other. Most psychotic experiences occurred in a context of affective dysregulation, and bi directional dose-response was apparent both with greater level of affective dysregulation and greater level of psychotic experiences. Persistence of psychotic experiences over time was progressively more likely to occur with greater level of (hypo) manic symptoms (OR linear trend = 1.51, 95% CI: 1.22,1.88; p<0.001) and depressive symptoms (OR linear trend = 1.15, 95% CI: 1.03,1.28;p = 0.012). Similarly, psychotic experiences of clinical relevance were progressively more likely to occur with greater level of affective dysregulation (depressive symptoms: OR linear trend = 1.28, 95%CI: 1.10,1.49; p=0.002; (hypo) manic symptoms: OR linear trend = 1.37, 95%CI: 1.02,1.83; p = 0.036). The findings suggest that correlated genetic liabilities underlying affective and non-affective psychotic syndromes may be expressed as correlated dimensions in the general population. In addition, affective dysregulation may contribute causally to the persistence and clinical relevance of reality distortion, possibly by facilitating a mechanism of aberrant salience attribution.

doi:10.1016/j.schres.2010.02.136
Weiser

A LONGITUDINAL COHORT STUDY
SELF-REPORTED PSYCHOTIC EXPERIENCES IN A-SYMPTOMATIC

doi:10.1016/j.schres.2010.02.137

differ from the more traditional ‘help-seeking’ prodromal risk group.

Further work is needed to characterize these ‘non-help-seeking’ symptoms in this sample also met criteria for a prodromal syndrome.

Conclusion: The psychosis screener did not distinguish between the groups.

Results: 9 adolescents (53% of those who reported ‘definite’ psychotic symptoms) met criteria for a prodromal syndrome, with the majority meeting criteria for Attenuated Positive Symptom Syndrome. Adolescents with a prodromal syndrome differed from adolescents with psychotic symptoms but who did not meet prodromal criteria on the measure of functional impairment only: CGAS score: 73.1 (sd=14.8) vs 85 (8.64); (p=0.03). There was no difference between the groups on gender, IQ score, positive family psychiatric history, current psychiatric diagnosis (K-SADS) or history of trauma. Initial score on the psychosis screener did not distinguish between the groups.

Conclusion: We conclude that prodromal risk syndromes may be diagnosed in non-help-seeking adolescents in the community. Approximately half of the adolescents with clinically-verified ‘definite’ psychiatric symptoms in this sample also met criteria for a prodromal syndrome. Further work is needed to characterize these ‘non-help-seeking’ prodromal subjects in the community and to determine how they differ from the more traditional ‘help-seeking’ prodromal risk group.

doi:10.1016/j.schres.2010.02.137

SELF-REPORTED PSYCHOTIC EXPERIENCES IN A-SYMPTOMATIC INDIVIDUALS SIGNAL RISK FOR SEVERE MENTAL ILLNESS; A LONGITUDINAL COHORT STUDY

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Background: It has been suggested that psychotic experiences identified in non-ill people signal risk for severe mental illness. The objective of this study was to provide evidence supporting this suggestion based on clinical diagnoses of non-affective psychotic disorders and other disorders.

Method: This is a longitudinal cohort study on psychotic experiences with outcome assessment (severe mental illness) obtained through linkage with a national hospitalization case registry; subjects were a random stratified sample of 4,914 Israeli community dwellers aged 25-34 who had been screened for psychopathology in the 1980’s, the mean follow-up was 24 years.

Results: Twenty-five percent of the cohort (n = 1183) reported one or more psychotic experiences during their lifetime. Self-reported psychotic experiences increased the risk of later hospitalization for non-affective psychotic disorders (ICD 10 F20.0-F29.9; OR = 3.04, 95% CI: 1.19-7.76) and non-psychotic disorders (OR = 2.49, 95% CI: 1.33-4.66) over the 25-year follow-up, with evidence for a dose-response relationship. The increased risk caused by self-reported psychotic symptoms was distributed evenly during the follow-up period, and was not only apparent in the years closer to the assessment. Risk of non-affective psychotic disorder was highest in those with evidence of poorer social functioning at baseline. Around a third of hospitalizations for psychotic and non-psychotic disorders could be attributed to prior psychotic experiences.

Discussion: Self-reported psychotic experiences in non-ill people signal risk for severe mental illness and psychotic disorder, particularly if combined with evidence of social impairment. Although psychotic experiences appear to be related to later psychiatric hospitalization, they cannot as yet be used for screening and prevention because of the rarity of the outcome and the distribution of risk over a very protracted period.

doi:10.1016/j.schres.2010.02.138

PSYCHOTIC-LIKE EXPERIENCES IN MAJOR DEPRESSION AND ANXIETY DISORDERS: A POPULATION-BASED SURVEY IN YOUNG ADULTS

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Objective: Population-based surveys have confirmed that psychotic-like experiences are prevalent in the community. However, it is unclear if these experiences are associated with common mental disorders. The aim of this study was to examine the prevalence of psychotic-like experiences in those with affective and anxiety disorders.

Methods: Subjects were drawn from the Mater-University of Queensland Study of Pregnancy. Delusional-like experiences were assessed with the Peters Delusional Inventory (PDI). The Composite International Diagnostic Interview (CIDI) was used to identify individuals with DSM IV lifetime diagnoses of major depression, anxiety disorder, substance use/dependence and psychotic disorders. The influence of affective and anxiety disorders on PDI and CIDI psychosis-related items scores were assessed with logistic regression, with adjustments for age, sex, and the presence of the other comorbid psychiatric diagnoses.

Results: Having either a lifetime diagnosis of major depressive disorder or an anxiety disorder was associated with significantly higher PDI total scores (highest versus lowest quartile adjusted Odd Ratio and 95% confidence intervals = 4.43, 3.09-6.36; 3.08, 2.26-4.20 respectively). The odds of endorsing any CIDI hallucination or delusion item was increased in those with a major depressive or anxiety disorder. The presence of current anxiety disorder symptoms was significantly associated with PDI score (OR 5.81, 95% CI 3.68-9.16).

Conclusion: While psychotic-like experiences are usually associated with psychotic disorders, individuals with depression and anxiety are also more likely to report these symptoms compared to well individuals. Psychotic-like experiences are associated with a range of common mental disorders.

doi:10.1016/j.schres.2010.02.139

Symposium 25
UPDATE ON DURATION OF UNTREATED PSYCHOSIS; ITS IMPACT ON OUTCOME, AND FINDING WAYS TO ITS REDUCTION
Co-Chairpersons: Lex Wunderink, Max Birchwood
Wednesday, 14 April, 2010 - 8:30 am - 10:30 am

Abstracts: Duration of untreated psychosis (DUP) has been shown to be an independent predictor of outcome in an overwhelming number of studies. However the precise nature of the
relationship between longer DUP and worse outcome is still unclear and the causality of this relationship has not yet been demonstrated. In DUP-outcome studies most attention has been paid to positive symptoms and related outcome measures, such as relapse rates, time to positive symptom response and positive symptom remission. The relationships of DUP with other outcome domains, such as negative symptoms have not been very well documented yet. In this symposium a meta-analysis will be presented showing an association of DUP and negative symptoms at baseline and throughout 5 years of follow-up. These relationships are of interest in view of the potential harm untreated psychosis might cause to the integrity of brain function. Findings from the London Institute of Psychiatry show that gray matter change is associated with poorer outcome and long exposure to antipsychotics, while DUP did not mediate these longitudinal brain changes. Though long DUP was associated with poor outcome, it was not shown to be related to the rate of secondary degeneration and cortical thinning as the disease progressed. Despite the current wide-spread implementation of early detection programs for first episode psychosis only few studies so far did address the effectiveness of these programs. Is it possible to reduce DUP, and if so, what specific ingredients do the job, and what were the achievements in terms of outcome? The TIPS study from Scandinavia still is the only quasi-experimental study in the field, revealing some unexpected results, while the Birmingham, U.K. experiences with early intervention shed a light on practical obstacles encountered when trying to reduce DUP in an urban area.

doi:10.1016/j.schres.2010.02.140

CHAIRPERSON
Lex Wunderink
Friesland Mental Health Services

OVERALL PANEL PROPOSAL: SPEAKER 1 ABSTRACT:
SPEAKER 2 ABSTRACT: SPEAKER 3 ABSTRACT:
SPEAKER 4 ABSTRACT:

REDUCING DUP IN A LARGE URBAN, MULTI-CULTURAL CITY:
WHY WE NEED TO USE AND UNDERSTAND DATA ON PATHWAYS TO CARE:

Max Birchwood1, Paul Patterson2, Swaran Singh3, Charlotte Connor2, Linda McCarthy2, Helen Lester4
1University of Birmingham, Birmingham, UK; 2Birmingham Early Intervention service & University of Birmingham; 3Birmingham Early Intervention service & University of Warwick, UK; 4Dept. Primary Care, University of Manchester, UK

Birmingham is the UK’s second largest city (pop 1.2M) and in a few years time will be populated by an ethnic majority. In spite of well developed secondary care early intervention services for first episode psychosis, DUP remains stubbornly high. In this paper we present data on DUP from over the last 2.5 years (N=350) and how these are systematically linked to different ethnic groups and geographical areas of the city. The Birmingham ‘DUP problem’ is essentially a problem of outliers (> 1 year DUP) and these are again over-represented in some ethnic groups, particularly the Muslim community, whose pathway to care nearly always involves the Mosques. I will also present data from a qualitative study of the construction of psychotic presentations by the Imams and other Muslim elders and how these may be linked to delays. Our NIHR ‘CLAHRC’ and ‘ENRICH’ projects will be described which aim to reduce DUP through a focused approach to care pathways and engaging directly with Birmingham’s cultural diversity.

doi:10.1016/j.schres.2010.02.141

DURATION OF UNTREATED PSYCHOSIS AND NEGATIVE SYMPTOMS: HOW DO THEY RELATE?

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1GGZ Friesland, Leeuwarden, Friesland, Netherlands; 2University Medical Center Groningen, Groningen, Netherlands

Negative symptoms are at the core of the schizophrenia syndrome. They have been referred to as primary or deficit symptoms and they are related to poor functional outcome. The association between duration of untreated psychosis (DUP) and poor outcome is overwhelming. In recent meta-analyses, DUP emerged as an independent predictor of the degree of recovery from an initial episode of psychosis, independent of potential confounders. However the causality of the association between DUP and poor outcome has not been proven: a later start of treatment might merely be a marker of other factors that contribute to poor outcome. So far both research and clinical programs mainly focus on the relationship between DUP and positive symptoms: early detection and intervention of psychosis, aiming at reducing the DUP, are focused on early positive symptoms and their precursors. Positive psychotic symptoms are easier to recognize and antipsychotic treatment is directed to reduce positive symptoms. Few studies report on the relationship between negative symptoms and DUP. It is unclear how strong this relationship is and whether there is a longitudinal relationship between positive and negative symptoms. If positive symptoms are causally related to negative symptoms then short DUP and better course of positive symptoms will be correlated with better course and outcome of negative symptoms. We conducted a meta-analysis on studies of first episode psychosis published after December 1992. We included all studies that quantitatively assessed DUP and assessed positive as well as negative psychotic symptoms by either PANSS, SAPS & SANS or BPRS at baseline and at least one follow-up assessment at 6 months or later. We included 29 studies from different countries. The main findings of this study are: 1) Long DUP is associated with more severe positive and negative symptoms throughout follow-up 2) There is no DUP x time interaction; the initial drawback of long DUP is still present at 96 months. These findings might indicate that early detection programs should not exclusively focus on the detection of positive psychotic symptoms but also on the presence of negative symptoms. The predictive value of rating these symptoms at an early stage, concurrent with positive symptoms, would have to be established, to determine the possibility of shifting the focus of early intervention teams from positive symptoms only to emerging negative symptoms as well.

doi:10.1016/j.schres.2010.02.142

BRAIN CHANGES FOLLOWING THE FIRST PSYCHOTIC EPISODE:
THE ROLE OF TREATMENT

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It remains unclear at what stage brain anatomical changes occur following the first episode of psychosis, and whether they are associated with poorer clinical and functional outcome. Furthermore, the role of
We investigated changes in brain volume and outcome 6 years after the first episode of psychosis. We additionally explored the role of treatment with antipsychotic drugs and of having experienced a long DUP on explaining brain changes. We collected an SPGR sequence acquired with a 1.5T scanner. Brain volumes were measured with a voxel-based automated method (Statistical Parametric Mapping, SPM5). We evaluated 49 patients (17 females; mean age 27 SD 9; 26 schizophrenia) and compared them with 46 healthy controls (21 females; mean age 31 SD 9). Mean length of follow up was 6.5 (SD 1.4) years.

Results: At first presentation, patients had significantly smaller grey matter volume than controls (p = 0.001), and significantly larger ventricular volumes (p = 0.01). Over time they showed similar reductions of grey matter, but a significantly larger increase in ventricular volumes (p = 0.02). More changes in grey matter and ventricular volumes were present in those patients with a poorer clinical outcome, and a longer exposure to antipsychotic medication after illness onset. In contrast, although a longer DUP was significantly associated with poorer outcomes at follow-up, it was not significantly related to any longitudinal tissue volume change.

Discussion: Further brain changes after illness onset particularly occur in patients who develop poorer outcome. Different progression rates may reflect the interaction with environmental insults, like antipsychotic medication, and are not mediated by a longer duration of untreated psychosis.

doi:10.1016/j.schres.2010.02.143

DURATION OF UNTREATED PSYCHOSIS, EARLY INTERVENTION AND SYMPTOM DEVELOPMENT IN FIRST-EPIODE PSYCHOSIS: EXPERIENCES FROM THE TIPS STUDY

Ingrid Melle, Tor Larsen, Ulrik Haahr, Svein Friis, Jan Olav Johannesen, Inge Joa, Stein Opjordsmoen, Bjørn Rund, Erik Simonsen, Per Vaglum, Thomas McGlashan
Oslo University Hospital, Oslo, Norway

The Scandinavian “Early Treatment and Intervention in Psychosis” (TIPS) study used broad mass-media information campaigns combined with focused education of first-line treatment personnel (GPs, school nurses) and low-threshold assessment teams to recruit patients with first episode psychosis to treatment at an earlier point of time. The study included consecutive FEP from four Scandinavian health care sectors over four years, half from two sectors with the early detection program (ED) and half from the two sectors without (NoED). A total of 281 patients (141 ED, 140 NoED) entered the study. At start of first treatment, patients from the ED area had a statistically significantly shorter duration of untreated psychosis and statistically significantly lower symptom levels across all symptom dimensions (positive, negative, depressive, excitative and cognitive) and also including severe suicidal behavior. Patients from both areas were offered a two-year comprehensive integrated treatment package mainly aimed at positive symptoms (antipsychotic medication algorithm, individual psychosocial treatment based on continuity-of-care with assertive outreach and psychoeducational family work). There were no significant differences in treatment received across the two-year period. Time to first remission was the same in the ED and NoED groups, and there were no differences in the number of patients in remission vs relapse at follow-up points. Parallel to this there were no differences in the levels of positive symptoms. Negative symptoms remained significantly lower in the ED area over the two year follow-up.

The course of excitative symptoms followed the course of positive symptoms, while the course of depressive and cognitive the course of the negative symptoms. Later studies from the ED area indicate that the reduction of DUP is linked to the information campaigns. The focused information program and the low threshold teams were continued after the study period, but the information campaigns were stopped. The DUP subsequently increased significantly, but went down again after the reinstatement of the campaigns.

doi:10.1016/j.schres.2010.02.144
nietic mechanisms impacting undisturbed neural processing in schizophrenia reporting their work on genomewide association scans (GWAS) associated genes (ZNF804A, CACNA1C) and their relationship to disturbances of the connectome in schizophrenia. Dr. David Lewis has agreed to be the discussant on the panel.

doi:10.1016/j.schres.2010.02.145

**BRAIN DEVELOPMENT IN CHILDHOOD ONSET SCHIZOPHRENIA: GENETIC AND ENVIRONMENTAL INFLUENCES**

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Structural neuroimaging studies in COS show profound parietofrontal cortical GM loss during adolescence in a pattern that appears to exaggerate of the normal GM maturation. At longer term follow up the GM loss slows with age and gets circumscribed to prefrontal and superior temporal cortices (n = 84,197 scans vs controls n = 86,220 scans; age range 8-28 yrs), mimicking a pattern seen in adult onset schizophrenia.

Longitudinal analyses on healthy COS siblings (n = 85,170 scans) also show prefrontal and temporal GM deficits in early ages, which normalize by age 20, suggesting that the GM trajectory itself could be a trait marker. Candidate gene analyses support these observations. For example, initial analyses comparing GM development in 75 COS subjects (176 scans), 44 healthy siblings (92 scans) and 166 healthy controls (402 scans) showed that COS subjects and their healthy siblings with val-COMT allele had accelerated GM loss across prefrontal, cingulated and temporal cortices compared to matched healthy controls who in contrast showed negative GM slow with the met-COMT genotype, suggesting the influence of genetic mechanisms impacting on distributed neural processing in schizophrenia.

Sub regional cerebellar maps in 85 COS subjects (206 scans), 78 healthy siblings, and 95 matched healthy controls (225 scans) show significant 'sub regional' decline in volume with age, while the vermal regions showed fixed deficits. The volume loss is shared by healthy COS siblings in the posterior inferior cerebellar regions (compared to the same set of controls) suggesting the trait nature of these changes at sub regional level.

Finally, it is important to understand the progressive nature GM changes in the context of underlying white matter (WM) development. Our recent 3-D maps of local WM growth rates in 12 COS patients and 12 healthy controls matched for age, gender and scan interval, over a 5-year period, show up to 2.2% slower WM growth per year in COS (P = 0.02, all P-values corrected). The deficits appear early in the frontal regions and later in the parietal regions suggesting a progressive abnormality that follows the normal front to back WM developmental pattern. In addition to highlighting significant WM growth deficits in COS, these findings also suggest that the cortical GM loss in schizophrenia is unlikely to be the result of WM encroachment.

doi:10.1016/j.schres.2010.02.146

**PROGRESSIVE BRAIN TISSUE LOSS IN MONOZYGOTIC AND DIZYGOTIC TWIN PAIRS DISCORDANT FOR SCHIZOPHRENIA**

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University Medical Center Utrecht, Utrecht, Netherlands

In contrast to common belief, human brain structure is highly plastic throughout life. That brains of young children and adolescents show constant development is widely accepted. In contrast, the adult human brain is said to be static, with changes being marginal. But can a static brain account for the continued development of people once they have become adults? That is unlikely. Indeed, recently we found evidence for structural brain plasticity in adulthood that promotes cognitive functioning. Moreover, since we conducted these longitudinal MRI studies in monozygotic and dizygotic twin-pairs, we were able to show that the genetic factors implicated in brain size differ from those implicated in brain structure change. In patients with schizophrenia, who experience cognitive problems, brain plasticity seems compromised. Evidence is accumulating that in patients with schizophrenia there is progressive brain tissue loss, not only in first-episode schizophrenia but also in chronically ill patients (Hulshoff Pol and Kahn, Sz Bull 2008). Recently, we found that the progressive brain changes in schizophrenia are also present in their non-psychotic co-twins, implicating that the progressive brain changes are influenced by genes involved in the disease (particularly in the frontal and temporal cortices), and not due to antipsychotic medication or other disease related circumstances (Brams et al, AGP, 2008). Interestingly, based on our cortical thickness change measurements progressive brain tissue loss in schizophrenia seems to occur predominantly in those brain areas that show continued cortical thickening in healthy adults. Thus, progressive brain tissue loss in adult patients may represent as yet unknown pathophysiology of adult human brain plasticity.

doi:10.1016/j.schres.2010.02.147

**LONGITUDINAL EFFECTS OF GENETIC RISK FACTORS ON BRAIN MORPHOLOGY**

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**Background:** Schizophrenia and bipolar disorder are highly familial disorders and previous studies suggest that the majority of this risk is shared across disorders. A recent investigation suggested that the effects of shared genetic liability may have longitudinal effects on brain structure. However, there is a lack of studies addressing the relationship between specific gene variants and brain developmental trajectories.

**Methods:** Using imaging data from studies of people at high familial risk of schizophrenia or bipolar disorder we will present evidence relating specific genetic variants to altered brain structure and function. In addition, we will consider the timing and longitudinal trajectories of these changes by examining differential relationships with age and by examining serial brain changes over 2-4 years follow-up.

**Results:** Cross-sectional and longitudinal effects of specific genetic variants in BDNF and NRG1 will be presented in studies of affected patients and closely related individuals at high risk of schizophrenia or bipolar disorder. This presentation will also include new data from the recent Scottish Bipolar Family Study.

**Discussion:** Bipolar disorder and schizophrenia are associated with longitudinal effects on medial temporal lobe volume and prefrontal structure that can, in part, be attributed to variants within replicated susceptibility genes common to both conditions.

doi:10.1016/j.schres.2010.02.148

**GENOME-WIDE SIGNIFICANT NEURAL RISK MECHANISMS FOR SCHIZOPHRENIA AND THE BRAIN CONNECTOME**

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Background: Recently, genome-wide significant risk variants for psychotic disorders have been discovered that afford an opportunity to establish neural mechanisms linked to genetic risk for schizophrenia and bipolar disorder through an imaging genetics approach. Methods: We use an imaging genetics approach in a sample of healthy German volunteers of German descent and a replication sample of similar ethnicity, recruited and assessed with a cognitive and resting fMRI and structural imaging battery in the context of the BMBF-Founded Mood's project. Results: ZNF804A and CACNA1C impact on cortical-subcortical connectivity with emphasis on hippocampus and prefrontal cortex. Cognitively specific and global abnormalities can be dissociated, indicating structural (maturational?) components and connectivity aspects relating to the specific type of information processed (working memory, theory of mind, episodic memory, emotional regulation). Discussion: Genome-wide significant variants impact on the brain regulation). (working memory, theory of mind, episodic memory, emotional regulation).

Tuesday, 13 April, 2010 - 9:30 am - 11:30 am

Methods: We use an imaging genetics approach in a sample of healthy German volunteers of German descent and a replication sample of similar ethnicity, recruited and assessed with a cognitive and resting fMRI and structural imaging battery in the context of the BMBF-Founded Mood's project. Results: ZNF804A and CACNA1C impact on cortical-subcortical connectivity with emphasis on hippocampus and prefrontal cortex. Cognitively specific and global abnormalities can be dissociated, indicating structural (maturational?) components and connectivity aspects relating to the specific type of information processed (working memory, theory of mind, episodic memory, emotional regulation).

Wednesday, 14 April, 2010 - 10:30 am - 12:30 pm

Overall Abstract: Performance-based assessment of functional abilities in schizophrenia has received considerable recent attention. Measurement of functional capacity, the ability to perform everyday living skills, vocational skills, and social skills in structured assessment situations, has been proposed as an alternative to the reliance on patient's self-reports of functioning, which are often not strongly related to performance on ability oriented tests, or the use of informants, who may also be unreliable. Most importantly, the FDA now requires that treatment trials aimed at cognition in schizophrenia have a co-primary outcome measure, with these performance-based functional capacity measures being widely employed. There may be problems with simply employing tests developed in the United States in international patient populations. In contrast to cognitive abilities, the topography of the necessary and appropriate everyday living and social skills varies considerably across different cultures. In order to address these issues, this symposium presents a multi-cultural perspective on the performance-based assessment. The presentations include detailed examination of variation in the validity of existing methods across different countries and cultures, the results of a systematic survey of the needs and challenges of performance-based assessments, a presentation on variation in gender roles across cultures and its functional implications as well as detailed information about differences in the functional skills that are measurable with validity across the age-range within American research participants. Philip Harvey will present the results of studies examining the performance-based measures of everyday living skills across American, Western European, and Chinese samples of healthy individuals and people with schizophrenia, showing that effects of education and rural upbringing are much salient in China and that performance differences between American and Western European populations were negligible. Dawn Velligan will present the results of the MATRICS-CT cross-cultural survey. This international survey conducted at 31 sites obtained opinions from experienced researchers about the cross-cultural applicability of for different measures of functional capacity that are currently utilized in the U.S. Investigators in each country rated the extent to which the measures applied to their culture in general and to specific subgroups within each culture. Investigators provided detailed comments about problems in cross-cultural applicability and suggested ways to alter the tests to better fit their culture. Delfina da Achaval will present a specific perspective on how the four different functional measures were rated at her site and how they would need to be altered to address the variation in cultures in South and North America. Terry Goldberg will present the results of studies aimed at developing functional capacity measures that are valid for older individuals. His results suggest that short forms that perform most suitably in older people assess different ability areas than those developed for younger people. Our Discussant, Richard Keefe, will comment on the presentations and present his own experience in implementing functional capacity assessments in clinical trials that were conducted in Russia, India, China, and other Asian countries. This truly internationally-oriented symposium will address a wide-ranging set of challenges and proposed solutions for increasing the validity of functional capacity assessments in multi-national settings.

doi:10.1016/j.schres.2010.02.149

doi:10.1016/j.schres.2010.02.150

PERFORMANCE BASED ASSESSMENT OF FUNCTIONAL DISABILITY: DIFFERENT CHALLENGES IN EASTERN AND WESTERN CULTURES

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Recent advances in the assessment of disability in schizophrenia have delineated the measurement of functional capacity (the ability to perform everyday functioning skills in structured assessments) from real-world functional outcomes. Studies of these functional capacity measures has indicated that they possess psychometric characteristics, including reliability, variability, and usefulness for repeated testing, that are very similar to those seen for neuropsychological (NP) tests. These measures are highly correlated with performance on NP tests and are often more strongly correlated with real world outcome than NP test results. However, functional requirements in the real-world clearly differ across countries and these differences may be accentuated in developing countries where there are wide variations in educational attainment, access to technology, and general complexity of everyday living requirements. This presentation will present the results of two studies examining functional capacity differences across different countries. The first study examined the similarity of performance-based assessments of everyday functioning, real-world disability, and achievement of milestones in people with schizophrenia in the United States (n = 244) and in Sweden (n = 146). The second compared the performance of healthy individuals and people with schizophrenia in Beijing. All research participants were assessed with the brief version of the UCSD Performance-based Skills Assessment (UPSA-B). Performance on the UPSA-B was essentially identical in the patients in the US and Sweden (New York, M = 13.84; Sweden, M = 13.30). In contrast, in China healthy controls (HC; n = 285) received an average score of 14.1 on the UPSA-B and patients with schizophrenia (n = 167) received an average score of 7.5. There was considerable evidence of biasing effects associated with educational history and other factors in this sample. There was a substantial Group x education interaction: F(3,435) = 7.97, p < .001, with no education effects in the schizophrenia sample and a substantial linear effect of age in HC sample. In the HC sample, the correlation between height and...
Velligan, M. Rubin, M.M. Frederick, S. Dube
Achával

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identified and present potential next steps including recommenda-
will present mean ratings for instruments as a whole as well as
the problems in adaptation and potential ways to address them. We
subgroup, raters were asked to make detailed comments describing
status. All test content areas are rated on a 7-point Likert scale. When
based on gender, geographic region, ethnicity and socioeconomic
applied to other cultures and to subgroups within those cultures
Russia, China, Spain, Argentina, Mexico, India and Germany. Raters
examined the cross-cultural applicability of the VIM intermediate
in influence the validity of an item as a measure of a person's skills. We
comfort with the form or content of the test items could potentially
reflect every day activities around the world. Lack of familiarity or
participants in the US, and it is clear that some of these items may not
activities queried with these instruments were developed for study
ing medications for improving cognition. The type of everyday
Functional Capacity, interview-based measures of cognitive problems
measures in 31 international sites. Participating countries included
in the MATRICS initiative to assess the reliability, validity, and utility of possible intermediate measures that have face validity for assessing functional outcome in schizo-
Mental Health Sciences Center San Antonio, TX, USA

For a medication to receive a treatment indication for improving
cognition in schizophrenia, regulatory agencies are requiring
evidence of improvement in functional outcome as well as cognition.
Because there are many factors that influence functional outcome in
this population, intermediate measures of functional outcome are
being pursued to meet this regulatory requirement. The Validation of
Intermediate Measures (VIM) study is being conducted as part of the
Measurement and Treatment Research to Improve Cognition in
Schizophrenia (MATRICS) initiative to assess the reliability, validity
and utility of possible intermediate measures that have face validity
for assessing functional outcome in schizophrenia. Measures chosen
for the validation study include, performance-based measures of
functional capacity, interview-based measures of cognitive problems
in every day life and global measures of cognition. Based on the VIM
study, recommendations will be made as to the best measure(s) for
use as co-primary measures in international clinical trials investigat-
ing medications for improving cognition. The type of everyday
activities queried with these instruments were developed for study
participants in the US, and it is clear that some of these items may not
reflect every day activities around the world. Lack of familiarity or
comfort with the form or content of the test items could potentially
influence the validity of an item as a measure of a person's skills. We
examined the cross-cultural applicability of the VIM intermediate
measures in 31 international sites. Participating countries included
Russia, China, Spain, Argentina, Mexico, India and Germany. Raters
were PIs and frontline research staff familiar with conducting clinical
medication trials. The Cultural Adaptation Rating Scale (C-CARS) is a
rating scale assessing the extent to which a measure is able to be
applied to other cultures and to subgroups within those cultures based
on gender, geographic region, ethnicity and socioeconomic status. All test content areas are rated on a 7-point Likert scale. When
a test subscale was rated as not working well in the culture or
subgroup, raters were asked to make detailed comments describing
the problems in adaptation and potential ways to address them. We
will present mean ratings for instruments as a whole as well as
ratings for individual subscales. We will describe the problems
identified and present potential next steps including recommenda-
tion of a "best" measure, the use of a brief measure composed of the
subscales of the instrument with the best psychometric properties
that works well across multiple cultural contexts, or the develop-
ment of a hybrid scale using the subscales from different instruments
that work well across cultures.

doi:10.1016/j.schres.2010.02.152

THE ADAPTATION OF INTERMEDIATE MEASURES OF FUNCTIONAL OUTCOME IN ARGENTINA

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The Validation of Intermediate Measures (VIM) study is being conducted as part of the Measurement and Treatment Research to
Improve Cognition in Schizophrenia (MATRICS) initiative to assess the
reliability, validity and utility of possible intermediate measures that
have face validity for assessing functional outcome in schizo-
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For a medication to receive a treatment indication for improving
cognition in schizophrenia, regulatory agencies are requiring
evidence of improvement in functional outcome as well as cognition.
Because there are many factors that influence functional outcome in
this population, intermediate measures of functional outcome are
being pursued to meet this regulatory requirement. The Validation of
Intermediate Measures (VIM) study is being conducted as part of the
Measurement and Treatment Research to Improve Cognition in
Schizophrenia (MATRICS) initiative to assess the reliability, validity
and utility of possible intermediate measures that have face validity
for assessing functional outcome in schizophrenia. Measures chosen
for the validation study include, performance-based measures of
functional capacity, interview-based measures of cognitive problems
in every day life and global measures of cognition. Based on the VIM
study, recommendations will be made as to the best measure(s) for
use as co-primary measures in international clinical trials investigat-
ing medications for improving cognition. The type of everyday
activities queried with these instruments were developed for study
participants in the US, and it is clear that some of these items may not
reflect every day activities around the world. Lack of familiarity or
comfort with the form or content of the test items could potentially
influence the validity of an item as a measure of a person's skills. We
examined the cross-cultural applicability of the VIM intermediate
measures in 31 international sites. Participating countries included
Russia, China, Spain, Argentina, Mexico, India and Germany. Raters
were PIs and frontline research staff familiar with conducting clinical
medication trials. The Cultural Adaptation Rating Scale (C-CARS) is a
rating scale assessing the extent to which a measure is able to be
applied to other cultures and to subgroups within those cultures based
on gender, geographic region, ethnicity and socioeconomic status. All test content areas are rated on a 7-point Likert scale. When
a test subscale was rated as not working well in the culture or
subgroup, raters were asked to make detailed comments describing
the problems in adaptation and potential ways to address them. We
will present mean ratings for instruments as a whole as well as
ratings for individual subscales. We will describe the problems
identified and present potential next steps including recommenda-
The effects of language and acculturation on measurement of functional capacity in schizophrenia are not yet fully understood. We assessed functional capacity using the UCSD Performance-Based Skills Assessment (UPSA), Social Skills Performance Assessment (SSPA), and Medication Management Ability Assessment (MMAA) in English-speaking (n = 210) and monolingual Spanish-speaking (n = 29) individuals with schizophrenia-spectrum disorders. The two groups did not differ on age, severity of positive, negative, and depressive symptoms, or Global Assessment of Functioning scores. However, the Spanish-speaking sample had less education, later age of onset of psychosis, lower Dementia Rating Scale scores, and lower dosages of antipsychotics; they were also more likely to be female, to have schizoaffective disorder (vs. schizophrenia), and to be married. The Spanish-speaking group performed better than did English speakers on the MMAA, but worse on the UPSA. The groups did not differ on the SSPA. In a multiple hierarchical regression controlling for group differences, DRS score (r = .61, .78, ps < .001) predicted UPSA performance (R = .74). Within the Spanish-speaking sample, higher levels of education and acculturation were both associated with better UPSA performance (rs = .61, .78, ps < .001), but did not explain variance in UPSA performance beyond that accounted for by DRS performance. These results suggest that measurement of functional skills can be strongly affected by language of test administration. Although acculturation is associated with functional capacity among monolingual Spanish-speakers with schizophrenia, it does not predict performance once cognitive performance is considered.

doi:10.1016/j.schres.2010.02.154

SEEING IS BELIEVING: A STRUCTURAL NEUROIMAGING PARADIGM OF GENE-ENVIRONMENT INTERACTIONS IN SCHIZOPHRENIA

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The study of gene-environment interactions is complicated because of the difficulty measuring environmental exposures. Developmental trauma and cannabis have been associated with schizophrenia risk, but reporting bias may play a role, causing spurious associations. We designed a new paradigm, using structural neuroimaging measures, to investigate GxE in schizophrenia in which reporting bias cannot impact on the findings. Neuroimaging measures in schizophrenia represent expression of genetic risk or better, given that genetic risk moderates environmental sensitivity, gene-environment interactions. Given the fact that biased measures of environmental exposures cannot impact on the brain, the use of neuroimaging phenotypes in studies of GxE may provide direct proof for environmental impact. We hypothesized that if GxE plays a role in the brain alterations in schizophrenia, a direct effect of developmental trauma and cannabis should be present in cases (as they carry schizophrenia genes causing differential sensitivity to environmental exposures) but not in controls. We used the measure of cortical thickness, arguably most sensitive for this purpose, to test these hypotheses in a sample of around 80 cases and 80 controls. For each person, 70 measures of cortical thickness were available. Analysis of the data revealed that both developmental trauma and cannabis impacted on cortical thickness in the cases, but not in the controls, strongly suggesting unconfounded and unbiased contributions of environmental exposures to GxE underlying brain alterations in schizophrenia.

doi:10.1016/j.schres.2010.02.156
STRESS AND HPA FUNCTIONING IN FIRST EPISODE PSYCHOSIS

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Two studies focusing on stress and HPA in first episode psychosis (FEP) will be presented. The first study prospectively investigated circulating cortisol, Dehydroepiandrosterone sulfate (DHEAS) and their ratio in FEP compared to healthy controls, and their relationship to psychotic, negative and mood symptoms. Blood cortisol and DHEAS levels were obtained in 39 neuroleptic-naive or minimally-treated FEP patients and 25 controls. Twenty three patients and 15 controls received repeat assessments after 12 weeks. At baseline, no differences were observed in cortisol, DHEAS or the cortisol/DHEAS ratio between patients and controls. Within FEP patients, decreases in cortisol and increases in DHEAS/DHEAS ratio over time were directly related to the improvement in depression (p = 0.031, p = 0.011), negative (p = 0.006, p = 0.008) and psychotic symptoms (cortisol only, p = 0.01). Perceived stress significantly correlated with DHEAS (r = 0.51; p = 0.019) and the cortisol/DHEAS ratio (r = -0.49; p = 0.024) in controls, but not patients, possibly reflecting an impaired hormonal response to stress in FEP patients. These findings furthe support the involvement of the stress system in the pathophysiology of psychotic disorders, with implications for treatment strategies that modulate these neurosteroids. The second study focused on the level of activity of the HPA axis in FEP and examined the cortisol response to the administration of low dose dexamethasone in FEP patients and its relationship to childhood trauma. Low (0.5 mg) and very low (0.25 mg) dose Dexamethasone Suppression Tests (DST) were performed in neuroleptic naive or minimally-treatment FEP patients and healthy control participants. Childhood traumatic events were assessed in all participants using the Childhood Trauma Questionnaire (CTQ) and psychiatric symptoms were assessed in patients using standard rating scales. In the 0.25 mg DST, FEP patients (n = 21) reported significantly higher rates of childhood trauma compared to controls (n = 20; p < 0.001), exhibited lower basal cortisol (p < 0.02) and an increased rate of cortisol hyper-suppression following dexamethasone compared to controls (33% (7/21) vs. 5% (1/20), respectively; p = 0.04). Similarly, in the 0.5 mg DST, a greater proportion of FEP patients suppressed cortisol compared to controls, although this was not significant (63% (5/8) vs. 36% (5/14), respectively; p = 0.4). This study shows for the first time that a subset of patients experiencing their first-episode of psychosis display enhanced cortisol suppression, similar to that observed in PTSD. These findings suggest there may be distinct profiles of HPA axis dysfunction in psychosis which should be further explored.

doi:10.1016/j.schres.2010.02.157

CAN WE EXPLAIN THE EPIDEMIOLOGY OF SCHIZOPHRENIA ON THE BASIS OF THE PATHOLOGY OF Dopamine?

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The relationship between epidemiology and pathogenesis has been established for many medical disorders eg. coronary artery disease, cancer; this is as it should be. In contrast, the two lines of investigation have remained quite separate in schizophrenia. Now much evidence suggests that the final common pathway to at least the positive symptoms of schizophrenia is dopamine dysregulation in the striatum. Furthermore, it has become clear that many of the risk factors associated with schizophrenia also impact the dopamine system. These include genes regulating the dopamine system such as DRD2 and COMT; not surprisingly some of the relatives of schizophrenic patients show similar abnormalities of striatal dopamine to patients. Furthermore, the risk-increasing effect of obstetric complications is well known, and these are known to be associated with dopamine dysregulation. The excessive use of stimulant drugs and cannabis also increases risk of schizophrenia, and once again this appears to be via their effect on striatal dopamine. Finally there is increasing evidence implicating exposure to adverse social factors including migration, urbanisation, and childhood maltreatment; it is suggested that such factors may have in common the experience of social defeat which in animals can be shown to influence the dopamine system. This presentation will therefore make the case that it is now time to integrate the epidemiology and pathogenesis of schizophrenia.

doi:10.1016/j.schres.2010.02.159

STRESS AND THE HIPPOCAMPUS SUBICULUM: KEY SITE FOR INTERVENTION IN THE PREVENTION AND TREATMENT OF DOPAMINE HYPER-RESPONSIVITY IN PSYCHOSIS

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Increasing evidence has implicated the anterior hippocampus (ventral subiculum in rats) in the pathophysiology of schizophrenia. Thus, imaging studies in humans have demonstrated hyperactivity in this region that correlates with psychosis, and postmortem studies have shown loss of parvalbumin interneuron staining. We have shown analogous changes using a rat neurodevelopmental disruption model of schizophrenia based on prenatal administration of the mitotoxin methylazoxymethanol acetate (MAM) during gestational day 15. In adult offspring of MAM-treated dams, we found that neurons were hyperactive, and this led to an increase in dopamine neuron population activity and hyper-responsivity to amphetamine. This hyperactivity correlated with a loss of parvalbumin interneuron staining and during behavioral tests this same region of the hippocampus showed selective loss of gamma rhythm activation to a conditioned tone. Our studies show that the ventral subiculum is also activated by known risk factors for schizophrenia. Thus, both amphetamine sensitization and stress activate the ventral subiculum-nucleus accumbens pathway, leading to increased dopamine neuron population activity and hyper-responsivity to amphetamine. Moreover, preliminary evidence shows that pharmacological reversal of ventral subicular hyperactivity in the MAM-treated rat by a novel GABA alpha-5 benzodiazepine agonist reversed the increased dopamine neuron population activity. Given that the ventral subiculum is potently driven by stressors, the strong drive of the hippocampus by the basolateral amygdale and the noradrenergic system, and the known susceptibility of the hippocampal formation to damage secondary to maintained stressors, we examined whether we could circumvent the pathological alterations observed in the ventral subiculum of MAM-treated rats. Our data show that MAM-treated rats that are administered diazepam intraperitoneally for 10 days spanning the time of puberty (postnatal days 31-40) fail to develop the increased dopamine neuron population activity that parallels the hyper-dopaminergic state observed in adults; no effect was observed in controls. These data suggest that treatment of the heightened responsivity to stress in at-risk individuals may be an effective means to circumvent the onset of psychosis.

doi:10.1016/j.schres.2010.02.158
Overall Abstract: For several decades, the biochemical targets used to monitor the brain molecular changes associated with psychosis were the monoamines dopamine, serotonin, and norepinephrine. However, an emerging new target appears to be GABAergic neurotransmission. One guiding hypothesis in schizophrenia (SZ) research is that a dysfunction of the telencephalic GABAergic system is a key component in the pathophysiology of this psychiatric disorder. Consistent with this hypothesis, various groups have shown that the expression of GAD67 and other GABAergic genes is downregulated in cortical, hippocampal, and basal ganglia GABAergic neurons of SZ postmortem brains. This downregulation is among the most robust and consistent findings reported by various groups in studies of post-mortem brains of SZ patients. Due to the prominent role of GABAergic neurotransmission in the maintenance of the normal function of telencephalic pyramidal circuits, we have inferred that very likely, GAD67 downregulation reflects a brain molecular mechanism underlying SZ symptomatology.

In this symposium, Dr. Weinberger will discuss genetic variation in GAD1 and its effects on GAD67 expression, GABA levels in living human brain, and risk for schizophrenia. Dr. Akbarian will present evidence for an aberrant epigenetic regulation of GAD1 in SZ. Dr. Mirnics will present data on the generation of several transgenic mice lines with cell-type specific downregulation of GAD67 protein in the NPY+, CCK+, and PV+ interneurons using exon-embedded miRNA to study downstream effects of GABAergic neurotransmitter dysfunction.

Dr. Guidotti will discuss new pharmacological strategies to correct GABAergic dysfunctions in SZ.

doi:10.1016/j.schres.2010.02.160

GENETIC REGULATION OF GABA ACTIVITY AND RISK FOR SCHIZOPHRENIA

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We have explored the association of genetic variation in GAD1 and risk for schizophrenia, related biologic intermediate phenotypes, interactions with other genes related to GABA neuronal activity, and GABA levels measured in vivo in human brain. We identified distorted transmission of single-nucleotide polymorphism (SNP) alleles in two independent schizophrenia family-based samples (Straub et al., Mol Psych 2007). In both samples, allelic association was dependent on the gender of the affected offspring, and in the CBBD/NIMH sample it was also dependent on COMT Val158Met genotype. QTDT analyses revealed that variation in GAD1 influenced multiple domains of cognition, including declarative memory, attention and working memory. A 5′ flanking SNP affecting cognition in the families was also associated in unrelated healthy individuals with inefficient MRI activation of dorsal prefrontal cortex (PFC) during a working memory task, a physiologic intermediate phenotype associated with risk for schizophrenia and altered cortical inhibition. A SNP in the 5′ untranslated (and predicted promoter) region that also influenced cognition was associated with decreased expression of GAD1 mRNA in the PFC of schizophrenic brain. We also observed evidence of statistical epistasis between the functional COMT Val158Met variant and SNPs in GAD1, suggesting a potential biological synergism leading to increased risk. This epistatic interaction was confirmed in normal subjects on fMRI measures of cortical inefficiency. We tested the effects of the six risk-associated SNPs in GAD1 and the COMT variant on GABA levels in the anterior cingulate cortex of 87 healthy volunteers measured with 3T magnetic resonance spectroscopy. There was a significant effect of genotype on GABA for three GAD1 SNPs and for COMT (all p < 0.05). The risk associated GAD1 × COMT interaction was also significant (p = 0.05). Surprisingly, risk alleles for schizophrenia in GAD1 were associated with higher GABA levels, and Val-Val homozygotes for COMT had higher GABA when on a GAD1 risk than on a non-risk genotype background. These coincident results implicate GAD1 in the etiology of schizophrenia and suggest that the mechanism involves altered cortical GABA inhibitory activity, perhaps modulated by dopaminergic function.

doi:10.1016/j.schres.2010.02.162

MOLECULAR DETERMINANTS OF DYSREGULATED GABAERGIC GENE EXPRESSION IN THE PREFRONTAL CORTEX OF SUBJECTS WITH SCHIZOPHRENIA

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Altered RNA expression, potentially affecting GABAergic neurotransmission and a wide range of other functions, is frequently observed in schizophrenia postmortem brain but the underlying molecular mechanisms remain poorly understood. Here, we provide evidence suggesting that multiple layers of regulation, including epigenetic control of gene expression and post-transcriptional inhibition via microRNA-mediated mechanisms, play a role in the underlying pathophysiology. For example, histone H3 lysine 4 methylation, an epigenetic mark regulated with transcriptional activity and regulation of promoters, is dynamically regulated at sites of GABAergic gene promoters during the extended period of normal development of prefrontal cortex, and altered in some cases with schizophrenia. These changes include GAD1 encoding 67KDa glutamic acid decarboxylase GABA synthesis enzyme. However, other GABAergic mRNAs frequently dysregulated in schizophrenia, including NPY (Neuropeptide Y) and SST (Somatostatin), show less robust chromatin changes in diseased tissue. Instead, expression of these mRNAs could be dependent on the local supply of Brain-derived Neurotrophic Factor (BDNF), which in turn is under control of multiple small non-coding RNAs targeting BDNF's 3′UTR for post-transcriptional regulation. In addition, BDNF promoters I and IV, frequently implicated in epigenetic regulation in the preclinical model, show progressive histone methylation changes during normal prefrontal development. These findings suggest that a complex network of intertwined molecular adaptations could contribute to dysregulated GABAergic gene expression as one of the final common pathways in the pathophysiology of psychosis. Acknowledgements: Supported by grants from the NIH. We would like to Dr. Ron Zielke and staff from BTB Maryland, Dr. William E. Bunney Jr. and Dr. Ted Jones (UC Davis and Irvine), and Dr. R. Roberts and Dr. R. Schwarz (Maryland Psychiatric Research Center), and Dr. Francine M. Benes (Harvard Brain Tissue Resource Center) for providing postmortem specimens.

doi:10.1016/j.schres.2010.02.162
GABA-ERGIC DYSFUNCTION IN SCHIZOPHRENIA: 
FROM POSTMORTEM STUDIES TO ANIMAL MODELS

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Nine years have passed since the first postmortem DNA microarray studies of schizophrenia were published, and it appears that this technology has generated several important leads that continue to shape translational neuroscience studies investigating the cellular/molecular bases of schizophrenia. Specifically, independently replicated expression profiling studies of the prefrontal cortex in schizophrenia revealed abnormalities in expression of genes encoding 1) synaptic proteins, 2) proteins related to GABA signaling, 3) immune/chaperone system proteins, 4) metabolic pathway components and 5) oligodendrocyte-related proteins. The GABAergic systemic dysfunction is perhaps the most consistently observed deficit associated with schizophrenia. At a molecular level, the PFC of humans with schizophrenia is characterized by an interrelated transcript deficit that consists of downregulation of BDNF, TRKB, GAD67, SST, NPY, PARV, CCK and GABRAD genes, clearly implicating the cortical GABAergic interneuron as a central component of the pathophysiology underlying the disease. Of these, reduction of the transcript encoding glutamic acid decarboxylase 67 kDa (GAD67) is the most robust and consistently replicated finding across different cohorts. GAD67, the critical GABA synthesis enzyme in the brain, is downregulated in distinct interneuron populations of the human cortex. Each of these affected cell types mediate a different kind of inhibition: 1) a chandelier-cell subpopulation of parvalbumin (PARV)-GAD67 neurons is responsible for regulating the output of projection neurons at the axon initial segment, 2) small basket and Martinotti cells containing GAD67+CALB+SST(±NPY) are responsible for the inhibition of the distal dendritic tree of pyramidal cells, and 3) GAD67+CALR(±CCK) interneurons regulate both the dendritic inputs of pyramidal cells as well as provide input to other GABAergic neurons. To understand the GABAergic dysfunction in schizophrenia we must develop animal models that modulate gene expression in a phenotypic and regional fashion. Therefore, we hypothesized that transgenic mouse models directed to cortical downregulation of GAD67 in distinct interneuron subtypes should both mimic the molecular and cellular human postmortem findings in schizophrenia, and have distinct consequences on cortical functioning. To test this hypothesis, we developed a novel BAC-driven transgenic mouse system that is capable of cell-type specific transcript downregulation using an endogenous miRNA processing cellular mechanism. We generated several transgenic mouse lines with cell-type specific downregulation of GAD67 protein in the NPY+, CCK+ and PV+ interneurons using exon-embedded miRNA. This transgenic approach allowed us rapid, cell type-specific in vivo downregulation of the transcripts of interest (reduction of GAD67 in specific interneuronal subpopulations), avoiding the labor-intensive and resource-demanding generation of conditional knockout animals. These animal models will allow us to gain a critical understanding of the mechanisms underlying cortical inhibition and the anatomical and behavioral consequences of disturbing this network. Furthermore, the mice generated in this proposal may be useful for testing current lead compounds with therapeutic indications for symptoms of schizophrenia, and aid in the knowledge-based development of drugs for this devastating disease.

Postmortem brain studies of schizophrenia (SZ) and bipolar (BP) disorder patients show a downregulation of glutamic acid decarboxylase-67 (GAD67) and other GABAergic genes (i.e., reelin) in specific populations of telencephalic GABAergic neurons. This downregulation may be caused by an epigenetic repression of GABAergic gene transcription very likely mediated by gene promoter hypermethylation or by an altered high-order chromatin structural remodeling. To correct GABAergic neuron deficits, we propose the following two principal strategies: 1) enhancement of defective GABAergic transmission by drugs active as selective positive allosteric modulators of GABA A action at pertinent GABA A receptor subtypes, and 2) use of drugs acting to correct chromatin remodeling abnormalities due to dysregulated epigenetic mechanisms. Elaborating on the first strategy, one may consider that benzodiazepines, which are devoid of intrinsic activity at GABA A receptors including α1 subunits and act exclusively at GABA A receptors expressing α2, α3, α5 subunit combinations, should counteract the GABAergic signal transduction deficit without eliciting sedation, amnesia, tolerance, or dependence liabilities. Benzodiazepines acting at α1-expressing GABA A receptor subtypes are prescribed for psychotic patients but there are problems related to their sedative action. One benzodiazepine devoid of intrinsic activity at GABA A receptors, including α1 subunits, but acting as a full allosteric modulator at α5 and perhaps also α2 and α3 subunits, is imidazaline. This drug is anxiolytic and anticonvulsant and moreover, fails to produce sedation or amnesia. Hence, we suggest that a combination of imidazaline with antipsychotics should be considered and eventually tested in the treatment of the GABAergic dysfunction operative in SZ and BP disorders. An alternative strategy to correct the GABAergic neuron deficit in SZ and BP disorder patients may be to use drugs that diminish the DNA-methyltransferase-1 (DNMT1) overexpression typical of these illnesses. One can speculate that a protocol to treat SZ and BP disorders may include inhibitors of DNMTs or nicotine acetylcholine receptor agonists such as A-85380 or varenicline to downregulate the expression of DNMT1. These agonists may be administered with valproate (VPA), which is used to inhibit HDACs and to activate chromatin transcriptional activity of selective GABAergic genes including, for example, GAD52. This is probably the reason why VPA is presently prescribed with antipsychotics as an augmentation strategy to treat multiple symptoms of BP and SZ syndromes. The site of action of the antipsychotics is not clear. Recent studies however, suggest that they may act on nuclear chromatin remodeling in GABAergic neurons. Hence, antipsychotic drugs and their coadjuvants (imidazaline, HDAC inhibitors) should be studied in animal experiments to evaluate their putative action on chromatin remodeling and their ability to correct the GABAergic downregulation typical in SZ and BP disorder with psychosis.

doi:10.1016/j.schres.2010.02.164

Symposium 30
IMPROVING OVERALL OUTCOMES - EXTENDING CBT TO COMPLEX PROBLEMS
Co-Chairpersons: Til Wykes, Emmanuelle Peters
Wednesday, 14 April, 2010 - 10:30 am - 12:30 pm

Overall Abstract: CBT for psychosis, now commonly called CBTp, was developed to try to reduce the positive symptoms of psychosis in those people whose symptoms seemed medication treatment resistant. Within the confines of this narrow remit the accumulated evidence is of such a high quality that CBTp has been included in treatment guidance both in the UK, Europe and USA. But despite this guidance there are a number of key issues that are as yet unresolved, particularly
those related to the provision of CBT within a health service framework and not in the context of a clinical trial. For instance is it as effective or cost-effective to provide therapy in a group rather than individually? Are the effects dependent on the expertise of the therapist? Should CBTp be confined to those who are treatment resistant who are often more chronic and stable patients or is it helpful to those who are also in the acute stage? This symposium will try to answer these questions and in particular investigate how CBT methodology has been extended for use with other groups and with targets other than positive symptoms. The speakers are experts both in research and practice in the field. They will report on new findings from meta-analyses, randomised controlled trials of new therapies as well as new smaller feasibility and pilot studies. The papers will provide evidence to guide researchers and clinicians in the next stages of trial design and service improvement. In particular it will aid the process of service development from the guidance of several countries. The speakers represent the cutting edge of cognitive behaviour therapy and are all practitioners from across Europe.

do:10.1016/j.schres.2010.02.165

HOW EFFECTIVE IS CBTP AND DOES THIS DEPEND ON YOUR THERAPIST?

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The most recent and thorough meta-analysis of cognitive behaviour therapy for psychosis (CBTp) suggests a modest effect size (Wykes, Steel, Everitt & Tarrier, 2008). Such outcomes are likely to contribute to the continued recommendation of CBTp within the routine clinical services of many countries. However, little is known about the level of training and supervision of the trial therapists who have contributed to this evidence base. If widespread dissemination of CBTp is to be carried out effectively, then such information is essential. Using an updated version of the studies included within our previous meta-analysis, we present data on the relationship between a number of therapist and supervision variables and outcome. These include the level of therapist training, supervision etc. As we have the methodological quality of the studies we calculated these effects after controlling for trial quality. Supervision but not therapist training appears to have an effect CBTp outcome. These results are discussed within the context of service delivery.

do:10.1016/j.schres.2010.02.166

WHAT WORKS FOR WHOM IN CBT FOR PSYCHOSIS

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The first case-study of CBT for psychosis (CBTp) was reported by Beck over 50 years ago. However it was not until the mid-90s that Randomised Controlled Trials (RCTs) and manuals started appearing in the literature. Fifteen years on, and there are nearly 40 trials published, a further 8 ongoing, and 15 manuals available. What is the status of the evidence so far? Has CBTp lived up to its promise, or do we need a different approach? In this review of the CBTp literature the service user factors associated with success include having stable persistent symptoms, being a help seeker, being cognitively flexible about your delusions and having a chink of insight and several admissions. In terms of therapy a good therapeutic alliance, more expert therapists, longer therapy and the presence of carers all seem to improve outcome. However, this still leaves a lot of unanswered questions about therapy such as the importance of formulation and homework and the significance of memory difficulties or thought disorder that can affect outcomes.

do:10.1016/j.schres.2010.02.167

COGNITIVE THERAPY TO REDUCE COMPLIANCE WITH COMMANDING HALLUCINATIONS WITHOUT CHANGING VOICE ACTIVITY: THE MRC COMMAND TRIAL

Max Birchwood
University of Birmingham Birmingham United Kingdom

Up to one-third of individuals with treatment resistant auditory hallucinations will experience their voices as commanding and many of these will comply or appease the voice, with serious consequences to themselves or others. Our cognitive model of voices has demonstrated in several studies and independent replications that it is the perceived power of the voice to harm or shame the individual if non-compliant, that motivates appeasement behaviour, compliance and distress/ depression. We have developed a method of helping the individual challenge the omnipotence and power of voices which appears in a pilot trial to reduce distress and ease compliance behaviour and distress. The MRC multi-centre COMMAND trial is a pragmatic RCT of CBT for individuals who have recently complied with their voices with serious and harmful consequences to themselves or others and predicts reductions in compliance behaviour and distress linked to changes in the power balance between the personified voice and the voice hearer. This paper will present the evidence for the model, the CBT approach and progress on the trial.

do:10.1016/j.schres.2010.02.168

COMPETITIVE MEMORY TRAINING (COMET) CAN CHANGE APPRAISALS OF VOICES

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Background: Dysfunctional expectations such as “I have to obey my voices to avoid punishment” can be cognitively discarded by verbal challenge and then emotionally experienced as not true with a behavioural experiment. Dysfunctional opinions and evaluations such as “I know that my voices cannot harm me, but they are right when they call me a looser, and then I feel depressed” can be challenged but a behavioural experiment is not at hand. So, a patient could know that the voices are wrong, but still feel depressed. In these cases the experiencing of incompatible positive feelings must be enhanced.

Method: Competitive memory training is a technique that uses imagery of successful moments in life to counterbalance the negative emotions induced by the voice content. The countertheme is over-learned until the positive feeling can be easily elicited by the patient. Four sessions are used to install the positive emotional network; three sessions are used to imagining the voices at the same time with feeling strong and competent. Participants were randomised into COMET (39) or TAU (38). COMET consisted of seven sessions, one each week. Pre and post measures were collected. Primary outcome measures were: Beliefs about Voices Questionnaire power subscale, Voice Acceptance and Activity Scale, Social Comparison Ranking Scale, Auditory
Hallucination Rating Scale cognitive interpretation subscale and Self-Esteem Rating Scale. Secondary outcomes were measured with Beck Anxiety Inventory, Beck Depression Inventory-2 and AHRS total score.

**Results:** Manova on five appraisal measures to avoid inflated type I error showed a significant benefit of therapy (Wilk's Lambda = .804; F (5) = 3.202, p = .012.) Separate Univariate GLM analyses on the post treatment measures, contrasting treatment allocation with the baseline measure as a covariate. Medium effect-sizes were found for: BaVQ power subscale $F(1,75) = 9.7, p < .005$, E-S = .50; SERS self-esteem $F(1,75) = 10.8, p < .005$, E-S = .53; SCS social ranking $F(1,75) = 7.9, p < .01$, E-S = .45. Small to medium effect-sizes were found as a tendency ($p < .05$) at the VAS $F(1,75) = 4.4, p < .05$, E-S = .34 and the AHRS cognitive interpretation $F(1,75) = 5.0, p < .05$, E-S = .36. Anxiety and AHRS total show no changes, but depression was lowered in the COMET group $F (1,74) = 5.01; p = .028$.

**Conclusions:** This study demonstrated that the attribution of power to voices can be diminished; that the social self-ranking to voices can become less submissive; that the voices become more accepted as a cognitive phenomenon; that positive self-esteem can be raised and that negative self-esteem can be diminished by the use of competitive memory training. This is achieved within a limited number of sessions.

doi:10.1016/j.schres.2010.02.169

**DISCUSSANT:**
Til Wykes
Institute of Psychiatry, King’s College London United Kingdom

**OVERALL PANEL PROPOSAL: SPEAKER 1 ABSTRACT:**
SPEAKER 2 ABSTRACT: SPEAKER 3 ABSTRACT:
SPEAKER 4 ABSTRACT:

Symposium 31
**GENE-ENVIRONMENT INTERACTIONS IN SCHIZOPHRENIA:**
ADVANCING BASIC AND CLINICAL RESEARCH
Co-Chairpersons: Jim van Os, Mikhail Pletnikov
Wednesday, 14 April, 2010 - 2:00 pm - 4:00 pm

**Overall Abstract:** The pathogenesis of schizophrenia likely involves multiple interactions between susceptibility genes of small effects and environmental factors. Gene-environment interactions (GEI) occur across different stages of neurodevelopment to produce heterogeneous clinical and pathological manifestations. One of the major obstacles for GEI studies has been the paucity of experimental methods. Recent advances in epidemiology, brain imaging and psychiatric genetics have stimulated the development of new basic and clinical approaches. The symposium will critically evaluate the existing difficulties in the field and will discuss emerging GEI research in schizophrenia. The symposium will include talks from two clinical and two basic scientists who are actively involved in investigation of GEI in schizophrenia. Dr. Jim van Os (Maastricht University, the Netherlands) will present his work on ‘intermediary phenotypes’ as useful targets for the study of GEI. Specifically, he will focus on stress-sensitivity, using momentary assessment technology to chart this phenotype and examine underlying GEI over the life course. Dr. Andreas Meyer-Lindenberg (Central Institute of Mental Health, Mannheim, Germany) will discuss his work from a translational genetics approach, with a focus on neuroimaging, delineating mechanisms of genetic risk through interaction of prefrontal cortex with striatum, midbrain and hippocampus. Using social status as an example, he will present his findings on dissociable neural responses to perceived social rank using functional magnetic resonance imaging (fMRI) in an interactive, simulated social context. He will also discuss validating epidemiologically identified GEI at the neural circuit level. The basic science part of the symposium will consist of two presentations on newly developed animal models of GEI in schizophrenia. The current study focused on stress-sensitivity, using mice which lack a candidate gene for schizophrenia, Neuregulin 1 (NRG1). He will show that Nrg1 heterozygous mice are more sensitive to the neurobehavioural effects of Δ9-tetrahydrocannabinol (THC), the major psychotropic component of cannabis. The new findings from his lab demonstrate that interaction between stress, cannabinoid exposure and Nrg1 genotype is necessary to alter stress-related circuitry in the brain. The possible molecular and neuronal mechanisms of these multiple interactions will be discussed. Dr. Mikhail Pletnikov (Johns Hopkins, USA) will conclude the symposium by describing his new mouse model of GEI relevant to aspects of the pathogenesis of schizophrenia. He will analyze a role of neuroimmune mechanisms in mediating adverse effects of environment in his transgenic mouse models of inducible expression of mutant human DISC1. By regulating timing of expression of mutant DISC1, he will focus on the time windows that are critical for GEI to determine variable phenotypic outcomes in transgenic mice. Dr. Mary Cannon (Royal College of Surgeons, Ireland) will be our discussant to overview the highlights of each presentations in the context of the new challenges in the field and directions for further investigation. The symposium is anticipated to be interesting to a broad audience of clinical and basic researchers seeking to advance translational studies of complex interactions between genetic and environmental factors in the pathogenesis of schizophrenia.

doi:10.1016/j.schres.2010.02.170

**MOMENTARY ASSESSMENT TECHNOLOGY TO ASSESS GENE-ENVIRONMENT INTERACTIONS UNDERLYING THE AFFECTIVE INTERMEDIARY PHENOTYPE OF STRESS SENSITIVITY IN SCHIZOPHRENIA**

Jim van Os, Inez Myin-Germeys, Marieke Wichers, Philippe Delespaul
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Research in twins and first-degree relatives of patients has shown that the genes predisposing for schizophrenia and related disorders impact on a number of heritable traits which underlie the illness: neurocognitive functioning, structural MRI brain volume measures, neurophysiological information processing traits and sensitivity to stress. These ‘intermediary phenotypes’, so-called because they are between the predisposing genes and the disease phenotype, may be closer to the action of genes than the diagnostic category of schizophrenia and related disorders itself, and therefore represent useful targets for the study if gene-environment interactions. The current study focused on stress-sensitivity, using momentary assessment technology to chart this phenotype and examine underlying GxE over the life course. It was hypothesized that the stress-sensitivity phenotype would be associated particularly with genetic risk for affective dysregulation and multiple, “sensitizing” environmental factors impacting over the life course (perinatal stress, childhood adversity and adult negative life events (NLE)). Twin pairs ($n = 779$) participated in a momentary assessment study (Experience Sampling Method, ESM), collecting appraisals of stress and negative affect (NA) in the flow of daily life. Prospective data on birth weight and gestational age, questionnaire data on childhood adversity and recent NLE as well as interview data on affective
dysregulation were used in the analyses. Daily Life Stress-Sensitivity was modelled as the effect of ESM daily life stress appraisals on ESM negative affect. All three developmental stress exposures were moderated by genetic vulnerability (modelled as DZ or MZ co-twin affective dysregulation status) in their effect on Daily Life Stress-Sensitivity: effects were much stronger in participants with MZ co-twins with affective dysregulation and a little stronger in participants with DZ co-twins with affective dysregulation, compared to those without co-twin affective dysregulation. NLE main effects and NLE genetic moderation were reducible to birth weight and childhood adversity. The findings are consistent with the hypothesis that adult daily life stress-sensitivity is the result of sensitization processes initiated by developmental stress exposures. Genes associated with affective dysregulation may underly the phenotype of stress-sensitivity by accelerating the process of stress-induced sensitization. Stress-sensitivity is likely shared with other psychiatric disorders such as depression and bipolar illness, suggesting the need for cross-diagnostic approaches.

doi:10.1016/j.schres.2010.02.171

MECHANISMS OF GEI IN SCHIZOPHRENIA

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Environmental factors and both common and rare genetic variants increasing risk for schizophrenia are being discovered, but the neural mechanisms that mediate their impact are only now coming into focus. We discuss work from a translational genetics approach, with a focus on neuroimaging, delineating mechanisms of genetic risk through interaction of prefrontal cortex with striatum, midbrain and hippocampus. Using social status as an example, we identify dissociable neural responses to perceived social rank using functional magnetic resonance imaging (fMRI) in an interactive, simulated social context. In both stable and unstable social hierarchies, viewing a superior individual differentially engaged perceptual-attentional, saliency, and cognitive systems, notably dorsolateral prefrontal cortex. In the unstable hierarchy setting, additional regions related to emotional processing (amygdala), social cognition (medial prefrontal cortex), and behavioral readiness were recruited. Furthermore, social hierarchical consequences of performance were neurally dissociable and of comparable salience to monetary reward, providing a neural basis for the high motivational value of status. Finally, we discuss GEI impacting on these circuits, with a focus on validating epidemiologically identified GEI on the neural circuit level.

doi:10.1016/j.schres.2010.02.172

AN ANIMAL MODEL OF A GENE-ENVIRONMENT INTERACTION: THE ROLE OF NRG1 IN CANNABIS-INDUCED SCHIZOPHRENIA

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Environmental factors may precipitate schizophrenia especially in individuals who have a genetic vulnerability to the disorder. Human and animal studies indicate that neuregulin 1 (NRG1) is a susceptibility gene for schizophrenia. Our research on gene-environment interactive mechanisms involved in the pathogenesis of schizophrenia has focussed on whether heterozygous deletion of the Nrg1 gene in mice modulates the neurobehavioural effects of environmental stressors and drug of abuse exposure. Specifically, our findings provide an animal model of genetic vulnerability to cannabis-induced psychosis. First, we showed that Nrg1 transmembrane-domain knockout mice (Nrg1 HET) were more sensitive to the neurobehavioural effects of Δ9-trtetrahydrocannabinol (THC), the major psychotropic component of cannabis. Surprisingly, we observed that THC selectively improved attentional function in Nrg1 HET mice, as measured by prepulse inhibition (PPI). We then demonstrated that THC increased c-Fos expression, a marker of neuronal activation, selectively in the ventrolateral septum (LSV) of Nrg1 HET mice - an effect that required the stress of behavioural testing. This implies that a three-way interaction between stress, cannabinoid exposure and Nrg1 genotype is necessary to alter stress-related circuitry in the brain. As the relationship between cannabis and schizophrenia is stronger in heavy, long-term cannabis users we then studied the effects of repeated cannabinoid exposure on the Nrg1 HET mice. These mice showed accelerated tolerance to cannabinoid-induced locomotor suppression and hypothermia. In the light-dark emergence test, similar anxiogenic effects of the cannabinoid were observed between Nrg1 HET and wild-type (WT) littermates on the first day of exposure. However, while WT mice became tolerant to these effects with repeated cannabinoid injections, Nrg1 HET maintained their avoidance of the light zone up to day 15 of exposure, highlighting a prolonged anxiogenic reaction only in Nrg1 HET mice. In the PPI model, cannabinoid administration differentially affected Nrg1 HET and WT mice on day 1, but both genotypes were completely tolerant to these effects by day 7 of exposure. We also examined the neuronal correlates of chronic cannabinoid-induced behavioural effects by measuring FosB/ΔFosB expression. Following 15 days of cannabinoind treatment, Nrg1 HET mice showed a significant increase in FosB/ΔFosB expression in the LSV compared to vehicle controls, an effect not observed in WT mice. In conclusion, our results show that Nrg1 may subserve an enhanced vulnerability to cannabinoid-induced schizophrenia and that the LSV is an important brain region involved in cannabinoid-Nrg1 interactions.

doi:10.1016/j.schres.2010.02.173

GENE-ENVIRONMENT INTERACTIONS IN SCHIZOPHRENIA: A NEW MOUSE MODEL

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Complex interactions between genetic and environmental factors seem to contribute to schizophrenia development. Identification of the molecular mechanisms of those gene-environment interactions (GEI) has been difficult due to paucity of appropriate experimental models. Recent discoveries in human genetics of schizophrenia had been instrumental in developing animal models of GEI based on interactions between relevant environmental factors and genes implicated in schizophrenia pathogenesis. We will describe our novel mouse model of interplay between inducible expression of mutant human Disrupted-In-Schizophrenia-1 (DISC1) and prenatal immune activation (Pletnikov, 2008). Mutant DISC1 is a protein product of the gene disrupted by the chromosomal translocation in a Scottish family (Millar, 2000). In pregnant mice, a synthetic analog of
viral double-stranded RNA, a polyinosinic-polycytidylic acid (poly IC) mimics aspects of viral infection in utero (Meyer, 2006). We studied immune and neurobehavioral alterations in mutant DISC1 and control mice treated with poly IC (5 mg/kg, ip) at embryonic day 9. We found that expression of mutant DISC1 modulated basal and poly IC-induced secretion of cytokines in fetal brains. Intriguingly, GEI in our model produced novel phenotypic manifestations that were not previously seen in DISC1 mice without prenatal challenge. Compared to saline-treated DISC1 mice, poly IC-treated DISC1 mice exhibited increased anxiety, decreased exploratory activity, depression-like responses and impaired spatial memory in Y maze. Prenatal challenge with poly IC produced a decreased linear density of dendritic spines of granule cells of the dentate gyrus of the hippocampus in DISC1 mutant mice only. We will demonstrate that the magnitude but not direction of neurobehavioral effects of GEI in our model depend on levels of expression of mutant DISC1. We will address the necessity of continuous expression of DISC1 for the GEI-produced neurobehavioral deficits to occur in adulthood. We will discuss our data in the context of GEI and will critically evaluate the strengths and drawbacks of the DISC1 model for future mechanistic investigations of GEI.

doi:10.1016/j.schres.2010.02.174

Symposium 32
SCHIZOPHRENIA AND HOMELESSNESS
Co-Chairpersons: Graham Thornicroft, Ezra Susser
Wednesday, 14 April, 2010 - 2:00 pm - 4:00 pm

Overall Abstract: This SIRS Symposium proposal is focused on schizophrenia and homelessness, both of which know no national boundaries. The social disability associated with schizophrenia renders its sufferers highly vulnerable to housing instability and subsequent homelessness. People with schizophrenia are in the group of disabled individuals most likely to fall into chronic homelessness, a situation that is often compounded by substance abuse and medical comorbidities. Awareness of how homelessness and housing instability can compromise the life chances of people with schizophrenia has prompted studies to increase the understanding of individual risk factors for homelessness, and the identification of the socioeconomic conditions across diverse cultures that can interact with individual characteristics to spawn new episodes of homelessness. Importantly, studies of service utilization by people with schizophrenia and the development of innovative service programs provide promising solutions so that people with schizophrenia can achieve recovery, lasting housing stability, and greater life fulfillment. It is this research, service, and policy advances that will define this symposium. In the first presentation, Robert A. Rosenheck and Greg A. Greenberg present findings on the association of personal risk factors, such as severe mental illness and substance abuse, with past homelessness, using data from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC), a large nationally representative survey of American adults conducted in 2001–2002. In the second presentation, Ezra Susser and colleagues from The Netherlands, Brazil, Argentina, and New York, expand the discourse on risk factors for homelessness to include broad societal issues such as social exclusion, income inequality, housing, migration, economic conditions, and family ties. Advocating for the prevention of homelessness as a global mental health initiative, mental health efforts in Brazil and Argentina are described to illustrate differing approaches in differing locales and cultures. In the third presentation, Michele Tansella, Francesco Amaddeo, and Valeria Donisi present findings on the influence of socio-economic variables on psychiatric service use, using census data and mapping technology applied to the Verona Health District to study the relationship of homelessness to where people live and their use of psychiatric services. In the fourth and final presentation, Sam Tsemberis describes the innovative Pathways “housing first” program that serves homeless people with severe psychiatric disabilities and addiction disorders by providing immediate access to housing without the requirement of participation in psychiatric treatment or sobriety as a precondition for housing. In closing, the Discussant, Graham Thornicroft, Professor of Community Psychiatry and Head of the Health Services and Population Research Department, Institute of Psychiatry, Kings College, London UK, will comment on the four presentations described above.

doi:10.1016/j.schres.2010.02.175

CORRELATES OF PAST HOMELESSNESS IN THE NATIONAL EPIDEMIOLOGICAL SURVEY ON ALCOHOL AND RELATED CONDITIONS

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Community telephone surveys have found that between 12 and 14% percent of US adults report past lifetime homelessness. While social and structural factors, e.g., the declining availability of low income housing or the reduced value of public support payments, may account for the number of homeless people at any given point in time, personal risk factors, i.e., sociodemographic, economic, and health characteristics, are likely to explain why some individuals are at greater risk for homelessness than others. In this study we use data from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC), a large nationally representative survey of 41,000 adults conducted in 2001–2002 to investigate the independent association of such personal risk factors, particularly mental illness and substance abuse with past homelessness. Homelessness was identified by a self-report question: “Since age 15 did you ever have a time lasting 1 or more months when you had no regular place to live?” Self-report data from the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM IV version (AUDADIS-IV) were synthesized into diagnostic categories based upon DSM-IV criteria but schizophrenia was addressed by a dichotomous self-report measure that indicated whether or not the respondent reported that a health professional had ever given them a diagnosis of schizophrenia. Altogether 0.76% of the sample responded positively to this question and this group was 11.7 times more likely to report past homelessness than others. Multivariate analyses, co-varying for socio-demographic and economic factors, showed that the factors most strongly related to past homelessness were diagnoses of behavioral health conditions: schizophrenia (Odd Ratio = 2.4) impulse control disorder or antisocial personality (OR = 3.4), substance abuse disorder (OR = 2.9) mood disorder (OR = 2.4), and other personality disorders (OR = 1.9). Psychiatric diagnoses showed consistently stronger associations than socio-demographic characteristics, measures of economic well being, or general health indicators. These nationally representative data from the US confirm findings of single site studies in that both schizophrenia as well as other psychiatric and substance abuse disorders are substantially over-represented among people who have been homeless.

doi:10.1016/j.schres.2010.02.176
SCHIZOPHRENIA, THE PREVENTION OF HOMELESSNESS, AND THE GLOBAL HEALTH MOVEMENT

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Available evidence suggests that individuals with schizophrenia and other severe mental illnesses are at increased risk for homelessness in contemporary societies with diverse cultures and socioeconomic conditions. Yet the prevention of homelessness among individuals with mental illness has rarely been a focus of global health programs. We propose that it should be. In any given society, the overall risk of homelessness will reflect broad societal factors such as income inequality, housing, migration, economic conditions, and family ties. We strongly advocate for addressing these societal causes of homelessness. We also believe, however, that we need to develop special programs in parallel to prevent homelessness among individuals with severe mental illness. We use historical examples to draw attention to ways in which individuals with mental illness have been – and still are – explicitly excluded from societies. We suggest that this social exclusion requires us to take special measures to protect the rights of individuals with mental illness, and to develop programs to ensure they have access to basic necessities including a home. The form these measures take will of necessity vary widely according to local conditions. We describe mental health initiatives in two middle-income countries (Brazil and Argentina) which illustrate different approaches, and allude more briefly to efforts being made in other countries including low-income countries. Finally, we consider some of the efforts that are already being made by various international groups to further this agenda within the global health movement.

doi:10.1016/j.schres.2010.02.177

HOUSING FIRST: ENDING HOMELESSNESS AND TRANSFORMING LIVES

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This presentation describes the Pathways’ Housing First program that serves people who are literally homeless and diagnosed with severe psychiatric disabilities and addiction disorders. The program offers immediate access to permanent independent apartments with intensive off-site clinical and support services like Assertive Community Treatment (ACT) teams. This approach stands in sharp contrast to the majority of programs that require psychiatric treatment and sobriety as a precondition for housing. The Housing First program emphasizes consumer choice and employs a harm reduction approach to managing symptoms and addictions. Program participants are not required to participate in psychiatric treatment or attain a period of sobriety as a precondition for housing. This program is has proved remarkably effective in ending homelessness for people who have been labeled by traditional providers as ‘treatment resistant’ or ‘hard to house.’ Housing First’s effectiveness is well documented in a number of research studies including randomized clinical trials reporting on quantitative and qualitative data. The program has been successfully replicated in numerous cities in the United States, Canada, and Europe. It is listed on the national registry for evidence based programs sponsored by the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA). The presentation will provide a description of the programs’ philosophical approach, essential
operating components, research evidence, and discuss issues of dissemination, program fidelity and system impact.

doi:10.1016/j.schres.2010.02.179

Symposium 33
CANNABIS, AMPHETAMINES AND EARLY PSYCHOSIS:
EVALUATING THE RISKS FOR PROGRESSION,
NEUROBIOLOGIC MODELS OF INTERACTION AND
IMPLICATIONS FOR TREATMENT
Chairperson: Douglas L. Noordsy
Wednesday, 14 April, 2010 - 2:00 pm - 4:00 pm

Overall Abstract: Substance abuse is common among people in early stages of schizophrenia spectrum disorders, and may exert adverse effects on the onset and course of illness. Patients with schizophrenia who use substances have an earlier age of onset, higher rate of relapse and poorer outcomes; and continued use after anti-psychotic treatment is associated with even worse outcomes. Numerous studies of early psychotic disorders note relationships to substance abuse, yet evidence on interactions between substance use and other risks factors for and outcomes of schizophrenia remains limited. This symposium will bring together investigators from around the globe to present emerging findings on the impact of substance use on high-risk individuals as well as on treatment outcomes of first episode patients. The symposium will begin with a brief presentation by the chair, Dr. Noordsy, to overview models to explain the high prevalence of substance use disorders in schizophrenia. He will focus on the reward deficiency model, a neurobiologic model linking dopamine dysfunction in the mesocorticolimbic circuit to both schizophrenia and vulnerability to addiction. Dr. Auther will then present a review of the literature on interactions between cannabis use and early psychosis, as well as results of a study of high-risk individuals with and without cannabis use and risk for progression to schizophrenia in New York. Dr. Linzen will then present data from Holland identifying relationships between cannabis use and symptoms and neuropsychological function among ultra-high risk individuals. Dr. LeComte will then present an analysis of a large sample of methamphetamine using individuals with psychosis from Canada. She will also describe treatment modules for addressing substance abuse in this population. Dr. Robinson will then present data on a first-episode sample from New York suggesting that substance use may be associated with both poorer initial response to antipsychotic treatment and also to longer term non-adherence and treatment dropout. Dr. Noordsy will then summarize and briefly present preliminary findings from a pilot study of clozapine treatment in first-episode patients with co-occurring cannabis use disorders. Finally, Dr. Kane will lead a discussion with the attendees and the panel. It is our hope that this symposium will serve to stimulate interest in the research community not only on the role of cannabis, amphetamine and other substance use in the onset and outcomes of schizophrenia, but also on the underlying mechanisms of co-morbidity that may have implications for a deeper understanding of the neurobiology of both disorders as well as the potential to lead to more effective treatments for individuals who suffer with these disorders. Reference: Green, Al, Drake RE, Brunette MF, Noordsy DL. Schizophrenia and co-occurring substance use disorder. The American Journal of Psychiatry, 164:402-408, 2007.

doi:10.1016/j.schres.2010.02.180

CANNABIS USE AND PRODROMAL SYMPTOMS OF PSYCHOSIS
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Background: Numerous clinical studies have documented high rates of cannabis use in persons with psychosis, amounting to approximately two times the rate in the general population. Furthermore, clinical studies have found cannabis use to be associated with positive & negative symptoms of psychosis, course of illness, and outcome but results vary among studies (Green et al, 2005). Epidemiologic studies also have found an increased risk of psychotic symptoms (OR 1.41) and psychotic disorders (OR 2.58) in cannabis users, especially in those with the highest frequency of cannabis use (OR 2.09; Moore et al, 2007). As a result, cannabis use has emerged as a potential risk factor for the development of psychotic symptoms in individuals predisposed to illness. The Recognition and Prevention (RAP) Program at The Zucker Hillside Hospital in New York, an NIMH funded longitudinal research program, has been investigating the patterns of cannabis use and prodromal symptoms of psychosis in adolescents/young adults.

Methods: Clinical High-Risk subjects with attenuated negative (n = 66) and attenuated positive symptoms (APS, n = 116) between the ages of 12-22 were compared to 68 healthy controls at baseline. Participants completed a self report substance use questionnaire and were interviewed to determine level of cannabis use and severity of symptoms. A subgroup was also followed for approximately one year.

Results: At baseline, subjects with attenuated positive symptoms (APS) had significantly higher rates of cannabis use than those with only attenuated negative symptoms and healthy controls. Among subjects with APS, cannabis users were more likely to be Caucasian, older, and less socially isolated than nonusers. Cannabis use was not significantly related to attenuated positive symptoms at baseline or to psychosis conversion at follow-up. Preliminary data on increased vs. stable vs. decreased cannabis use over follow up was analyzed and no interaction between time and pattern of use was found.

Discussion: In the RAP Program, no relationship was found between cannabis use and emerging positive symptoms or conversion to psychosis. These results will be compared to other published studies of cannabis use in prodromal samples, the results of which have been mixed.


doi:10.1016/j.schres.2010.02.181

SYMPTOMATOLOGY AND NEUROPSYCHOLOGICAL FUNCTIONING IN CANNABIS USING SUBJECTS AT ULTRA HIGH RISK FOR DEVELOPING PSYCHOSIS AND HEALTHY CONTROLS

Don Linszen, Nikkie Korver, Dorien Nieman, Hiské Becker, J. van de Flert, Peter Dingemans, Lieve de Haan, Mark Spiersing, Nicole Schmitz
AMC Academic Psychiatric Center, Amsterdam, Netherlands

Objective: The relationship between cannabis use and psychosis has been studied intensively. However, few data are available on the relationship between cannabis use, ultra high risk for developing psychosis and neurocognition. The aim of the present study is to investigate the relationship between cannabis use, ultra high risk
symptoms and cognitive functioning in ultra high risk patients and healthy controls.

**Methods:** 63 Ultra high risk patients (34 cannabis users) and 58 control subjects (28 cannabis users) were assessed with clinical measures and a neuropsychological test battery. Patients were eligible for the study if they were between the ages of 12 and 35 years and if they fell in one or more of the following inclusion groups: familial risk and reduced functioning, attenuated psychotic symptoms, brief limited intermittent psychotic symptoms and basic symptoms. Control subjects were eligible for the study if they were between the ages 12 and 35, had no present or past psychiatric illness, no family history of psychiatric illness, no drug use in the non cannabis using group and use of at least 4 joints per week in the cannabis using control group.

**Results:** In the UHR and the control group, cannabis users experienced more basic symptoms and UHR symptoms than the non cannabis users. Moreover, cannabis users in the control group performed at the level of the UHR subjects on a test of verbal memory and verbal fluency. Frequency of cannabis use correlated with UHR and basic symptoms.

**Conclusions:** Our results show that cannabis using UHR patients have more basic symptoms than non using patients. In addition healthy cannabis users have more subclinical UHR and basic symptoms and more neuropsychological dysfunctions than non cannabis users. Our results show that more frequent cannabis use is related to increased severity of basic and UHR symptoms.

doi:10.1016/j.schres.2010.02.182

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**THE METHAMPHETAMINE AND PSYCHOSIS STUDY (MAPS) – INDIVIDUAL PROFILES AND TREATMENT NEEDS**

**Tania Lecomte**

*Université de Montréal, Quebec, Canada*

**Background:** Multiple studies are investigating the impact of substance abuse on early psychosis. Stimulants such as methamphetamine (MA), while known to precipitate psychosis, are understudied. The prevalence of MA abuse in young individuals showing signs of early psychosis is dramatically high in Western North America, as is the prevalence of psychosis in young MA abusers. MA lifetime use by youth diagnosed with psychosis ranges from 21–33%. Common reasons for drug misuse in first episode clients range from increased pleasure, reduced depression and anxiety, and enhanced social facilitation. Individuals who abuse drugs, particularly stimulants such as MA, tend to have their first hospitalization earlier than non-misusing peers with schizophrenia, present with more severe symptoms, and have more problems in areas of interpersonal relationships, motivation, role functioning and activities. For many people, the substance abuse may precede the onset of the illness, whereas for others MA abuse may coincide with the onset, or even follow the onset of psychosis. Sixty–90% of first episode psychosis youth have abused drugs prior to their first psychiatric contact, suggesting a strong connection between psychosis and substances. Recent studies suggest that MA users with psychosis are much more likely to experience psychotic symptoms again if they use MA, and are also more likely to have a psychotic relapse when confronted with stressful situations, even years after cessation of MA use. MA users with persistent or recurrent psychotic symptoms become vulnerable to stress and may benefit from antipsychotic medication the same way individuals with schizophrenia do.

**Method:** Our study aimed at describing the profiles of individuals with MA abuse and psychotic symptoms. We also wished to determine patterns of abuse and psychotic symptoms over time. 295 participants were interviewed following at least one episode of acute psychotic symptoms linked to MA abuse, and followed with monthly measures of substance abuse and psychiatric symptoms for six months.

**Results:** Most participants lived in transitional housing or were homeless. Only 13% had no family history of mental illness or substance abuse. Close to 70% had a previous diagnosis of a mental illness. Antisocial personality disorder (68%), depression (67%), and post-traumatic stress disorder (49%) were highly prevalent. Risk factors and trajectories of substance abuse and psychotic symptoms will also be presented.

**Treatment:** Integrated dual-disorder treatment, where the mental health team works in collaboration with the substance abuse counsellors, is considered the evidence-based treatment for individuals presenting with co-occurring substance abuse and severe mental illness. Such treatments include step-wise interventions, often using CBT and motivational interviewing components, and can be found in various settings, including assertive community treatments. However, only some of the difficulties presented by participants in our study are addressed in these programs. Our team is currently working on developing modular programs for people with early psychosis and various concurrent disorders. Some examples of these treatment modules will be presented.

**doi:** 10.1016/j.schres.2010.02.183

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**CLOZAPINE VS. RISPERIDONE FOR PEOPLE WITH FIRST EPISODE SCHIZOPHRENIA AND CO-OCCURRING CANNABIS USE DISORDER**

**Douglas Noordsy, Jessica, Alan Green**

*Dartmouth Medical School, Hanover, NH, USA*

**Background:** Schizophrenia with comorbid substance abuse disorder is associated with increased morbidity and mortality. Early in the course of schizophrenia, cannabis is one of the most commonly abused substances. Patients with schizophrenia who use cannabis have earlier age of onset, higher rates of relapse and poorer outcomes. Repeated relapse has been associated with progression of schizophrenia to a more treatment resistant illness. Clozapine is the most effective antipsychotic and has been shown to increase time in remission for first episode patients. Clozapine has also been shown to decrease cannabis use in patients with schizophrenia. Thus, patients with first episode schizophrenia and co-occurring cannabis use disorder (CUD) may be candidates for the use of clozapine first-line, in an attempt to improve the long-term course of this disorder. This pilot study is assessing whether treating patients with first episode schizophrenia and comorbid CUD with clozapine will lead to increased abstinence from cannabis and better illness outcomes as compared to those treated with risperidone over 24 weeks of treatment.

**Methods:** We are aiming to recruit 21 subjects, age 17-45, meeting DSM-IV criteria for schizophrenia and for cannabis abuse or dependence, who have less than 16 weeks of prior antipsychotic treatment, and demonstrate use of cannabis in past 35 days. Participants are randomized to flexible-dose treatment with clozapine or risperidone for 24 weeks. The lowest dose of antipsychotic necessary for treatment of psychotic symptoms is used. Medication drop-outs are followed in intent-to-treat fashion. A lifestyle intervention including education, goal setting and behavioral log of diet, exercise and stress management is provided to minimize metabolic changes. Weight, waist circumference, laboratory values and symptom, side effect and functional rating scales are administered at regular intervals.

**Results:** Fourteen participants have been randomized to medication thus far, 13 have taken study medication. Mean age is 23 years, 57% male, all Caucasian. Mean daily doses are 75 mg for clozapine, and 3.1 for risperidone. Of 7 participants assigned to clozapine, 3 (43%) completed the study on clozapine and 4 terminated prior to 24 weeks. Of 7 participants assigned to risperidone, 4 (57%)
completed on risperidone, 2 terminated early, and 1 never took medication. All clozapine completers chose to continue clozapine at study termination (for up to 2.5 years), while 2 of 4 risperidone completers chose to discontinue antipsychotic treatment and a third changed antipsychotics at study termination. Substance use, psychopathology, cognitive and functional outcomes will be analyzed at the completion of the study.

Discussion: About half of participants in the clozapine group have discontinued treatment early, a rate similar to previous first-episode schizophrenia studies in the US. There were no discontinuations due to lack of efficacy in either group, but several discontinuations due to inability to tolerate medication side effects in clozapine group. Patients with first-episode schizophrenia and CUD can be recruited into a randomized trial of clozapine. A subset of participants in each group is able to complete a 6-month trial of their assigned medication. Clozapine completers have demonstrated strong interest in remaining on this medication.

doi:10.1016/j.schres.2010.02.184

Symposium 34
NEWER ANTIPSYCHOTIC DRUGS IN EARLY-ONSET PSYCHOSIS: A TRANSLATIONAL VIEW
Co-Chairpersons: Sanjiv Kumra, Frank Tarazi
Wednesday, 14 April, 2010 - 2:00 pm - 4:00 pm

Overall Abstract: Due to the relative rarity of schizophrenia in children and adolescents, the conduct of antipsychotic treatment studies with informative sample sizes in this population has proven difficult. The overall goal of this panel is to improve the design and conduct of clinical trials in pediatric schizophrenia. The panel will bring together clinical investigators and translational scientists to evaluate the evidence for existing treatments for pediatric schizophrenia and the latest information on the effectiveness and safety of antipsychotic treatments that are relevant to pediatric schizophrenia in order to identify the most urgent clinical questions in this area. There have been a number of recently completed placebo-controlled and active comparator trials of new antipsychotic drugs in children and adolescents. We review this experience to identify the unique developmental aspects associated with the treatment of pediatric schizophrenia; and the challenges and the lessons that have been learned in conducting clinical trials in this population. Lastly, we will examine some new animal data that provide insights into understanding the observed age-related differences in side effect profiles of antipsychotic drugs between young and adult patients. Key objectives of this symposium are to summarize authoritatively and succinctly the important recent advances in pharmacological and clinical understanding of newer antipsychotics in young patients, and to integrate the available basic and clinical findings so as to guide future research efforts. This symposium will contribute to improved understanding of cerebrobehavioral mechanisms of this important class of psychotropic agents, and of emerging principles aimed at improved treatments for early-onset psychotic and major affective disorders.

doi:10.1016/j.schres.2010.02.185

IS THERE A ROLE FOR CLOZAPINE IN CHILDREN AND ADOLESCENTS WITH SCHIZOPHRENIA?
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Background: In adults with schizophrenia, neuroleptic resistance is associated with an early onset of psychosis. A recent study in youth with schizophrenia revealed high rates of treatment discontinuation during an 8-week trial to all three randomized drugs (e.g., clozapine, risperidone, olanzapine). However, serious concerns about metabolic adverse side effects to olanzapine were raised. A previous study demonstrated that clozapine was superior to haloperidol. Because olanzapine has been shown to have superiority to other typically used 'first-line' agents in adults with schizophrenia, the present study compared the effectiveness and safety of clozapine versus "high-dose" olanzapine in treatment-refractory adolescents with schizophrenia.

Methods: Children, ages 10-18 years, who met DSM-IV criteria for schizophrenia and who were resistant or intolerant to at least two antipsychotic drugs were randomized to receive 12 weeks of double-blind flexibly dosed treatment with clozapine (n = 18) or "high-dose" olanzapine (up to 30 mg/day) (n = 21). The primary efficacy measure was response (improvement), defined as a decrease of 30% or more in total BPRS score from baseline and a CGI scale improvement rating of "1" (very much improved) or "2" (much improved). Patients were then followed in a 12-week open-label trial to monitor adverse effects.

Results: Significantly more clozapine-treated adolescents met response criteria (66%) compared with olanzapine-treated subjects (33%) during the double-blind portion of the study. Clozapine was superior to olanzapine in terms of reduction of the psychosis cluster scores and negative symptoms from baseline to endpoint. However, both treatments were associated with significant weight gain and related metabolic abnormalities at 12- and 24-weeks post-treatment.

Conclusion: This double-blind randomized comparison of two second-generation antipsychotic drugs for treatment-refractory adolescents with schizophrenia supports clozapine as the agent of choice. The results are similar to a recent NIMH completed double-blind comparison of clozapine vs. ‘standard-dose’ olanzapine, and do not support a hypothesis that metabolic side effects associated with olanzapine are dose-related. We will also present long-term safety data and pilot data regarding potential mechanisms underlying clozapine-induced weight gain.

doi:10.1016/j.schres.2010.02.186

EFFICACY AND SAFETY OF ANTIPSYCHOTICS IN ADOLESCENTS WITH EARLY-ONSET SCHIZOPHRENIA

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Background: Until recently, controlled safety and efficacy data of antipsychotics in youth with schizophrenia have been scarce. This has changed with the completion of a number of placebo-controlled and active controlled trials. We aimed to provide an overview of the available and emerging controlled efficacy and safety data of antipsychotics in youth with pediatric schizophrenia.

Methods: Systematic review and summary of published and unpublished data from randomized placebo-controlled and active-controlled studies of antipsychotics in children and adolescents. Results. 14 randomized, controlled trials (n = 1,155) were found. Six trials had a placebo comparator and evaluated haloperidol (N = 2, n = 67), loxapine (N = 1, n = 51), aripiprazole (N = 1, n = 301), quetiapine (N = 1, n = 220), risperidone (N = 1, n = 160), and olanzapine (N = 1, n = 107), and one trial (n = 279) used low dose risperidone (0.15-0.6 mg/day) as pseudo-placebo comparator. 7 trials (n = 275) compared antipsychotics head-to-head, including thiothixene vs thioridazine (N = 1, n = 21), haloperidol vs olanza-
pine vs risperidone (N=1, n=50), molindone vs olanzapine vs risperidone (N=1, n=119), haloperidol vs clozapine (N=1, n=21), clozapine vs olanzapine (N=2, n=64), and olanzapine vs quetiapine (N=1, n=50). All newer antipsychotic trials completed since 2005 showed superiority on PANSS all studied doses. The numbers-needed-to-treat for response ranged from 4-10 for aripiprazole, olanzapine, quetiapine and risperidone. Across the 7 active-controlled trials, the only significant group differences were in favor of clozapine compared to haloperidol, regular dose olanzapine (up to 20 mg/day) and high-dose olanzapine (10-30 mg/day). While response rates were lower in adolescents compared to adults, youth were more sensitive to antipsychotic adverse effects, such as sedation, EPS (except for akathisia), withdrawal dyskinesia, prolactin abnormalities, weight gain and metabolic abnormalities, with significant differences among the studied antipsychotics. By contrast, diabetes and tardive dyskinesia were less prevalent in pediatric samples, at least during the relatively short observation periods and at lower doses than used in adults.

Conclusions: Data from large placebo-controlled studies support statistically significant superiority of all studied antipsychotics vs. placebo in pediatric schizophrenia. Except for superiority of clozapine, efficacy differences among antipsychotics are small, and response rates are lower than in adults. In contrast, adverse effects are more pronounced in youth and differ across antipsychotics. To achieve generalizability and follow patients for sufficiently long periods of time, large practical trials and long-term cohort studies should also be conducted to complement randomized controlled trials.

do:10.1016/j.schres.2010.02.187

SIMILAR EFFICACY RESULTS IN SHORT-TERM AND LONG-TERM STUDIES OF ADULT AND ADOLESCENT PATIENTS WITH SCHIZOPHRENIA TREATED WITH ARIPIPRAZOLE

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Learning Objectives. (1) To facilitate informed consideration and discussion of the rationale and scientific basis for extrapolating long-term efficacy data from adult studies to adolescents with schizophrenia who received aripiprazole treatment. (2) Review and discuss long-term safety and efficacy of aripiprazole in adolescents with schizophrenia, ages 13-17. Objective. Post-hoc was analyses were performed to assess the similarity of short- and long-term efficacy in adolescents and adults with schizophrenia treated with aripiprazole.

Background: There are limited published, controlled data on the long-term efficacy of antipsychotics in adolescents with schizophrenia. Schizophrenia, when properly diagnosed in younger adolescent patients, carries a high degree of diagnostic continuity. Regardless of age, after diagnostic criteria are met, a threshold has been reached where the stage of the illness and its progression can be defined with a high degree of reliability.

Methods: A comparison between the adolescent and adult efficacy data was conducted, including analyses of short- and long-term treatment effects on the PANSS scores; response rates; and remission rates.

Results: Comparable short and long-term treatment effects were observed on the PANSS Total and subscale scores, demonstrated by overlapping 95% confidence intervals. Percent of adolescents achieving remission at 27-32 weeks (82%) on open label treatment was similar to that in adult studies at week 26 (76%) and at week 52 (79%) on double blind treatment. Remission was maintained at 27-32 weeks in 91% of adolescents who achieved remission at 6 weeks of double-blind treatment compared to 95% and 92% of adults after 26 and 52 weeks of treatment, respectively.

Conclusions: The validity of extrapolating long-term efficacy from adult aripiprazole studies to adolescents as acknowledged by the FDA is supported by the continuity of schizophrenia and similarity of efficacy results across adolescents and adults.

do:10.1016/j.schres.2010.02.188

DIFFERENTIAL EFFECTS OF ANTIPSYCHOTIC DRUGS IN DEVELOPING VS. MATURE ANIMALS

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Background: Long-term effects of dissimilar antipsychotic drugs on neuronal elements in developing vs. mature rat brain require further investigation.

Methods: Juvenile [PD 22] and adult [PD 70] Sprague-Dawley rats were treated with representative first- [fluphenazine (FLU); 1 mg/kg/d] and second-generation [clozapine (CLZ); 40 mg/kg/d, olanzapine (OLZ); 5 mg/kg/d, and risperidone (RSP); 3 mg/kg/d] antipsychotic drugs. At the end of treatment, subjects were sacrificed and brains were collected and processed for in dopamine (DA) and serotonin (5-HT) receptor autoradiography.

Results: Repeated treatment with FLU, OLZ and CLZ decreased DA D1 receptors in cerebral cortex of juvenile, but not adult rats. All four antipsychotic agents selectively increased D2 receptors in cerebral cortex of adult animals and D2 receptors in hippocampus of juvenile animals. The four agents also increased D4 receptors in nucleus accumbens and caudate-putamen in both aged groups, but the effects were more profound in developing animals. D3 receptors were not altered by any treatment in any brain region at either age. CLZ, OLZ, RSP, but not FLU, increased 5-HT1A and decreased 5-HT2A receptors in cerebral cortex of both developing and mature animals but with different magnitudes. In addition, CLZ, OLZ, RSP treatment increased 5-HT1A receptors in juvenile and not adult animals.

Conclusions: Similar doses of antipsychotic drugs exert different effects on Da and 5-HT receptor subtypes. Young animals are more sensitive than adults to the long-term effects of dissimilar antipsychotic drugs. Developmental differences in DA and 5-HT receptor responses may account for differences in clinical effects of antipsychotic drugs between young vs. adult psychiatric patients.

do:10.1016/j.schres.2010.02.189

Symposium 35 INTEGRATION OF STRUCTURAL, FUNCTIONAL AND NEUROCHEMICAL BRAIN CHANGES PRIOR TO THE ONSET OF PSYCHOSIS

Co-Chairpersons: Phillip McGuire, Christos Pantelis
Wednesday, 14 April, 2010 - 2:00 pm - 4:00 pm

Overall Abstract: Recent neuroimaging studies of the prodromal phase of psychosis have shown that structural, functional and neurochemical alterations predate the onset of illness. However, to
ABERRANT SALIENCE IN SUBJECTS AT HIGH RISK OF PSYCHOSIS RELATED TO ALTERED DORSOLATERAL PREFRONTAL FUNCTION

Jon Roiser
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Background: The “aberrant salience” hypothesis proposes that psychosis is, at least in part, driven by dysregulated dopamine transmission, resulting in the inappropriate assignment of importance to irrelevant environmental stimuli (Kapur 2003). Consistent with this hypothesis, we used the Salience Attribution Test (SAT; Roiser et al 2009) to demonstrate that first-episode schizophrenia patients suffering from delusions exhibited significantly greater aberrant salience than patients without delusions. However, interpretation of these results was complicated by the fact that almost all the patients were taking antipsychotic medication.

Methods: We used multi-modal imaging to investigate the neural mechanisms of aberrant salience in unmedicated individuals with an At-Risk Mental State for psychosis (ARMS). Eighteen ARMS individuals and 18 controls performed the SAT, during which haemodynamic responses were measured using functional magnetic resonance imaging (fMRI). The SAT is a quick-response game using relevant and irrelevant cue features, on which participants earn rewards (money). It produces implicit (Reaction Time (RT) based) and explicit (Visual Analogue Scale (VAS) based) measures of adaptive and aberrant salience. On a separate occasion, all participants underwent an [18F]-DOPA Positron Emission Tomography (PET) scan to assess pre-synaptic dopamine synthesis capacity. Symptoms were assessed in ARMS individuals using the Comprehensive Assessment of At Risk Mental States (CAARMS).

Results: At the behavioural level, ARMS individuals exhibited significantly higher levels of aberrant salience than controls, but did not differ in terms of adaptive salience, suggesting a specific difficulty in salience attribution, as opposed to a general learning impairment. Schizotypy ratings across all participants, and symptoms on the positive sub-scale of the CAARMS in the ARMS individuals, correlated with the severity of aberrant salience. As with the behavioural data, neural responses relating to adaptive salience did not differ between the groups. Both groups also showed a similar response in the ventral striatum to measures of aberrant salience. However, in the dorsolateral prefrontal cortex (DLPFC) there was a significant group difference in the responses relating to aberrant salience. In ARMS individuals, irrelevant stimulus features erroneously linked with lower reward probabilities evoked greater DLPFC responses, whereas subjective reward probability had no bearing on the DLPFC response to irrelevant stimuli in controls. In both ARMS subjects and controls, presynaptic dopamine synthesis capacity in the associative striatum was correlated with aberrant salience-related responses in the hippocampus. However, the correlation in the ARMS group was negative, whereas in controls the correlation was positive.

Discussion: These data are consistent with the aberrant salience hypothesis of psychosis, and suggest that circuits including the DLPFC, ventral striatum and hippocampus, interacting with a dysregulated dopamine system, may play a crucial role in the production of positive psychotic symptoms.

doi:10.1016/j.schres.2010.02.190

glutamate in the at risk mental state

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Background: Since the 1980s, glutamatergic abnormalities have been hypothesised to occur in schizophrenia. Recent findings from genetics, neuroimaging and post-mortem studies support the role of glutamate in the development of psychosis. Individuals with an At Risk Mental State (ARMS) experience attenuated psychotic symptoms, and are at high risk of transition to frank psychosis (20-40% within 2 years). The role that glutamate dysfunction might play in the very early stages of psychosis was investigated in this group using MR spectroscopy.

Methods: Subjects meeting PACE criteria for the ARMS (n=27) and controls (n=27) were studied using a 3T MRI scanner. MR spectra were acquired in ROIs in the thalamus, anterior cingulate gyrus and the hippocampus. Volumetric MRI data were acquired from the whole brain. MRS data were collected again using the same methods after approximately 12 months. MRS data were analysed using LCM model version 6.1-4F. Volumetric data were analysed using SPM.

Results: At presentation, ARMS subjects had significantly lower levels of glutamate than controls in the thalamus (p<0.05), but higher glutamine in the anterior cingulate (p<0.05). Within the ARMS group, the level of thalamic glutamate was directly correlated with grey matter volume in the medial temporal cortex and insula (p<0.01). Preliminary analysis suggests that within the ARMS sample, there is a difference in the longitudinal change in glutamate levels according to whether or not subjects developed psychosis.

Discussion: This study provides the first evidence that brain glutamate function is perturbed in people with prodromal signs of schizophrenia, and that glutamatergic dysfunction is associated with a reduction in grey matter volume in brain regions thought to be critical to the pathogenesis of the disorder. These findings suggest that drugs affecting the glutamate system may be useful in the early stages of psychotic illness.

doi:10.1016/j.schres.2010.02.192

VIRAL LOAD AND BRAIN STRUCTURE IN PEOPLE AT ‘ULTRA-HIGH RISK’ OF DEVELOPING PSYCHOSIS: A VOXEL-BASED MORPHOMETRY STUDY

Thomas Whitford
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Background: There is now a considerable body of evidence indicating that structural brain changes precede the onset of psychotic symptoms in people who subsequently go on to develop a psychotic illness, such as schizophrenia or bipolar disorder. However, the question remains unresolved as to what environmental and genetic factors can trigger the onset of such prodromal cerebral alternations. Answering this question is one of the most important challenges currently faced by psychosis prevention and early-intervention programs. It has been suggested that prodromal exposure to one or more specific viral pathogens may trigger the structural brain changes that have been observed in people with a diathesis for psychosis who go on to develop the disorder.

Methods: The present study aimed to test this suggestion by investigating the relationship between brain structure and viral load in a large sample (n=84) of people at ‘ultra-high risk’ (UHR)
of developing psychosis. All subjects underwent both a blood-draw and a T1-weighted structural MRI scan on a 3T system. Viral load (i.e., virons per milliliter) was calculated for each subject for several common viruses, namely Herpes Simplex Virus 1, Herpes Simplex Virus 2, Cytomegalovirus and Epstein-Barr virus, and also for the Toxoplasmosis parasite. Voxel-based morphometry in SPM2 was used to address two specific questions: 1) what is the relationship between brain structure and viral load in people at UHR of developing psychosis, and 2) is there a consistent difference in the viral load between UHR subjects who transition to psychosis (UHR-P) and those who do not (UHR-NP).

**Results:** The results revealed a complex set of interactions between viral load and regional grey matter density.

**Discussion:** These findings may shed light on the environmental triggers for psychosis onset.

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**ABNORMAL PREFRONTAL ACTIVATION RELATED TO STRIATAL Dopamine Dysfunction in People at Clinical Risk for Psychosis**

Paolo Fusar-Poli
University of Pavia, Italy

**Background:** The pathophysiology of schizophrenia is incompletely understood, but two of the most robust abnormalities are elevated striatal dopamine activity and prefrontal cortical dysfunction. To investigate the relationship between these abnormalities in the prodromal phase of the illness, we combined functional Magnetic Resonance Imaging and 18F-Dopa Positron Emission Tomography in the same subjects.

**Methods:** We studied 22 subjects who met PACE criteria for the At Risk Mental State and 16 healthy volunteers. Prefrontal activation was studied using functional MRI while subjects performed a verbal fluency task. Striatal dopamine function was studied using 18F-Dopa Positron Emission Tomography (PET). All subjects were medication naive. Data were analysed using SPM.

**Results:** When performing a verbal fluency task, subjects with an At Risk Mental State showed greater activation in the inferior frontal cortex than controls (FWE p < 0.05). Dopamine function in the associative subdivision of the striatum was greater in the At Risk group than in controls (p < 0.05). Within the At Risk group there was a direct correlation between the degree of left inferior frontal activation and the level of striatal dopamine function (r = 0.681, p = 0.001). There was no significant correlation in the control group (r = -0.261, p = 0.368, R2 = 0.068). The between-group difference in the respective correlations was significant (Fisher’s r to z transformation p = 0.005).

**Discussion:** The key finding from the present study is that in individuals at very high risk of schizophrenia, altered prefrontal activation during a task of executive function was directly related to striatal hyperdopaminergia. This provides in vivo evidence of a link between dopamine dysfunction and the perturbed prefrontal function which may underlie the deficits in executive processing evident in people with prodromal symptoms of psychosis. These abnormalities reflect an increased vulnerability to psychosis and predate the first episode of frank psychosis.

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**Oral Presentations**

**ORAL PRESENTATION 1 – GENE ENVIRONMENT INTERACTIONS IN THE PREDICTION OF PSYCHOSIS**

**Chairperson:** Lynn DeLisi

**Tuesday, 13 April, 2010 - 1:30 pm - 3:30 pm**

**Overall Abstract:** Topics Include: Animal Models, Brain Imaging - functional, Brain Imaging - structural, Children & Adolescents

**DEVELOPMENTAL VITAMIN D DEFICIENCY (DVD) AND BRAIN Dopamine Ontogeny**

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2Queensland Brain Institute, University of Queensland Brisbane, Qld, Australia; 3Dept Psychiatry, University of Queensland Brisbane, Qld, Australia

**Background:** Low maternal vitamin D is a risk factor for schizophrenia. For the past 8 years our group has been developing a rodent model of Developmental Vitamin D (DVD) deficiency. This model is associated with both spontaneous hyper-locomotion and enhanced response to psychomimetics. Our most recent studies indicate that the absence of this vitamin during development also alters the way dopaminergic neurons develop.

**Methods:** Vitamin D deficiency is induced in female Sprague-Dawley rats by dietary restriction. Females are then mated with vitamin D normal males and the pregnant females are maintained on their respective diets during this period. At birth all maternal animals are placed on a vitamin D normal diet. The period of DVD-deficiency is therefore restricted to the gestational period only. Resultant DVD-deficient progeny were examined either as embryos, neonates or adults.

**Results:** Studies in embryonic brains have indicated that the vitamin D receptor (VDR) appears first in the superior colliculus (the proto-basal ganglia) (Embryonic day E12). Immunohistochemical studies have confirmed that VDR is present in the nuclei of these developing dopamine neurons. Therefore we investigated the expression of genes relevant for dopamine neuron development in this region. We have found that mRNA for Nurr-1 (a crucial nuclear transcription factor in dopamine neuron development) is significantly reduced in the embryonic DVD-deficient mesencephalon at both E12 and E15. At birth, Catechol-O-methyl transferase (COMT, a major catabolic enzyme for dopamine converting DOPAC to HVA) was significantly reduced in the male DVD deficient rat brain. Correspondingly the ratio of DOPAC/HVA was increased consistent with the lower production of HVA. In adult males this reduction in COMT persists in the prefrontal cortex with an apparent reduction in tyrosine hydroxylase positive neurons in the substantia nigra. In contrast, female adult DVD animals do not have changes in COMT activity or TH positive cell count, but show a significant increase in dopamine transporter density and/or affinity (all P < 0.05 n ≥ 8).

**Discussion:** Developmental absence of vitamin D is associated with altered dopamine neuron ontogeny. There is now a convergence of findings in other epidemiologically plausible developmental animal models of schizophrenia that are also describing alterations in dopamine development. Developmental changes in dopamine signalling/connectivity may therefore represent an “Early” rather than a “Final” common pathway linking dysregulated dopamine function and schizophrenia.

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**DOE 1016/j.schres.2010.02.193**
IN VIVO PET IMAGING OF CEREBRAL TYPE 1 CANABINOID RECEPTOR AVAILABILITY IN PATIENTS WITH SCHIZOPHRENIA

Jenny Ceccarini1, Marc De Hert2, Ruud van Winkel2, Dagmar Koethe3, Guy Bormans3, Markus Leweke3, Joseph Peuskens3, Koen Van Laere1
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Background: Increasing evidence supports the idea that the human endocannabinoid system (ECS), an important and abundantly present neuromodulator in the brain, may be involved in psychiatric disorders such as schizophrenia (SCZ), as supported by biochemical and post-mortem studies. In particular, as the cerebral type 1 cannabinoid receptor (CB1R) presynaptically modulates other neurotransmitters such as glutamate and dopamine, it may contribute to the pathogenesis of SCZ or neural circuit dysfunctions responsible for its symptomatology. In this study, we used positron emission tomography (PET) and the selective, high-affinity radioligand [18F]MK-9470, to assess whether in vivo binding of this CB1R ligand is altered in medication-free and monotherapy treated patients with schizophrenia (SCZ), in comparison to healthy controls.

Methods: 58 patients with SCZ (38 ± 9 yrs, 38 M/20F), with (n = 49, SCZ1) and without (SCZ0, n = 9, n = 5 drug-naïve, n = 4 after washout) antipsychotic treatment, and 12 healthy volunteers (36 ± 14 yrs, 12 M/4F), were investigated using [18F]MK-9470 PET. All subjects underwent 60 minutes PET scanning with 303 ± 57 MBq of [18F]MK-9470 at 120 min postinjection. Spatially normalized, parametric images using a modified standardized uptake value (mSUV), reflecting CB1R availability, were calculated. Changes in CB1R availability were analyzed by statistical parametric mapping (SPM2) and predefined volume-of-interest analysis.

Results: Compared to controls, treated and untreated SCZ patients showed a significant increase of CB1R availability in the mesocorticolimbic circuitry, especially in the nucleus accumbens (+ 13.6%, p = 0.01 for SCZ1, and + 15.7%, p = 0.03 for SCZ0). Regional analysis (normalized to individual whole-brain availability), confirmed this in both groups and in addition, schizophrenics treated with antipsychotic monotherapy presented increased relative CB1R binding in the insula (+ 2.2%, p = 0.03) and anterior cingulate cortex (+ 1.8%, p = 0.04). A correlation analysis showed that CB1R uptake was positively associated with the positive PANSS subscale ‘conceptual disorganization’ in the insula (r = 0.60, P<0.001) and nucleus accumbens (r = 0.55, P<0.001). In a cluster encompassing the amygdala, hippocampus and putamen, CB1R availability was negatively correlated to psychomotor speed and attention (Trial Making Test), but > 0.60, P<0.001.

Discussion: We provide evidence for the involvement of the ECS in the mesocorticolimbic circuitry of patients with SCZ, especially in the nucleus accumbens, an important key region involved in several cognitive, emotional and psychomotor dysfunctions encountered in SCZ. These increases are differentially modulated by antipsychotics, but not normalized compared to the control conditions. Furthermore, mesolimbic functional disturbances in ECS may be correlates of the psychopathological symptoms and cognitive processing deficits observed in SCZ. The mechanisms by which these results can lead to limbic hyperdopaminergia or prefrontal hypodopaminergia, and involvement of the glutamatergic hypothesis, needs further study. Research support: Merck & Co., Inc. is acknowledged for the availability of the precursor for [18F]MK-9470 and partial sponsoring of the study. KVL is Senior Clinical Investigator of the Flemish Fund of Scientific Research.

doi:10.1016/j.schres.2010.02.196

PROGRESSIVE LATERAL VENTRICULAR ENLARGEMENT IN SCHIZOPHRENIA: A META-ANALYSIS OF LONGITUDINAL MRI STUDIES

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Background: Lateral ventricular enlargement is one of the most consistent findings in patients with schizophrenia; however whether progressive ventricular dilation occurs during the course of the illness has been controversial. To clarify this we conducted a meta-analysis of longitudinal studies measuring the lateral ventricles in patients with schizophrenia and a control group.

Methods: The MEDLINE database was searched from 1980-2009 for longitudinal MRI studies of patients with schizophrenia. We identified 13 studies which measured the lateral ventricles in both patients and controls and these were included in a random effects meta-analysis. The effect of various clinical variables was investigated in a meta-regression analysis.

Results: Patients showed evidence of progressive ventricular enlargement after illness onset greater than that seen in controls (Effect size = 0.45, 95%CI 0.19-0.71, p = 0.0006). A sub-analysis of chronic patients with schizophrenia with a mean duration of illness of 7.6 years at baseline scan also showed progressive ventricular enlargement (p = 0.002). The results were robust to inclusion criteria, and no significant effect of age of onset, duration of illness, or age at baseline scan, was found in the meta-regression analysis.

Discussion: The meta-analysis shows progressive changes in ventricular volume a number of years after illness onset and challenges an exclusively neurodevelopmental model of schizophrenia.

doi:10.1016/j.schres.2010.02.197

DEFAULT NETWORK AND MEDIAL PREFRONTAL CORTEX DYSFUNCTION IN SCHIZOPHRENIA AND IN FIRST DEGREE RELATIVES OF PERSONS WITH SCHIZOPHRENIA

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Background: MRI studies of patients with schizophrenia have found consistent evidence of gray matter reduction in the right anterior cingulate cortex (ACC) and in bilateral medial prefrontal cortex (mPFC). In these studies, findings have been more consistent in chronic patients with schizophrenia than in first degree relatives of persons with schizophrenia (FDR). In addition, there is evidence of progressive atrophy in the ACC and mPFC over a period of years.
Background: Persons at risk for schizophrenia have subtle brain abnormalities (possible endophenotypes) well before the acute psychosis begins. Amongst the variety of abnormalities observed, understanding dysfunction of the default network, particularly the medial prefrontal cortex (mPFC), has potential to help understand the nature of the pathophysiology of schizophrenia. Here we report on 3 of our studies in which brain structure or function, as measured by MRI, was found to be abnormal in nonpsychotic relatives of persons with schizophrenia.

Methods: We examined the volume, using MRI morphometry, of the mPFC in a middle aged (mean age 40.4) sample of 45 first-degree relatives compared to 48 controls, and in a second younger sample (mean age 18.4) of 27 nonpsychotic relatives and 48 controls. We also examined the status of the neural network mediating the default mode of brain function, which typically exhibits greater activation during rest than during task, in 13 patients in the early phase of schizophrenia and in 13 young first-degree relatives of persons with schizophrenia.

Results: Significant volume reductions were found bilaterally in the mPFC in the two independent groups of relatives of persons with schizophrenia. During functional magnetic resonance imaging (fMRI), patients, relatives, and controls alternated between rest and performance of working memory tasks. As expected, controls exhibited task-related suppression of activation in the default network including mPFC and posterior cingulate cortex (PCC)/precuneus. Patients and relatives exhibited significantly reduced task-related suppression in mPFC, and these reductions remained after controlling for performance. Increased task-related mPFC suppression correlated with better working memory performance in patients and relatives with and without psychotic symptoms, (3) reduction in prefrontal lobe volume due to failure to gain white matter volume in those who will develop full-blown schizophrenia and no others.

Discussion: From the demonstration more than 30 years ago that brain structure in schizophrenia was different from that of normal people we have been able to explore the progress of the changes over time. We have been able to show that those who actually develop schizophrenia, in addition to showing that those who would go on to develop schizophrenia and to a lesser extent those who had transient and partial psychotic symptoms lost grey matter volume in a way that the controls and those who remained well did not (2005). Using a second cohort at enhanced risk for cognitive rather than genetic reasons the predictive value of temporal lobe grey matter loss was more confirmed (2009). Finally, having overcome the difficulties of combining scans from different machines and using approximately 500 scans taken over the 10 years of the study we were able to show that those who actually develop schizophrenia, in addition to losing temporal grey matter volume, will lose volume in the prefrontal lobes in a way that all other groups do not and that this finding is largely due to the fact that those who will become ill show no increase in prefrontal white matter volume while all other groups do show such increases over time.

Discussion: From the demonstration more than 30 years ago that brain structure in schizophrenia was different from that of normal people we have been able to explore the progress of the changes over time and with the technological advances that have occurred. Our tentative view of the sequence of development of change is (1) reduced thalamic size in those at genetic risk, (2) progressive reduction in grey matter volume in those with psychotic symptoms, (3) reduction in prefrontal lobe volume due to failure to gain white matter volume in those who will develop full-blown schizophrenia and no others.

Abstracts

THE TIME SEQUENCE OF STRUCTURAL BRAIN ABNORMALITIES IN SCHIZOPHRENIA

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Background: This presentation is an explanation of the nature, site and sequence of development over time of the brain structural changes in schizophrenia. Using a population of patients with established schizophrenia we demonstrated with CT in 1976 that the brain substance was less and ventricular volume greater than in controls. Examining samples who had and had not had various forms of treatment we were able in 1985 to demonstrate unequivocally that the findings were due to the illness that the patients suffered and not the treatment that they received. Following some of these subjects up to post-mortem in 1990 we were able to show that the imaging findings were paralleled by pathological change.

Methods: The early studies were done with CT and standard histological methods. From the late 1980s studies were done with MRI and examined with ROI, VBM, TBM and machine implementation of hand tracing. Standard and detailed psychological and clinical methods were used throughout.

Results: More recently we have studied a population of young people, initially well, at enhanced genetic risk of schizophrenia, in comparison with well controls. Baseline scans showed those at risk of schizophrenia to have smaller thalami (1999) and later follow up showed reduced thalamic size to be the best baseline imaging predictor of the later development of schizophrenia although compared to personality and behavioural measures it was not a strong predictor (2005). Serial imaging studies initially using ROI then VBM indicated that those who would go on to develop schizophrenia to a lesser extent those who had transient and partial psychotic symptoms lost grey matter volume in a way that the controls and those who remained well did not (2006). Using a second cohort at enhanced risk for cognitive rather than genetic reasons the predictive value of temporal lobe grey matter loss was more confirmed (2009). Finally, having overcome the difficulties of combining scans from different machines and using approximately 500 scans taken over the 10 years of the study we were able to show that those who actually develop schizophrenia, in addition to losing temporal grey matter volume, will lose volume in the prefrontal lobes in a way that all other groups do not and that this finding is largely due to the fact that those who will become ill show no increase in prefrontal white matter volume while all other groups do show such increases over time.

Discussion: From the demonstration more than 30 years ago that brain structure in schizophrenia was different from that of normal people we have been able to explore the progress of the changes over time and with the technological advances that have occurred. Our tentative view of the sequence of development of change is (1) reduced thalamic size in those at genetic risk, (2) progressive reduction in grey matter volume in those with psychotic symptoms, (3) reduction in prefrontal lobe volume due to failure to gain white matter volume in those who will develop full-blown schizophrenia and no others.

doi:10.1016/j.schres.2010.02.198

THE STAR CONSORTIUM: DO GENES OR ENVIRONMENT EXPLAIN THE ASSOCIATION BETWEEN SCHIZOPHRENIA AND A SMALLER BRAIN?

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Background: Structural brain abnormalities are consistently observed in schizophrenia, and appear associated with the familial risk for the disorder. Unaffected family members show comparable
decreases in brain volume, albeit to a lesser extent than probands. Whether these volume abnormalities are mediated by genetic or shared environmental factors remains unclear. The Schizophrenia Twins And Relatives (STAR) consortium aims to define the relative contributions of genetic and non-genetic factors to the association between structural brain abnormalities and schizophrenia in a uniquely powered cohort.

Methods: We obtained Magnetic Resonance Imaging (MR) brain scans from twin pairs in London (UK), Utrecht/Amsterdam (the Netherlands), Helsinki (Finland) and Jena (Germany). A total of 841 subjects is included. The sample consists of 208 monozygotic (MZ) and 138 dizygotic (DZ) twin pairs, 35 of their full siblings and 114 healthy control singletons. The pairs are either concordant (26 MZ and 1 DZ) or discordant for schizophrenia (57 MZ and 40 DZ), or healthy (125 MZ and 97 DZ). Intracranial volume and cerebral gray and white matter volumes were estimated from all images, while total brain, cortical gray matter of the frontal, temporal, parietal, and occipital lobes, cerebellar, third and lateral ventricular volumes were measured in all images, except for the Helsinki twins. We showed earlier in a calibration study that volumetric data from Utrecht, London, and Jena can be validly and reliably pooled. As the images from Helsinki were processed differently (using the UCLA processing pipeline) the data from the calibration study was used to calculate intra-class correlations (ICCs) between the volumes acquired using the two processing methods (Utrecht and Los Angeles). The ICCs showed that findings from both analyses methods were comparable. We used structural equation modeling to estimate the additive genetic and common and unique environmental contributions to brain volume variance. The analyses for cerebral gray and white matter were covaried for age, gender, intracranial volume and scan site (i.e., London, Utrecht, Helsinki, Jena).

Results: The heritabilities for all brain structures were significant, ranging from 0.45 (cerebral gray matter volume) to 0.77 (total brain volume). Preliminary analyses show significant negative correlations between schizophrenia and volumes of the whole brain, cerebral gray and white matter; and cortical gray matter in the frontal, parietal, and temporal lobes. Bivariate structural equation modeling using cross-trait/cross-twin correlations revealed a significant phenotypic correlation between schizophrenia and cerebral gray matter (-0.14; 95% confidence interval [CI], -0.16 to -0.06), with significant additive genetic (-0.09; 95% CI, -0.16 to -0.01) and unique environmental contributions (-0.05; 95% CI, -0.09 to -0.02).

Discussion: With the largest multi-site schizophrenia twin sample to date we have found highly suggestive evidence that cerebral gray matter volume represents a promising endophenotype for schizophrenia. Further analyses will explore the anatomical specificity of this association. The study was underpowered to detect a genetic association between schizophrenia and for example total brain volume, which shows a similar correlation pattern with schizophrenia as cerebral gray matter volume. The smaller cerebral gray matter volume found in patients with schizophrenia and their unaffected co-twins can at least partly be attributed to genetic factors related to the illness.

Background: Cerebral grey matter volume reductions are progressive in schizophrenia, with larger grey matter volume decreases associated with cannabis use. It is unknown whether this grey matter loss is globally distributed over the entire brain or more pronounced in specific cortical brain regions.

Methods: Fifty-one patients with recent-onset schizophrenia and 31 matched healthy subjects were included. For all subjects, magnetic resonance imaging scans were obtained at inclusion and at 5-year follow-up. Nineteen patients (ab-)used cannabis but no other illicit drugs; 32 patients and the healthy comparison subjects did not use any drugs during the 5-year follow-up. At follow-up, clinical outcome was measured. To evaluate the local differences in cortical thickness change over five years between the two groups regression analysis was carried out over the cortical surface.

Results: At inclusion cortical thickness did not differ between patients and controls and between cannabis-using and non-using patients. Over the follow-up period we found excessive thinning of the right supplementary motor cortex, inferior frontal cortex, superior temporal gyrus, angular gyrus, occipital and parietal lobe in patients relative to controls after controlling for cannabis use. Patients who used cannabis showed additional thinning in the left dorsolateral prefrontal cortex (DLPFC), left anterior cingulate cortex (ACC) and left occipital lobe as compared to those patients that did not use cannabis during the scan interval.

Discussion: First-episode cannabis-using schizophrenia patients show a more pronounced cortical thinning than non-using patients in areas known for their high density of CB1 receptors, such as the ACC and the DLPFC.

CANNABIS USE AND PROGRESSIVE CORTICAL THICKNESS LOSS IN AREAS RICH IN CB1 RECEPTORS DURING THE FIRST FIVE YEARS OF SCHIZOPHRENIA

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CHILDHOOD AND ADOLESCENCE PREDICTORS OF PSYCHOSIS IN THE GENERAL POPULATION -BASED NORTHERN FINLAND 1986 BIRTH COHORT

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Background: Prodromal phase usually precedes frank psychosis. Prospective general population based studies about which kind of specific symptoms predict psychosis are lacking. The aim was to identify, in general population of adolescents, whether a questionnaire psychopathology assessment could predict the onset of psychosis.

Methods: Members (N = 9,215) of the Northern Finland 1986 Birth Cohort, an unselected general population cohort (Järvelin et al. 1993), were invited to participate in field surveys. The 8-year field study included Rutter B2 questionnaire for teachers (Rutter 1967). The 16-year field study in 2001 included a 21-item PROD-screen questionnaire screening prodromal symptoms for last six months. (Heinimaa et al. 2003). The Finnish Hospital Discharge Register was used to find out new cases of hospital treated mental disorders during 2002-2005.

doi:10.1016/j.schres.2010.02.200

doi:10.1016/j.schres.2010.02.201
Results: There were 37 new cases of psychosis (0.45%) during 1998–2005. High scores in Rutter B2 total and antisocial and neurotic symptoms in 7-8 year-olds did not associate with later psychosis. Of the subjects 17 (0.3%) were treated due to first episode psychosis and 95 (1.5%) due to non-psychotic disorder during the follow-up period for prodromal features in 2002-5. Those who developed psychosis had more positive, negative and general symptoms than those who developed non-psychotic disorder and also those without mental disorder. Negative symptoms were reported by 53% of the later psychotic subjects, by 10% of those hospitalized for non-psychotic disorder and by 8% of the ‘healthy’, without psychiatric hospital treatment (Fisher’s exact test: psychosis vs. healthy p<0.0001, psychosis vs. non-psychosis p<0.001, and non-psychosis vs. healthy p=0.35).

Discussion: This study may one of the very few studies exploring prospectively symptoms predicting onset of psychosis in general population of adolescents. The findings emphasize the importance of negative symptoms in the development of psychosis.

Acknowledgements: The Academy of Finland, the National Institute of Mental Health, the Signe and Ane Gyllenberg Foundation and the Sigrid Juselius Foundation, Finland.


STRESS-INDUCED DOPAMINE RELEASE IN SUBJECTS AT CLINICAL HIGH RISK FOR PSYCHOSIS AND IN ANTIPSYCHOTIC NAIVE PATIENTS WITH PSYCHOSIS: A [11C]-(+)-PHNO PET STUDY

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Background: Dysregulation of the biological stress response is a potential etiological factor in dopamine (DA) related human disorders, including drug-induced psychosis and schizophrenia. However, the underlying neural event(s) leading to an exaggerated response to stressors are unknown. One proposed model suggests neurochemical sensitization of the mesolimbic DA system. According to this model, repeated exposure to sensitizing life stressors (or dopaminergic drugs) leads to progressive increases in stress related neurochemical activations, mainly hypothalamic-pituitary-adrenal hormones (HPA) and DA, which in turn may precipitate illness in vulnerable individuals and relapse in those diagnosed with schizophrenia. The aim of this work is to investigate whether stress induces more DA release in subjects at clinical high risk (CHR) i.e., putatively prodromal for psychosis, and in antipsychotic-naive patients with psychiatric disorders, as compared to matched healthy volunteers.

Methods: Twelve CHR, and six with psychotic disorder (SCZ) were recruited. Diagnosis was obtained with the Structured Interview for Prodromal Syndromes (SIPS), as per the Yale Criteria of Prodromal Syndromes (COPS), and with the Structured Clinical Interview for DSM disorders (SCID) respectively. In addition, we recruited ten matched healthy volunteers. All subjects underwent 2 PET scans at the same time of the day on two different days: one while undergoing the Montreal Imaging Stress Task (MIST) (Pruessner et al, 2004), and one while undergoing a Sensory-Motor Control Task (SMCT). The simplified reference tissue model (SRTM) was used to obtain BPND in each striatal subdivision based on its functional connections to the limbic, frontal executive and motor brain regions: limbic striatum (LST, ventral striatum), associative striatum (AST; dorsal caudate and precommissural dorsal putamen) and sensorimotor striatum (SMST, postcommissural putamen). Stress-induced DA release (indexed as a reduction in [11C]-(+)-PHNO BP ND) between CHR, SCZ and HV was tested with ANOVA. Perceived stress (psychological with scales and physiological with salivary cortisol) was used to test the effectiveness of the stress paradigm.

Results: Stress-induced DA release was increased in both CHR and SCZ compared to HV (F=6.84 p=0.01). There was no difference between CHR and SCZ (F=7.45 p=0.009), but both were significantly more than HV (F=7.46 p=0.009) and less relaxed.
The Role of Glucocorticoids in the Emergence of Psychosis: Potential Genetic and Epigenetic Mechanisms

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Background: Advances in the field of molecular genetics have broadened our understanding of the mechanisms involved in epigenetic processes. Hormones, including glucocorticoids, play a significant role in the signaling cascades that alter the expression of genes governing neuronal function. In particular, the HPA axis involves a neurohormonal signaling path via glucocorticoid receptors in the brain that is influenced by both environmental factors and intrinsic developmental programs. Research on patients with schizophrenia and other psychotic disorders indicates HPA hyperactivity that may be related to symptom severity. To date, glucocorticoid secretion during the prodrome, prior to clinical onset, has not been examined. We present data on the relation of glucocorticoid secretion with progression to psychosis in prodromal youth, and genetic factors that might contribute to this progression.

Methods: Longitudinal data on cortisol secretion were obtained on 130 adolescents who were followed for 4 years. Of these, 56 met criteria for the prodrome to psychosis as measured by the Structured Interview for Prodromal Syndromes (SIPS). 36 were help-seeking but not prodromal, and 38 were healthy controls. Genotyping was conducted for several candidate genes that have been linked with the expression of psychosis, including COMT and BDNF. Diagnostic status was measured over the course of 4 years with the Structured Clinical Interview for DSM (SCID).

Results: There was a significant longitudinal increase in cortisol secretion through the course of adolescence, and it is more pronounced among individuals who meet criteria for the prodrome. Further, when comparing the 14 prodromal youth who converted to Axis I psychotic disorder with those who did not, the longitudinal increase is greater for those who converted within 4 years of baseline. Data on the role of candidate genes in modulating developmental changes in HPA activity are also presented.

Discussion: Neurodevelopmental changes in the HPA axis that increase glucocorticoid secretion during adolescence appear to be linked with conversion to psychosis. Potential neural mechanisms mediating the relation between HPA activity and prodromal progression will be discussed. In particular, plausible genetic and epigenetic factors in the neuropathological cascade, as well as implications for future research on preventive intervention, will be considered.

doi:10.1016/j.schres.2010.02.205
that using transition to psychosis as the primary outcome measure in UHR research may be misleading and may result in the failure to target a number of individuals who never transition to psychosis but may nevertheless benefit greatly from intervention.

doi:10.1016/j.schres.2010.02.206

STATIC AND DYNAMIC COGNITIVE DEFICITS IN CHILDHOOD PRECEDE ADULT SCHIZOPHRENIA: A 30-YEAR STUDY

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Background: Premorbid cognitive deficits in schizophrenia are well documented, and have been interpreted as supporting a neurodevelopmental etiological model. We investigated 3 unresolved questions about premorbid cognitive deficits: (a) What is their developmental course? (b) Do all premorbid cognitive deficits follow the same course? (c) Are premorbid cognitive deficits specific to schizophrenia or shared by other psychiatric disorders?

Methods: Participants were members of a representative 1972–1973 birth cohort of 1,037 males and females in Dunedin, New Zealand, who were followed up to age 32 with 96% retention. We compared the cognitive development of three groups of children: those who developed schizophrenia, recurrent depression, and healthy controls.

Results: Children who developed adult schizophrenia exhibited developmental deficits (i.e., static cognitive impairments that emerge early and remain stable) on tests indexing verbal and visual knowledge acquisition, reasoning and conceptualization. In older, they lag further and further behind their peers in working memory, attention and processing speed. These two premorbid cognitive patterns were not observed in children who later developed recurrent depression.

Discussion: These findings suggest that the origins of schizophrenia include two interrelated developmental processes evident from childhood to early adolescence. Future schizophrenia cases enter primary school struggling with verbal reasoning and, as they get older, they lag further and further behind their peers in working memory, attention and processing speed.

doi:10.1016/j.schres.2010.02.207

WORKING MEMORY NOT PROCESSING SPEED IS THE BASIS OF HIGHER-ORDER PLANNING DEFICITS IN FIRST EPISODE SCHIZOPHRENIA

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Background: Patients with schizophrenia have deficits in many cognitive domains which impact on social and occupational function. Working memory and processing speed are particularly affected and it is possible that impairments of these basic cognitive processes are fundamental to the deficits in higher order cognitive functions employed in every day life. Accordingly we tested the degree to which planning ability was affected by working memory and processing speed.

Methods: Eighty-eight first-episode schizophrenia patients and controls, matched for age, sex and premorbid IQ, performed a computerised version of the Tower of London task (CANTAB SOC). Subjects: a) planned and executed a series of moves so that a test arrangement of balls matched a goal arrangement on 12 problems which varied in difficulty; b) performed a yoked psychomotor task in which they simply followed the computer in performing the exact same moves they had previously used when solving the planning problems; c) performed other tests of processing speed (digit symbol), working memory, visual memory and IQ.

Results: Patients spent less time planning their moves than controls across all trials. When they solved problems perfectly, i.e. in the minimum number of moves possible, patients spent more time than controls executing each move suggesting that they were actively compensating for their shorter planning times. Patients were not impulsive; like controls, they modulated their planning times according to how difficult they found particular problems. Instead, reduced planning and increased execution times on perfect solutions were entirely related to working memory and general cognitive capacity (IQ); these relationships were absent in controls. Processing speed on the planning task was generally slower in patients but neither this nor digit-symbol processing speed or visual memory contributed to the planning impairment.

Discussion: Healthy volunteers planned their moves before they made their first response and then quickly executed the solution. Patients, on the other hand, seemed to lack the ability to plan all the necessary moves at the same time and instead adopted a strategy of planning moves while they executed the problem. As patients solved less problems than controls overall, this strategy was ultimately disadvantageous. Performance on the control tasks suggested that this was not due to perceptual or motor slowing. Rather, the planning impairment seemed to be particularly due to deficient working memory manipulation. These results suggest that the cognitive difficulties experienced by patients in everyday situations which commonly require planning reflect the well known working memory impairment seen in this disorder. Remedial strategies should target working memory with the aim of improving social and occupational function via its impact on higher order cognitive functions such as planning.

doi:10.1016/j.schres.2010.02.208

THE RELATIONSHIP BETWEEN NEUROPSYCHOLOGICAL FUNCTIONING AND SYMPTOM DIMENSIONS IN FIRST-EPISTODE PSYCHOSIS

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Background: There is increasing focus on dimensional approaches to classification of psychotic disorders as a useful adjunct or alternative to categorical classification. Studies exploring the relationship of symptom dimensions to performance on neuropsy-
chological tasks have underlined their potential role in mapping distinct brain alterations and pathophysiological processes. To date, most relevant neuropsychological studies have focused on non-affective psychosis, and primarily on schizophrenia in relation to two symptom dimensions positive and negative. Therefore exploring cognitive deficits in relation to a broader range of psychopathological dimensions and in a wider spectrum of psychoses is particularly worth undertaking.

**Methods:** Data was collected as part of the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study, and included a cohort of 166 first episode psychotic patients. Symptoms were assessed using the Schedule and Clinical Assessment in Neuropsychiatry (SCAN). Based on a recent factor analytic study by the AESOP group (Demjaha et al., In Press), patients were rated on five symptoms dimensions: Mania, Reality Distortion, Negative Symptoms, Depressive Symptoms and Disorganization. Participants were also administered a neuropsychological battery designed to assess the following cognitive domains: Verbal Memory, Visual Memory, Attention-Concentration and Processing Speed, Executive Functions and Working Memory, and Language. Premorbid (NART) and current IQs (WAIS-R) were also assessed.

**Results:** More severe negative symptoms were associated with poorer memory, attention and IQ. This was exemplified by significant negative linear associations between the negative symptoms dimension score and full-scale IQ ($r = - .23$, $p = .005$), Verbal Memory ($r = -.22$, $p = .005$) and Attention-Concentration-Processing Speed ($r = -.23$, $p = .004$) scores. The relationship between mania symptoms and neuropsychological performance was positive, i.e., more severe mania symptoms associated with better neuropsychological performance.

Yet, this relationship was predominantly non-linear ($p < .01$): high mania symptoms were associated with better performance on Attention-Concentration and Processing Speed and on Executive Functions and Working Memory.

**Discussion:** Symptom dimensions are differentially associated with neuropsychological functions. Some of these relationships are non-linear. This suggests that different brain mechanisms may underlie the dimensions of negative and manic symptoms.

**Background:** Early detection and prospective evaluation of clinical high-risk (CHR) individuals who may develop schizophrenia or other psychotic disorders is critical for predicting psychosis onset, assessing disability and for testing preventive interventions. The goal of this study was to elucidate the neuropsychology of the CHR syndrome, to determine the association of neuropsychological function with conversion to psychosis and family history (FH) of psychosis, and to examine whether baseline neuropsychological functioning predicts subsequent psychosis.

**Methods:** Longitudinal study with 2 1/2 years follow-up of 304 prospectively identified CHR individuals meeting Structured Interview for Prodromal Syndromes (SIPS) criteria, 52 non-CHR persons with a FH of psychosis in first- or second-degree relatives (‘Family HR’/FHR), and 193 normal controls with neither a FH of psychosis nor a CHR syndrome, all of whom had baseline neuropsychological evaluations, recruited across eight centers as part of the North American Prodrome Longitudinal Study (NAPLS). The main measures used were a neurocognitive composite score, eight individual neuropsychological measures, an IQ estimate, and HR status.

**Results:** Global (‘composite’) neuropsychological functioning was comparably impaired in CHR and FHR groups compared to controls, but profiles differed significantly between groups. Neuropsychological functioning in the CHR group was significantly lower in persons who progressed to psychosis than in those who did not, and worst in the subgroup with a FH of psychosis. Tests of processing speed and verbal learning and memory were most sensitive in discriminating CHR from controls, although reductions were less severe than in established schizophrenia. Neuropsychological functioning did not contribute uniquely to the prediction of psychosis beyond clinical criteria, but worse verbal memory predicted more rapid conversion.

**Discussion:** These findings document that CHR individuals have significant neuropsychological difficulties, particularly those who later develop psychosis. This dysfunction is generally of moderate severity but less than in first episode schizophrenia, suggesting that a further decline may occur after baseline CHR assessment.
with alarms, signs, and checklists established in the home environment to bypass cognitive deficits in patients who have difficulty following a medication regimen.

Methods: In study I, 95 outpatients with schizophrenia were randomly assigned to 1) Full-CAT (CAT focused on many aspects of community adaptation), 2) Pharm-CAT (CAT focused only on medication and appointment adherence) or 3) treatment as usual (TAU). Treatment lasted for 9 months, and patients were followed for 6 months after the withdrawal of home visits. In study II, a translation study, CAT treatment was delivered by case managers in a community mental health center to 124 consumers for a 9 month period. In study III, in a sample of 92, we compared TAU, to PharmCAT, to a group using smart pill containers that download adherence data to a secure website that can be checked by case management staff.

Results: Study I: Results of mixed effects regression models indicated that both CAT and PharmCAT treatments were superior to TAU for improving adherence to prescribed medication. These differences remained significant when home visits were withdrawn. Survival time to relapse or significant exacerbation was significantly longer in both CAT and PharmCAT in comparison to TAU Study II: Adherence improved significantly in the treatment group compared to a group of control individuals in the same clinic. Issues in the implementation of CAT by community agencies were identified and addressed. Assessments were simplified and visit frequency adjusted to fit state mandated guidelines that would allow reimbursement. Adequate reimbursement for time spent in supervision and preparation for visits was also problematic. Study III: Individuals in both the PharmCAT group and the group who received smart pill containers improved with respect to medication adherence in comparison to treatment as usual after only 3 months.

Discussion: Interventions using technology may be easier to use in over-burdened delivery systems. Novel treatments to improve adherence delivered in standard community settings may provide a foundation for the individual to more successfully pursue broader goals in their own process of recovery.

doi:10.1016/j.schres.2010.02.212

EFFECTS OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON PROBABILISTIC FEEDBACK LEARNING IN PEOPLE WITH SCHIZOPHRENIA

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Background: Probabilistic feedback learning relies on fronto-striatal activation in healthy adults and generally elicits a deficit associated with prefrontal cortex dysfunction in people with schizophrenia (Poldrack et al. 1999 Neuropsychologia 13, 564-74; Weickert et al. 2009 Journal of Neuroscience 29, 1244-54). Anodal transcranial Direct Current Stimulation (tDCS) of the left dorsolateral prefrontal cortex was shown to improve probabilistic feedback learning in healthy adults (Kincses et al. 2003 Neuropsychologia 42, 113-7). The aim of the current study was to evaluate the ability of weak anodal tDCS of the left dorsolateral prefrontal cortex to reverse probabilistic feedback learning deficits in people with schizophrenia.

Methods: Following a baseline session without stimulation 19 people with schizophrenia entered the single-blind, randomized, counter-balanced, cross-over, with-in subjects study in which sham stimulation or anodal tDCS at an intensity of 2.0 mA was administered continuously for 20 minutes to the left dorsolateral prefrontal cortex during probabilistic feedback learning. People with schizophrenia were classified as good or poor learners on the basis of their ability to show sustained improvement over time during the baseline assessment.

Results: Of the 19 participants, 11 people with schizophrenia were classified as good learners and 8 people with schizophrenia were classified as poor learners at baseline. An ANOVA of those people with schizophrenia classified as good learners at baseline revealed a significant condition (active versus sham) X trial interaction, F(49, 2980) = 1.37, p = .002. Post hoc LSD test revealed significant improvement in performance in active tDCS relative to sham conditions within the first 12 trials in those people with schizophrenia classified as good learners at baseline (all p’s <.02). There was no significant condition X trial interaction in those people with schizophrenia classified as poor learners at baseline. F(49, 2086) = 1.16, p = .10.

Discussion: These results suggest that acute tDCS may have an immediate beneficial effect to improve cognitive function in some people with schizophrenia. Further studies are needed to test the effects of repeated tDCS treatment to sustain the potential therapeutic benefit.

doi:10.1016/j.schres.2010.02.213

A BOTTOM-UP BIOFEEDBACK REMEDIATION IMPROVES EMOTION RECOGNITION IN SCHIZOPHRENIA: EVIDENCE FROM A VISUAL SCAN PATH PILOT STUDY

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Background: Cognitive deficits in schizophrenia are now widely accepted as both a core feature of schizophrenia and an area lacking effective treatment regimes. Their resistance to the effects of antipsychotic medications, association with functioning and apparent separateness from positive symptoms demonstrates the need for efficacious treatments targeting cognition. To date, remediation strategies have adopted a largely top-down remediation approach. This is despite extensive evidence for bottom-up sensory training resulting in downstream, higher order improvements. However, this has largely been ignored in the schizophrenia remediation literature. The rationale for the present study was that in order for the brain to assign meaning to face emotion stimuli it must first generate reliable neurological responses relating to the location and sampling of sensory information. Utilizing a novel remediation strategy derived from the neurosciences, we predicted that visual scanpath performance would be altered (with patients recording a less restricted viewing strategy and increased fixations) with a downstream improvement in emotion recognition.

Methods: Twenty five participants with schizophrenia were randomly allocated to a emotion recognition treatment program (METT/SETT) or a biofeedback based treatment. Participants completed training weekly for 6 weeks. At baseline, post treatment
LEARNING TO SELF-REGULATE INSULA CORTEX MODULATES EMOTION RECOGNITION AND NEURAL CONNECTIVITY IN SCHIZOPHRENIA

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Background: Brain computer interfaces (BCI) are novel techniques that allow subjects to achieve self-regulation of brain activity. BCI based on functional magnetic resonance imaging (fMRI-BCI) has recently become feasible, and studies have demonstrated that self-regulation of circumscribed brain areas can be achieved by healthy subjects, leading to specific behavioural modifications. So far, and despite its potential therapeutic applications, no studies have attempted to apply fMRI-BCI in schizophrenia. Objective: We attempted for the first time to apply fMRI-BCI on schizophrenic patients. The first aim of this study was then to evaluate if schizophrenic subjects can achieve volitional regulation of anterior insula cortex activity by fMRI-BCI training, and to explore the relationship between the capability to self-regulate and other aspects of the symptomatology. Insula cortex was chosen as the region of interest based on the increasing evidence for the hypothesis that insula dysfunction might be critically involved in different aspects of the psychopathology. Secondly, we explored whether self-regulation is associated with a behavioural modification over face emotion recognition. Finally, we explored whether learned self-regulation can modulate the functional connectivities of the emotional brain network.

Methods: Nine schizophrenic patients - mean age (DS): 26.3 years (4.5)- from the community and rehabilitation settings were recruited. They were moderately symptomatic, and under antipsychotic medication. The training consisted in twelve sessions of fMRI-BCI, in which patients were trained to self-regulate insula by online visual feedback of bilateral anterior insula activity, on a Siemens 3.0T body scanner. A face emotion recognition task for disgust and happy faces was conducted after the training, and during insula self-regulation and non-regulation blocks, to explore the effect of self-regulation on behaviour. Changes in the functional connectivity were measured by Granger Causality Modelling.

Results: After few sessions of training, patients were able to learn to self-regulate the BOLD response in the insula cortex. The capability to self-regulate was negatively correlated with the severity of negative symptoms and the duration of the illness. During the learned self-regulation, patients detected significantly more disgust faces than during non-regulation, in line with the extensive evidence of the role of insula cortex in disgust recognition. However, patients detected less happy faces during self-regulation, an outcome that was not expected according to our original hypothesis. Volitional control of insula was also associated with a modulation of the perception of emotion intensity. Volitional self-regulation led to a significant enhancement of the functional connectivities arising from insula cortex on both hemispheres, and of the emotional network in general.

Discussion: Our results show that with enough training, schizophrenic subjects are able to learn volitional regulation of the insula cortex by fMRI-BCI. Learned self-regulation led to changes in the perception of emotional faces, one the hallmarks of schizophrenic dysfunction, showing that behavioural modulation by this new technique in schizophrenia is possible. The enhancement of the connectivities in brain emotional network, suggests that fMRI-BCI can be used to “re-connect” the schizophrenic abnormal neural connectivities. This finding, and current new developments of BCI methodology, opens the door for further studies of fMRI-BCI in psychiatric population, and for possible therapeutic applications.

doi:10.1016/j.schres.2010.02.215

THE FIVE YEAR COURSE OF OBSESSIVE-COMPULSIVE SYMPTOMS IN FIRST EPISODE SCHIZOPHRENIA

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Background: The five year course of obsessive-compulsive symptoms (OCS) and obsessive-compulsive disorder (OCD) and its relationship with other characteristics in patients with first episode schizophrenia, schizoaffective disorder or delusional disorder is insufficiently known.

Methods: Consecutively hospitalised patients with a diagnosis of a first episode of schizophrenia, schizoaffective disorder, obsessive-compulsive disorder or delusional disorder were screened for obsessive – compulsive symptoms and if present measured with Yale Brown Obsessive Compulsive Scale (Y-BOCS) at admission, six weeks after admission, three and five years after admission. Positive and Negative Syndrome Scale (PANSS) and Montgomery Åsberg Depression Rating Scale (MADRS) were used to assess other symptoms at first three assessments. Course of three and five year symptoms, psychotic relapse, substance use, and social functioning was assessed with the Life Chart Schedule (LCS).

Results: 186 patients were included. Three years after admission of 177 patients OCS status could be assessed. Five years after admission of 172 patients OCD could be assessed. 91 patients 48.9% had no OCS symptoms on any of the assessments. 14.5% had only initial OCS, 13.4% had enduring OCS, 8.0% had no OCS at first assessment but developed OCS subsequently, and 15.1% had intermittent OCS. Percentage patients diagnosed with current co-morbid OCD at 4 assessments varied between 7.3% and 11.8%. OCD was associated with less severe negative symptoms, and OCD was associated with more severe depressive symptoms and poorer premorbid functioning. OCS was negatively associated with smoking status. OCS/OCD during admission did not predict time to psychotic relapse, nor remission, nor social functioning.

Discussion: The five year course of OCS/OCD in patients with first episode schizophrenia or related disorders is variable. About one
out of ten patients has enduring OCS symptoms and is diagnosed with co-morbid OCD. OCS/OCD co-morbidity was not associated with a more severe course of psychotic symptoms and relapse, although premorbid functioning and social outcome of patients with OCD and enduring OCS symptoms is worse.

Discussion: The rate of recovery (15.7 %) and working or studying (29.8%) contradicts the presumption that psychosis or schizophrenia is a chronic or progressive deteriorating illness. The predictors are consistent with earlier findings, which suggest that a stable social life with a normal level of social functioning (a partner, friends, kids) have a predictive value on good outcome. These measures might be a pseudo measurement of negative symptoms and thus not having a protective value in their own. But in the multivariate analysis with negative symptoms included they still stand out.

doi:10.1016/j.schres.2010.02.216

LONG TERM FOLLOW UP OF AN ULTRA HIGH RISK ("PRODROMAL") GROUP

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Background: Criteria have now been developed that identify individuals at "ultra high risk" (UHR) or clinical high risk (CHR) of psychotic disorder. That is they are thought to be in the prodromal stage. These individuals have been found to have a rate of "transition" to psychotic disorder of about 35% over 1 year, with risk decreasing over the next 2.5 years. The longest follow up to date of a UHR cohort has been 3.5 years. In this study we sought to determine the longer term (5-15 year) outcome of a UHR sample.

Methods: An extensive tracking procedure was followed to trace individuals who had previously participated in research studies at the PACE UHR Clinic in Melbourne Australia (n=416). At the time of the original research studies (conducted between 1994 and 2006) participants had given consent for long term follow up. The CAARMS (Comprehensive Assessment of At Risk Mental States) was used to determine whether transition to a previously defined psychosis threshold had occurred, and if so the date of onset.

Results: 311/416 individuals (74.8%) were directly assessed by interview. Taking into account all sources (interview, clinical database, past research), data on transition status was available for 411 subjects (98.8%). Rates of transition to psychotic disorder were: within the first year after entry: 17.1%, within 2 years after entry: 20.9%, within 3 years after entry: 25%, within 5 years or more after entry: 29.3%. Rates of transition tailed off after 5 years. The overall transition rate was lower than expected. Thus we then assessed whether year of recruitment affected transition rate, as we have previously found that transition rates are decreasing over time. It was found that the participants recruited earlier, between 1994 and 2000, had a significantly higher transition rate than later cohorts, recruited between 2001 and 2006.

Discussion: This long term follow up study suggests that UHR individuals continue to be at risk of psychosis even 5 years and more after initial presentation. However the risk is greatest in the early years after recruitment. The transition rate appeared to have decreased over the past 15 years. This may be partly because later cohorts have not yet moved through the period of greatest risk, especially given the reduced period of time between symptom onset and entry into PACE. For example, previously we had found that subjects recruited before 1998 had a significantly higher transition rate compared to those recruited between 1998 and 2000. However this longer term follow up found that the transition rate in the 1998-2000 cohort caught up to the earlier cohort, suggesting a lead time effect. It is also possible that changes in recruitment and clinical practice over time may have decreased the rate of transition to psychotic disorder.

doi:10.1016/j.schres.2010.02.218
Background: An increasing amount of evidence has grown in detecting early markers as predictor of antipsychotics response. Early markers may be used in usual clinical practice in order to identify those patients who require an early switch to a more effective treatment. Although previous studies have reported models based in non-response rates during the first weeks of treatment, the optimal thresholds and the time point at which early response should be assessed varied considerably. Additionally, most of the samples studied comprised chronic and previously treated patients. We aimed to identify the optimal thresholds of response to antipsychotics in the first four weeks of treatment that best predicts subsequent non-response at six week point in never treated first episode psychosis patients.

Methods: Data were obtained from 174 consecutive patients with a first episode of schizophrenia-spectrum disorders admitted to treatment in a multicompontent treatment program in which antipsychotic treatment was randomly assigned to haloperidol, olanzapine or risperidone followed-up weekly during the first four week of treatment and an end point at six week. The non-response criterion was a less than 40% BPRS reduction from baseline. We used 10%, 20% and 30% thresholds in BPRS and in the psychotic, disorganized and negative dimensions of the SANS-SAPS in the first four weeks of follow-up and diagnosis, age of onset, duration of untreated psychosis (DUP) as possible predictors of non-response. Those variables that were initially associated with the response (assessed with a chi square o a student's T analysis) were introduced in a logistic regression analysis (backward: wald method). Receiver-Operator Curves (ROC) were used to predict non-response by the early response in BPRS in the four first weeks in order to establish the best point to assess the early response and the threshold with a best accuracy.

Results: The model obtained in the logistic regression was statistically significant (R2=0.479; Chi Square: 6.8,252; p < 0.001) and classified correctly 80% of the patients. The variables included in the model were the thresholds of 30% in BPRS at week 3 and 4 and the disorganized dimension at week 3 and DUP. ROC curves showed significant Areas Under the Curve (AUC) for the response in BPRS in weeks 1 (AUC=0.655; p = 0.001), 2 (0.740; p < 0.001), 3 (0.802) and 4 (0.840), but only at week 3 it was possible to establish a threshold with adequate sensibility and specificity (Threshold of 31.91% of BPRS at week 3, Sensibility: 0.78, Specificity: 0.76, Youden’s Index:0.54)

Discussion: Our data suggest that early response can be used as an accurate predictor of subsequent response-non response. However, response at first two weeks seem to have low specificity, being the third week the optimal point for assessing the early response and the improvement of 31.91% in BPRS the most accurate threshold.

doi:10.1016/j.schres.2010.02.219
SOCIAL DISADVANTAGE: CAUSE OR CONSEQUENCE OF IMPENDING PSYCHOSIS?

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Background: Those with long-standing psychotic mental disorders experience very high rates of unemployment, more often live alone, and fail to establish long-term relationships. However, there remains a lack of data on the social circumstances of patients before they became ill. Using data from a case-control study of first-episode psychosis, we set out to compare the prevalence of specific indicators of current and long term social disadvantage and isolation (unemployment, living alone, being single and low education achievement) in patients suffering their first episode of psychosis and in a healthy control sample.

Methods: We collected data relating to current and past social circumstances using the MRC Socio-demographic Schedule from a sample of 209 individuals with their first episode of psychosis and 167 healthy volunteers from the local population. We dichotomized the above variables to indicate the presence or absence of an indicator, with a score of 1 for present (e.g. unemployed) and 0 for absent. This produced a potential range on the current index and on the long-term index of 0 to 4. Where possible, we distinguished between current and long-term (> 1 year and > 5 years) circumstances.

Results: 74.64% (N = 156) of patients compared to 24.55% (N = 41) controls reported two or more markers of social disadvantage/ isolation (cumscore ≥ 2), p < 0.001. Applying logistic regression, we calculated the OR for a cumscore ≥ 2 (OR = 9.04; 95% CI 5.25-15.57). We repeated these analyses for long standing social disadvantage (one year and five years previously) and found that cases were 5.47 (CI 3.29-9.10) times more likely than controls to report social disadvantage one year previously and 3.39 (CI 2.05-5.61) times more likely to have experienced social disadvantage than controls 5 years previously.

Discussion: All the indicators of social disadvantage and isolation that we considered were more prevalent in cases than controls at the time of presentation to psychiatric services. The association was still significant but less strong for one and five years previously indicating that the disadvantage and isolation was not simply a consequence of the patients having been in the prodrome of their illness.

doi:10.1016/j.schres.2010.02.221

INDIVIDUALS, SCHOOLS AND NEIGHBOURHOODS: A MULTILEVEL LONGITUDINAL STUDY OF VARIATION IN INCIDENCE OF PSYCHOTIC DISORDERS

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Background: The incidence of schizophrenia and other non-affective psychoses is greater in urban compared to rural areas, but the reason for this is unclear. Few studies have been able to examine whether both individual and neighbourhood characteristics can explain this association. Furthermore, the effect of individual characteristics may depend upon neighbourhood context, whereby, for example, the risk of schizophrenia associated with being of a minority ethnic status varies depending upon the proportion of people within that neighbourhood who are also of a similar minority ethnic status. We report results from a study that aims to examine: i) whether individual, school or area level characteristics are associated with psychosis, and whether these can explain the association between schizophrenia and urbanity; and ii) whether effects of individual characteristics on risk of psychosis vary according to school context (that reflects both peer group and neighbourhood effects).

Methods: This is a population-based, multilevel, longitudinal study of all individuals born in Sweden in 1972 & 1977. Diagnoses were identified through linkage with The Swedish National Patient Register until 31st December 2003. There were 203,829 individuals, with data at individual, school, municipality, and county levels. We examined any non-affective psychosis, including schizophrenia as our primary outcome (N = 881; 0.43% cumulative incidence). However, for the study of interactions, we examined any psychosis (including affective as well as non-affective psychoses) as our outcome (N = 1,944; 0.95%) to maximise statistical power.

Results: Almost all the variance in risk of non-affective psychosis was explained by individual-level rather than higher-level variation. An association between urbanicity and risk of non-affective psychosis

doi:10.1016/j.schres.2010.02.222

STRATEGIES FOR THE STUDY OF GENE-ENVIRONMENT INTERACTIONS IN SCHIZOPHRENIA

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Background: Gene-environment interactions are believed to be major contributors to the etiology of schizophrenia. The direct empirical evidence of specific GxE interactions, however, is sparse. Most studies have been based upon broad measures of familial risk for schizophrenia and broad “exposures” as, e.g., place of birth. A few studies have included a few candidate genetic markers, that alone will account only for a limited amount of familial risk. If GxE interactions are important the incomplete measurement of genetic and environmental risk factors in theory should mean that most genetic and epidemiological studies are producing biased results that are difficult to interpret.

Methods: We compare studies of fetal exposures to Herpes Simplex type 2, where we use detailed family history, candidate snp’s, and GWAS-data as alternative means of studying GxE interactions.

Results: Family history data are relevant as confounders. Much of the confounding, however is related to parental mental illnesses that generally are not considered to be part of the schizophrenia spectrum. The power of family histories as an indicator of genetic liability in the study of GxE interactions is limited, compared to candidate markers and GWAS data.

Discussion: Accurate measurement of environmental exposures as well as genetic markers is essential to the study of GxE interactions.

doi:10.1016/j.schres.2010.02.222

Abstracts

IMPENDING PSYCHOSIS?

SOCIAL DISADVANTAGE: CAUSE OR CONSEQUENCE OF
was explained by higher-level characteristics, primarily school-level social fragmentation. We observed cross-level interactions between individual- and school-level markers of ethnicity, social fragmentation, and deprivation on risk of developing any psychotic disorder, all with qualitative patterns of interaction; in other words, the effects of ethnicity, social fragmentation, and deprivation were all reversed in contrasting neighbourhood contexts.

**Discussion:** The association between urbanicity and psychosis appears to be a reflection of the increased social fragmentation present within cities. The qualitative interactions indicate that any characteristic that defines an individual as being different from most other people in that local environment may increase the risk of psychosis. These findings have important implications both for understanding aetiology of psychotic disorders, and for informing social policy.

doi:10.1016/j.schres.2010.02.223

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**ON THE PATHWAY FROM STRESS TO PSYCHOSIS**

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**Background:** Evidence will be presented for an “affective pathway to psychosis”. Sensitivity to stress in daily life is hypothesized to be a vulnerability marker underlying the positive symptom dimension of psychotic disorder. Three main questions will be addressed: (i) is sensitivity to stress a marker of genetic risk?, (ii) how is this stress-sensitivity linked to the psychosis symptom dimensions, and (iii) does stress-sensitivity cluster within families?

**Methods:** Daily life stress-sensitivity (measured with Experience Sampling Method – a structured diary technique) and (sub-)clinical psychotic symptoms (measured with the Community Assessment of Psychotic Expressions and Positive And Negative Syndrome Scale) were assessed in (i) a general population twin sample (N = 535), (ii) a sample of patients with non-affective psychosis (N = 67), and (iii) a patient-sibling sample (N = 47). A series of multilevel linear regression analyses were performed investigating the association between stress-sensitivity and (sub-)clinical psychotic symptoms. Cross-trait, across-twin and – sibling analyses allowed for testing of the association in an non confounded and uncontaminated way.

**Results:** Cross-trait cross-twin analyses showed that stress-reactivity in twin 1 was significantly moderated by subclinical experiences in the co-twin (B = 0.09, 95%CI 0.02; 0.14, P = 0.03). Higher levels of stress-reactivity were associated with higher levels of positive symptoms (B = 0.09, 95%CI 0.05; 0.12, P = 0.00) and lower levels of negative symptoms (B = 0.03, 95%CI -0.05; 0.01 P = 0.00) in patients with non-affective psychosis. Third, stress-sensitivity clusters within families of patients with high scores on positive symptoms (B = 0.05, 95%CI 0.02; 0.09, P = 0.00).

**Discussion:** From these results we can conclude that (i) stress-sensitivity is a non confounded indicator of genetic risk for psychosis, (ii) is especially linked to the positive symptoms of psychosis (i.e. delusions, hallucinations, formal thought disorder), and (iii) there is a possible genetic contribution to stress-sensitivity specifically underlying the positive symptom dimension. The results will be discussed within a theoretical framework of an “affective pathway to psychosis”. Novel clinical strategies will be discussed aimed at the “on-line” monitoring of the influence of daily life stress on symptoms/ outcome and giving feedback to patients on an individual level.

doi:10.1016/j.schres.2010.02.224

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**DETERMINING THE LONG-TERM RISK OF SUICIDE AND PREMATURE DEATH FOLLOWING A FIRST EPISODE OF PSYCHOSIS: AN INCIDENCE COHORT APPROACH**

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**Background:** Following an influential meta-analysis in the 1970s (Miles 1977), the lifetime risk of suicide in schizophrenia has been estimated at 10% and this figure is still routinely quoted in the literature. The increased risk of premature death following first episode psychosis is also well recognised, but both risks may have been misjudged by studying unrepresentative cohorts. These have often been based on prevalence rather than incidence cohorts, made an arbitrary distinction between schizophrenia and other psychoses and been biased towards more severely ill, hospitalised patients (Palmer et al 2005). A long-term follow-up study of three unique incidence cohorts will be presented to illustrate the risk of suicide and premature death compared to that expected for a general population.

**Methods:** Three compatible cohorts of all first episode psychosis patients from three geographical catchment areas in London (1965-2004; n = 2056), Nottingham (1997–1999; n = 203) and Dumfries and Galloway (1979-1998; n = 464) were studied. Case tracing with the Office for National Statistics (England and Wales) and General Register Office (Scotland) was used to identify those patients who had died up to 31st March 2007 and their causes of death. Survival analyses involving lexis expansion and Poisson regression was used to establish person-year rates of suicide. Indirect standardisation was used to calculate Standardised Mortality Ratios (SMRs) for suicide and other causes of death, standardised for age and gender.

**Results:** Of the 2723 patients in the merged cohort traced after a mean of 11.5 years, 444 had died, 53 by suicide. This meant case fatality from suicide was considerably lower than expected from previous studies: 13% (53/2723), although proportionate mortality was 11.9% (53/444). Although the rate of suicide was highest in the first year after presentation, risk persisted late into the follow-up period, with median time to suicide being 5.6 years; 12 suicides occurred a decade or more after first presentation: a time when there may be less intensity clinical monitoring of risk. Suicide occurred approximately 12 times more than expected in the general population of England and Wales (SMR 11.65; 95% CI 8.73-15.24), and 49 of the 53 suicides were excess deaths. There was a significantly elevated all cause mortality SMR of 1.84 (95% CI 1.67-2.02) with apparent widening of the differential mortality gap over calendar time. Of the 444 deaths, 203 were excess deaths. Of the natural causes of death, diseases of the respiratory system and certain infectious diseases had the highest SMR (2.32; 95% CI 1.83-2.91).

**Discussion:** The highest risk of suicide following a psychotic episode occurs soon after presentation, yet clinicians should still be vigilant in assessing risk of suicide later in the course of illness. Teaching that “10% die from suicide” is misleading as careful scrutiny of the previous literature shows it refers to proportionate mortality, not “lifetime risk”: it is much better to know how risk compares to the general population using standardised mortality ratios. There has been an apparent increase in the all cause mortality gap amongst patients with first episode psychosis compared to the general population over the last four decades.

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EVIDENCE FOR THE BEHAVIORAL SENSITIZATION HYPOTHESIS OF PSYCHOSIS: AN 8-YEAR LONGITUDINAL COHORT STUDY INVESTIGATING THE EFFECTS OF CASCADING PSYCHOLOGICAL STRESSORS ON PSYCHOSIS OUTCOME

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Background: Recent studies have suggested that early adverse events, such as childhood trauma, accentuate vulnerability for psychosis, and stressful life events, occurring later in the vulnerable individual may move the individual towards the tipping point of psychosis. This would, alongside the contribution of genetic factors, suggest that environment x environment (ExE) interactions play a decisive role in psychosis development, with vulnerability being determined by cascading events within the stress-trauma pathogen. However, establishing causality of these environmental dynamics requires prospective studies that are adequately powered, which are currently lacking in the literature. The Early Developmental Stages of Psychopathology (EDSP) study, a longitudinal study of a population sample of 3021 adolescents and young adults, was designed to provide answers about prevalence, incidence, risk factors, comorbidity and course of mental disorders. We used data from this study to examine whether there was a synergistic interaction between early life trauma and occurrence of later life events on the risk of outcome of psychosis, taking into account the moderating or mediating effects of cannabis abuse and urbanicity.

Methods: We analyzed the association between childhood trauma (retrospectively assessed at T0), negative life events occurring between T0 and T2, and psychosis at T3, defined as either (i) having a total score above the 90th centile on the psychoticism subscale of the SCL-90, or (ii) having displayed impairment or helpseeking behavior in response to the occurrence of psychotic symptoms at T3, or (iii) being diagnosed as having a psychotic disorder at T3, according to the explicit diagnostic criteria of the DSM-IV. Associations were expressed as odds ratios from logistic regression models. All analyses were a priori adjusted for age, sex, urbanicity and cannabis abuse. Furthermore, all participants fulfilling criteria for psychosis liability prior to T3 were excluded from analysis.

Results: The experience of life events between T0 and T2 significantly increased the risk to develop psychosis at T3 (OR: 2.37; 95% CI: 1.68-3.38; p=0.000). This risk was larger in subjects who were exposed to trauma in their childhood (OR: 5.92; 95% CI: 2.37; 95% CI: 1.68-3.38; p=0.000), compared to those who did not experience childhood trauma (OR: 1.88; 95% CI: 1.25-2.82; p=0.002). The observed risk difference in the trauma group was significantly larger than the risk difference in the non-trauma group (14.9% and 4.4% resp.; test for interaction: χ2(df = 1676) = 7.59, p = 0.006).

Discussion: Results from this longitudinal study indicate that the occurrence of early life trauma moderates the effect of later life events on the risk of psychosis, taking into account the moderating or mediating effects of cannabis abuse and urbanicity. The experience of trauma at an early point in life, thus, increases risk of responding with psychotic symptoms to later life adverse events. Our findings point in the direction of a behavioral sensitization model of psychosis in which, alongside genetic contributions, dynamics within the environment (ExE) can be of crucial relevance.

doi:10.1016/j.schres.2010.02.226

PRIMARY AND READJUDICATION MORTALITY RESULTS FROM ZODIAC, A LARGE SIMPLE TRIAL OF ZIPRASIDONE VS. OLANZAPINE IN PATIENTS WITH SCHIZOPHRENIA

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Background: At the time of Ziprasidone’s regulatory approval, it was unknown if ziprasidone’s modest increase in the QTc interval was associated with increased morbidity and mortality in the population of treated patients with schizophrenia. In this symposium, we present the result of a large simple trial comparing the risk of non-suicide and other mortality endpoints associated with ziprasidone versus olanzapine in real-world use. The content will focus on two sets of analyses: the initial results submitted to the FDA and the readjudication of all mortality events using ICD 10 guidelines for the secondary outcome of sudden death, as further requested by the FDA.

Methods: ZODIAC, an open-label, randomized, postmarketing study, enrolled patients with schizophrenia from routine clinical practice settings in 18 countries. A total of 18,154 subjects were randomized to either ziprasidone or olanzapine. Patients received the selected medication in an unblinded fashion, and no further study-related interventions were made. Demographics, medical and psychiatric history, and concomitant medication use were collected at baseline using a physician-administered questionnaire, and a brief follow-up questionnaires elicited data on incidence of patient hospitalization since the last study visit, vital status, study medication continuation, and concomitant antipsychotic medication(s) use. The primary outcome was non-suicide mortality during the year after treatment initiation. The secondary objectives of this study were to estimate the relative incidence among users of ziprasidone and olanzapine of all-cause mortality, mortality due to suicide, cardiovascular mortality, mortality due to sudden death, as well as of all-cause hospitalization, hospitalization for arrhythmia, MI, or diabetic ketoacidosis, and to determine the rate of discontinuation of randomized treatment. One of the secondary outcomes, sudden death, was readjudicated according to ICD10 criteria per FDA.

Results: The incidence of nonsuicide mortality within one year of initiating therapy was 0.9% (n = 83) for the ziprasidone group (n = 9,077) compared with 0.9% (n = 81) for the olanzapine group (n = 9,077) yielding a relative risk (95% confidence interval) of 1.02 (0.76, 1.39). This finding was robust in numerous secondary and sensitivity analyses. Data from the post-hoc readjudication of sudden death were consistent with the study's initial findings (i.e., RR = 0.67, 95% CI: 0.11, 3.99; n = 2 for ziprasidone, n = 3 for olanzapine). The risk of sudden cardiac death and sudden death NOS (I46.1, R96.0 and R96.1) was 1.11 (0.45, 2.77) (n = 9 for

doi:10.1016/j.schres.2010.02.225

**Poster 2**

**EXAMINING PATIENT VALIDITY FOR CLINICAL: A POST-HOC ANALYSIS OF PLACEBO RESPONDERS**

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**Background:** It is well documented that placebo response rates for CNS studies conducted in the United States have gradually increased and that many clinical trials fail to achieve statistical significance. Numerous factors have been attributed to these failed clinical trials including misplaced site enrollment incentives, inflated entry scores, and the use of inappropriate or “professional” patients. Hence, it has been argued that some enrolled patients have not been truly valid treatment candidates for the study.

**Methods:** We began a post-hoc analysis of unblinded data from 12 adult clinical trials conducted for different pharmaceutical sponsors between 2002 and 2009. All studies were conducted by CRIWW (Mount Laurel, New Jersey). Therapeutic areas included Generalized Anxiety Disorder (GAD), Major Depressive Disorder (MDD), Bipolar Depression, and Schizophrenia. We examined the available data from all patients relative to demographic variables, baseline efficacy measures, psychopharmacologic treatment history, psychiatric history and co-morbid medical diagnoses, as well as their previous participation in clinical trials. Analysis of the data included general descriptive statistics and T-tests for equality of variance.

**Results:** Data relative to the following questions will be presented:

1) Do any demographic variables predict placebo response? 2) Does a previous history of psychopharmacologic treatment affect placebo response? 3) Do co-morbid medical or psychiatric diagnoses affect placebo response? 4) Does previous participation in clinical trials affect placebo response?

**Discussion:** In this preliminary analysis of a small sample of unblinded clinical trials, there was no relationship between treatment outcome in the current trial with patient demographic variables, co-morbid medical or psychiatric diagnoses, or previous participation in a clinical trial. Of note, it was difficult to obtain unblinded data from sponsors and fewer than 15% of studies conducted by CRIWW between 2002 and 2009 had available data for review. Prior to 2006, it was uncommon to collect systematic data about previous participation in clinical trials or detailed treatment response histories. CRIWW has begun a program to collect this data on all patients in all studies going forward. The analysis of unblinded treatment outcomes from CNS trials relative to patient demographic characteristics and past clinical trials experience can improve our understanding of patient selection variables and enhance the precision of patient selection for future trials.

**doi:** 10.1016/j.schres.2010.02.230

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**Poster 3**

**IMPROVEMENT OF PHENOTYPING IN GENOME WIDE ASSOCIATION STUDIES ON SCHIZOPHRENIA: AN APPLICATION OF LATENT CLASS FACTOR ANALYSIS**

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**GROUP XX**

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**Background:** Genetic factors explain a large proportion (81%) of the variation in schizophrenia. Nevertheless, the identification of specific
genes is not very successful as the enormous investments that are made on the genotypic level (e.g., genotyping ~ 1,000,000 SNPs) are not matched by similar investments on the phenotypic level. We aim to improve the assessment of individual differences in schizophrenia.  

**Methods:** We performed Latent Class Factor Analysis on 76 Comprehensive Assessment of Psychiatric History (CASH) symptoms in a sample of 2,290 patients with schizophrenia, schizotypal disorder, bipolar disorder or depression, and 1,888 healthy controls from the Netherlands. IQ was assessed in a subsample (N=2,373).  

**Results:** Exploratory factor analyses show that variation in schizophrenia symptoms is best represented by five latent dimensions (positive, negative, mania, disorganisation, and depression). For each individual, factor scores were estimated on each of these five dimensions. Latent class analysis was applied to the individual factor scores and showed the existence of eight clusters of subjects. Patients diagnosed with a psychotic disorder were assigned to three of these classes which were separated based on the scores on the disorganisation and negative dimensions while scores on the remaining dimensions were high irrespective of class. Controls and subjects with depression were most often assigned to healthy or moderately affected classes, but were also assigned to the three “affected” classes. Linear regression analyses, with diagnosis included as a covariate, showed that IQ was significantly associated with the dimensions negative, depression, and disorganisation. A relatively high IQ was associated with low scores on the negative and disorganisation dimensions and a high score on depression. Univariate analyses of variance showed differences between latent classes. Within the schizophrenia and schizoaffective patients, IQ scores were below average in the two classes which obtained high scores on the negative dimension, and were about average in the class which obtained a low score on the negative dimension. Within controls (including subjects diagnosed with depression), subjects who were assigned to one of the three “affected” classes, obtained lower IQ scores than subjects who were assigned to a relatively healthy class.  

**Discussion:** Despite the fact that schizophrenia is a highly heterogeneous disorder, gene finding studies collapse patients with different symptom patterns into one group. However, if in reality these patients have distinct genetic vulnerabilities, this would dramatically decrease the statistical power to detect functional genetic variants. We show large phenotypic heterogeneity both within patients with a psychotic disorder and within controls. This phenotypic heterogeneity is associated with IQ. Future Genome Wide Association studies should take this heterogeneity into account.  

doi:10.1016/j.schres.2010.02.231

**Poster 4**  
**Poster not available**  


**Poster 5**  
**DEVELOPMENT OF A BRIEF SELF-REPORT QUESTIONNAIRE FOR SCREENING THE AT RISK STATE OF PSYCHOSIS IN TAIWAN**  

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**Background:** The prodromal symptoms of schizophrenia are difficult to be differentiated from other common psychiatric illnesses or stress reactions. Despite newer instruments have been developed, non-specificity and low prediction rates are still the major barriers for early identification of at-risk subjects. Screening in the general population is thought to be infeasible; however, mental health campaigns inevitably were expected to provide some easy, handy questionnaires for self evaluation and referral.  

**Methods:** 151 subjects age between 16 and 32 years old with informed consent from the study on psychopathological progress of early schizophrenia-like disorder (ESLD) (SOPRES) in Taiwan were assessed by the researchers to determine their clinical severity at four hypothetical hierarchical psychopathological stages: first episode psychosis (n = 40), very high risk state (n = 41), intermediate risk state (n = 33), and very early state (n = 37), together with 129 age and gender comparable normal subjects and 96 non-at-risk psychiatric outpatients. All 376 participants filled a self-administered 231-item Mandarin version Schizophrenia Prone Scale Composed by 110-item Wisconsin psychotc prone scale, 74-item schizotypal personality questionnaire, 33-item basic symptoms, and 14-item cognitive symptoms. Items showing best discriminating power, estimated by Chi-square statistics and matrix visualization, were extracted to form a brief version self-report questionnaire. A two-stage cut-off approach by putting more emphasis on three designated items was applied to maximize the sensitivity and specificity. The feasibility of this approach was also estimated by a 10-fold cross-validation procedure.  

**Results:** Reduced from the original 231 items, a 15-item self-report questionnaire was developed. The final version is comprised by 5 interpersonal difficulty/social anxiety symptoms, 3 negative symptoms, 4 self-depreciating descriptions, and 3 subthreshold psychotic experiences. Respondents who have checked at least 8 items or have checked 3 to 7 items which included any one of the three items referring to intolerable to stress in crowd (item 1), paranoid ideation (item 14), and perceptual disturbance (item 15) would be considered as at risk of ESLD. Using these criteria, the sensitivity is 0.737 and the specificity is 0.732. The positive predictive value for at-risk state is 65.1%, and the negative predictive value is 80.8%. The validity of this cut-off selection estimated by a 10-fold cross-validation procedure revealed the sensitivity and specificity at 0.713 and 0.717 respectively. The two cut-points (3, 8) has been chosen 940 times and the three variables (item 1, 14, 15) been chosen 697 times in 1000 permutations.  

**Discussion:** A 15-item self-report questionnaire was demonstrated to have good sensitivity and specificity for screening among a group of subjects at-risk of psychosis, a comparison group of non-at-risk psychiatric outpatients, and normal controls. There are certain overlaps remained among these three groups in their response patterns, and we still failed to differentiate subjects at earlier risk stage from those at higher risk or first episode psychosis. Nonetheless, this questionnaire can act as an appealing feature to arouse the lay public’s attention to psychotic prodrome and serves as a handy tool for self-screening and referral, given careful wording for instructions while using this questionnaire. Test of the validity of this questionnaire is pending in another sample from help-seeking psychiatric patients and the general population.  

doi:10.1016/j.schres.2010.02.233

**Poster 6**  
**WHY HEARING VOICES IS DISSOCIATIVE IN ORIGIN, NOT PSYCHOTIC IN KIND**  

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**Background:** Voice hearing (VH) is considered a major symptom of schizophrenia. This is despite estimates that ten times more people experience VH than receive treatment for psychotic disorder.
First-episode patients with schizophrenia were found to perceive hostility, has been reported to be associated with paranoia dimension of schizotypy may not only be present in first-episode psychotic patients but may already have evolved prior to the onset of frank psychotic symptoms. A biased attribution style may play a pivotal role in the persecutory process during the prodromal phase as well as patient’s first schizophrenic episode.

doi:10.1016/j.schres.2010.02.235

Poster 8
CORRELATES OF SCHIZOTYPY CLUSTERS IN A LARGE NON-CLINICAL SAMPLE

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Background: Correlational methods, unlike cluster analyses, cannot take into account the possibility that individuals score highly on more than one symptom dimension simultaneously. This may account for the inconsistency found in the correlates of schizotypy dimensions. This study explored the clustering of positive and negative schizotypy dimensions in nonclinical subjects and whether schizotypy clusters have meaningful patterns of adjustment in terms of psychopathology, social functioning, and personality.

Methods: Positive and negative schizotypy dimensional scores were derived from the Wisconsin Schizotypy Scales for 6,137 college students and submitted to cluster analysis. Of these, 780 completed the NEO-PI-R and Social Adjustment Scale-self report version, and further 430 were interviewed for schizophrenia-spectrum, mood, and substance use psychopathology.

Results: Four clusters were yielded: low, high positive, high negative, and mixed (high positive and negative) schizotypy. The positive-schizotypy cluster presented more psychotic-like experiences and schizotypal and paranoid symptoms, had more affective and substance abuse pathology, and were more open and extraverted. The negative-schizotypy cluster had more negative and schizoid symptoms, worse social adjustment, high conscientiousness and low agreeableness. The mixed cluster was the most deviant on almost all aspects.

Discussion: Our cluster solution is consistent with that of few previous cluster analyses in schizotypy and schizophrenia, indicating that meaningful profiles of schizotypy features can be detected in nonclinical populations. The clusters displayed a distinct and meaningful pattern of correlates across different domains, thus providing construct validity to the schizotypy types defined. The phenomenological similarity between schizotypy and schizophrenia in terms of their underlying dimensions and associated correlates in a general population sample supports the fully-dimensional conceptualization of schizotypy.

doi:10.1016/j.schres.2010.02.236

Poster 9
AN EXAMINATION OF NEUROTICISM AS A MODERATING FACTOR IN THE ASSOCIATION OF SCHIZOTYPY DIMENSIONS AND PSYCHOPATHOLOGY IN A NON-CLINICAL SAMPLE

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Background: Affective temperament-based personality traits such as neuroticism have been found to be related to schizophrenia and...
schizotypy. However, studies thus far have not clarified the differential association of neuroticism with individual schizotypy dimensions and the role it plays in the expression of schizophrenia-spectrum phenomena.

**Methods:** 204 nonclinically ascertained participants completed self-report questionnaires assessing neuroticism and the positive and negative schizotypy dimensions, and underwent structured interviews assessing schizophrenia-spectrum psychopathology (psychotic-like experiences, negative symptoms, cluster A personality disorders), mood episodes, substance abuse, and global functioning.

**Results:** Results indicated that neuroticism predicted positive symptoms of schizophrenia and depression, over and above the effects of both schizotypy dimensions. Also, neuroticism moderated the association of positive schizotypy with interview measures of psychopathology and functioning.

**Discussion:** The results of this study support other research indicating that neuroticism is etiologically relevant for spectrum psychopathology and that it cannot be considered solely a ‘secondary effect’ of spectrum disorders. Current psychological models of psychosis can accommodate the finding of neuroticism being a shared vulnerability factor for affective and psychotic disorders.

doi:10.1016/j.schres.2010.02.237

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**Poster 10**

**THE PSYCHOMETRIC EVALUATION OF THE AUDITORY VOCAL HALLUCINATION RATING SCALE (AVHRS)**

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**Background:** Assessing characteristics of auditory vocal hallucinations (AVH) is a key issue both for clinical practice and research purposes. Questioning patients thoroughly about different aspects of their voices creates a solid base for therapeutic interventions, whereas reliable instruments are essential for outcome assessment and research. Aim of this study is to examine the psychometric properties of the Auditory Vocal Hallucination Rating Scale (AVHRS) in terms of inter-rater agreement, internal consistency and face validity. Also a first step in investigating concurrent validity was made.

**Methods:** Sixty-two patients of the Voices Outpatient Department of the University Medical Center Groningen were interviewed about past month voice hearing. Besides, a sample of 347 non-clinical voice-hearing children (7/8 years) was interviewed about past year voice hearing. In both of these samples internal consistency rates were examined. Inter-rater agreement was assessed in 23 patient interviews and in the children’s follow-up study. Concurrent validity was analysed by comparing an AVHRS severity index with the (adult) patients’ Symptom Checklist (SCL-90) indices. Adult patients were also questioned about face validity.

**The AVHRS interview:** The AVHRS is a structured 16-item interview, with the following items: number of voices (speaking separately or simultaneously), hypnagogic/hypnopompic voices (only voices when falling asleep or at waking up), frequency, duration, localization (inside or outside the head), loudness, attribution of origin (internal attribution, e.g. ‘they could be my own thoughts and feelings’ or ‘could be caused by stress’, or external attribution, e.g. ‘the voices are caused by deceased persons or extraterrestrials’), amount of negative content, severity of negative content, frequency of suffering, intensity of suffering, interference with daily functioning, control over voices (i.e., the patient can dampen the voices or has at least some influence on their occurrence), anxiety, interference with thinking and form of address. Items are scored on a 5-point scale. For experienced therapists and researchers in the field of psychopathology, no extensive training in administering the AVHRS is required. Duration of administering the AVHRS is around 20 minutes.

**Results:** Agreement analyses showed weighted (Cohen’s) kappa’s of .84 (patients) and .88 (follow-up study of the children). Internal consistency (Cronbach’s alpha) was .84 (adult sample), respectively .77 (children’s sample). Pearson’s correlation coefficients with the SCL-90 were r = .66 with the psychoticism dimension and r = .62 with the SCL-90 total score. According to patients face validity was good.

**Discussion:** Thus far, analyses showed that the AVHRS is a comprehensive instrument with good psychometric properties, for a thorough assessment of characteristics of auditory vocal hallucinations. It is useful in both clinical and research settings, and also suitable (with some adjustments in language) for children.

doi:10.1016/j.schres.2010.02.238

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**Poster 11**

**MOTOR BEHAVIOR ABNORMALITIES IN DRUG-NAÏVE PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS**

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**Background:** Most previous studies of motor abnormalities have been typically conducted in patients with different degrees of chronicity and exposure to antipsychotic medication. This might dramatically affect motor abnormalities' prevalence and correlates, since motor signs in treated patients likely represent a mixture of primary and secondary abnormalities. Despite the fact that motor features are thought to be core manifestations of the psychotic illness and that basal ganglia dysfunction is increasingly involved in the pathophysiology of schizophrenia, the characterization of motor disorders in first-episode psychotic disorders has been a neglected area of research, and there is a lack of studies comprehensively examining motor abnormalities in drug-naïve patients.

**Objectives:** This study was aimed at examining the prevalence, syndromic structure and response to antipsychotic medication of a broad array of primary motor abnormalities.

**Methods:** Two-hundred antipsychotic-naive patients with schizophrenia spectrum disorders [schizophrenia (n = 94, 47%), schizoaffective disorder (n = 36, 18%), brief psychotic disorder (n = 38, 19%), other psychotic disorders (n = 32, 16%)] were examined for motor abnormalities using the Modified Rogers Scale. Thirty-one motor signs were subjected to factor analysis and the resulting factor structure was examined for treatment response in 189 patients who were reassessed after a 4-week trial with antipsychotic medication [haloperidol (n = 23), risperidone (n = 93), olanzapine (n = 57) or a mixed pattern of antipsychotic drugs (n = 16)].

**Results:** One hundred and thirty-three patients (66.5%) showed at least one motor sign, 92 patients (46%) showed two or more signs and 73 patients (36.5%) showed three or more signs. Motor signs clustered together into 7 clinically interpretable factors: abnormal phenomena, excited catatonia, catalepsy and parkinsonism. All motor domains but parkinsonism were inter-related. Change scores in
motor domains after antipsychotic treatment indicated improvement (p < 0.01) for abnormal involuntary movements, hypokinesia, retarded catatonia, excited catatonia and echophenomena, and worsening (p < 0.01) for parkinsonism.

**Discussion:** Our findings extend the concept of motor abnormalities of schizophrenia as a highly prevalent and intrinsic component of schizophrenia, which reflects a disease process involving basal ganglia dysfunction. On the basis of our findings, it could be hypothesized the existence of some type of hyperdopaminergia in the nigroestriatal circuitry responsible for the generation of those motor domains improving with antipsychotic drugs, which is compensated by treatment. On the other hand, parkinsonism would be the expression of a hypodopaminergic state that is worsened by drug-induced dopamine D2-receptor blockade. However, the coexistence of several types of motor disorders suggests that the mechanisms involved are more complex than simple hypo- or hyperdopaminergia. In this respect neuromotor dysfunction in schizophrenia may involve multiple frontal-subcortical circuitries and neurotransmitters systems, which are also potentially involved in the nonmotor manifestations of schizophrenia.

**Acknowledgments:** This study was partly funded by a grant of the Government of Navarra (946/2005 and 55/2007).

doi:10.1016/j.schres.2010.02.239

**Poster 12**

**SCHIZOPHRENIA TRAVELER TYPE**

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**Background:** DSM-IV-TR classifies schizophrenia in several types: disorganized, paranoid, catatonic, undifferentiated and residual. This classification is focused on the symptoms one could identify into the consequence of illness was not statistically significant when compared with the other group.

**Results:** The patients with an extensive travel pattern had more symptoms and neurotransmitters systems, which are also potentially involved in the nonmotor manifestations of schizophrenia.

**Discussion:** There are several ways to look at this phenomenon: 1. There could be differences in insight earlier in the illness, partially leading to same discrepancies described in duration of untreated psychosis studies which in turn could lead to a worse or different prognosis; 2. The illness have a different course likely as result of hallucinations that lead to changes in behavior, such as extensive travel patterns.

**Acknowledgments:** This study was partly funded by a grant of the Government of Navarra (946/2005 and 55/2007).

doi:10.1016/j.schres.2010.02.240

**Poster 13**

**SAME OR DIFFERENT? AUDITORY VERBAL HALLUCINATIONS IN HEALTHY AND PSYCHOTIC INDIVIDUALS**

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**Background:** Whereas auditory verbal hallucinations (AVH) are most characteristic for schizophrenia, their presence has frequently been described in a continuum, ranging from severely psychotic patients through schizotypal personality disorder to otherwise healthy subjects. It remains unclear whether AVH at the outer borders of this spectrum are indeed the same phenomenon. Furthermore, specific characteristics of AVH may be important indicators of a psychotic disorder.

**Methods:** To investigate differences and similarities in AVH in psychotic and non-psychotic individuals, the phenomenology of AVH in 118 psychotic patients was compared to that of 111 otherwise healthy individuals, both experiencing AVH at least once a month. Characteristics of AVH were quantified using the PSYRATS Auditory Hallucinations Rating Scale.

**Results:** The Wilk's lambda multivariate test of overall differences among groups was significant (p < 0.001). A significant main effect for group was present for the following variables: The patients experienced less control, more frequently heard voices talking in the third person, and were older (mean difference of 9 years) when they first heard a voice, and scored significantly higher on frequency, duration, distress and emotional valence of content. No differences were found for perceived location (i.e. inside/outside the head), loudness, number of different voices, and personification. A binary logistic regression model was used to investigate which characteristics best predict whether a person experiencing AVH has a psychotic disorder. The optimal model had a satisfactory fit ( Hosmer and Lemeshow test, Chi-square = 13.7, df = 8, p = 0.09), and the Nagelkerke approximation of R² was high: 0.77). Having control over the AVH for most of the time, hearing voices less than once a day, age of onset before 16 years of age, and hearing voices with a predominantly positive content are good predictors that a person does not have a psychotic illness. The sensitivity as well as the specificity of this model were 92 percent (implying that there is a 92% probability of a correct diagnosis using these characteristics). An explorative binary logistic regression was carried out with only the strongest predictor (emotional valence of content of AVH), age and gender, and group membership (having a psychotic disorder or not) as the dependent variable. Emotional valence of content provided a better fit and substantial explained variance ( Hosmer and Lemeshow test, Chi-square = 8.7, df 8, p = 0.37), and the Nagelkerke approximation of R² was high: 0.64. When only emotional valence is included in the model, there is a sensitivity of 80% and 87% specificity using only this characteristic. The positive predictive value was 88 percent.

**Discussion:** The most prominent differences between AVH in healthy and psychotic individuals were the emotional valence of the content, the frequency of AVH, and the control subjects had over their AVH. In our sample, the emotional valence of the content of AVH (defined as more than half of the AVH with a negative content) could accurately predict the presence of a psychotic disorder in 88% of the subjects. This implies that inquiring after the emotional content of AVH may be a crucial step in the diagnosis of psychotic disorders in individuals hearing voices. Most other characteristics of AVH, such as voices heard inside or outside the head, loudness,
number of voices, and attribution of the voices to a real or familiar person were similar in both groups, consistent with AVH being the same phenomenon in both groups. However, onset of AVH was at a much younger age in the healthy subjects, which could point to a different mechanism of origin.

doi:10.1016/j.schres.2010.02.241

**Poster 14**
EDUCATIONAL LEVEL OF RATERS IMPACTS INTERVIEW QUALITY IN INTERNATIONAL ANTIPSYCHOTIC CLINICAL TRIALS

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**Background:** In clinical trials agreement among raters and ultimately signal detection may be complicated by variations in raters’ credentials and interview skills. The Positive and Negative Syndrome Scale (PANSS) is the most widely recognized and utilized measure in schizophrenia clinical trials. There is no universal agreement regarding the level of professional credentials required to rate the PANSS. We have previously reported substantial regional differences in the use of doctorate level PANSS raters with the lowest use in the United States compared to the rest of the world (1). The impact of educational level on the quality of the ratings interview in clinical trial settings is not well defined.

**Methods:** We examined the relationship between the educational level (doctorate vs. non-doctorate) of 432 PANSS raters and competency to conduct an interview as measured by the total score on the Research Interview Assessment Scale (RISA). All raters were undergoing training to rate in multi-center international schizophrenia clinical trials. The RISA is a 16 item scale that assesses four domains of interview quality, demonstrates high levels of inter-rater and intra-rater reliability and is highly correlated with other measures of interview competency (2).

**Results:** For the world as a whole the mean total RISA score of doctorate level raters (mean = 26.99, n = 367) was higher than non-doctorate raters (mean = 25.86, n = 65) (t = 1.95, df = 74, p < .06, [unequivalent variance]). In the US subset of raters the mean total RISA score of doctorate level raters (mean = 27.8, n = 45) was higher than non-doctorate raters (mean = 26.2, n = 55) (t = 2.3, df = 94, p < .02). The variance in the total RISA score of the non-doctorate raters in both of the above situations was larger than that of the doctorate variance by a factor of 2.2 (p < 0.001). In the European subset of raters the mean total RISA score of doctorate level raters (mean = 27.62, n = 184) was not significantly different from non-doctorate raters (mean = 28.00, n = 2), however there were only two non-doctorate raters.

**Discussion:** The current findings are consistent with the notion that in clinical trials PANSS raters with doctorate degrees on the whole exhibit higher quality interview skills than raters without doctorate degrees. In addition, there was significantly more variance in the total RISA score (reflecting variation in interview quality) among non-doctorate compared to doctorate level raters. Interview quality is an important factor in the validity and consistency of clinical trials ratings. The current findings must be viewed in light of the relatively small sample size of non-doctorate raters outside the United States particularly in Europe. Also, the possibility of sampling bias must be considered because all the raters were trained by United BioSource Corporation (UBC). This analysis was paid for by UBC. REFERENCES: 1) David D, Bartko J, Sartorius N et al: Regional and Temporal Differences in the Use of Doctorate Level PANSS Raters in Multicenter Clinical Trials. Proceedings of the New Clinical Drug Evaluation Unit Annual Meeting, Boca Raton, Florida, June 14, 2006.

doi:10.1016/j.schres.2010.02.242

**Poster 15**
COGNITIVE AND NEGATIVE SYMPTOM DIMENSIONS IN THE AT RISK MENTAL STATE PREDICT SUBSEQUENT TRANSITION TO PSYCHOSIS

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**Background:** The At Risk Mental State (ARMS) is associated with a very high risk of psychosis but it is difficult to predict which individuals will later develop psychosis on the basis of their symptoms at presentation. We investigated psychopathological dimensions in subjects with an ARMS and examined whether particular symptom dimensions predict subsequent transition to psychosis.

**Methods:** The sample comprised 122 subjects (aged 16-35) meeting PACE criteria for the ARMS recruited through OASIS in London, UK. A Principal Axis Factor analysis was performed on symptom scores, obtained from presentation from the Comprehensive Assessment of the At Risk Mental State (CAARMS), using Varimax rotation. The relationship between dimension scores and transition to psychosis during the following 24 months was then examined employing Cox Regression Analysis.

**Results:** Factor analysis gave rise to a five factor solution of negative, anxiety, cognitive, self-harm and manic symptom dimensions, accounting for 37% of the total variance. Both the negative and the cognitive dimension scores were significantly associated with transition to psychosis during subsequent follow up (p = 0.044 and p = 0.005 respectively).

**Discussion:** The symptoms of the At Risk Mental State have a dimensional structure similar to that evident in patients with schizophrenia. The association between scores on the cognitive and negative dimensions and later transition is consistent with evidence that formal thought disorder, subjective cognitive impairments and negative symptoms are linked to subsequent development of psychosis.

doi:10.1016/j.schres.2010.02.243

**Poster 16**
CO-MORBID SUBSTANCE MISUSE DOES NOT HAVE AN EFFECT ON COGNITIVE FUNCTION AT TEN YEAR FOLLOW-UP OF FIRST-EPIsode PSYCHOSIS PATIENTS

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**Background:** Co-morbid substance misuse and a first-episode psychotic disorder are highly prevalent and have been associated with a poor prognosis including more hospitalisations, treatment non-compliance and higher relapse rates. There is also concern that comorbid substance misuse may be associated with a greater
improvement in cognitive function in this population. Impairment in memory, learning and executive function has been demonstrated as a result of substance misuse in healthy individuals. However, similar results have not been demonstrated in first-episode psychosis patients. This study aims to investigate the effect of substance misuse on neuropsychological test performance in first-episode psychosis patients after a ten year follow-up period.

Methods: A battery of neuropsychological tests were administered to 29 individuals at their first-episode of psychosis and again at ten year follow-up. Information on substance misuse was obtained from participants self report using an amended version of the World Health Organisation Life-Chart and the Schedules for Clinical Assessment in Neuropsychiatry and was supplemented from information in clinical case notes. Substance misuse was defined as frequent or regular illegal drug use (more than once a month) or meeting ICD-10 criteria for harmful use or dependence of substances. A repeated measures ANOVA was used to compare participants with a history of substance misuse and those without for their neuropsychological test performance, at baseline and at ten year follow-up.

Results: A history of co-morbid substance misuse was present in 48.3% (14/29) of the participants. Cannabis was the most common substance misused with 71.4% (10/14) of participants having misused it. Those with a history of substance misuse were significantly younger ([t(18) = 2.834, p = 0.011] and more likely to be male (Fisher's Exact test, p = 0.035) compared to those without a history of substance misuse. There was no difference between groups with a history of substance misuse and those without for ethnicity (Fisher's Exact test, p = 1.00), diagnosis (Fisher's Exact test, p = 0.109) or pre-morbid IQ measured using the National Adult Reading Test at baseline assessment ([t(25) = 1.687, p = 0.104]). The length of the follow-up period between neuropsychological assessments ranged from 360-510 weeks and there was no difference between groups. A repeated measures ANOVA was conducted with the factors of time (baseline and follow-up) and group (no substance misuse and substance misuse) with covariates of age and gender, to examine change in neuropsychological test performance over time. There was no main effect of time (p > 0.05) for any measure with the exception of WAIS full scale IQ (F(1,123) = 4.537, p = 0.034) where there was significant reduction between baseline and follow-up. There was no significant main effect of group (p > 0.05) for any measure. The group x time interaction effect was not significant for any measure (p > 0.05).

Discussion: Cognitive function remained stable over time from the first-episode of psychosis with the exception of IQ which diminished over the follow-up period in this sample. Co-morbid substance misuse did not have an impact on cognitive function over time in those with a psychotic disorder. The sample size for this study was small, however, the re-contacting of participants in the original first-episode cohort continues and it is anticipated that these results will be replicated in the larger sample of participants.

doi:10.1016/j.schres.2010.02.244

Poster 17

INTERIM ANALYSIS OF THE CAPOUS TRIAL: A RANDOMIZED, PARALLEL-GROUP, OBSERVER-BLINDED CLINICAL TRIAL OF SPECIALIZED ADDICTION TREATMENT VERSUS TREATMENT AS USUAL FOR YOUNG PATIENTS WITH CANNABIS ABUSE AND PSYCHOSIS

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Background: Studies have shown increased cannabis-use prevalence in patients with schizophrenia and related disorders. Use of cannabis among patients with psychosis can maintain and worsen the psychotic symptoms, and is associated with lack of compliance to treatment, poorer treatment effect, and with more rehospitalizations. Two reviews have concluded that positive evidence exists for integrated treatment with motivational interviewing, cognitive behavioral therapy, and a harm-reduction approach. Authors of a recent Cochrane review concluded that insufficient evidence exists to show that any psychosocial treatment method for comorbid schizophrenia and substance abuse is superior to others. The CapOpus trial We are currently conducting a trial which for a six-month period combines motivational interviewing, psycho-education, cognitive behavioral therapy, and social skills training in addition to treatment as usual, is compared with treatment as usual. One early interim analysis indicated that CapOpus lowered the median number of cannabis-smoking days by fifty percent. At the present conference, we expect to be able to present an interim analysis of at least 75 patients. In addition, a number of longer-term follow-ups will have been conducted, and we will be able to present results on level of psychopathology, cognitive functioning etc. as well.

Methods: The trial is designed as a two-armed, parallel-group, observer-blind randomized trial. Patients are randomized to receive either specialized CapOpus treatment or treatment as usual (TAU). The randomization procedure is stratified by degree of cannabis use disorder and for type of TAU (e.g. OPUS teams, community mental health centres, etc.). CapOpus is an add-on treatment to TAU. CapOpus incorporates motivational interview, cognitive behavior therapy, social skills training, and also involves both the patients’ families and existing case managers. CapOpus is given for six months, with an assertive approach to get weekly contacts with the patients. TAU has no manualized way of treating cannabis use disorders. Inclusion and exclusion criteria for the CapOpus trial are: "Diagnosis of schizophrenia spectrum disorder (F2 in ICD-10) and cannabis use disorder (F12 in ICD-10) "Living in the Copenhagen area "Other types of alcohol or substance use disorders allowed, but cannabis must dominate the clinical picture."

Data collection: Data collection takes place at baseline (pre-randomization), after six months and ten months. Primary outcome measure is number of days with cannabis use in the past 30 days, measured using the Timeline Followback instrument. Secondary outcomes include PANSS rated psychopathology, cognitive functioning, quality of life, and disability assessment, all using validated psychometric instruments.

Results: Not ready at time of abstract submission.

Discussion: If positive effects of CapOpus are demonstrated at the end of data collection, and differences are statistically significant, CapOpus-treatment may be considered for future implementation in treatment of patients with comorbid cannabis use disorder and schizophrenia spectrum disorders.

doi:10.1016/j.schres.2010.02.245

Poster 18

SOCIAL NETWORK CHARACTERISTICS AND EFFECT ON SEVERITY OF PSYCHOSIS IN A COMMUNITY SAMPLE WITH HIGH PREVALENCE OF STIMULANT USE


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Background: Urban environments include neighbourhoods with high prevalence of serious and persistent mental illness, substance...
abuse and communicable infectious disease. As little is known about these particular social networks, one objective of this study was to collect descriptive information with the goal of identifying strategies for more effective health care intervention. A second objective was to determine if social network size had a buffering effect on the severity of psychotic symptoms.

Methods: Participants were recruited from two single-room occupancy hotels in Vancouver (from November 2008 to October 2009) and completed structured interviews to provide information on demographics, substance use, mental health and social network characteristics. The specific components of the interview that were used included: a socio-demographic survey, the Maudsley Addiction Profile, Substance time-line follow back, urine drug screen, Positive and Negative Symptoms Scale (PANSS), Beck Depression Inventory (BDI) and the Arizona Social Support Interview Schedule. Regression analysis was used to determine whether there was a correlation between network size and symptoms of psychosis.

Results: The study population (n = 135) was: 25% female, 74% male, 0.7% transgendered and had an average age of 44 years old (range 24-63 years). The substance use characteristics within the month preceding interview are as follows: 95% stimulant use, 54% opiate use, 52% cannabis use, 53% used both stimulants and opiates, 13% consumed alcohol at least weekly and 51% reported current intravenous drug use. The mean total PANSS score was 73 (SD 20), with positive subscale mean 17 (SD 7) and negative subscale mean 18 (SD 7). Using a categorical approach and PANSS items related to delusions, hallucinations and thought disorder, 57% of subjects were determined to be psychotic at the baseline interview. The mean BDI score was 14 (SD 11). Using a threshold of $\geq 21$ on the BDI as indicating clinical depression in a substance-using sample, 26% of subjects were depressed at baseline. The mean available network membership (ANWM) was 4.1 (range 0-14) and the mean utilized network membership (UNWM) was 2.98 (range 0-14) people. Regression models were used to predict total PANSS score, with predictors ANWM score, gender, and an ANWM by gender interaction. Statistically significant results were obtained for ANWM ($p=0.001$) and the ANWM x gender interaction ($p=0.002$). A larger ANWM predicted less severe total PANSS score, and this effect was strongest in women. Generally similar patterns of effects were observed for positive or negative symptoms as outcomes, and for UNWN as a predictor rather than ANWM. In contrast to the protective effects of a larger network on severity of psychotic symptoms, no such relationship was observed for severity of depression. For BDI score, only gender was a statistically significant predictor ($p=0.01$), with scores higher in women.

Discussion: The social network size of participants was similar to those reported in other samples with high prevalence of psychiatric illness or IVDU. Studies of schizophrenia showed relationships between network size and negative symptom severity. However, in the present sample, network size was related to total, positive and negative symptom severity. Of note, the protective effect of social network size was most prominent in women. In an environment where exposure to stimulant drugs increases the risk of psychosis, social network size appears to be a protective factor that could be a target for future development of interventions.

doi:10.1016/j.schres.2010.02.246

Poster 19

CANNABIS USE AND COGNITION IN SCHIZOPHRENIA: A LITERATURE REVIEW

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Background: People with schizophrenia frequently report cannabis use, and cannabis may be a risk factor for schizophrenia, mediated through effects on brain function and biochemistry. Thus, it is conceivable that cannabis may also influence cognitive functioning in this patient group. Data from our laboratory that showed paradoxical positive effects of cannabis on cognition prompted a review of the existing literature on the relationship between cannabis use and cognitive functioning in schizophrenia.

Methods: We performed a PubMed search on all combinations of the search words: cannabis, substance, schizophr*, psychos*, cognit* and neuropsych*, and searched the reference lists for all included papers of other studies covering this topic. This resulted in 23 studies comparing schizophrenia and related psychoses with and without cannabis use (alone or in combination with other substances) on cognitive performance. The following characteristics were noted for each study: The number of subjects in the drug group/no-drug groups, whether multiple drugs were used, diagnostic characteristics of the subjects (including the presence of a substance use disorder), whether the drug use was current or former, and overall group differences in regard to cognitive performance.

Results: Fourteen of the studies reported that the cannabis user groups showed better cognitive performance than the no-cannabis groups. Eight of the studies reported no or minimal differences in cognitive performance between the two groups, and one study reported better cognitive performance in the no-cannabis group compared to the drug group.

Discussion: A majority of the reviewed studies report better cognitive functioning in cannabis-using patients with schizophrenia and psychosis groups compared to non-cannabis groups. This paradoxical finding may have several explanations. We suggest that cannabis causes a transient cognitive breakdown (also supported by preliminary longitudinal data from our laboratory) enabling the development of psychosis, imitating the typical cognitive vulnerability seen in schizophrenia. This is further supported by an earlier age of onset and fewer neurological soft signs in the cannabis-related schizophrenia individuals, suggesting an alternative pathway to psychosis. It is suggested that the effects of cannabis on cognition and brain functioning model the cognitive vulnerability in schizophrenia, and understanding this cognitive breakdown may provide a unique window to understanding schizophrenia neurodevelopment.

doi:10.1016/j.schres.2010.02.247

Poster 20

DRUG USE AND FIRST EPISODE PSYCHOSIS: EXPLORING ASSOCIATIONS WITH OCCUPATIONAL EXPECTATIONS AND ACHIEVEMENTS

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Background: Schizophrenia and other psychoses are reliably associated with high rates of unemployment at first presentation, although occupational expectations may remain undiminished. Whilst a causal relationship has not been established, unemployment in this population is linked to poor clinical course and compromised social functioning. Similarly, drug use has been independently linked to reduced employment rates, a relatively lower income and low academic attainment and aspirations. Given that substance misuse rates are elevated in individuals presenting with first episode...
psychois, the question therefore remains as to whether the presence of both first episode psychosis and drug use has a cumulative effect upon individuals’ occupational expectations and achievements.

**Methods:** Secondary analysis was carried out on cross sectional data collected in Nottingham (UK) between 1997 and 2003 for the Aetiology and Ethnicity of Schizophrenia and Other Psychoses study (AESOP). Data was drawn from control and case participants who provided information upon both drug use and occupational related variables (n = 163). Perceptions of current occupational achievement and prior occupational expectations were rated by participants on identical 10 point scales with point 10 representing the highest level of achievement. The outcome measure was derived by subtracting scores on achievement from those on expectations to provide a new variable representing the ‘achievement-expectation gap’. This was dichotomised into the following groups: Those who had met or exceeded their expectations (scores 0 to 9) and those who had failed to attain them (scores -1 to -9). Illness status (cases versus controls) and drug use (drug use versus no drug use) were entered separately into a regression model to ascertain their independent contribution to the outcome variable. An interaction term was calculated to investigate the cumulative impact of both drug use and psychoses upon the achievement-expectation gap.

**Results:** Pearson’s Chi-Square analysis indicated that the four groups (cases with drug use, cases with non use, controls with drug use, controls with non use) differed significantly according to gender (χ²(3, n = 163) = 9.29, p = .026) and age (χ²(3, n = 163) = 35.56, p = .001). This finding was not replicated for either education or ethnicity. Binary logistic regression analysis revealed no significant effect of age or gender upon the outcome variable. Subsequently, the binary logistic regression analysis was rerun with these predictors excluded from the model. This analysis revealed a significant association between drug use and a relatively higher gap between occupational achievements and expectations (OR = 3.62; 95% CI = 1.29 – 10.130, p = .014). Specifically, individuals with self reported drug use were three times more likely to have not met, or exceeded, their employment expectations. Illness status (case or control) was not significantly associated with this outcome (OR = 1.11; 95% CI = 0.31 – 3.923, p = .877). There was not a significant interaction between drug use and illness status with regard to prediction of the achievement-expectation gap (OR = 0.55; 95% CI = 0.123 – 2.426, p = .426). A post hoc test of analysis of variance revealed that drug users had significantly higher occupational expectations relative to non drug users (F(1,159) = 6.45, p = .012).

**Discussion:** There was no association between psychosis and a heightened gap between occupational expectations and achievements. Independent of illness status, drug users were three times more likely to report failing to attain, or exceed, their desired occupational status. This was attributable to the presence of significantly higher employment expectations in this population.

doi:10.1016/j.schres.2010.02.249

**Poster 21**

**COGNITIVE PERFORMANCE AND SMOKING IN FIRST EPISODE PSYCHOSIS: THE SELF-MEDICATION HYPOTHESIS**

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**Background:** The self-medication hypothesis attempts to explain the extraordinary high levels of cigarette smoking in schizophrenia. It rests on three main explanations: patients may smoke as an attempt to reduce their cognitive deficits, their symptoms or the antipsychotic side-effects. In a previous report, our team detected a beneficial attentional and working memory performance in smoking first episode psychosis patients compared to non-smokers soon after their stabilization.

**Methods:** In the present analyses we examine differences in the course of those deficits 12-months after the instauration of the antipsychotic treatment, exploring also smoking associations to symptoms and medication side-effects. Neuropsychological assessments were performed at baseline, month 6 and 12, using a computerized battery that included measures of sustained attention (Continuous Performance Test CPT-O), selective attention (Stroop Interference task) and working memory (CPT-XO). Patients included met the criteria of fitting in the same smoking category throughout the study: non-smoker (n = 15; 0 cigarettes/day), smoker (n = 26; > 15 cigarettes/day).

**Results:** Smoking patients lost their superior baseline performance, which probably was obtained through nicotinic stimulation, at the 6–12 months assessments due to a static course of deficits. The non-smoking patients showed significant improvements, probably derived from the antipsychotic treatment.

**Discussion:** Nicotine in tobacco smoking might improve attention and working memory in a similarly modest degree than atypical antipsychotics. Smoking might reflect an effort to ameliorate these cognitive dysfunctions. Smoking was not associated with fewer extrapyramidal side-effects or symptoms. Moreover, nicotine consumers worsen their symptoms over the first year, result that supports smoking as a marker of a more severe illness.

doi:10.1016/j.schres.2010.02.250
Poster 23  
CEREBELLAR GREY MATTER DEFICITS, CANNABIS USE AND FIRST-EPIPOSE SCHIZOPHRENIA IN ADOLESCENTS AND YOUNG ADULTS

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Background: Epidemiological data suggest a link of juvenile cannabis use to the prevalence of psychosis and schizophrenia while a potential contributing or even causative effect of adolescent cannabis use to the neuropathology of schizophrenia remains controversial. First-episode schizophrenia (FES) presents with regional grey and white matter changes in the brain, including a distinct pattern of regional grey matter loss in the cerebellum. The cerebellum also presents with a high density of cannabinoid type 1 receptors involved in the neuronal diversification of the developing brain. Cannabis abuse may interfere with this process during adolescent brain maturation and thereby leading to “schizophrenia-like” cerebellar brain pathology.

Methods: By employing cortical pattern matching, the current magnetic resonance imaging study investigated cerebellar grey and white matter in 17 young cannabis users (mean age of 22.7 SD 2.4 years), starting consuming at a mean age of 15.2 (SD 2.4) years and totalling an average of 22,800 (SD 16,400) individual life-time doses of cannabis over 7.6 (SD 2.6) years.

Results: We found life-time dose-dependent regional reduction of grey matter in the right lobules III, IV, and V and a tendency of more profound grey matter reduction in lobule III with a younger age at onset of regular cannabis use. However, the overall regional grey matter changes in cannabis users were within the normal variability of grey matter distribution when compared to 17 age, gender, and handedness pair-wise matched healthy control subjects. By contrast, 13 age-matched remitted FES subjects (<2 years duration of illness and without substance use history) presented with lower total cerebellar grey to white matter ratios and marked grey matter loss in vermis, pedunculi, flocculi and lobules III, IV, V, VI, and IX when compared to 13 pair-wise matched healthy control subjects. This pattern and the degree of grey matter loss did not differ from 6 age-matched FES subjects with co-morbid cannabis use history.

Discussion: Our findings indicate small dose-dependent effects of juvenile cannabis use on cerebellar neuropathology but no evidence that cannabis use is associated with (or contributes to) the cerebellar grey matter deficits found in FES.

doi:10.1016/j.schres.2010.02.251

Poster 24  
SEASONALITY AND SCHIZOPHRENIA ADMISSIONS IN GALIZA

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Background: Previous studies on schizophrenia admissions were no consistent to find a connection with seasonality, neither in the first admissions, proposing further work in order to clarify the impact of latitude and meteorological factors on this topic. This preliminary study was conducted to determine if seasonality in schizophrenia admissions follows an specific pattern in a sample of galician inpatients from Santiago de Compostela (42.5 N / 8.33 W). The weather in its area is warm and wet, with a mean temperature about 12.6°C, its mean rainfall over 1700 l/m²; and a daylength range between 9 hours per day (January) and 15 hours per day (July).

Methods: A retrospective and descriptive study was designed. Sample studied was randomized among the all inpatients with diagnosis of schizophrenia (DSM-IV), admitted from spring 2003 to spring 2008 in the psychiatry department because acute symptoms. So, medical history of half of these schizophrenic inpatients were reviewed.

Results: 132 admissions with DSM-IV diagnosis of schizophrenia were studied (paranoid type 75%, disorganized type 11.4%, catatonic type 0.7%, undifferentiated type 9.1% and residual type 3.8%). Seasonal admissions distribution for the whole sample was: spring 20.5%, summer 32.6%, autumn 15.9% and winter 31%. Statistically significant differences were not found, with an only monthly peak in July (13.6%). The group of paranoid type admissions (n = 99) presented the following seasonal pattern: spring 17.2%, summer 32.3%, autumn 18.2% and summer 32.3%, with a peak in summer and winter. First admissions (n = 20) were distributed as follows: spring 20%, summer 25%, autumn 25% and winter 30%, without displaying a seasonality pattern.

Discussion: Neither the whole schizophrenia admissions sample nor first admissions showed a definitive seasonal pattern, suggesting that strong variables other than climate and latitude, are related to acute episodes in this chronological psychosis, too in galician inpatients.

doi:10.1016/j.schres.2010.02.252
Discussion: The results of this study confirm the association between MPA and schizophrenia. The excess of MPAs in schizophrenia is in agreement with the neurodevelopmental hypothesis of this disorder that posits a role for genetic and environmental factors in the development of the disorder during critical intrauterine and perinatal periods.

doi:10.1016/j.schres.2010.02.253

Poster 26
IMPROVING DETECTION OF FIRST EPISODE PSYCHOSIS BY MENTAL HEALTH CARE SERVICES USING A SELF REPORT QUESTIONNAIRE

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Background: To examine the utility of the Community Assessment of Psychic Experiences (CAPE)-42, a self report questionnaire, to improve detection of the first episode psychosis in new referrals to mental health services.

Methods: At first contact with mental health care services patients were asked to complete the CAPE-42 and were then routinely diagnosed by a clinician. Standard diagnosis were obtained by means of the mini- Schedule for Clinical Assessment in Neuropsychiatry.

Results: Of the 246 included patients, 26 (10.6%) were diagnosed with psychosis according to the mini- Schedule for Clinical Assessment in Neuropsychiatry. Only 10 of them were recognized by clinical routine, and 16 psychotic patients were not properly identified. Using an optimal cut-off of 50 on the frequency or distress dimension of the positive subscale of the CAPE-42, detected 14 of these misdiagnosed patients. The sensitivity of the CAPE-42 at this cut-off point was 77.5 and the specificity was 70.5.

Discussion: We found that in routine clinical practice patients were not appropriately recognized leaving a substantial number of psychotic patients undetected. Implementation of systematic screening using a self report questionnaire for psychotic symptoms improves routine detection of psychotic patients when they first come into contact with mental health services.

doi:10.1016/j.schres.2010.02.254

Poster 27
PARENTAL AGE AND THE RISK OF PSYCHIATRIC DISORDERS

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Background: It has been suggested that increased parental age is a risk factor for developing psychiatric disorders. Parental age may be linked to increased de novo germline mutations or epigenetic changes affecting neurodevelopment and leading to increased susceptibility to schizophrenia and other neuropsychiatric disorders in the offspring.

Methods: Patients with the diagnoses schizophrenia, bipolar disorder, major depression disorder, and autism are collected through a patient registry from the central part of The Netherlands. From these patients, date of birth, sex, birth order, and ethnicity are collected. Date of birth from their parents is received from the database of Statistics Netherlands (CBS). Social Economic Status (SES) of the residential area is taken as a proxy for parental education. A fourfold number of matched control subjects is collected from the CBS population database, matched on month and year of birth, residential area, sex, and ethnicity. Parental ages at time of birth of the proband is calculated in days and logistic regression is carried out using the following equation/parameters: Psychiatric diagnoses - age_father*b1 + difference_in_years_with_age_mother*b2 + SES*b3.

Results: In total, 2,627 Schizophrenic, 2,329 Autistic, 8,634 Major depression, and 1,133 Bipolar disorder patients were available for analyses. Data on parental age and the risk for developing these disorders will be presented. We hypothesize that the risk for developing a psychiatric diagnosis increases linearly with age of the father, adjusted for age of the mother, age difference between parents and socio-economic status. Previous studies indicated that schizophrenia is associated with higher paternal age, whereas bipolar disorder and autism seem to be associated with both paternal and maternal ages. Thus far, no studies reported an association between parental age and the risk for major depression disorder.

Discussion: Although schizophrenia, bipolar disorder, autism, and major depression are heterogeneous disorders, results from the parental age analyses could give more insight in the etiology of these diseases. If advanced parental age is associated with risk to developing psychiatric disorders, we should examine whether de novo genetic mutations or epigenetic mechanisms may contribute to this effect. As far as we are aware, this is the first large-scale population-based study to compare the four main psychiatric diagnoses on parental age in a single cohort.

doi:10.1016/j.schres.2010.02.255

Poster 28
IS TRAUMATIC BRAIN INJURY A RISK FACTOR FOR PSYCHOSIS? A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Traumatic brain injury (TBI) has long been implicated in the development of a range of neuropsychiatric disturbances, such as cognitive impairments, mood disorders, anxiety disorder and behavioural problems. However the question of whether TBI is a risk factor for psychosis remains somewhat controversial. To help clarify the evidence we conducted a systematic review and meta-analysis of available studies on psychosis among individual who have suffered TBI.
Methods: We searched for papers that reported on prevalence rates of psychosis following traumatic brain injury or allowed calculation of prevalence rates from data provided in the paper. We did computer-assisted searches, scanned reference lists, searched journals and corresponded with authors where necessary. We included case-control studies, cohort studies and family studies. Estimates of prevalence of psychosis from different studies were combined using fixed or random-effects meta-analysis, as appropriate, with the data presented in forest plots. Heterogeneity among studies was estimated.

Results: Our literature search and search of reference lists yielded 10015 references. The search was then limited to humans, which resulted in 9131 studies. Of these, 162 were considered to be potentially relevant. We excluded 154 studies, which did not meet inclusion criteria. We identified 8 studies which met our inclusion criteria, of which two were family studies, two were nested case-control studies and four were cohort studies. The overall pooled data revealed a significant association between TBI and subsequent psychosis (adjusted odds ratio = 1.15, 1.04-1.26). However there was significant heterogeneity between the studies (Heterogeneity $\chi^2 = 30.70$ (d.f. = 7); p = 0.000; $I^2 = 77.2\%$). Therefore, we decided to examine the family studies and case-control/cohort studies separately. Overall, pooled data from the 6 population-based cohort and case-control studies showed an increased risk of development of schizophrenia or psychotic disorder in individuals who had been exposed to TBI (adjusted odds ratio = 1.1, 1.005-1.231). However there was significant heterogeneity between the studies (Heterogeneity $\chi^2 = 26.43$ (d.f. = 5); p = 0.000; $I^2 = 81.1\%$). Pooled data from the two family studies show an increased risk of schizophrenia after TBI in individuals who have a family history of schizophrenia or psychotic disorder in individuals who had been exposed to TBI (adjusted odds ratio = 1.1, 1.005-1.231). However there was significant heterogeneity between the studies (Heterogeneity $\chi^2 = 26.43$ (d.f. = 5); p = 0.000; $I^2 = 81.1\%$). There was no significant heterogeneity between the two studies. We were not able to examine the influence of location or age at onset of head injury.

Discussion: We report an increased risk of psychosis following TBI. The increase among the general population is small - about 10% but the relative risk of psychosis from different studies were combined using fixed or random-effects meta-analysis, as appropriate, with the data presented in forest plots. Heterogeneity among studies was estimated. We were not able to examine the influence of location or age at onset of head injury. There was significant heterogeneity between the two studies. We were not able to examine the influence of location or age at onset of head injury.

Acknowledgements: This work was supported by a Clinician Scientist Award to M. Cannon from the Health Research Board (Ireland).

doi:10.1016/j.schres.2010.02.256

Poster 29
THE HIGH RISK CHILDREN OF MOTHERS WITH SCHIZOPHRENIA AND OTHER SEVERE MENTAL ILLNESS: DOES A MOTHER’S MENTAL ILLNESS INCREASE THE RISK OF SUDDEN INFANT DEATH SYNDROME?

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Background: Webb R et al (in press 2009) found an excess risk of Sudden Infant Death Syndrome (SIDS) for infants born to women with psychotic illness, including schizophrenia. For infants of women with psychotic illness, the absolute risk of SIDS has fallen since the global “Reducing the Risks” (RTR) campaign. However, the relative risk of SIDS in these women’s infants has increased compared with infants born to other women in the general population. We aimed to determine whether infants born in Western Australia (WA), to women with psychotic illness, were at greater risk of SIDS than other infants.

Methods: A population based record linkage case cohort study of infants (n = 472,772) born in WA from 1980 to 2001 inclusive, to 249,145 women. Of the live born, singleton infants 20,209 were born to women with severe mental illness (case mothers) and 436,725 to women with no mental illness (control mothers).

Results: Mothers of the 587 SIDS infants were compared with mothers whose infants were alive at one year.

Discussion: Infant’s sleep position, young maternal age, maternal smoking, single motherhood, maternal socioeconomic disadvantage, male infants and preterm birth are among the established risk factors for a SIDS death. During the study period, the Australian RTR for SIDS campaign validated stressed parental behavioural risk factors: safe infant sleeping posture; avoidance of smoke exposure and not over-wrapping the baby. In this study, the major risk factors for SIDS for infants born to women with psychotic illness, when compared with other women were: low birth weight, preterm birth, current or prior teenage and/or single motherhood, smoking in pregnancy and obstetric complications, all potentially modifiable risk factors. Of the RTR target behaviours, only smoking in pregnancy was available in our dataset, and only for 1998 to 2001 inclusive, making pre and post-RTR campaign comparisons difficult. However, unless rates of smoking during pregnancy had declined for women with psychotic illness, then we would not expect obstetric complications to be modified by the RTR. The next step in this program of work is to examine separately data for maternal illness onset prior to the infant’s birth compared with post-partum illness onset.

doi:10.1016/j.schres.2010.02.257

Poster 30
VRINT: A NEWLY DEVELOPED EARLY PSYCHOSIS SERVICE IN BELGIUM

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Background: Early detection and intervention services have been developed in different countries. In Belgium there is no tradition, nor funding of specialized treatment for early psychosis outside the mental hospital. The prolonged delay in accessing effective treatment often results in forced treatment starting in the context of severe behavioural crisis. After discharge lack of community care is among the reasons responsible for the frequent relapses after the first episode. These considerations were an argument to start in January 2009 with an early psychosis pilot project "VRINT". The first objective is to describe the structure and the organisation of VRINT, as well as the methods of inclusion, assessment and treatment. The
second objective is to describe the first epidemiological, inclusion, diagnostic, treatment and outcome data.

Methods: The project is based on 1) existing literature, 2) cooperation with projects for early intervention worldwide and 3) cooperation with other pilot projects in Belgium. A prospective and systematic collection of the epidemiological, inclusion, diagnostic, treatment and outcome data is conducted.

Results: The project serves a semi-urban population of 300,000 inhabitants. VHFRT applies a systematic and integrative model for assessment and treatment. Providing specialized, phase-specific, need-adapted and integrated care is crucial and particular attention is given to service accessibility for the patient and his family through a case management approach. To avoid early stigmatisation dimensional diagnoses are used. Psychotherapy according the Open Dialogue Model of Seikkula is an important issue. The project is organised for young patients between 14 and 35 years and offers engagement, assessment and treatment for at least five years. After 10 months 79 patients were referred to the project. 66 patients enrolled the engagement and assessment phase; 3 patients refused contact, resulting in only contacts with their help-seeking families; 4 patients did not meet criteria for early psychosis and 1 patient was referred to another specialised setting. Of the 58 patients included 20 are still in the engagement or assessment phase; 12 meet criteria for increased risk for psychosis, 19 for a first episode and 7 for the critical period of five years after the first psychosis.

Discussion: Significant numbers of young people were referred to this newly developed early psychosis service. More than half of them were in an at risk mental state or had already suffered a first psychotic episode.

doi:10.1016/j.schres.2010.02.258

Poster 31
THE PREVALENCE OF PSYCHOTIC SYMPTOMS IN CHILDREN AND ADOLESCENTS IN CLINICAL SETTINGS: A SYSTEMATIC REVIEW

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Background: There is evidence that psychosis exists on a continuum in the population in both adult and child and adolescent samples. A large number of studies have been carried out examining the prevalence rates of psychotic symptoms in adult populations; however studies in child and adolescent samples are scarcer. To date, no systematic review of the literature on psychotic symptoms specifically in childhood and adolescence has been carried out, solely in a clinical sample. This review aimed to establish prevalence rates of psychotic symptoms in children and adolescents.

Methods: A systematic review of all published literature up to February 2009 on the prevalence of psychotic symptoms in children and adolescents was conducted using electronic databases Ovid Medline, Pubmed and Psychinfo with an agreed battery of search terms: young people, adolescents, teenagers, child, psychotic symptoms, psychosis, paranoia, delusions, grandiosity, unusual beliefs/ideations, bipolar, positive and negative symptoms, dissociative disorders, prevalence. Reference lists of the relevant papers were examined to identify further articles. We included both clinical and community samples of children and adolescent. We excluded studies reporting prevalence rates in first episode schizophrenic studies and in specific prodrome or early intervention services for psychosis. We also excluded all studies of psychotic symptoms in children and adolescents with organic illnesses. In total 126 papers were located. Twenty nine relevant studies were identified: 14 from clinical and 15 from community settings. Methods used to identify psychotic symptoms included self-report questionnaires, clinical interview, standardised interview instruments and review of patient charts or a combination of methods.

Results: Reported prevalence of psychotic symptoms for clinical samples ranged from 0.4% to 81% across ages 2 to 19 years (outpatient samples 0.4 to 28%, inpatient samples 1.1 to 81%). Prevalence rates in community samples varied from 2% to 58.9% spanning ages 7 to 19 years (rates determined by questionnaire 6% to 58.9% and rates determined at interview 9% to 50%).

Discussion: Differing methodology across studies is reflected in a wide variation of rates of psychotic symptoms both within and across clinical and community samples. Research in this area would benefit from a standardised developmentally appropriate screening instrument with high sensitivity for identifying psychotic symptoms in children and adolescents. Future studies could employ a two stage process to screen large samples of children and adolescents and determine rates of psychotic symptoms at interview.

Acknowledgement: This work was funded by a Clinician Scientist Award to M.Cannon from the HRB (Health Research Board, Ireland).

doi:10.1016/j.schres.2010.02.259

Poster 32
ONSET OF PSYCHOTIC ILLNESS: NEGATIVE SYMPTOMS INCREASING RISK FOR POSITIVE SYMPTOMS INCREASING RISK FOR IMPAIRMENT?

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Background: Cognitive and negative symptoms associated with schizophrenia may represent alterations in brain development associated with distributed genetic risk, influencing a final common pathway of neurotransmitter dysregulation resulting in the onset of positive psychotic symptoms, particularly when combined with environmental exposures such as cannabis, developmental trauma and urbanicity. The epidemiological predictions of this model were tested.

Methods: A prospective cohort study was conducted in a sample of originally n = 3021 adolescents and young adults, aged 14-24 years at outset, over a period of 8.4 years, in Munich, Germany (Early Developmental Stages of Psychopathology Study). Measures of psychopathology and clinical relevance were assessed by clinical psychopathology and clinical relevance were assessed by clinical psychologists using the Composite International Diagnostic Interview (DIA-X/M-CIDI).

Results: Both positive and negative psychotic symptoms were frequent (5-year cumulative prevalence rates of around 12%) and occurred in combination more often than predicted by chance. Negative symptoms revealed a pattern of socio-demographic associations indicative of developmental impairment, whereas the positive symptoms were associated with environmental risk factors such as trauma, cannabis use and urbanicity. Negative symptoms predicted positive symptoms over time, and co-occurrence of positive and negative symptoms for schizophrenia was strongly related.
negative symptoms was predictive of clinical relevance in terms of secondary functional impairment and help-seeking behaviour.

**Discussion:** Results suggest that the liabilities underlying negative features of psychotic illness are distributed at a population level and drive the ontogenesis of positive psychotic experiences after exposure to environmental risks, increasing the likelihood of impairment and need for care.

doi:10.1016/j.schres.2010.02.260

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**Poster 33**  
**TO COMPARE MORTALITY IN 1175 PATIENTS WITH PSYCHOSIS AND THEIR FIRST DEGREE RELATIVES TO CORRESPONDING GROUPS OF MENTALLY HEALTHY CONTROLS**

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**Background:** The Malmö Preventive Study is a general health-screening program that started in 1974. Over 33 000 (approximately 70%) of the middle aged Malmö (Sweden) population at the time entered the study.

**Methods:** A case control sample of 1175 PS patients (202 (17%) with SC and 158 (13%) with BP), and 5000 age and sex matched C was identified from the Malmö cohort. Further, 2701 first-degree relatives (parents, siblings, and children) to the PS and 14518 for SC and 158 (13%) with BP, and 5000 age and sex matched C was identified from the Malmö cohort. All subjects were record linked to the Swedish Hospital Discharge and Cause of Deaths registers until Dec 2006 (mean follow-up of 11.2 yrs). Odds ratios (OR) and 95% Confidence Intervals (CI) were calculated.

**Results:** Overall 1218 (24.4%) natural death occurred among C vs. 351 (29.9%) in PS, OR 1.32, (1.15-1.52). CVD caused death for 10.0% of C vs 13.0% of PS, (1.35, 1.11-1.64). Corresponding number was significantly higher among SC (19.3% (2.16, 1.50-3.10) but not among BP (9.5% (0.95, 0.55-1.62). RES was the cause of death in 1.7% of C and in 3.7% of PS (2.28, 1.57-3.30) with higher proportions but with similar distributions in SC (4.5%) and BP (4.4%). Of the first degree relatives 3744 (25.8%) related to C and 723 (26.8%) to PS subjects died a natural death (1.05, 0.96-1.15). Corresponding numbers of deaths were 12.6% and 13.2% (1.05, 0.94-1.19) for CVD and 2.4% and 2.3% (0.97, 0.74-1.27) for RES, respectively.

**Discussion:** Death caused by CVD was significantly more frequent in PS vs C subjects. This was most frequent among SC; less frequent than C among BP. RES as cause of death was also more common among PS vs C but without substantial differences between SC and BP. No major differences were seen for frequency or cause of death between all first-degree relatives to PS vs C subjects. Further studies will focus on analyses of co morbidity in siblings.

doi:10.1016/j.schres.2010.02.261

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**Poster 34**  
**PRODROMAL SYMPTOMS: DIFFERENTIAL EFFECTS OF SEX AND FAMILY HISTORY**

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**Background:** Family history and sex differences have been implicated in some of the heterogeneity in clinical symptom presentation in schizophrenia and other psychotic disorders. To date, studies of the joint effects of sex and family history of disorder have focused on clinical populations. Yet the recent finding that sex differences in age at onset of schizophrenia are only observed among patients without a positive family history (Esterberg et al., submitted) suggests the importance of examining the joint effects of family history of disorder and sex on the earliest stages of the illness. Accordingly, this report examines the joint impact of family history and sex on the severity and profile of prodromal symptoms in individuals at-risk for psychotic conversion.

**Methods:** Participants included 325 young adult (mean age = 18.19) prodromal patients from the multi-site North American Prodromal Longitudinal Study (NAPLS). Family history was determined by participant interview and corroborative data from available family informants. Eighty-nine percent of the sample reported a FH of mental illness (42% psychosis; 47% non-psychotic Axis-I disorder). Participants were grouped on the basis of a family history of mental illness in a 1st or 2nd degree relative (psychotic illness, non-psychotic mental illness, and no FH of mental illness). Prodromal symptoms were assessed at baseline, and 6- and 12-month (N = 133) follow up periods, using severity ratings from the Structured Interview for Prodromal Syndromes (SIPS).

**Results:** ANOVA and student t-tests explored the main effects of family history and sex on baseline prodromal scores for positive, negative disorganized and general symptoms. Results showed that a family history of psychosis or other Axis I disorder did not significantly differentiate baseline prodromal symptoms. However, there was a trend for patients with a 1st-degree relative with a psychotic disorder to have a greater severity of negative symptoms than prodromal patients with a 1st-degree relative with an Axis I disorder (t = 1.359, p = 0.088). Significant main effects were found for sex, with male participants having significantly greater negative symptoms than female participants (t = -2.28, p = 0.01), and female participants having more general symptoms than male participants (t = 2.41, p = 0.01). A two-way MANOVA revealed a trend for an interaction between sex and family history status (F = 1.798, p = 0.08), suggesting that family history was associated with positive and negative prodromal symptoms in a sex-differentiated manner. For male patients, baseline negative symptoms were more severe among those with a family history of psychosis than those with a family history of a nonpsychotic Axis I disorder (t = 2.93, p < 0.01), and there was a trend for baseline general symptoms to be more severe among those with a family history of psychosis relative to those with no family history (t = 1.52, p = 0.067). For female patients, baseline general symptoms were greater in those with a family history of an Axis I disorder relative to those with a family history of a psychotic disorder (t = -1.68, p = 0.05).

**Discussion:** The current study highlights the importance of sex and family history in the presentation of the psychosis prodrome. Further study of the relation of sex and family history with prodromal symptom presentation, course, and conversion will not only identify those at greatest risk for developing a psychotic disorder, but will also aid in the identification of new treatment targets.

doi:10.1016/j.schres.2010.02.262
Poster 35
AWARENESS OF WEIGHT STATUS AND DESIRE FOR WEIGHT CHANGE AMONG PSYCHOTIC PATIENTS WITH SEVERE MENTAL ILLNESS

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Background: Obesity among patients with chronic mental illness is a significant issue and is coming under increasing scrutiny, especially with studies documenting significant weight gain associated with antipsychotic and mood stabilizing medications. There have been few studies examining the perspectives of patients themselves on their weight status and desire for change.

Methods: Northcoast Behavioral Healthcare System is a hospital for the mentally ill in Ohio, consisting of long-term forensic patients as well as acute care patients. Staff asked patients' perceptions of their weight status, their concern about their weight, their level of desire to lose weight, as well as documenting their stages of change for weight loss. All refusals to participate were noted, as well as the patient's most recent BMI (Body Mass Index). We separated patients into two groups—those with psychotic diagnoses (schizophrenia, schizoaffective disorder, and bipolar disorder with psychotic features), and non-psychotic disorders (e.g. major depression, adjustment disorder, substance abuse disorders, etc).

Results: Eight forensic units and seven acute care units were included in the survey. A total of 259 patients were interviewed. There were 246 completed surveys by patients. Of these, there were 193 psychotic patients, consisting of 153 males (79%), 40 females (21%); 49% black and 49% white. The mean age of the psychotic patients was 42.6. Among 89 psychotic patients, 23.3% of were normal weight (BMI <25 kg/m²), 30.1% were overweight (BMI >/= 25 kg/m², <30), and 46.1% were obese (BMI >/= 30). When 177 psychotic patients were asked about their efforts to lose weight, 58.2% were in the precontemplation stage, 7.3% were in the contemplation stage and 35.4% were in the action/maintenance stage. Among the 82 obese psychotic patients, there was no significant difference in the stages of change for weight loss. Among 89 psychotic obese individuals, 7.9% believed they were below their ideal weight, 16.9% believed they were at their ideal weight, 60.7% believed they were above their ideal weight and 14.6% were unsure. Among 89 psychotic obese, 52.8% were not concerned about their weight, 22.5% were a little concerned, 15.7% were concerned and 9.0% were very concerned. Among 87 psychotic obese, 43.7% wanted to lose weight, 31.0% did not want to lose weight, and 25.3% were unsure.

Discussion: Our research demonstrates that patients with psychotic illness have significant problems with overweight and obesity, and that their perceptions about their weight status vary considerably. These perception disparities may be an important limiting factor to consider when developing interventions to reduce obesity among this patient population.

doi:10.1016/j.schres.2010.02.263

Poster 36
EMOTIONAL AND BEHAVIOURAL SYMPTOMS OF PSYCHOPATHOLOGY AMONG ADOLESCENTS WITH PSYCHOTIC-LIKE EXPERIENCES

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Background: Psychotic-like experiences (PLEs) in childhood and adolescence are associated with increased risk for adulthood psychiatric illness, including psychotic disorder. However, little is known about the psychopathological profile associated with PLEs in the general adolescent population.

Methods: Behavioural and emotional symptoms were assessed in a general population sample of 681 school-going adolescents aged 11 – 13 years using the Strengths and Difficulties Questionnaire. History of PLEs was assessed using the Adolescent Psychosis-like Symptom Screener (APSS), which has previously been shown to be a valid instrument for identifying PLEs in the general adolescent population.

Results: 6.6% of the total sample scored in the abnormal range on the SDQ. Adolescents who reported PLEs were significantly more likely to have an abnormal SDQ score (OR = 4; p < 0.001), including significantly higher rates of emotional, conduct and attention deficit/hyperactivity symptoms and peer problems (all p < 0.001). There were no differences in scores for prosocial behaviour.

Discussion: Adolescents with PLEs are at significantly increased risk for a wide range of psychopathological problems. Longitudinal research is necessary to determine what effect comorbid emotional and behavioural symptoms have on risk for adulthood psychosis among this population.

doi:10.1016/j.schres.2010.02.264

Poster 37
SELF-REPORTED PSYCHOTIC SYMPTOMS AMONG THE GENERAL POPULATION OF BUENOS AIRES CITY

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Background: There is evidence that psychosis is not an all-or-nothing phenomenon and that psychotic disorders are continuous with psychotic symptoms in the general population. The aim of this study was to assess the prevalence of psychotic symptoms among the general population of Buenos Aires city.

Methods: A sample of 1036 individuals aged 18 to 91 years were surveyed at 15 different neighborhoods of Buenos Aires city. Their psychiatric-like experiences were assessed by several questions about unusual experiences in the last week and by the paranoid ideation subscale of the Symptom Checklist-90 Revised (SCL-90-R). The calculated response rate for the survey was 67.6%.

Results: Eighteen percent of the surveyed revealed that they had experienced one or more psychotic symptoms in the previous week. Auditory hallucinations were reported by 7.2% of the surveyed population; visual hallucinations by 9.7%, reference ideation by 5.6%, paranoid ideation by 4.2%, influence experiences by 3.1%, thoughts stolen by 2.8% and thoughts inserted by 1.4%. Three or more psychotic symptoms were reported by 4.6% of the surveyed. Almost half of them were on psychological or psychiatric treatment, a third were medicated and 25% believed they had a mental illness. There were no significant differences by sex or age between the individuals that had psychotic symptoms or not. Almost 19% had an index compatible with risk of having pathology and 0.7% had an index that suggests severe pathology according to the SCL-90-R subscale. There was a significant correlation between the paranoid ideation subscale and the number of psychotic symptoms. Almost 45% of the individuals that reported at least one psychotic symptom had experienced a stressful situation the week before. Compared with persons without psychotic symptoms, individuals with psychotic symptoms were significantly more likely to report recent stressful
situations (81% vs 29%). Level of education and stress were factors associated with psychotic symptoms.

**Discussion:** A high percentage of the general population of Buenos Aires city reported psychotic symptoms. This supports the hypothesis that psychosis exists in the population as a continuum rather than just a categorical diagnosis.

doi:10.1016/j.schres.2010.02.265

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**Poster 38**

**SUICIDE ATTEMPTS AT THE TIME OF FIRST ADMISSION AND DURING EARLY COURSE SCHIZOPHRENIA: A POPULATION BASED STUDY**

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**Background:** Early schizophrenia is a period of increased suicide risk, yet past research does not use national population based data to examine the extent of suicide attempts in first admission schizophrenia and risk factors associated with subsequent suicide attempts. This study aims to examine suicide attempt rates at time of first admission and risk factors for subsequent suicide attempts over the early course of illness in national population-based data.

**Methods:** All first admissions for schizophrenia in a national population based Israeli cohort from 1989 to 1992 were followed through 1996 (n = 2293). The data were from the National Psychiatric Hospitalization Case Registry of the State of Israel, a complete national registry of psychiatric admissions that includes suicide attempt data prior to admission.

**Results:** Attempted suicide rates were: 8.5% (n = 196) at the time of first admission and 6.6% (n = 151) over the follow-up period. Of those with a suicide attempt at first admission, 31.6% (n = 62) made a subsequent suicide attempt during the follow-up period (OR = 10.44, 95% CIs = 7.22 to 15.09). Binary logistic regression modeling showed that protective factors of subsequent attempts included being female, aged 36 to 40 at time of first hospitalization, completion of more formal education, whereas a suicide attempt at first hospitalization increased risk ten-fold. Risk profiles from recursive partitioning were derived to predict sub-groups of patients at risk of a subsequent suicide attempt. For example, those characterized by an attempt at time of first admission, college educated, female and not married were at salient risk (45.9% (17/37), OR = 13.46, 95% CIs = 6.89 to 26.3). The risk profiles together correctly classified 90.7% (137/151) of subsequent suicide attempts.

**Discussion:** Suicide attempts at time of first admission and premorbid years of education have long-term prognostic utility and risk profiles are available.

doi:10.1016/j.schres.2010.02.266

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**Poster 39**

**CONCORDANCE RATES AND EARLY RISK FACTORS IN SCHIZOPHRENIA: A TWIN STUDY**

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**Background:** From early twin studies the concordance rates for schizophrenia is 33-78% in MZ twins and 8-28% in DZ. More recent twin studies have estimated rates of 41-65% in MZ twins and 0-28% in DZ. There is empirical evidence for these methodological procedures being systematically associated with concordance rates, so that register based sample selection and zygosity determination by genetic testing significantly lower concordance rates. Environmental factors have been shown to increase the risk of developing schizophrenia, including perinatal events, CNS infections in childhood, adverse childhood experiences and drug abuse. It is likely that there is an additive effect of several risk factors. 2/3 of all MZ twin pairs share placenta and chorion while the other 1/3 have separate placenta and this may be a key environmental factor. One study indirectly showed that mono-chorionic MZ twins have a higher concordance for schizophrenia than di-chorionic MZ twins. This could indicate, that a refinement of concordance rates based on chorion status may be plausible.

**Purpose:** The overall purpose of this planned study is to examine clinical endophenotypes and early risk factors in a twin study design. There are 2 specific aims of the present part of the twin study: 1) To establish concordance rates in the included twins after a validation of diagnosis (SCAN), zygosity (blood sample) and chorion-placental status (birth records), which, to our knowledge, has not been done before. Also we want to examine whether the concordance rates differ for twins with and without a family history of schizophrenia. 2) To identify early risk factors for schizophrenia and examine whether there is a synergistic effect of several risk factors towards developing schizophrenia and, to identify environmental predictors of discordance in twins.

**Method:** Twins, concordant and discordant for schizophrenia, will be included from the Danish Twin Register, and we plan to include min. 40 MZ pairs matched with an equal no. of DZ twin pairs and healthy twin pairs. Data on risk factors from the Danish registers of known high quality will be linked and combined with the most recent neurobiological examination methodology.

doi:10.1016/j.schres.2010.02.267

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**Poster 40**

**SUNLIGHT, NEUROULATION AND THE “MADNESS-CREATIVITY” NEXUS: A SCHIZOPHRENIA-LIKE BIRTH-MONTH EFFECT AMONG ARTISTS AND MATHEMATICIANS**

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**Background:** Schizophrenia studies dealing with patients mostly born during the first half of the 20th century, a period of more intimate human exposure to seasonal factors such as sunlight, found the “birth-month effect,” a tendency among the afflicted to have been born most often in late winter and least often in late summer. Based on comparable early 20th-century birth data, we (Marzullo & Fraser, 2005, 2009) found the same birth rhythm first among children with neural-tube defects (NTDs) and later among baseball players with extreme left-handedness and other manifestations of cerebral asymmetry deficits. We also noted that when viewed in terms of conceptions rather than births, the rhythm showed an intriguing correlation with annual photoperiod: i.e., it pointed to a conception maximum in late May, a month before the summer solstice, and a minimum in late November, a month before the winter solstice. These timings, coupled with evidence that a) schizophrenia is associated with cerebral symmetry deficits, and b) left-right asymmetries are established concomitantly with neural-tube closure during the early fourth embryonic week, led us to a hypothesis implicating mother’s blood-mediated sunlight actions capable of inhibiting both processes. Based on evidence that the embryonic processes of asymmetry development and neural tube closure are both uniquely sensitive to free-radical
inhibition, a mechanism envisaged for those sunlight actions involved the ability of intense UV and visible light to deplete skin and blood antioxidants. Prompting the present creativity studies was the ages-old notion of a nexus between “madness” and “genius” coupled with many laterality studies associating more intuitive modes of thought with the right hemisphere.

**Methods**: Based on 48,038 biographies found in a 1970 edition of *Who's Who in America* (WWA), an initial study was a general test of association between month of birth and success in different kinds of occupations. This study having shown a remarkable birth-month difference between “artist” and “un-artist” occupations, subsequent studies used more specific artist databases (e.g., *Contemporary American Painters, American Composers, American Writers*) to test whether, upon stratification, a difference would be found between more successful subgroups (e.g., artists with longer biographies) and less successful ones (e.g., those only briefly mentioned). The WWA study having also indicated a birth-month contrast between biologists and mathematicians, this effect was pursued with a study of all life-scientists and mathematicians found in the *Dictionary of Scientific Biography* (DSB), a 17-volume compendium covering all major figures in the history of western science.

**Results**: In the WWA study, a group representing 3,533 “VPL-Artists” (all those engaged in Visual, Performing and Literary fields) showed the same birth-month rhythm as the schizophrenics. A group representing 4,042 “BAB-Pragmatists” (mostly Business Administrators and Bankers) showed a diametrically opposite rhythm. A group representing 812 “para-Artists,” i.e., art onlookers rather than creators (art critics, historians, curators, etc.) showed the BAB-Pragmatist rhythm. In stratification studies, the top, more “important” classes of painters, actors, composers, or writers showed high, positive ratios of May-Jun to Nov-Dec conceptions; the bottom, more mediocre classes showed negative ratios. In the DSB study, a group representing 787 biologists (mean birth year: 1781) showed the BAB-Pragmatist type of rhythm; a group representing 576 mathematicians (mean birth year: 1784) showed the VPL-Artists rhythm.

**Discussion**: (See Marzullo & Boklage, this conference).

doi:10.1016/j.schres.2010.02.268

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**Poster 41**

**THE AUSTRALIAN SCHIZOPHRENIA RESEARCH BANK (ASRB): QUALITY ASSURANCE AND CONTROL FOR A COMPREHENSIVE CLINICAL, NEUROPSYCHOLOGICAL, GENETIC AND NEUROIMAGING DATABASE FOR RESEARCHERS**

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**Background**: The Australian Schizophrenia Research Bank (ASRB) is an example of a large scale database comprising clinical, cognitive, neuroimaging and genetic data for schizophrenia probands and healthy controls. Procedures have been developed to ensure the quality and integrity of the ASRB data. The quality assurance procedures for data acquisition, storage and distribution stages will be described.

**Methods**: Comprehensive training in all clinical and neuropsychological measures was completed for staff involved with the data collection component of the study. Clinical and neuropsychological batteries were recorded for training and subject to inter-rater reliability analysis between clinicians, and comparison with a “gold standard” rater. Random sampling of clinical interviews was also completed and diagnostic inconsistencies taken for review by chief investigators on this project. Clinical assessment software for automated data entry that also contains fixed data input parameters to reduce data entry errors has been utilised. Once electronically uploaded to a centralised database, data is further reviewed before final inclusion in the active dataset. With regards to blood samples, OD readings are undertaken on each genomic DNA sample using a Nanophotometer to obtain A260:A280 ratios > 1.8 as an indication of the DNA quality. Prior to sending samples to researchers, DNA quantitation may be checked using PicoGreen assay for dsDNA. For brain scans, a Siemens head coil phantom is regularly used at each participating site to establish and monitor scanning quality across sites. After scanning acquisition, data is transferred to a central processing office where it is checked for artefacts and general image quality.

**Results**: For the diagnostic assessment (97 DIP questions), raw agreement across all raters was 85.3%, with a mean kappa for all items of 0.6 (range = 0.42-0.86). For MRI scans (N = 398), 19% (N = 76) were found to have artefacts (e.g., movement, ringing), however these were retained as they did not exceed threshold. Incidental findings were reported for 8 participants (0.2%). Blood samples were collected in all participants (N = 717), and where DNA did not meet sufficient ratio, sample were redrawn (0.03%).

**Discussion**: Comprehensive quality control procedures are in place for the ASRB with systematic reporting and review processes.

doi:10.1016/j.schres.2010.02.269
Poster 43
METABOLIC ALTERATIONS IN THE CORTEX OF A MOUSE MODEL WITH GLUTATHIONE DEFICIT – RELEVANCE TO SCHIZOPHRENIA

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Background: Glutathione (GSH) is a major redox regulator and antioxidant and is decreased in cerebrospinal fluid and prefrontal cortex of schizophrenia patients [Do et al. (2000) Eur J Neurosci 12:3721]. The genes of the key GSH-synthesizing enzyme, glutamate-cysteine ligase catalytic (GCLC) and modifier (GCLM) subunits, are associated with schizophrenia, suggesting that the deficit in GSH synthesis is of genetic origin [Gysin et al. (2007) PNAS 104:16621]. GCLM knock-out (KO) mice, which display an 80% decrease in brain GSH levels, have abnormal brain morphology and function [Do et al. (2009) Curr Opin Neurobiol 19:220]. Developmental redox deregulation by impaired GSH synthesis and environmental risk factors generating oxidative stress may have a central role in schizophrenia. Here, we used GCLM KO mice to investigate the impact of a genetically dysregulated redox system on the neurochemical profile of the developing brain.

Methods: The neurochemical profile of the anterior and posterior cortical areas of male and female GCLM KO and wild-type mice was determined by in vivo 1H NMR spectroscopy on postnatal days 10, 20, 30, 60 and 90, under 1 to 1.5% isoflurane anaesthesia. Localised 1H NMR spectroscopy was performed on a 14.1 T, 26 cm VNMRS spectrometer (Varian, Magnex) using a home-built 8 mm diameter quadrature surface coil (used both for RF excitation and signal reception). Spectra were acquired using SPECIAL with TE of 2.8 ms and TR of 4 s from VOIs placed in anterior or posterior regions of the cortex [Mlynárik et al. (2006) MRM 56:965]. LCModel analysis allowed in vivo quantification of a neurochemical profile composed of 18 metabolites.

Results: GCLM KO mice displayed nearly undetectable GSH levels as compared to WT mice, demonstrating their drastic redox deregulation. Depletion of GSH triggered alteration of metabolites related to its synthesis, namely increase of glycine and glutamate levels during development (P20 and P30). Concentrations of glutamine and aspartate that are produced from glutamate were also increased in GCLM KO animals relative to WT. In addition, GCLM KO mice also showed higher levels of N-acetylaspartate that originates from the acetylation of aspartate. These metabolites are particularly implicated in neurotransmission processes and in mitochondrial oxidative metabolism. Their increase may indicate impaired mitochondrial metabolism with concomitant accumulation of lactate in the adult mice (P60 and P90). In addition, the GSH depletion triggers reduction of GABA concentration in anterior cortex of the P60 mice, which is in accordance with known impairment of GABAergic interneurons in that area. Changes were generally more pronounced in males than in females at P60, which is consistent with earlier disease onset in male patients.

Discussion: In conclusion, the observed metabolic alterations in the cortex of a mouse model of redox deregulation suggest impaired mitochondrial metabolism and altered neurotransmission. The results also highlight the age between P20 and P30 as a sensitive period during the development for these alterations.

doi:10.1016/j.schres.2010.02.270

Poster 44
THE DIFFERENCES OF 2ND TO 4TH DIGIT LENGTH RATIO BETWEEN SCHIZOPHRENIA PATIENTS AND NORMAL CONTROLS

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Background: The ratio of 2nd to 4th finger(2D:4D) is known to be an indirect measure for prenatal sex hormone exposure. Sex hormone influences the brain development through structural and epigenetic modifications of neuron. We examined 2D:4D in schizophrenia patients and normal controls to investigate the relationship between prenatal sex hormone exposure and genesis of schizophrenia.

Methods: The subjects were 187 schizophrenia patients(male:94, female:93), and 190 normal controls(male:95, female:95). Hand- edness was measured with Edinburgh Handedness Inventory. Age of onset was examined by clinical records or questioning directly to the patients. The length of digit was measured by vernier caliper. T-test, ANOVA and ANCOVA were performed to analyze the data.

Results: There were no significant differences of the 2D:4D between schizophrenia and normal controls. Also, there was no significant correlation between 2D:4D and the age of onset. Among normal controls, 2D:4D was significantly higher (more feminized) in females than in males (F = 4.937, p = .027). But, there were no significant sex differences of 2D:4D among schizophrenia patients (F = 3.429, p = .066).

doi:10.1016/j.schres.2010.02.271
Discussion: These results imply that sex hormone changes during fetal period might play some roles in the development of schizophrenia.

doi:10.1016/j.schres.2010.02.272

Poster 45
VERBAL AND VISUAL MEMORY IMPAIRMENTS AMONGST YOUNG OFFSPRING AND HEALTHY ADULT RELATIVES OF PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR-DEPRESSION: SELECTIVE GENERATIONAL PATTERNS INDICATE DIFFERENT PREDICTIVE PATHWAYS

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Background: Memory deficits have been shown in patients affected by schizophrenia (SZ) and bipolar/mood disorder (BP). We recently reported that young high-risk offspring of an affected parent were impaired in both verbal (VEM) and visual episodic memory (VisEM). Understanding better the trajectory of memory impairments from childhood to adult clinical status in risk populations is crucial for early detection and prevention. Focusing on multi-generational families affected by SZ or BP, we aimed to compare the memory impairments observed in the young non-affected high-risk offspring to memory functioning in control adults, non-affected adult relatives and patients.

Methods: For 20 years, we followed up numerous kindred in the Eastern Quebec population. After having characterized the DSM phenotypes, we assessed cognition (N = 381) in three subsamples in these kindred and in controls: 60 young high-risk offspring of a parent affected by SZ or BP and, in the adult generations, 92 non-affected relatives and 40 patients affected by SZ or BP. VEM was assessed with the CVLT and VisEM with the Rey figures.

Results: The VEM deficits observed in the young offspring were also found in non-affected adult relatives and in adult patients. In contrast, the VisEM impairments observed in the offspring were present only in adult patients, not in the non-affected relatives.

Discussion: This is the first study to use cross-sectional family data to inspect potential different generational patterns between VEM and VisEM impairments across generations, i.e., in the period preceding disease onset up to adulthood. Implications for prevention and gene identification were derived from our observations regarding VEM and VisEM as they showed distinct generational patterns. A VEM deficit would better fit an intermediate phenotype model, allowing the detection of false negative among non-affected adult relatives and unaffected offspring, i.e., gene carriers not expressing the DSM syndrome. In contrast, VisEM deficit were found exclusive to patients and offspring, suggesting its potential use as an early precursor of later disease. Future research should take into account that these observed differences in generational patterns might reflect two relatively independent or heterogeneous developmental pathways with different gene-environmental risk mechanisms from the early years to adulthood. Even though this was not the main goal of our study, it is noteworthy that impairments in VEM and VisEM were shared in the SZ and BP patients, as well as in the non-affected relatives and offspring of SZ and BP patients, a commonality between SZ and BP already reported in former studies.

doi:10.1016/j.schres.2010.02.273

Poster 46
SPECIFICITY AND SEVERITY OF PRE-PsYCHOTIC JUVENILE BEHAVIOR: A 20-YEAR FOLLOW-UP STUDY

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Background: Psychosis is generally considered a disorder of early adulthood, but the pathological processes predisposing psychosis may already be present earlier in life. In comparison to the majority of studies comparing normal subjects with (pre)psychotic subject, the current study includes children aged 3 to 18 years showing all kinds of juvenile behavioral, emotional and social pathological abnormalities. This therefore allows us to address the question on specificity of a very wide spectrum of pre-psychotic behavioral abnormalities in comparison to their non-psychotic psychiatric counterparts.

Methods: The current study is a longitudinal follow-up study of psychosis of a cohort of 6700 psychiatrically assessed children at the Department of Child and Adolescent Psychiatry in Utrecht, The Netherlands, between 1984 and 2004 who are now on adult age. Both specificity for psychosis of pre-psychotic behavioral abnormalities by means of all or none categorical juvenile DSM diagnosis but also using a dimensional model focusing on symptom severity in terms of juvenile CBCL subscales and age and sex related risk for psychosis are discussed.

Results: This juvenile psychiatric cohort shows extreme high risk for psychosis. More specific, some juvenile psychiatric disorders are actually more at risk than others. Especially persistent disorders of childhood are at high risk for psychosis and surprisingly high risks were found for ‘odd and incongruent children’ with deferred and no diagnosis at all. Further, distinction in gender and age of assessment (childhood versus adolescence) and their prevalence for psychosis revealed different developmental pathways. Results derived from the CBCL total and subscale scores shows that pre-psychotic children are more severely impaired than their non-psychotic peers.

Discussion: The results emphasize the developmental dynamics of psychosis by the extreme high prevalence and therefore general elevated vulnerability for psychosis of this juvenile psychiatric cohort. Further, behavioral abnormalities such as thought, attention and social problems are specifically elevated in pre-psychotic subjects. These results are most pronounced in early childhood. The results of this study show further that the psychosocial outcome in adult life of pre-psychotic subjects must be considered rather poor even in comparison to their non-psychotic psychiatric peers and thereby underscore the severity of psychosis.

doi:10.1016/j.schres.2010.02.274
Poster 47
THALAMUS VOLUME AND SHAPE IN MALE ADOLESCENTS WITH EARLY-ONSET FIRST-EPISTODE PSYCHOSIS

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Background: Post-mortem and in vivo research in adult patients with first-episode psychosis indicate volume deficits in anterior, mediodorsal and posterior thalamic subnuclei. In adolescent patients with psychosis, it is unclear if these thalamic subregions are affected. The study was designed to compare whole and regional thalamus volume between a sample of minimally treated male adolescents with early-onset first-episode psychosis (EOP) and male healthy controls.

Methods: Baseline Magnetic Resonance Imaging (MRI) brain scans were obtained from 49 adolescent EOP patients, and 34 healthy controls. Subjects were younger than 19 years (age range 12-18 years), and EOP patients had the first psychotic symptoms before the age of 18 years. All patients had less than six months of psychotic symptoms at study enrollment. All patients had a two-year clinical follow up assessment including a K-SADS-PL interview. At the two year follow up, 13 patients had schizophrenia, 17 patients had bipolar I disorder, 16 patients had another psychotic disorder, and 3 patients did not fulfill K-SADS-PL criteria for psychosis. At baseline, all patients were on antipsychotic medication, the mean daily chlorpromazine equivalent (CPE) dose of the patient sample was 401. To ensure that our MRI findings were not dependent on scan preprocessing, two different automated procedures were used to assess thalamus volume (FreeSurfer and Fmrib Software Library-FIRST, both freely available). Regional thalamic shape analysis using Spherical Harmonics (SPHARM) was used to localize regional thalamic volume deficits.

Results: Within patients, right and left thalamus volumes were not correlated with dose of CPE. After controlling for total brain volume and age, EOP was associated with a significant volume deficit in the right thalamus. After a Bonferroni correction for multiple comparisons, the shape analysis showed surface deflation in a right anterior mediiodorsal subregion in EOP patients, meaning that in this anterior mediiodorsal region the surface of the patients sank inside the surface of controls. A volume deficit. Both volume and shape measures were not correlated with positive and negative PANSS symptom ratings.

Discussion: Thalamus volume deficits are present in minimally treated male adolescent EOP patients. Hyperfrontality in the right thalamic anterior mediiodorsal subregion was observed in male adolescent-onset EOP, indicating particular involvement of the individual anterior and mediiodorsal subnuclei at the onset of psychosis.

doi:10.1016/j.schres.2010.02.275

Poster 48
DISORDERS OF THE BASIC SELF AS A MARKER OF VULNERABILITY FOR SCHIZOPHRENIA: PRELIMINARY EMPIRICAL SUPPORT FROM NON-PSYCHOTIC HELP-SEEKING ADOLESCENTS

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Background: A recent first person account in Schizophrenia Bulletin (Koen, 2009) suggests that schizophrenia is fundamentally a self-disturbance. The overarching goal of this presentation is to report and discuss preliminary empirical support for the idea that a disorder of the basic self is indeed a core defect in schizophrenia that precedes its acute onset. More specifically, we will: 1) briefly present our analysis of the main limits of current research on early markers of risk for schizophrenia; 2) explain why we believe that a phenomenologically informed empirical exploration of subjective experience holds out the promise of addressing these limitations; and 3) present a pilot study among 87 non-psychotic help seeking adolescents that tested this hypothesis.

Methods: The prevalence and nature of basic self disorders was assessed with the Examination of Anomalous Self-Experience (EASE; Parnas et al, 2005). Next, to assess the relationship between disturbances of the basic self and current high-risk markers, the presence and severity of prodromal symptoms were screened with the Prodromal Questionnaire (PQ; Loewy et al, 2005) that was followed by a full Structured Interview for Prodromal Symptoms (SIPS: Miller et al., 2003) for participants who scored above the cut-point for probable prodromal syndrome on the PQ. Finally, deterioration in psychosocial functioning was assessed with Cornblatt et al.’s (2007) Social and Role functioning scales that were specifically developed to assess psychosocial functioning in the prodrome.

Results: A wide range of anomalous self experiences at different levels of severity has been reported by about two thirds of the sample. However, only less than one quarter (23%) was judged to suffer from anomalies of self experience at a clinically meaningful level. This proportion was smaller than the number of participants (32%) who met diagnostic criteria for a prodromal syndrome. The degree of overlap between the two conditions was moderate (14%) but not significant (c2(1)=2.9, p=.09). Similarly, an exploratory factor analysis with oblique rotation revealed that anomalies of self experience load of a different factor than prodromal symptoms, but that there is a modest correlation between the two factors. Interestingly, deterioration in social functioning loaded more highly on the anomalous self experiences factor than on the prodromal symptoms one.

Discussion: These preliminary findings suggest that anomalous self-experiences can enrich current early detection models by providing a means of further “closing in” on a smaller subgroup of individuals truly at high risk of schizophrenia spectrum disorder.

doi:10.1016/j.schres.2010.02.276

Poster 49
IMPAIRED MOTOR CONTROL IN ADOLESCENTS AT HIGH RISK FOR SCHIZOPHRENIA

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Background: We present evidence from the Harvard Adolescent High Risk Study designed to determine the association between
motor control and lateralization performance and risk for schizophrenia. A frequent observation in high-risk studies has been that a significant number of individuals who are at risk for or who have developed schizophrenic disorder have experienced motor symptoms or impairment of motor control, especially fine motor coordination, prior to the onset of psychosis. Prior work has suggested that motor control, specifically coordination and precision of movement as measured with a line drawing task, is associated with an earlier age of diagnosis, and with higher scores on psychometrically estimated schizotypy in normal young adults.

Methods: In contrast to many earlier studies, this investigation employed quantitative measures of motor behavior and a sample of younger high risk subjects. The study sample was composed of three groups, biological children and siblings of schizophrenia patient probands, biological children and siblings of affective psychosis patient probands and biological children and siblings of community control subject probands. All high risk and community control participants were between the ages of 13 and 25. Subjects were assessed psychiatrically and with an extensive battery of neuropsychological measures. We used the line drawing measure and standard assessments of handedness to estimate motor control and lateralization. We hypothesized that participants at risk for schizophrenia would exhibit deviant performance distinct from that of controls.

Results: The results are consistent with predictions. They demonstrate that compared to controls, measures of motor control and lateralization among the high risk participants are significantly different and similar to previous observations in schizophrenia and schizotypy.

Discussion: These findings add plausibility to the notion that increased vulnerability to schizophrenia, reflected in a greater degree of motor abnormality, could be associated with earlier recognition and diagnosis of the manifest psychotic disorder. The refinement of a profile of measures to detect high levels of vulnerability to schizophrenia may have value in the development of preventive interventions that might delay and/or mitigate the disorder.

doi:10.1016/j.schres.2010.02.277

Poster 50
GENETIC MODELLING OF CHILDHOOD SOCIAL DEVELOPMENT AND PERSONALITY IN TWINS AND SIBLINGS WITH SCHIZOPHRENIA

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Background: Abnormalities in early social development and schizotypal personality can be detected in patients with schizophrenia and also in their unaffected relatives. This study was designed to establish and quantify the degree to which these childhood and adolescent developmental abnormalities are genetically determined and the degree of shared genetic aetiology with schizophrenia.

Methods: We used a combined twin and family study design (n = 531) to retrospectively assess childhood and adolescent social adjustment and schizotypal personality traits in 98 MZ and DZ twin pairs (n = 196) varying in their concordance for schizophrenia as well as 156 sibling clusters (n = 335) varying in their concordance for schizophrenia. Data were analysed using both regression and genetic model fitting approaches.

Results: Schizophrenia was significantly associated with childhood and adolescent deficits in social adjustment and personality, with additive genetic effects being the main source of these phenotypic correlations.

Discussion: Abnormalities of social adjustment and personality are present in children and adolescents who later develop schizophrenia. These deficits reflect in part the influences of genetic risks that are shared with the disorder itself.

doi:10.1016/j.schres.2010.02.278

Poster 51
CHILDHOOD TRAUMA MAY BE RELATED TO TRANSITION TO PSYCHOSIS IN ULTRA HIGH RISK INDIVIDUALS

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Background: Childhood trauma (CT) are commonly endorsed by individuals with schizophrenia, and associated with psychotic symptoms, little is known about childhood trauma in UHR samples. In our previous study (Ucok et al, 2007) we found that childhood abuse and neglect was related to positive but not negative symptoms at first admission in patients with first-episode schizophrenia (FES). We compared 38 patients on ultra high risk for psychosis (UHR) with 65 patients with FES by using Childhood Trauma Questionnaire (CTQ), BPRS, SAPS, SANS and Calgary DSS. UHR defined based on Melbourne criteria, and transition to psychosis was defined by using CAARMS.

Results: There was no difference between groups in terms of physical, emotional, sexual abuse, and physical, and emotional neglect scores of CTQ. We found that emotional, and sexual abuse (p = 0.04), emotional (p = 0.009) and physical neglect (p = 0.05) was correlated to SAPS score. But, none of the CTQ subscale and total scores was found to be related to positive or negative symptom severity in UHR group. There was also no difference between brief limited intermittent psychotic symptoms (BLIPS) and attenuated psychotic symptoms groups on CTQ. However, we found that severity of emotional trauma was higher in those who transformed to psychosis (n=9) during the follow-up (p = 0.001).

Discussion: Our findings suggest that although the UHR group report CT as severe as FES group, the relationship between CT and symptoms of UHR state different from those with FES. However, our findings also suggest that CT might be one of the factors which contribute to transition to psychosis in UHR people.

doi:10.1016/j.schres.2010.02.279

Poster 52
ABNORMAL NEURODEVELOPMENT IN ATTENTION NETWORKS AND EXECUTIVE FUNCTIONS IN SCHIZOPHRENIA

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Background: Schizophrenia is a neurodevelopmental disorder with cognitive alterations involving attention, set shifting and working
memory. Until recently, tasks to assess these abilities were providing global performance measures without opportunity to investigate continuous performance measures from childhood to adulthood. Interaction of attentional networks as well as specific batteries of cognitive control and executive functions can be sensitive enough to detect developmental changes in normal children, adolescents and adults. In a previous study we tested 21 chronic schizophrenic patients aged 31(8) years old with predominantly negative symptoms using an adapted version of the interaction of attention network task (ANT) to increase the independence of these networks. We found a reduction of alertness with a positive influence on the executive control of attention.

**Method:** A group of 24 younger schizophrenia patients 25 (3) years old, with comparable disease duration was assessed with the attention network task and a short battery sensitive to the maturation of executive functions (Davidson et al. 2006). In this latter tests cognitive flexibility as well as spatial incompatibility, ability to hold in mind two elementary rules, task switching, and working memory were evaluated. The different tasks permitted to analyze performance with respect to gradual levels of inhibition control demands and memory load.

**Results:** The patients displayed no executive control of attention nor alerting impairment but an orienting deficit. Concerning executive functions, patients showed no impairment in the low and intermediate level of inhibitory control demand, while they demonstrated more errors in a spatial incompatibility task with a high demand of inhibitory control. In the working memory task, patients had comparable reaction times but committed more errors than controls in the low memory load condition (2 items to remember). In the high memory load condition (6 items), reaction times were longer and number of errors was elevated.

**Discussion:** With reference to the control group values established by Davidson’s et al (2006) using similar tests, our study clearly demonstrates a dysmaturation in inhibitory control and working memory. Overall, young schizophrenic patients showed pre-attentive disabilities in conjunction with impairments in cognitive tasks demanding more cognitive resources. Also while one level of executive control involved in working memory or spatial incompatibility might be impaired, other levels implicating the executive control of attention can simultaneously be preserved. Brain-imaging studies could provide further information about the different structures involved in these tasks. Behavioural studies evaluating patients in tasks sensitive to changes in neurodevelopment could be fruitful to understand cognitive alterations especially in the different stages of psychosis. Davidson et al. 2006: development of cognitive control and executive function from 4 to 13 years: evidence from manipulation of memory, inhibition and task switching. Neuropsychologia 44:2037-2078.

doi:10.1016/j.schres.2010.02.280

**Poster 54**

**DYSFUNCTION IN A DISCRETE CORTICOSTRIATAL CIRCUIT REFLECTS LIABILITY TO SCHIZOPHRENIA**

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**Background:** Three studies examining corticostriatal circuits will be presented. We tested the hypothesis that patients with schizophrenia have dysfunction in a specific corticostriatal circuit by examining skill learning. Two circuits were examined. A motor skill circuit that originates in the supplementary motor area and includes the supplementary motor area, putamen, globus pallidus and thalamus was studied using the Serial Reaction Time task (SRT). A cognitive skill circuit involving the caudate nucleus/dorsolateral prefrontal cortex and ventral striatum/orbitofrontal cortex was studied using the Procedural Classification Task (PCT).

**Methods:** Results: In the first study (Foerde et al 2009) we examined motor and cognitive skill learning in patients with schizophrenia and normal controls. Patients and controls were trained on both a motor skill (SRT) and a cognitive skill (PCT). We examined development of automaticity, using a dual task paradigm, across three training sessions for each task. Patients with schizophrenia were impaired at learning on the PCT compared to controls. Controls showed the greatest gain in performance within the first session, whereas patients only improved gradually across all three sessions and never reached the performance level of controls. In contrast, patients were not impaired at learning on the SRT relative to controls. These results suggest that patients with schizophrenia may have dysfunction in a specific corticostriatal sub-circuit. We conducted analyses that demonstrated that the differential deficit noted above was not due to psychometric differences between the two tasks. We examined the normal development of these two circuits in normal children and adolescents. Paralleling the results of the first study we found developmental differences in cognitive but not motor skill learning. While children tended to have slower reaction times.

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times on the SRT, they benefited as much as adolescents from the
sequenced trials and showed a similar decrement in performance in the
dual task condition. In contrast, adolescents learned faster and achieved
higher levels of accuracy on the PCT than the children. Both children
and adolescents showed little effect of the dual task, implying that both
groups automated the task well. These results provide additional
evidence of the independence of these two circuits. A third study tested
the hypothesis that deficient cognitive skill learning is associated with
liability to schizophrenia. Non-psychotic first degree relatives of
patients with childhood onset schizophrenia showed a slower rate of
learning on the PCT and a greater decrement in performance on the PCT
when performing a secondary task than age matched controls.
Discussion: These results indicate that dysfunction in the cognitive
skill learning circuit is associated with liability to schizophrenia.

doi:10.1016/j.schres.2010.02.282

Poster 55
THE REPEATABLE BATTERY FOR THE ASSESSMENT OF NEUROPSYCHOLOGICAL STATUS (RBANS) IN PATIENTS WITH SCHIZOPHRENIA: A PRELIMINARY STUDY IN ARMENIA

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Background: Objective. Psychiatric research in Armenia is attempting
to modernize its approach to research and treatment of schizophrenia. There is a paucity of resources regarding standar-
dized cognitive tests and no normative data to interpret tests results. The purpose of the present study was to translate the
Repeatable Battery for the Assessment for Neuropsychological Status (RBANS; Randolph et al., 1998) into Armenian, and examine the
validity of the translated version in a clinical sample.

Methods: A sample of 11 patients that met the DSM IV diagnosis
criteria for schizophrenia or schizoaffective disorder was recruited from
a state psychiatric hospital to participate in the study. An Armenian translated version of the RBANS was used to assess five
cognitive domains: immediate memory, visual-constructual ability,
language, attention, and delayed memory, as well as a global
measure, RBANS total score.

Results: Test performance was compared to US data from a non-
clinical healthy sample (N = 540) and patients with schizophrenia
(N = 59). The BRANS total score (M = 62) was more than two
standard deviations below the U.S. non-clinical sample, and 8-
points lower than the U.S. clinical sample. Patients’ performance on
indices of attention, immediate and delayed memory, was lower in
comparison to language and visual-constructual ability.

Discussion: Patients with schizophrenia demonstrated impairment
on all RBANS domains and exhibited a cognitive profile similar to
those reported in previous studies (e.g., Wilk et al., 2004). The low
RBANS total score in our sample in comparison to the U.S. clinical
sample (62 versus 70.5, respectively) may reflect the greater use of
conventional rather than atypical antipsychotics in Armenia’s
psychiatric state hospitals. Our results indicate that the RBANS is
a sensitive tool in identifying cognitive impairment in the
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by Fulbright scholars grant 49414540 (AA) from U.S. Department of
State Bureau of Educational and Cultural Affairs.

doi:10.1016/j.schres.2010.02.283

Poster 56
ACCESSIBILITY TO THE SEMANTIC ATTRIBUTES OF NON RECALLED WORDS IN SCHIZOPHRENIA

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Background: Many observations suggest that when people cannot
retrieve a solicited target from memory, they can still provide some
partial information about it. Patients with schizophrenia suffer from
several deficits of cognitive processes. In particular, they have impaired
memory, and impairments in the processing of contextual information.
They also suffer from a specific impairment in conscious recollection.
We examined the nature of the semantic information that schizo-
phrenia patients can access about words that they failed to retrieve.

Methods: Schizophrenia patients and their matched healthy controls
participants (according to age, gender, and education) had to learn
words of a putative foreign language, ‘somali’. Participants learned the
french translations of a list of 30 pseudo-Somali words. After several
learning sessions, they were tested by having to recall the french word
in response to the presentation of the Somali word. When they failed
(either after an omission or after an incorrect recall), they were asked to
determine the meaning of the somali word with respect to one of the	hreedimensions of the semantic differential —evaluation (good-
bad), potency (strong–weak), and activity (active–passive). Explicit
access to semantic attributes of the word was inferred from the
accuracy of these judgments. In addition, indirect access was inferred
from the tendency to make commission errors that have the same
polarity on the respective dimension as the correct word.

Results: The performances of correct recalls were equated in the
two groups. The identification of the contextual information related
to of the nonrecalled target items was at chance in both groups after
an omission error of the target. However, after having provided an
incorrect target recall, healthy participants remained able to
correctly identify the semantic attribute of the failed target item,
whereas schizophrenia patients were not.

Discussion: Schizophrenia patients had more difficulties to access
to the semantic dimensions of evaluation, potency and activity of a
failed target when they have previously provided an incorrect recall
when asked to retrieve the target answer. In addition to the
previously identified deficits in context processing, schizophrenia
patients also present specific impairments in the processing of
semantic attributes of words that cannot be recalled.

doi:10.1016/j.schres.2010.02.284

Poster 57
TRAUMATIC BRAIN INJURY AND SECONDARY PSYCHOSIS

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Background: The relationship between psychotic symptoms and
traumatic brain injury (TBI) is unclear, with an estimated prevalence
ranging from 0.7% to 9.8%. This dual diagnosis results in significant patient distress and disability, and can complicate broader aspects of rehabilitation. Despite this, our understanding of psychosis following TBI (PFTBI) is poor.

**Methods:** Twenty-four papers on PFTBI were reviewed.

**Results:** Studies show a highly variable range of psychosis onset, progression and course. Existing clinical, neurocognitive and localisation data suggested the absence of negative symptoms as a potential diagnostic distinction for PFTBI, revealed common deficiencies in language, verbal memory and verbal learning, and a higher prevalence of frontal and temporal (both left and right) lesions. However, substantial and potentially confounding methodological weaknesses were inherent in the majority of this research.

**Discussion:** Conceptualisations of the precise relationship between psychosis and TBI, and features of PFTBI, are premature until the considerable methodological limitations shown in the existing literature are addressed in comprehensive and standardised research. We anticipate initiating the first comprehensive investigation of clinical and cognitive/neuropsychological symptoms in PFTBI. Symptom trends that are distinctive of psychosis secondary to TBI may indicate the potential for a separate diagnostic category. Identification of potential risk factors may aid the detection of those at a higher risk for psychosis and allow management strategies to be implemented early, prior to the onset of advanced symptoms.

**Poster 58**

**MEMORY PROFILES IN SCHIZOPHRENIA: CATEGORIZATION VALIDITY AND STABILITY**

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**Background:** Distinct memory profiles in schizophrenia corresponding to Nearly-Normal (NN), Subcortical impairment (Sub) and Cortical impairment (Cort) have been identified by several investigators using cluster analytic techniques.

**Methods:** Neuropsychological assessments were obtained from 151 outpatients with schizophrenia or schizoaffective disorder from an urban community mental health center participating in a study of cognitive and vocational rehabilitation. Specific aims of the current study were to (1) perform a K mean cluster analysis using Hopkins Verbal Learning Test –II scores (2) create a decision rule for classification based upon cluster distributions and expected memory profiles for NN, Sub and Cort memory profiles and to determine the concordance between the observed clusters and the rational classification; (3) explore differences among classified groups on demographic features and illness characteristics and in neurocognitive and social cognitive domains; and (4) determine the stability of the classifications 12 months later.

**Results:** Empirically derived clusters were produced that corresponded to profiles of those of the three expected subgroups. Using simple decision rules, rationally-derived groups were created and had 90% classification agreement with cluster groups (Cramer’s V = .86; Gamma = .99). Comparison of groups in neurocognitive and social cognitive domains revealed significant group differences with NN>Cort and NN>Sub in all domains except visual/motor speed. Sub>Cort in verbal working memory and Sub did not differ from NN on Digit Span. NN>Cort in social cognition. NN performed within normal limits on all tasks except Digit Symbol Substitution.

Rationally derived groupings showed fair stability at 12 month follow-up with 65% classification agreement (Cramer’s V = .49, Gamma = .77). Specificity was good for NN (82.4%), fair for Cort (71.4), and poor for Sub (45.5%).

**Discussion:** Results replicated the presence of three distinct profiles using cluster analysis. Simple decision rules were created that successfully achieved excellent agreement with cluster membership. Neurocognitive and social cognitive findings supported the validity of the classifications. The simple rules created in this study can be used by other investigators to classify participants for neuroimaging and other studies investigating the significance of verbal memory profiles. This is the first study to investigate the stability of memory profile membership and found mixed results with best stability in the Nearly-Normal group. Possible sources of variance that reduced stability for Subcortical and Cortical groups include marginal cases, particularly for the Subcortical group, and issues such as motivation that may affect performance differentially at two points in time. These findings lend further support to the hypothesis that verbal memory may be an important source of heterogeneity in schizophrenia.

successful completion of the computerized cognitive testing (Cogtest), suggesting that this battery is an efficient measure of cognitive functioning in multicenter multinational clinical trials.

doi:10.1016/j.schres.2010.02.287

Poster 60
SOCIAL COGNITION IN SCHIZOPHRENIC PATIENTS: EFFECTS OF SEMANTIC AND PROSODY IN THE COMPREHENSION OF EMOTIONAL DISCOURSE

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Background: Social communication is a major problem in schizophrenia. Emotion recognition expressed during conversation is one of the components of social interaction. In healthy subjects, this recognition relies on the processing of ortholinguistic (semantics) and para-linguistic (emotional prosody) elements (Beaucousin et al. 2007, Cereb. Cortex). In patients, if comprehension impairments has already been evidenced separately for emotional prosody (Hoekert et al. 2007, Schizophr. Res.) and neutral semantics (Dollfus et al. 2008, Schizophr. Res.), no studies investigated the interaction between both elements in schizophrenic patients during emotional speech. We tested the hypothesis that schizophrenic patients present lesser performances in semantic and/or prosodic processes during emotional speech comprehension than healthy subjects.

Methods: The paradigm previously published (Beaucousin et al. 2007, Cereb. Cortex) is based on a corpus of sentences characterized by emotional semantic content. The selected emotions were anger, happiness and sadness. The sentences were expressed with (50%) or without (50%) emotional prosody to evaluate the effect of prosody. The performances in 16 stable schizophrenic DSM IV outpatients were analyzed and compared with 16 healthy controls matched on age, sex and educational level. Assessments included the Positive and Negative Syndrome Scale, the Thought Language and Communication and a verbal IQ. A three factor analysis of covariance (ANCOVA) was used with group (patients/controls), emotional category (anger, happiness and sadness), and prosody (with or without) as factors, the verbal IQ and the age as covariates.

Results: The ANCOVA showed an effect of group for the response rate (F1,30 = 12,4504; p = 0,0015). Patients were significantly impaired compared with controls. There was an effect of prosody with a higher response rate for sentences expressed with prosody than those without prosody (F1,30= 118,4318; p<0,0001). An effect of category was found for both the response rate (F2,60= 46,9887; p<0,0001) and the response time (F2,60= 218,7368; p<0,0001). Happiness was better recognized than anger and sadness. Sadness was the least easy and the slowest recognized emotion. There was a group x prosody interaction for the response rate (F1,30 = 7,0904; p = 0,0123) due to the fact that prosody improved more the performances of patients than controls. There was a prosody x category interaction for both the response rate (F2,60 = 11,4632; p<0,0001) and the response time (F2,60 = 10,0548; p = 0,0002) due to the fact that sadness was less recognized compared to other emotions even more when the sentences did not contain emotional prosody.

Discussion: Patients performed significantly lesser than controls whatever the presence of emotional prosody. This is the first time that impaired semantic comprehension with emotional content was evidenced. Emotional prosody improved performances in both groups but even more in patients than in controls. Moreover sadness was the emotion the most difficult to process for the patients. Consequently, these impairments could be one of the major components of their social inabilities. As patients took more advantage than healthy subjects of emotional prosody adjunction in the discourse, focusing attention to emotional prosody could be a way of cognitive remediation to improve social communication.

doi:10.1016/j.schres.2010.02.288

Poster 61
OLFACtORY IDENTIFICATION DEFICITS ARE A FEATURE OF SCHIZOPHRENIA AFTER IDENTIFICATION AS ULTRA-HIGH RISK AT THE PACE CLINIC

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Background: We have previously reported that olfactory identification (OI) deficits are a promising premorbid marker of transition from ultra-high risk (UHR) to schizophrenia, but not of psychotic illness more generally (Brewer et al, 2003). This finding is consistent with suggestions of arrested prefrontal neural development (reflected by OI deficits) in a subgroup of UHR clients, putatively reflecting a greater biological relative to psychological compromise. We propose that to understand the role of OI in schizophrenia, deficits need to be interpreted in the context of dynamic prefrontal maturational changes occurring during adolescence, whereby those UHR patients who are most likely to develop schizophrenia are also more likely to be ‘growing into a deficit’. Our previous findings also suggest the OI deficits remain stable (Brewer et al, 2001). In the current follow-up study, we investigated whether OI in a group of individuals identified as UHR at the Personal Assessment and Crisis Evaluation (PACE) Clinic discriminated between those who made the transition to schizophrenia relative to those who did not.

Methods: Transition data was collected from the first 254 individuals (Age=26.1 [S.D=5.1]) who were seen at PACE (from 1994 - 2006), all of whom received the University of Pennsylvania Smell Identification Test (UPSIT). Sixty-eight (26.8%) made the transition to psychosis (UHR-P) and of these, twenty-three (31.1%) received a diagnosis of schizophrenia (UHR-Scz). None have made the transition in the last 2.5 years.

Results: OI was significantly reduced in the UHR-Scz group at follow-up (Mean = 30.26 [S.D=5.2]) relative to those who either did not make the transition or who received a psychosis-spectrum diagnosis (Mean = 32.30 [S.D=4.0]); t(252) = 2.28, p<.05. OI could not be used to differentiate those who transitioned to psychosis (UHR-P; Mean = 31.57 [S.D = 4.57]), t(252) = 1.27, p = .21. In this adult cohort, comparison with UPSIT norms suggests that OI deficits in the UHR-Scz group are equivalent to a functional level that would already be interpreted as being impaired in a normal early adolescent cohort.

Discussion: Our follow-up UPSIT results provide further evidence that suggests increased likelihood of receiving a diagnosis of schizophrenia in a UHR cohort reflects greater degree of OI deficits.
In the context of tracking maturation of prefrontal neural regions during adolescence, it appears that the UPSIT may be a non-invasive probe for detecting orbitofrontal developmental arrest in those UHR patients who are at higher risk for developing schizophrenia. Brewer et al., (2001) AMJP, 158:107; Brewer et al., (2003) AMJP, 160:1790.

doi:10.1016/j.schres.2010.02.290

Poster 62
RELATIONSHIP OF NEUROCOGNITIVE FUNCTION AND IMPAIRMENT OF INSIGHT IN FIRST EPISODE SCHIZOPHRENIA

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Background: Impairment of insight is one of the common features of schizophrenia with clinical importance because of its relationship with treatment compliance and hence clinical outcomes. However, its etiology remains poorly understood. Various studies have suggested the link of poor insight with the neurocognitive functions particularly executive function and memory. The present study aims at evaluating the association between insight and measures of executive functions and working memory in patients with first episode schizophrenia and explore the contribution of these neurocognitive functions to the variance of insight.

Methods: Consecutive patients between ages 18 and 55 with first episode schizophrenia based on DSM-IV diagnostic criteria were recruited from adult psychiatric services covering a defined catchment area in Hong Kong. All the assessments were conducted within six months of starting treatment. Clinical symptoms were evaluated using Positive and Negative Syndrome Scale (PANSS). The Scale for Assessment of Unawareness of Mental Disorder (SUMD) was used to assess insight. Executive functioning was measured by the Wisconsin Card Sort Test (WCST) and Verbal fluency. Working memory was measured by the Letter Number Sequencing (LNS) test from the Wechsler Adult Intelligence Scale (WAIS).

Results: There were 79 patients completed the study. The average score of the first three items of SUMD were used as overall insight rating. Individual items were analyzed separately. After correction for multiple testing, WCST categories completed was found to be significantly correlated with overall insight rating (r = -0.337, p = 0.003). After analyzing the sub-scale of SUMD in detail, both WCST categories (r = 0.315, p = 0.006) and WCST perseverative error (r = -0.291, p = 0.011) were significantly correlated with awareness of consequence of mental illness (SUMD item 2) but not the awareness of having mental illness (SUMD item 1) and the awareness of need for medication (SUMD item 3). No significant correlations were found with other neurocognitive functions. While the symptomatology explained 26.8% of variance in the awareness of consequence of mental illness, WCST categories completed and perseverative errors explained 5.7% of the variance.

Discussion: The current study shows a significant association of WCST performance, particularly categories completed and perseverative errors, with poor insight in patients with first episode schizophrenia. No other neurocognitive functions were found to be significantly associated. This is in line with previous findings in both chronic and first episode patients. Though the contribution of these neurocognitive functions to the variance of insight is small, the consistence of the finding indicating that executive function could be one of the important elements of underlying neurocognitive deficit explaining poor insight. Further studies are needed to explore the etiological models for poor insight.

doi:10.1016/j.schres.2010.02.290

Poster 63
COUNTERFACTUAL THINKING IN SCHIZOPHRENIA PATIENTS

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Background: Thinking about what might have been, about alternatives to our own pasts, is central to human thinking and emotion. Such thoughts are called counterfactual thoughts (CFT). In healthy persons CFT is associated with learning, behavioral regulation, planning and correcting mistakes as part of an automatic cognitive pathway involving counterfactuals, intentions, and implementation of behaviors. CFT is uniquely associated with prefrontal (especially orbitofrontal) activation. Although the role of prefrontal cortex in schizophrenic symptoms has been extensively studied, it remains unclear as to how different aspects of prefrontal functioning is fractionated in schizophrenia and into specific behavior and cognitive performance.

Methods: The aim of our study was to examine the role of counterfactual thinking in schizophrenic patients. We used the model of Roese et al. (2008) that relates CFT and behaviour (figure 1). The present research examined the firsts and second link in this process: the activation of the CTF (link 1) and the automatic activation of intentions (link 2) by CFT. 2.1 Subjects Forty subjects who met DSM-IV criteria for schizophrenia and 40 healthy control participants were recruited. Exclusion criteria for both groups of participants were head injury, neurological disorders, and history of substance use. The two groups were matched in age, education, IQ and handedness. 2.2 Procedure To investigate the generation of CTF (link 1) we used two tasks. In the first task, we presented to the patient one history with 4 different scenarios. After the presentation of the history, we asked to the patient that list alternatives to solve the problem presented in the history. The second counterfactual measure was centered on inference resulting from the Counterfactual Inference Test (CIT; adaptation by Hooker et al., 2000). With the CIT we investigated the relation between CFT and judgment regarding social events.

To investigate the link 2 (automatic activation of intentions), we used a sequential priming paradigm to assess the automatic activation of the intentions by CFT (adaptation of Roese et al., 20008).

Results: In the study of generation of CTF, we obtained differences between the two groups. In the first task, schizophrenic patients generated less responses of CFT than controls. In the second task, the schizophrenic patients’ responses were different that the controls’ responses, indicating that the difference between the two groups was related with the difference in social functioning that were mediated by variation in CFT. When we investigated the link 2, the results showed that schizophrenic performed similarly to controls. Schizophrenic patients showed higher RTs than control subjects in both conditions. However, schizophrenic showed the same overall pattern than controls. Counterfactual judgements facilitated intention RTs relative to control judgements (Ms = 1737, 6 ms vs. 1911, 82 ms), t(15) = -3.404, p = .001.

Discussion: The present research focused on links 1 and 2. Our results were different that the obtained by Roese et al. (2008) in link 2. We found that the schizophrenic patients showed this same overall
pattern than controls. Whereas, in the link 1 the results obtained were similar to the showed by Hooker et al. (2000). The fact that the link 2 was preserved in schizophrenic suggests that could be efficacy the countereffectual therapy designed to increase or dramatize CFT oriented toward everyday social interactions. Regular practice with such CFT might produce improvement in social functioning.


**Poster 64**

ANXIETY COMORBIDITIES AND COGNITIVE EVOKED POTENTIAL IN PATIENTS WITH SCHIZOPHRENIA ANXIETY COMORBIDITIES AD COGNITIVE EVOKED POTENTIAL IN PATIENTS WITH SCHIZOPHRENIA

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**Background:** Anxiety disorders are common in patients with schizophrenia. The presence of such symptoms may influence the presence of core psychotic symptoms and may be correlated to the cognitive activities characteristics. Social Anxiety has been reported as highly frequently comorbid (Pallanti et al., 2004) and if its impact in the outcome and rehabilitation is becoming more evident, its meaning in term of “social cognition” deserves further investigation. Accumulating evidence suggests that anxiety and related disorders play a significant role in patients with schizophrenia, but few studies have examined multiple types of anxiety, and how they interact with different symptoms of schizophrenia. Obsessive-compulsive disorder (OCD) is a common comorbidity in schizophrenia, with prevalence rates ranging from 7.8% to 40.5%, both in first-episode schizophrenia and in chronic schizophrenia. (Attia et al., 2000; Poyurovsky et al., 2000, 2001; Tibbo et al., 2000) It has been suggested that obsessions and compulsions represent a separate symptom dimension of schizophrenia based on neuropsychological functioning or that OCD and schizophrenia share common pathophysiological features (Berman et al, 1998; Hwang et al, 2000; Lysaker et al, 2002; Cavallaro et al, 2003; Poyurovsky et al, 2005). Investigations, on the matter of this link between psychosis and anxiety beyond the clinical level are scarce. In schizophrenia research electrophysiological measures have been investigated to identify biomarkers of the disorder, indices enabling differential diagnosis among psychotic disorders, prognostic indicators or endophenotypes. An approach for eliciting neurophysiological correlates of cognitive functioning. The P300 evoked related potential is an index of endogenous cognitive processes elicited by infrequent sensory stimuli that are either novel or task relevant. It reflects a variety of cognitive processes elicited by a change in the sensory environment. These include directed attention, the contextual updating of working memory, and the attribution of salience to a deviant stimulus. (Turetsky et al., 2007).

**Methods:** P300 “oddball” and go/no-go paradigms to register frontal functionality dysfunctionliness criticized due to the limited efficacy in measuring frontal functionality (Towey et al.,1990; Morault et al., 1998). In the go/no-go paradigm, the greater wave amplitude that occurs when the subject has to stop (no-go signal) could be affected by the warning stimulus, not only by inhibitory activity. It is not clear if inhibitory activity itself (without a warning stimulus) is sufficient to produce greater wave amplitudes (Ritter et al., 1983). To emphasize the aspects of activation and inhibition a task similar to a go/no-go paradigm was chosen, but the task lacked a warning signal.

**Results:** We present preliminary data recorded from a sample composed by of DSM-IV Schizophrenia (n = 14) and/or OCD. Schizo-OCD (n = 11) subjects had simultaneous diagnoses of OCD and Schizophrenia and patients with OCD (n = 16), with a severity threshold of 0-16 points on the Y-BOCS (absence of psychotic symptoms).

**Discussion:** Schizo-OCD patients showed a distinct ERP patterns compared to both OCD and schizophrenic patient groups: a lower non-target P300 similar to SCH patients as an expression of a response inhibition deficit, but a higher amplitude compared to SCH patients without comorbid OCD. Schizophrenic and Schizo-OCD patients showed a decreased performance for reaction times compared to OCD patients and healthy controls (n = 12). N100 target amplitude higher in Schizo-OCD patients than in SCH patients may be interpreted as schizo-OCD patients having a better performance in terms of initial orientation response (selective attention) compared to SCH patients without comorbid OCD. Schizo-OCD patients showed a target stimulus response similar to OCD patients with no differences between target- and non-target P300, while SCH pts showed a spared difference. This may be interpreted as an expression of the same abnormal attentional shift observed in OCD patients. This results suggest that schizo-OCD may not only be a distinct clinical entity from pure OCD and schizophrenia, but it may also be characterized by a distinguishable neurophysiological pattern.

doi:10.1016/j.schres.2010.02.292

**Poster 65**

P300 EVENT-RELATED POTENTIAL AND NEUROPSYCHOLOGICAL OUTCOME IN DELIRIOUS AND NON-DELIRIOUS SCHIZOPHRENIA

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**Background:** Schizophrenia is a prolonged and severe mental illness with a great variability in symptomatology and neural abnormalities. The appearance of positive symptoms, such as delirium, may interfere with proper neurocognitive processing and the subjacent neurophysiology. The objective of this work is to study the differential relation between neuropsychological and neurophysiological outcome in two groups of patients with and without prominent delirious symptoms.

**Methods:** 35 schizophrenic patients aged from 23 to 65 years took part in the study. Inclusion criteria were a stable phase of the disease and no changes in pharmacological treatment in the last 3 months. Two groups of patients were composed: Delirious schizophrenia group consisting of 14 patients (12 males; mean age of 46.9) and Non-delirious schizophrenia group consisting of 21 patients (19 males; mean age of 43.6). All patients were assessed by a comprehensive neurophysiological (P300-ERP, P3ab Three-stimulus paradigm) and neuropsychological (MATRICS and WCST) battery. Statistical analysis consisted of a comparison of means (t-test) for independent samples.

**Results:** Delirious schizophrenia patients showed a significant decrease in frontal (Fz: t=2.307; p<0.05) and central (Cz: t=2.139; p<0.05) P300 amplitude in response to distracter stimuli (P3a), as well as a significant increase in the parietal P300 latency (Pz: t=-2.116; p<0.05) in response to target stimuli (P3b). Regarding to neurocognitive measurements, delirious patients obtained better results in the WCST; with a lower number of trials administered (t=2.143; p<0.10) and errors committed both
perseverative ($t = 2.618; p < 0.05$) and non-perseverative ($t = 3.412; p < 0.01$), and a higher number of correct answers ($t = -2.059; p < 0.10$) and categories completed ($t = -5.633; p < 0.01$).

**Discussion:** Modern models (eg, Polich, 2007), consistent with a neural inhibition hypothesis of stimulus processing, establish that the P300 comprises an early attention process stemming from a frontal working memory representational change to produce the P3a. The attention-driven stimulus signal will be then transmitted to temporal and parietal structures related to P3b. In this context, our results confirm that delirious schizophrenia patients require less early frontal attention/working memory activity for the inhibition of a distracter stimulus. These results are consistent with the much better outcome of this particular sample in the cognitive flexibility task (WCST). However, in response to a target, prominent delirious symptoms seem to slow down the later parietal processing of the stimulus. Future research should be directed towards the investigation of the role of negative symptoms in non-delirious patients as a possible explanation for the higher needs of frontal processing, as well as understanding how delirious symptoms decelerate the later parietal processing.

doi:10.1016/j.schres.2010.02.293

**Poster 66**
THE COURSE OF COGNITIVE DEFICITS IN SCHIZOPHRENIA FROM ILLNESS ONSET TO 6 YEARS POST ONSET: PRELIMINARY RESULTS FROM A PROSPECTIVE LONGITUDINAL STUDY

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**Background:** The course of cognitive deficits in schizophrenia has been found to be relatively stable in the years following illness onset. However, most previous studies have used brief follow-up intervals, and/or included patients that were medicated at baseline assessments.

**Methods:** A cohort of first-episode schizophrenia patients were included and examined when drug-naive, and were re-examined after 6 years. A matched healthy control group was also assessed at baseline, and after 6 years.Thirty-one patients were included at baseline. Of these, 17 were re-examined after 6 years (±0.7 years). Twenty-nine healthy controls were included at baseline; of these, 19 completed the follow-up assessment. Repeated measures analyses were performed to assess differential cognitive changes over time in patients compared to controls. Post-hoc analyses examined within-group changes in both groups.

**Results:** All patients were re-diagnosed with schizophrenia at follow-up. PANSS scores showed improved positive symptoms at follow-up. Results indicated relative stability of cognitive deficits within most domains assessed. However, the course of verbal memory functions in patients differed significantly from controls, indicating deterioration in the patient group, and stability in the healthy control group.

**Discussion:** These preliminary analyses found cognitive deficits to be largely stable from illness onset until 6 years post onset, with the exception of differential deterioration of verbal memory in the patients.

doi:10.1016/j.schres.2010.02.294

**Poster 67**
SOCIAL COGNITION AND PSYCHOTIC SYMPTOMS

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**Background:** Cognitive deficits are associated with psychotic symptoms and may play a causal role in their formation and persistence. Still, the evidence is ambiguous across the different cognitive domains and symptom clusters. Some associations seem most robust for the negative and disorganized symptom cluster, yet several studies have reported associations between specific cognitive deficits and positive symptoms. The aetiology of any association remains unclear. This study uses a genetically sensitive design to investigate whether social cognitive impairment is associated with the presence and severity of (clinical/subclinical) symptoms in patients and their first degree relatives and whether any association between cognition and symptoms is due to a familial aetiology.

**Methods:** A sample of 1036 patients with non-affective psychosis, 1024 of their healthy first-degree relatives and 579 control subjects from the general population was recruited within the national multicenter study Genetic Risk and Outcome in Psychosis (GROUP-project) to investigate the nature of the associations between social cognitive impairment and symptomatic expression in psychosis. All subjects completed a cognitive battery including IQ (WAIS-III), mentalizing (hinting task), degraded facial affect recognition (DFAR) and the Benton Facial Recognition test (BFRT). Positive and negative symptoms were assessed with the Positive and Negative Syndrome Scale.

**Results:** All groups differed significantly in IQ and mentalizing performance. Siblings did not perform differently from controls on DFAR and the BFRT, but both outperformed patients significantly. Within patients all cognitive measures were consistently and significantly associated with disorganized symptoms ($\beta$'s = .20 -.31, all $p < .01$) and to a lesser extent with negative symptoms ($\beta$'s = .11 -.19, all $p < .05$). Associations between cognitive performance and positive symptoms were statistically significant, but small ($\beta$'s = .08 -.11, all $p < .05$). Within-trait cross-sibling analyses between 1009 patient-sibling pairs showed that all cognitive measures clustered within families ($\beta$'s = .09 -.42, all $p < .05$). Cross-trait cross-sibling analyses were performed to investigate associations between symptoms in patients and cognitive performance in siblings. None of the associations were significant.

**Discussion:** The findings show that patients’ social cognitive deficits are primarily associated with disorganized and negative symptoms. Performance on social cognitive tasks shows substantial familial clustering, indicative of genetic factors contributing to social cognitive functioning. However, the lack of any familial covariation suggests that the overlap with symptoms and social cognitive dysfunctions is due to individual rather than shared factors.

doi:10.1016/j.schres.2010.02.295
**Poster 68**

RESULTS OF PHASE 2B EAGLE TRIAL; A DOUBLE BLIND PLACEBO CONTROL STUDY EVALUATING THE EFFICACY AND SAFETY OF BL-1020, A GABA ENHANCED ANTIPSYCHOTIC FOR THE TREATMENT OF SCHIZOPHRENIA

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**Background:** BL-1020 is a new chemical entity that combines dopamine antagonism with GABAergic activity. PK studies demonstrate that BL-1020 enters the brain, increases dopamine release in the prefrontal cortex and hippocampus and has the ability to reverse cognitive impairment induced by PCP in animal's behavioral models. Pre-clinical and clinical studies show that BL-1020 effectively reduces psychotic behavior with significantly fewer side effects.

**Methods:** The EAGLE (Effective Antipsychosis via GABA Level Enhancement) study was conducted under a U.S. FDA, IND application at 40 sites in U.S., Europe and India. In this 6-week study, 363 patients were randomized equally to treatment with low (10 mg/day) or high dose (20-30 mg/day) of BL-1020, risperidone (2-8 mg/day) or placebo. The study was designed to demonstrate statistically significant superiority of the BL-1020 high dose to placebo on the primary efficacy measure: the total score of the PANSS. Key secondary efficacy measures included the CGI-S, CGI-C, RDQ and an exploratory end point: Effect on cognition as measured by the Brief Assessment of Cognition in Schizophrenia (BACS).

Risperidone at a dose of 2-8 mg was included as a positive control. Patients included were diagnosed with schizophrenia using the DSM-IV-TR experiencing an acute exacerbation of their psychosis, as evident from the following: PANSS total score ≥ 70; persistent positive symptoms; PANSS score ≥ 4 on conceptual disorganization, hallucinations, delusions, grandiosity, or suspiciousness; CGI-S rating of ≥ 4 (moderately ill); and duration of current episode less than one month.

**Results:** The results in the ITT population using the LOCF for the primary efficacy measure, the total PANSS scores, indicated that treatment with BL-1020 high dose (LS mean -23.6; 95% CI-28.4; -18.8), was statistically significant superior (p = 0.002) to placebo; (LS mean -14.4; 95% CI -19.1; -9.7). Risperidone treatment also was associated with significant improvement (LS means-26.2; 95% CI -31.0; -21.3) to placebo. BL-1020 low dose did not separate from placebo. There were no statistically significant differences between BL-1020 high dose and risperidone (p = 0.390). The BL-1020 high dose was also statistically significantly superior for PANSS positive symptoms (p<0.001) and general psychopathology (P = 0.003) and showed a trend for significance (P = 0.067) for negative symptoms compared to placebo. These positive results on the PANSS, supported by the findings on the CGI-S and CGI-C. BL-1020 high dose showed significant increase in the number of 'responders' compared to placebo. The effect of BL-1020 on cognition provided evidence of a statistically significant and clinically relevant benefit. Analysis of the BACS composite score indicated significant superiority of the BL-1020 high dose group compared to placebo (p = 0.027) and risperidone (p = 0.027) at the end of study, with an effect size of 0.5 compared to placebo. The maximum change from baseline in the ESRS score was comparable to that of risperidone. BL-1020 increase in prolactin was significantly lower than that of risperidone (p<0.001). There were no statistically significant or clinically relevant changes in the measurements of the ECG, laboratory or vital signs (BP, HR. Temp). There were no statistically significant or clinically relevant AEs of body weight gain, glucose increases, and changes in lipids.

**Discussion:** These results are consistent with BL-1020 preclinical profile of an effective, safe and well tolerated, antipsychotic with GABA activity and a potential to improve cognition.

doi:10.1016/j.schres.2010.02.296

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**Poster 69**

ARE LATE-ONSET PSYCHOTIC SYMPTOMS POTENTIAL PRECURSORS OF DEMENTIA?

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**Background:** Data are sparse and controversial regarding the cognitive profile and progression of individuals presenting with late-onset psychotic symptoms (LOPS). Some studies reported a preserved cognitive profile and no evidence of neurodegeneration over time in patients presenting with LOPS compared to patients with early-onset schizophrenia (EOS). Other studies found specific and/or comparable cognitive deficits and an unfavourable evolution in LOPS. Consequently, the objectives of the present study were to characterize the cognitive profile and evolution of patients presenting with LOPS.

**Methods:** This was an historical cohort study following patients over periods from 0 to 17 years (mean = 5.33 ± 5.25 years) after the diagnosis of LOPS. The neuropsychological profile and clinical evolution of 17 patients presenting psychotic symptoms for the first time after the age of 50 years old (LOPS) were compared to those of 17 patients aged 50 years and older who had received a diagnosis of schizophrenia before the age of 40 years old (EOS) and to those of two control groups (n=11 in each group). The neuropsychological battery included tests measuring general cognitive function (MMSE, 3MS, Dementia Rating Scale-II), working and episodic memory (Span, California Verbal Learning Test-II), attention and executive functions (Trail Making Test, Stroop Interference Color-Word Test, Clock drawing, Verbal fluency). An independent consensual diagnosis procedure involving a geriatric psychiatrist and a neuropsychologist both blinded to the initial psychiatric diagnosis of the patients was applied in order to verify if the LOS were developing more dementia over time than the EOS.

**Results:** No statistical differences were obtained between LOPS and EOS groups (raw and standardized scores) on any of the neuropsychological tasks administered. The comparison of the two patient groups with their respective control groups revealed specific cognitive deficits. The EOS patients presented more episodic memory (encoding) and executive deficits (speed, flexibility, strategic evocation) than controls matched with patients according to age, education, gender and language. An analysis of covariance (for age and education) revealed that the performances of the LOPS were comparable to those of their controls matched according to gender and language. Dementia diagnoses were not significantly more reported in the LOPS than in the EOS group (4/17 cases in the LOPS versus 1/17 case in the EOS), even when the disease duration was taken into account (LOPS <2 years versus LOPS >3 years). However, mild cognitive impairment was diagnosed by the consensual procedure in more LOPS (6/17; 35.3%) than in EOS cases (1/17; 5.8%).

**Discussion:** The present study is in favour of a relatively preserved cognitive profile in patients presenting with LOPS compared to elderly patients with EOS. Furthermore, the neurodegenerative
hypothesis of LOPS cannot be confirmed on the basis of the present results but a longer delay could have revealed a unfavourable evolution of the LOPS patients who received a supplementary diagnosis of mild cognitive impairment which is commonly considered as a prodromic state of dementia.

doi:10.1016/j.schres.2010.02.297

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**Poster 70**

**SOCIAL COGNITIVE ENDOPHENOTYPES FOR PSYCHOTIC DISORDERS?**

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**Background:** Accumulating evidence of common genetic vulnerability for schizophrenia and bipolar disorder has led to investigations of shared cognitive endophenotypes for these disorders. The status of social cognitive deficits as candidate endophenotypes remains to be determined, and must be considered with respect to potential relationships with executive function as a well-established candidate for genetic association. In this study we aimed to (a) compare the performance of bipolar disorder and schizophrenia patients on simple and complex social cognitive skills, and (b) examine differential relationships between social cognition and executive function in each of these groups.

**Methods:** Preliminary analyses were conducted for 22 schizophrenia patients, 22 bipolar disorder patients, and 17 healthy controls. The Awareness of Social Inference Test (TASIT) was used to assess basic affect perception and higher order mental state inference (MSI) from short videos of sincere, sarcastic, and deceitful social exchanges. The Intra/Extradimensional Set Shift (IED) task from the CANTAB was used to measure executive function.

**Results:** The perception of affect from short video clips of actors engaged in scripted communication was impaired in schizophrenia but not bipolar disorder, compared with healthy controls. In addition, MSI impairments in schizophrenia were evident in all social exchanges involving sarcasm (compared to controls), while MSI impairments in bipolar disorder were limited to complex social exchanges incorporating paradoxical sarcasm and deception (compared to controls). Regarding associations with neurocognition, the number of IED errors prior to the extra-dimensional shift were negatively associated with the ability to perceive affect and comprehend sarcasm in schizophrenia, but were related only to sarcasm perception in bipolar disorder. In addition, for bipolar disorder, comprehension of all social exchanges (i.e., sincere, sarcastic, and deceitful) were positively associated with the number of IED stages completed and negatively associated with the total number of IED errors (adjusted for stages completed), while there were no associations between these IED variables and social cognition in schizophrenia.

**Discussion:** Social cognitive deficits appear to be more extensive and severe in schizophrenia, relative to those demonstrated in bipolar disorder. Executive dysfunction in schizophrenia may contribute to deficits in basic emotion perception as well as higher order social inferences, yet more consistent links between executive function and higher order social cognition were evident in bipolar disorder in this study. The contribution of executive dysfunction to social cognitive deficits should be acknowledged when pursuing social cognitive endophenotypes for psychotic disorders; these findings implicate a combination of multiple candidate genes that contribute to prefrontal cortex and subcortical temporal functions in association with potential social cognitive endophenotypes for psychosis.

doi:10.1016/j.schres.2010.02.298

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**Poster 71**

**PERCEPTION OF AFFECTIVE PROSODY IN REMITTED PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER I**

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**Background:** The ability to accurately perceive, interpret, and process emotion from prosodic intonation (affective prosody) is an important aspect of human social communication. Psychiatric disorders, like schizophrenia and bipolar disorder I, have been associated with deficits in the recognition of affective prosody, which appear to contribute directly to social dysfunction by leading to difficulties in interpersonal relations, occupational functioning, and hygiene. To the best of our knowledge, this ability has not yet been directly contrasted in remitted patients with schizophrenia and bipolar disorder I.

**Methods:** Forty patients with schizophrenia and sixty patients with bipolar disorder I from public outpatient mental health services as well as forty healthy control subjects between the ages of 19 and 60 will be included into a cross-sectional study. All patients are diagnosed according to ICD 10 criteria. Diagnoses are confirmed with the Mini International Neuropsychiatric Interview (M.I.N.I.). In order to ensure symptom recovery, schizophrenia patients have to be remitted according to the remission criteria defined by Andreasen et al., while patients with bipolar disorder I have to score ≤ 8 on the Montgomery-Asberg Depression Rating Scale (MADRS) and the Young Mania Rating Scale (YMRS). Affective prosody is assessed by using subtest 8 of the Comprehensive Affect Testing System (CATS). One sentence is read at a time and the subject selects which emotion (happiness, sadness, anger, fright or neutrality) the voice expresses.

**Results:** So far, 33 remitted patients with schizophrenia, 44 remitted patients with bipolar disorder I, and 40 healthy control subjects have been included into the study. The mean age is 39.9 ± 8.0 years in the schizophrenia group (60.6% males), 43.6 ± 12.9 years in the bipolar I group (40.9% males), and 40.8 ± 10.2 years in the control group (72.5% males). Compared to the control group, the bipolar I group comprises older subjects as well as more females. Accordingly, analysis of covariance with adjustment for age and gender was employed. With regard to affective prosody perception the mean accuracy was 59.1% ± 15.6% in schizophrenia patients, 56.3% ± 16.7% in bipolar I patients, and 67.5% ± 13.9% in healthy control subjects. Consequently, the perception of affective prosody was comparable in patients with schizophrenia and bipolar disorder I. However, the control subjects achieved significantly higher CATS scores than the two patient
Poster 72
WHAT FACTORS PREDICT AWARENESS OF COGNITIVE PROBLEMS IN PEOPLE WITH SCHIZOPHRENI A?

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Background: People with a diagnosis of schizophrenia demonstrate a range of cognitive difficulties at all stages of illness. What is less clear is the extent that they notice and report these difficulties on subjective measures. Awareness of cognitive difficulties may facilitate engaging participants in therapies that aim to target cognitive problems, such as cognitive enhancing medication or cognitive remediation therapy. Recent studies (Stip et al. 2003; Medalia et al. 2008) have found weak or absent relationships between objective performance on neuropsychological tests and self-reported cognitive complaints.

Methods: The purpose of the current study was to compare self-reported cognitive complaints on an established scale - the Cognitive Failures Questionnaire - with neuropsychological test performance. We additionally sought to determine if other non-cognitive variables—such as self-esteem, depressed or anxious mood—could predict self-reported cognitive problems in people with schizophrenia. To address these issues, fifty-five people with a diagnosis of schizophrenia were administered the Cognitive Failures Questionnaire (CFQ), range of neuropsychological tests (digit span, WCST and CVLT and FAS), the Rosenberg self-esteem questionnaire, and the Hospital Anxiety and Depression scale.

Results: There were no significant correlations between CFQ scores and any of the neuropsychological tests. However, CFQ scores showed significant positive correlations with self-esteem ($r=0.37$), and both anxious ($r=0.45$) and depressed mood ($r=0.42$). A multiple regression was performed with CFQ scores as the dependent variable, and the composite score neuropsychological tests score and emotional measures as predictors. This analysis revealed that one variable—anxiety—had an independent relationship with CFQ score.

Discussion: The data reported above replicate previous studies that have reported no association between subjective cognitive complaints and objective cognitive impairments. People with schizophrenia who have significant objective cognitive impairment appear to show limited awareness of these problems. However, greater cognitive complaints were associated with anxiety indicating that awareness of cognitive problems may reduce perceived coping in people with schizophrenia.

doi:10.1016/j.schres.2010.02.300

Poster 73
ATTENTIONAL MODULATION OF EXTERNAL SPEECH ATTRIBUTION IN PATIENTS WITH HALLUCINATIONS AND DELUSIONS

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Background: A range of psychological theories have been proposed to account for the experience of auditory hallucinations and delusions in schizophrenic patients. Most influential theories are those implicating the defective monitoring of inner speech (Firth et al., 1987; Johns et al, 2001). However, some recent studies measured response bias independently of self-monitoring and found the results inconsistent with the defective self-monitoring model, but explained by an externalizing response bias (Allen et al., 2004). We investigated the role of attentional biases in external misattribution of source by modulating participant's endogenous expectancies.

Methods: Comparisons were made between patients with paranoid schizophrenia (N=23) and matched healthy controls (N=23), who participated in two different versions of the audiovisual task, which differed based upon level of the cue predictiveness. The first experimental run consisted of 50% valid and 50% invalidly cued trials (unpredictive cue condition). The second experimental run consisted of 80% validly and 20% invalidly cued trials (predictive cue condition). Participants passively listened to recordings of single adjectives spoken in their own and another person's voice (alien) preceded by their own or another person's (alien) face and made self/nonself judgments about the source. The acoustic quality of recorded speech was experimentally manipulated by altering the pitch (distorted).

Results: The patients showed increased error rates comparing to controls, when listening to the distorted words they spoke, misidentifying their own speech as spoken by others. Importantly, patients made significantly more errors across all the conditions in which the cue was invalid, but were particularly prone to misidentify their own undistorted speech as alien, when preceded by an alien face.

Discussion: We confirmed the presence of the externalizing bias in patients with hallucinations and delusions listening to their own voice, that was moreover amplified when they were cued with an alien face. The patients experience uncertainty during invalid cueing of the voice stimuli, especially when the majority of the other cues is valid (predictive cue condition). This finding supports our assumption that patients with positive symptoms are less able than controls to inhibit the top-down information that is guiding them at the expense of the bottom-up attention, which could be responsible for the misattribution of the ambiguous sensory material.

doi:10.1016/j.schres.2010.02.301

Poster 74
MECHANISMS OF PSYCHOMOTOR SLOWING IN SCHIZOPHRENIA

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Background: Psychomotor slowing has been documented in schizophrenia. Nevertheless, the slowing of Reaction Time (RT) has been documented; the mechanism of the slowing remains largely unknown. A few studies suggest the presence of general slowing or attentional disorders \(^1\). However, they did not examine separately rapidity of processes involved in RT tasks such as perceptual, motor, decisional processes and attention \(^2\). The objective of this study was to examine mechanisms of RT slowing in schizophrenia, specifically, to determine whether RT lengthening is due to global slowing or specific alteration of perceptual, motor, decisional processes or of attention.

Methods: Participants were 16 patients meeting the DSM-IV criteria for schizophrenia (mean age: 38.6 years, SD = 10.9 ; mean education: 10.3, SD = 2.4) and 16 age and education-matched controls (mean age: 38.9 years, SD = 11.1 ; mean education: 10.6 years, SD = 2.3). On general, neuropsychological assessment showed that 30% schizophrenia patients suffered from episodic memory disorders and 40% from a deficit of executive functions although no patient had a deficit of oral comprehension or capacity of visuo-spatial exploration. 4 tasks were used to assess rapidity of (1) motor processes using finger tapping test; (2) perceptuomotor integration; (3) attention using Simple RT (SRT); and (4) binary decision processes using Choice RT (CRT). Group comparison study was performed using SRT data and additional analyses of SRT distribution using validated method \(^4\).

Results: Analyses of variance showed in schizophrenia patients slowing of (1) finger tapping (3.7± 1.1 Hz) (p = 0.007); (2) SRT (442.8± 281 msec) (p = 0.001); (3) CRT both in AD (782.6± 260.7 msec) (p = 0.002) without increase of error. Additional analyses of SRT distribution indicated that SRT lengthening in schizophrenia patients was mainly due to impaired attentional index (p = 0.004).

Discussion: The schizophrenic patients were investigated in the present study displayed a significant psychomotor slowing on the reaction time test. This study supports the presence of slowing in schizophrenia and the profile of performance indicates that its slowing is due to disorders of attention and visual processes.


doi:10.1016/j.schres.2010.02.302

Poster 75
INVESTIGATION INTO COGNITIVE FUNCTION IN FIRST EPISODE PSYCHOSIS PATIENTS

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Background: Cognitive dysfunction has been identified as a core feature of schizophrenia (Bartok et al., 2005). Despite a number of studies looking at the relationship between impaired memory function in patients with a diagnosis of schizophrenia, there have been few that have investigated cognitive dysfunction in patients with first episode psychosis with only some studies reporting predictive relationships with social and clinical outcomes (Leeson et al., 2009). This study aims to investigate cognitive function in patients with a first episode in psychosis and to determine the impact of treatment on cognition and quality of life for the patient.

Methods: A group of 50 consenting participants who present with first episode psychosis are being recruited from the Bradford District Care Trust through the Early Intervention in Psychosis Service. Each participant is assessed for pre morbidity IQ using the Wechsler Test of Adult Reading (WTAR), allowing us to control for intelligence and to provide information on cognitive functioning before a diagnosis of mental illness was made. A PANS assessment is undertaken to assess symptom expression. Immediately following this procedure each participant is tested on 5 subtests of the Cambridge Neuropsychological Test Automated Battery (CANTAB) assessing the following domains: visual memory, executive function and attention. Each participant’s weight, height and percentage of body fat were measured to further assess the influence of medication on their body weight and physical health. Samples of saliva are collected and analysed for selected genetic polymorphisms. All of these procedures (excluding the WTAR and Saliva collection) will take place twice 6 months apart with each meeting lasting approximately 1 hour 45 minutes. A group of 50 sex and age matched healthy volunteers with no history of mental illness are being recruited as a comparison group. Both groups undergo identical procedures (excluding the PANS for the comparison group).

Results: Preliminary analysis of the results suggests that the cognitive deficits are significantly more profound in the patient sample compared to the healthy volunteer group Very early results indicate that all patients showed significant deficits in all aspects of cognitive functioning as assessed by CANTAB, including Pattern Recognition Memory (PRM) and Spatial Recognition Memory (SMR) which assess visual and spatial aspects of memory, Intra-Extra Dimensional Shift (IED) and Stockings of Cambridge (SOC) which assess executive function, working memory and planning. However, interestingly the preliminary results also indicate that patients’ mean initial thinking time is equivalent to the control group in the presence of cognitive deficits, which may suggest that patients are more susceptible to impulsiveness. Early investigation of the age ranges of the patients tested indicates a mean of 25± 1. Analysis of BMI and % body fat results further suggests that patients are in a high risk group with a mean BMI of 28.75± 4.0 (over-weight) and 31.36± 2.8 for Body Fat (increased % of body fat).

Discussion: Preliminary results suggest that patients who have presented with a first episode in psychosis show significant deficits in all aspects of cognitive functioning compared to a control population, which is in agreement with previous findings (Ayres et al., 2006).

doi:10.1016/j.schres.2010.02.303

Poster 76
NEUROCOGNITIVE FUNCTION IN SCHIZOPHRENIA AND BIPOLAR DISORDER: A FIVE-YEAR FOLLOW-UP STUDY

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Background: People with schizophrenia and bipolar disorder have been shown to have a wide range of cognitive deficits, but the longitudinal course of these deficits remains unclear. Some studies have suggested that cognitive function deteriorates over time,
whereas others have reported stability or even an improvement in some functions. The objective of the present study was to examine the longitudinal course of cognitive function in a cohort of patients with schizophrenia and bipolar disorder compared with a control group.

**Methods:** Forty-three patients with bipolar disorder, 50 patients with schizophrenia and 24 healthy controls were assessed twice with a neurocognitive battery (Executive Functions, Working Memory, Verbal Memory, Visual Memory, Vigilance and Motor Speed tasks), clinical scales (the Positive and Negative Symptom Scale, the Hamilton Rating Scale for Depression and the Young Mania Rating Scale) and functional outcome measures (WHO’s Disability Assessment Scale and occupational adaptation level, and Quality of Live Scale) over a five-year follow-up period.

**Results:** Repeated measures analysis demonstrated no differences between patients and controls in degree of change in neuropsychological performance over this time period: Executive Functions; F = 1.27; p = 0.280; Working Memory F = 0.68; p = 0.511; verbal fluency; F = 0.033; p = 0.718; Verbal Memory, learning: F = 1.30; p = 0.278; V Verbal Memory, recall: F = 1.30; p = 0.278; Visual Memory: F = 0.117; p = 0.842; Vigilance: F = 2.71; p = 0.103.

**Discussion:** We conclude that in both group of patients, with schizophrenia and bipolar disorder, cognitive impairment remains stable. Overall, the findings are more consistent with a neurodevelopmental model of schizophrenia than with a neurodegenerative model.

doi: 10.1016/j.schres.2010.02.304

**Poster 77**

**AUTOBIOGRAPHICAL MEMORY DEFICITS AND THEIR RELATIONSHIP WITH SYMPTOM DIMENSIONS IN OLDER PATIENTS WITH CHRONIC SCHIZOPHRENIA**

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**Background:** Patients with schizophrenia display numerous memory impairments. Recently some studies have described a reduction in accessing specific episodic - but not semantic - autobiographical information in schizophrenic patients. It is suggested that there is a strong relationship between autobiographical memory retrieval and executive functions. A key neuropsychological proposal in schizophrenia is that negative symptoms are associated with different pattern of impairment on executive tasks. However, the direct relationship between autobiographical memory deficits and psychopathological symptom dimensions are widely unknown. Because of the fundamental role of executive functions for autobiographical memory retrieval we hypothesized, that patients with negative symptom pattern show marked difficulties in the episodic aspects of autobiographical memory.

**Methods:** Up to now 49 old-age chronic schizophrenics (mean age 58 years) were explored psychopathological with the SAPS and SANS. Personal semantic and episodic memories from five lifetime periods were assessed by using the Bielefelder Autobiographical Memory Inventory, which differentiates between a semantic and an episodic score. Information about executive functions were achieved with Trail Making Test, verbal fluency tasks, digit span and the Clock drawing Test.

**Results:** Exploratory factor analysis with oblique rotation yielded a tree dimensional model with a negative, a delusion/hallucination and a disorganisation factors. The negative symptom dimension showed significant correlations with all executive tasks and as expected also with the episodic score of the Bielefelder Autobiographical Memory Inventory.

**Discussion:** These preliminary results confirm that older chronic schizophrenic patients show deficits in autobiographical memory, which only involve personal episodic memories. This deficits affect mostly patients with marked negative symptoms and reduced executive functions. This findings support the view that frontal function, which is impaired in patients with negative symptoms and associated with executive functions, have an important role for autobiographical memory retrieval.

doi: 10.1016/j.schres.2010.02.305

**Poster 78**

**GENETICS OF SCHIZOPHRENIA: CLINICAL AND NEUROBIOLOGICAL IMPLICATIONS**

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**Background:** Schizophrenia (SZ) occurs throughout the world with a prevalence of 1%. As much as 80% can be attributed to genetic factors. Individuals with SZ reproduce at a lower rate: females produce 50% as many children as normal; males 25%. Genetic factors accounting for SZ should therefore behave like highly lethal genes. Laws of Hardy-Weinberg equilibrium predict that SZ should disappear from the human gene pool. How can we explain the persistence of SZ at a constant frequency of 1%?

**Methods:** Clinicians appreciate that the natural course of SZ varies widely from patient to patient and cannot be predicted. The Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) concluded that the response of any individual with SZ to treatment with 2nd generation antipsychotic agents cannot be predicted: either the effectiveness of the treatment or the myriad of possible side effects. Each clinical intervention is a clinical trial. More than 50 candidate genes have been identified within kindreds with high frequencies of SZ. There is no identified candidate gene common to all afflicted patients. The development of nucleic acid hybridization technology has revised our understanding of the structure and function of the human genome. Several recent publications have identified chromosomal rearrangements of large coding and non-coding regions including certain candidate or neurodevelopmental genes. Structural variations such as microdeletions and/or duplications range from 100 KB to 15 MB. Microduplications may include copy number variants Importantly, these chromosomal variants were not found in parental genomes. They are post fertilization or in vivo mutations. In vivo mutations are found in control DNA at a frequency of 5%, in SZ DNA at a frequency of 15%, and among children with the most severe childhood-onset SZ (COS) a rate of 22%.

**Results:** Balanced polymorphism is the hypothesis explaining how non-adaptive genetic factors are maintained in natural populations in combination with other genes to confer increased fitness to the entire population, thus insuring their preservation in the gene pool. Diverse evidence suggests a neurodevelopmental model of SZ, the autism spectrum, Asperger’s Syndrome, and others. A family of genes has been identified that are activated by diverse extracellular mechanisms. They are the interface between the organism and its environment, at the cellular and organismic level. An example of such a regulatory gene is Disrupted in Schizophrenia (DISC-1) Neurodevelopmental genes account for the organization of complex neuronal networks that are analogous to...
organogenesis In vivo mutations are a normal part of the development of the brain but occur more frequently in patients with SZ and most frequently among patients with COS. In vivo mutations are not passed on to the next generation.

Discussion: Genetic elements which are adaptive must exist to account for the persistence of SZ as well as its familial pattern of inheritance. A different class of neurodevelopmental genes in SZ must exist to increase the rate of in vivo mutations within the CNS and must, in combination with other genetic elements, be adaptive to account for their preservation in the human gene pool. Such a gene, operating outside the CNS, would be expected to be highly lethal by generating oncogenes. These hypotheses, in conjunction with the findings of CATIE raise the possibility that each patient with SZ may be genetically unique, a phenocopy.

doi:10.1016/j.schres.2010.02.306

Poster 79
EXECUTIVE DYSFUNCTION IN SCHIZOPHRENIA: POSSIBLE ROLE OF SAITOHIN GENE

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Background: Saitohin (STH) is an intronless gene nested within the human tau gene, that contains a single nucleotide polymorphism (A/G), suggested to be involved in the physiopathology and clinical course of several neurodegenerative and neuropsychiatric diseases. Recently it was reported an association between this polymorphism and frontal hypoperfusion and clinical prognosis in frontotemporal dementia. The present study sought to evaluate the possible role of the STH polymorphism as a concurring factor of cognitive decline in schizophrenia, a disease sharing both early psychotic manifestations, both a core deficit of executive functions and hypofrontality with frontotemporal lobe dementia.

Methods: 220 clinically stabilized patients with schizophrenia were assessed with the Wisconsin Card Sorting Test (WCST) for evaluation of executive functions. 38 patients affected by frontotemporal dementia were used as control sample to compare STH allele frequency. All patients were genotyped for STH polymorphism.

Results: We observed a significantly greater frequency of G allele among both patients with frontotemporal dementia (p = .04) and schizophrenia patients with poor performances of WCST (p = .04), compared to schizophrenia patients with best WCST performances. Among patients with schizophrenia, stratified for age and gender, the STH polymorphism resulted a significant predictor of WCST performance (p = .007).

Discussion: These results confirm the hypothesis of a possible contribution of STH gene products on the heterogeneity of core frontal executive functions deterioration, probably through complex interactions with mechanism involved in neurodevelopment and neurodegeneration.

doi:10.1016/j.schres.2010.02.307

Poster 80
PSYCHOSIS BIOLOGICAL MARKERS AND THEIR GENETIC INFLUENCES

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Background: Psychotic disorders are highly heritable, however proposed candidate genes like neuregulin1, COMT and BDNF have not been unequivocally replicated yet. Furthermore, little is known about the mechanism of action of these candidate genes. Biological markers of risk of developing psychosis such as enlarged lateral brain volumes or EEG traits such as the P300 wave could help us to identify genes for psychosis and to better understand their function.

Methods: Biomarkers obtained by structural MRI or EEG were collected in a large sample of families with members affected with psychotic disorders. SNPs in Neuregulin1, COMT and BDNF were examined for association with the biomarkers using multilevel modelling.

Results: Neuregulin 1, Dysbindin, COMT and BDNF do not exert a significant influence on lateral ventricles, whole brain or hippocampal volumes. Neuregulin-1 SNP8NRG221533 had a significant influence on P300 latency and the higher the number of C alleles carried, the greater the latency delay [Coef. = 32.4 ms; 95%CI: 13.2 to 51.6 ms; p = 0.001].

Discussion: Contrary to our prediction, the genes examined did not influence our brain morphometry phenotypes. The P300 latency reflects the speed of neural transmission. We hypothesise that variation in NRG1 may convey risk for schizophrenia by disrupting neural connectivity, possibly white matter integrity, and leading to a slower speed of cognitive processing. This is a preliminary finding and requires replication.

doi:10.1016/j.schres.2010.02.308

Poster 81
IDENTIFICATION OF TWO DNA COPY NUMBER VARIATIONS (CNVS) SEGREGATING WITH SCHIZOPHRENIA SPECTRUM DISORDERS IN TWO FAMILIES

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Background: Schizophrenia is a complex mental disorder that has a high genetic component in its causes. The genetic underpinnings may be attributed to the joint effects of many common genetic variants with small effects (common variant hypothesis), or rare mutations with high clinical penetrance, and these rare mutations might be of recent origin and specific to single cases or families (rare mutation hypothesis). Recent employment of array-based comparative genomic hybridization (array CGH) technology has discovered several DNA copy number variations (CNVs) predisposing to schizophrenia. These pathogenic CNVs are usually de novo mutations found in sporadic cases.

Methods: We screened CNV in several multiplex families affected with schizophrenia spectrum disorders using array CGH, and confirmed them using fluorescent in situ hybridization (FISH), and real-time quantitative PCR.

doi:10.1016/j.schres.2010.02.307
Results: Two CNVs were detected in two respective families. One was an approximately 5 Mb DNA segment at chromosome 15q11.2-13.1 segregating in a family with the mother being diagnosed as schizophrenia, and her daughter schizoaffective disorder. The other one was a deletion of an approximately 4.4 Mb segment at chromosome 6q12-13 in a family segregating with affected members diagnosed as schizophrenia or schizoaffective disorder. These CNVs were further confirmed by fluorescent in situ hybridization, and real-time quantitative PCR, and the breakpoints were delineated by chromosome-specific high-resolution array CGH.

Discussion: Our findings not only expand the allelic spectra of schizophrenia, but also indicate that pathogenic CNVs may also be present in familial type of schizophrenia. Furthermore, many genes located at or near the CNV regions can be considered as candidate genes of schizophrenia, and further studies are warranted.

doi:10.1016/j.schres.2010.02.309

Poster 82
THE XY HYPOTHESIS OF GENETIC PREDISPOSITION TO PSYCHOSIS: PRESENT STATUS

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Background: Deviations in language, lateralization constitute a genetic risk for schizophrenia (Li et al., 2007). Contrary to the near universal assumption that predisposition is coded in the DNA sequence of multiple autosomal genes, is the hypothesis that it relates to a determinant of human brain development on the X and Y chromosomes (DeLisi & Crow 1989) accounting for a) an association with sex chromosome aneuploidies (DeLisi et al, 1994), b) the same sex concordance effect, c) sex differences in age of onset and form of psychosis (Crow, 1993).

Methods/Results: The defining characteristic of the human brain - the “torque” - the right frontal to left occipital bias, shows reciprocal deviations in X0 and XXY syndromes implicating an XY determinant (Rezaie et al, 2009). The region of homology between 4q21.3 and Ypl1.2 was established by a duplication dated to 6 million years, the time of separation of the chimpanzee and hominid lineages (Williams et al, 2006). Within this gene pair Protocadherin 11X/Y codes for cell surface adhesion proteins expressed in the germinal cell layer of the cortex, and elsewhere. PCDH11Y has been subject to two deletions, a paracentric inversion and 16 amino-acid substitutions, but remains in-frame and has been under positive selection. PCDH11X has undergone 5 amino-acid substitutions, the most radical (R>C) in ectodomain 5 (Williams et al, 2006).

Discussion: Variation associated with the PCDH11XY gene pair likely arises in male meiosis from the mechanism now recognised as meiotic suppression of unpaired chromosomes (MSUC) in an epigenetic process dependent upon adhesion of histones rather than the DNA sequence. Thus the XY hypothesis identifies a class of variation that (as W Bateson recognised in 1909) is non-Mendelian, species-specific, and relates to the most characteristically human of abilities language. By tracing the phenomena of psychosis to the speciation of modern Homo sapiens the theory accounts on the one hand for the relationship between schizophrenia and the faculty of language (Crow, 2000, 2007; Delisi, 2001), and on the other for the failure of linkage and association studies to identify the genetic basis of psychosis (Crow, 2007). References Crow TJ (1993) Sexual failure of linkage and association studies to identify the genetic basis of psychosis (Crow, 2007). References Crow TJ (1993) Sexual failure of linkage and association studies to identify the genetic basis of psychosis (Crow, 2007).

Poster 83
MTHFR GENOTYPE AND DIFFERENTIAL EVOLUTION OF METABOLIC PARAMETERS AFTER INITIATION OF A SECOND GENERATION ANTIPSYCHOTIC

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Background: Most second-generation antipsychotics (SGA) induce metabolic disturbances, but large differences exist in the degree to which individual patients develop these. Little is known about genetic factors associated with this differential liability. Cross-sectional studies suggested an association between polymorphisms in 5,10-methylenetetrahydrofolate reductase (MTHFR) and metabolic syndrome in patients with schizophrenia. This study aims to assess whether the C677T or A1298C polymorphism in the MTHFR gene predict differential evolution of metabolic parameters over the course of a 3 month follow-up period after initiation of an SGA.

Methods: 104 Initiations of SGA in patients with schizophrenic disorder were measured at baseline, 6 weeks and 3 months. MTHFR A1298C and C677T genotype were measured.

Results: MTHFR A1298C, but not C677T, genotype predicted post-baseline increases in weight (b = 2.5, SE 0.92, p = 0.006), waist circumference (b = 2.0, SE 1.0, p = 0.050), fasting glucose (b = 2.8, SE 1.2, p = 0.024) and glucose at 120 minutes during the Oral Glucose Tolerance Test (OGTT; b = 10.7, SE 4.5, p = 0.018) following a de novo metabolic challenge with a specific SGA. A1298C-allele carriers consistently displayed the most unfavorable evolution of metabolic parameters. MTHFR A1298C genotype may explain part of the individual liability to metabolic disturbances in patients with schizophrenia.

Discussion: The MTHFR protein is vital for the availability of methyl groups in the brain, necessary for the methylation of DNA. Several SGA’s are known to decrease DNA methylation. It is therefore possible that drug-induced epigenetic changes, in combination with a genotype that may reduce the availability of methyl groups, increases the liability for metabolic disturbances in patients with schizophrenia.

doi:10.1016/j.schres.2010.02.311
SEGMENT-WISE GENOME-WIDE ASSOCIATION ANALYSIS IDENTIFIES A LIMITED NUMBER OF REPLICABLE CANDIDATE REGIONS ASSOCIATED WITH SCHIZOPHRENIA

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Background: Genetic factors explain a large proportion (81%) of the variation in schizophrenia. Nevertheless, the identification of specific genes is not very successful as the enormous investments that are made on the genotypic level (e.g., genotyping ∼1,000,000 SNPs) are not matched by similar investments on the phenotypic level. We aim to improve the assessment of individual differences in schizophrenia.

Methods: We developed a novel method in which we performed a X² test for each SNP and counted the number of nominally significant tests in a segment. We then assigned a p-value to each segment using a binomial test to determine whether this region contained significantly more nominally significant SNPs than expected by chance. This binomial test was adjusted for linkage disequilibrium.

Results: One region of meta-significance on chromosome 5q (128 - 140 Mbp) was found to be significantly associated with schizophrenia in all three samples and was robust for segment width.

Discussion: This region was found to contain a high density of disease associated genes. Interestingly, this region flanks a region with suggestive evidence for linkage with schizophrenia. The fact that a relatively large segment of the chromosome is associated with schizophrenia supports earlier findings which suggest that the location on the genome may be of more importance than that suggested by genetic code alone. In conclusion, our findings suggest that region-specific patterns and possibly three-dimensional structures may play a role in the genetic architecture of complex diseases such as schizophrenia.

doi:10.1016/j.schres.2010.02.312

ZNF804A DELINATES A SCHIZOPHRENIA SUBTYPE CHARACTERISED BY RELATIVELY SPARED COGNITIVE PERFORMANCE AND BRAIN VOLUME

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Background: The Zinc Finger Protein 804A gene (ZNF804A) has been implicated in schizophrenia (SZ) susceptibility by several genome-wide association studies (GWAS). ZNF804A is brain-expressed, but of unknown function. We investigated whether the identified risk allele at the disease associated single nucleotide polymorphism (SNP) rs1344706 is associated with (1) variation in symptom severity, (2) variation in neuropsychological performance in patients and controls, and (3) variation in brain volume.

Methods: In our neuropsychological study we tested for association between ZNF804A rs1344706 and cognitive functions known to be impaired in schizophrenia (IQ, episodic memory, working memory, and attention) in an Irish discovery sample (n = 297 cases and n = 165 controls). We then tested significant results in a German replication sample (n = 251 cases and n = 1472 controls). Life time symptom severity data (based on OPCRIT and BADDSS) was also available for analysis in the Irish sample (∼900 cases). In our volumetric brain study we used voxel-based morphometry to investigate the effects of ZNF804A on brain structure in a sample of 82 patients and 39 controls.

Results: In the Irish samples ZNF804A genotype was associated with better performance on all measures of episodic and working memory in patients but not controls. These findings replicated in the same direction in the German sample. Furthermore, in both samples, when patients with lower IQ were excluded the association between ZNF804A and schizophrenia strengthened. Correspondingly, we found that carriers of the ZNF804A risk variant had significantly higher hippocampal volumes relative to non-carriers, again in patients but not controls. Finally, factor analysis of clinical symptom scores available in the Irish patients indicated a significant but subtle increase in manic symptoms in risk carriers.

Discussion: In a disorder characterized by heterogeneity, a risk variant at ZNF804A appears to delineate a patient subgroup characterized by relatively spared cognitive ability and brain volume, and slightly elevated manic symptoms. Further work is required to establish if this represents a discrete molecular pathogenesis that differs from other patient groups and whether this also has consequences for nosology, illness course or treatment.

doi:10.1016/j.schres.2010.02.313

DOES THE DYSBINDIN GENE INFLUENCE HIPPOCAMPAL VOLUME IN PSYCHOSIS?

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Background: Hippocampal volume deficits have been commonly reported in both schizophrenia and psychotic bipolar disorder. The dysbindin gene (DTNBP1) has also been associated with these disorders. We investigated the effect of two SNPs of DTNBP1 on hippocampal volume in psychosis.

Methods: 364 participants consisting of patients with psychoses, their unaffected family members, and unrelated healthy controls of white European ancestry contributed both MRI and DNA data. The SNPs...
doi:10.1016/j.schres.2010.02.314

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VARIABILITY OF CANDIDATE GENES (COMT, CNR1 AND CHRNA7) IN RELATION TO CANNABIS USE AND PSYCHOTIC SYMPTOMS IN AN ADOLESCENT PSYCHIATRIC POPULATION

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Background: Different studies have confirmed the association between cannabis use and psychosis (Henquet 2005) and the relationship between age at onset of cannabis use and age at onset of psychosis (Barnes 2006, González-Pinto 2008). These associations have been suggested to be mediated by genes involved in the dopaminergic, cannabinoid and cholinergic systems (Agrawal 2008). The aims of our study were to investigate: i) the effect of variability at COMT, CNR1 and CHRNA7 genes on, both, cannabis use and psychotic symptoms appearance, ii) the correlation between cannabis use and the age at onset of psychotic and non-psychotic disorders and whether this relationship is modulated by the genetic variability at these three genes.

Methods: The sample consisted of 171 Caucasian adolescent psychiatric patients (mean age 16.8(3.56)), diagnosed following DSM-IV-TR criteria and classified into two groups: i) patients with a psychotic disorder (n = 84; 45% schizophrenia, 8% schizophreniform, 10% schizoaffective and 37% psychosis not otherwise specified), ii) patients with non-psychotic disorders (n = 87; 58% conduct, 31% affective and 12% personality disorders); 137 young healthy controls were included (mean age 22.9(4.67)). Cannabis use was assessed in patients with UNICA-A and DGS scales (Nurnberger 1994), and in controls with AIS (Grau & Ortel 1999). All individuals were classified in consumers (n = 180). COMT Val158Met (rs4680), CNR1 (rs1049353) and CHRNA7 (rs6494223) SNPs were genotyped using Taqman 5′-exonuclease assay. The distribution of all genotypes was in Hardy-Weinberg equilibrium.

Results: Cannabis use was more frequent in patients (48%) than in controls (19.2%) (χ² = 25.3 p < 0.001). Carrying the GG genotype of CNR1 gene appeared to increase significantly the risk for consuming cannabis (β = 0.63 p = 0.03 OR(95%CI) = 1.9(1.13-3.12)). This effect was observed to be marginally significant in the psychotic disorders’ group (p = 0.07), significant in the non-psychotic disorders’ group (p = 0.025) and non significant in controls. Being an A allele carrier of the SNP at CHRNA7 was observed to increase significantly the risk for developing psychotic symptoms, independently of cannabis or tobacco use (β = 0.86 p = 0.02 OR(95%CI) = 2.36(1.13-4.19)). Psychotic patients had a higher frequency of the allele compared to non-psychotic (χ² = 6.68 p = 0.009) and to controls (χ² = 9.73 p = 0.008). Within patients groups, a positive relationship between age at onset of cannabis use and age at first psychiatric symptoms was observed both in psychotic (β = 1.44 p < 0.001) and non-psychotic patients (β = 0.56 p = 0.001). An interaction effect was found between age at first cannabis use, Val158Met genotype and onset of the psychotic symptoms only (β = 0.93 p = 0.05), with Val/Val carriers showing an earlier onset.

Discussion: Our results suggest the interest of further analyses in larger samples to understand the role of genetic variability in CNR1 and CHRNA7 in modulating the individual sensibility to cannabis use and the risk for developing psychotic symptoms. Moreover, the association between age at onset of cannabis use and age of the first psychiatric symptoms highlights the importance of timing of brain development and maturation when exposition to cannabis occurs. The interaction between the age at first cannabis use and the COMT functional polymorphism in the prediction of the first psychotic symptoms, suggests that Val158Met could be a risk factor for psychosis, especially in individuals exposed early to cannabis.


do:10.1016/j.schres.2010.02.315

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GENETIC VARIABILITY IN DYSBINDIN-1 GENE (DTNBPI) CONTRIBUTES DIFFERENTIALLY TO EARLY AND ADULT ONSET FUNCTIONAL PSYCHOSES AND IT IS ASSOCIATED WITH THE FAMILIAL TRANSMISSION OF IQ AND PREFRONTAL COGNITIVE DEFICITS

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Abstracts
Background: Genetic variability at dysbindin-1 gene (DTNBP1) has been reported to be associated not only with schizophrenia and bipolar disorder but also with particular phenotypes such as cognitive functioning, negative symptoms, and premorbid adjustment (i.e. Straub 2002, Fanous 2005, Gornick 2005, Burdick 2006, Riley 2009). However, the specific genetic variants involved in these core features of functional psychoses remain unclear. Therefore, in a family-based approach we investigated the association of DTNBP1 variability with age of onset and neurocognitive impairment.

Methods: The sample consisted of 894 Caucasian individuals from 268 Spanish families (268 patients with DSM-IV diagnosed functional psychosis, 483 parents and 143 siblings). Considering the age at onset of the first psychotic symptoms (KSADS and/or Symptom Onset in Schizophrenia inventory), 154 patients were defined as early onset patients (first psychotic episode before 18 years). A sample subgroup (80% of individuals) performed a neurocognitive battery including: i) estimated IQ (WAISIII/WISC-IV), ii) executive functioning evaluation (TMT-B, WCST, Verbal Fluency). According to previous association and expression studies, 10 SNPs distributed along the gene were selected to cover the genetic variability of DTNBP1. They were genotyped using Taqman 5’ exonuclease assays. Genotype distributions of all SNPs did not depart significantly from the Hardy–Weinberg equilibrium. Haploview was used to estimate linkage disequilibrium (D’) between SNPs (Barrett 2005). Family association analyses were conducted using the TRANSMIT and UNPHASED programs (Dudbridge 2003, Clayton 1999), to test the DTNBP1 genetic variability associated with: i) the risk for psychosis, ii) patients’ age at onset. The effect of the genetic variability on the neurocognitive variables was tested by using the quantitative DTD (QTDT, Abecasis 2000).

Results: In the 268 families, the T allele of the SNP rs760666 was significantly associated with the risk for psychosis (p<0.02) and two haplotypes were observed to be over-transmitted to patients, the C-G-G (rs760761-rs2743864-rs1011313) and the C-T (rs2619539-rs760666). When the analyses were conducted separately in early and adult onset families, a 5-marker haplotype encompassing introns 1 to 4 appeared to be significantly over-transmitted to early onset cases (C-T-C-G-G: rs1018381-rs2619522-rs760761-rs2743864-rs1011313; p=0.009 with UNPHASED). However, a 3-marker haplotype corresponding to the region defined by intron 4 to 7 was specifically over-transmitted to adult onset patients (A-C-T: rs3212107-rs2619539-rs760666; p=0.005 with both UNPHASED and TRANSMIT). In the global sample, the SNP rs760666 was associated with the familial transmission of the estimated IQ. Specifically in early onset families, we detected: i) a marginal effect of a functional polymorphism (rs2743864) on the estimated IQ (p=0.029, non significant after adjusting for multiple testing), ii) a significant association of the rs2619522 marker with estimated IQ (p=0.006, non significant after multiple testing).

Discussion: Our findings confirm the role of dysbindin-1 gene in the risk for functional psychosis and its associated cognitive deficits and describe a differential haplotypic risk pattern between early and adult onset families. These results are in line with the definition of dysbindin-1 gene as a mixed susceptibility/modifier gene (Fanous 2008), which increases the susceptibility to psychosis, but to certain presentations more than others. Further studies are required to confirm and extend our findings. Acknowledgements: la Fundació La Marató de TV3 (014430/31); Fundación Alicia Koplowitz (2006); Fundació Seny; CIBERSAM.

doi:10.1016/j.schres.2010.02.316

Poster 89
NO RELATIONSHIPS BETWEEN NICOTINE DEPENDENCE AND SCHIZOTYPAL FEATURES IN UNAFFECTED FIRST-DEGREE RELATIVES OF SCHIZOPHRENIC SUBJECTS AND HEALTHY CONTROLS

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Background: Subjects suffering from schizophrenia have very high rates of cigarette smoking. Several hypotheses have been suggested concerning the relationship between nicotine and etiopathogeny or treatment of schizophrenic symptoms, but the results remain controversial. Many factors can explain these controversial results, such as heterogeneity of studied populations, the use of inadequate measures of nicotine dependence or influence of pharmacological treatment. Conversely, less is understood about the relationship between nicotine consumption and milder phenotypes related to schizophrenia, such as schizotypy. Furthermore, first-degree relatives are free from the multiple artefacts that potentially confound research in schizophrenia, including the effects of long-term and usually ongoing medication, treatment, multiple hospitalizations, etc...

Methods: Consecutively admitted probands meeting DSM-IV criteria for schizophrenia are recruited from a university-affiliated hospital (Psychiatry Department, Paris XII University). Their unaffected first-degree relatives were contacted and asked to participate in the study. We also recruited healthy controls among blood donors. Relatives and controls were interviewed with the French version of the Diagnostic Interview of Genetic Studies (DIGS) to confirm the absence of diagnosis of schizophrenia. We used the validated French translation of the self-rating Schizotypal Personality Questionnaire (SPQ) to measure schizotypal dimensions. Subjects also completed the French translation of the Fagerström Test for Nicotine Dependence (FTND). Differences between groups were tested using the Mann-Whitney test for continuous variables and a chi-2 (or exact Fischer) test for discrete variables. The relationships between schizotypal dimensions and smoking dependence were analyzed by partial correlation to control for the potential confounding influences of sex and age.

Results: The samples were composed of 98 first-degree relatives and 110 healthy controls. Relatives present a higher rate of smokers (44.9% vs 23.6% ; p=0.001) and a higher level of nicotine dependence on the FTND (2.66±2 vs 1.65±1.9; p=0.03) than normal controls. We did not find any relationship between nicotine dependence and levels of schizotypy or schizotypal dimensions in relatives or normal controls.

Discussion: We find a greater proportion of smokers and a greater level of nicotine dependence in relatives suggesting that nicotine consumption may be associated with a familial vulnerability to schizophrenia, and raising the possibility that family members are at greater risk of smoking due to their genetic predisposition to schizophrenia. We failed to find a relationship between smoking status or nicotine dependence and level of schizotypy in the two groups and in the entire sample.

doi:10.1016/j.schres.2010.02.317
**Poster 90**

RETHINKING THE GENETIC ARCHITECTURE OF SCHIZOPHRENIA

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**Background:** For many years, the prevailing dogma has stated that schizophrenia (SZ) is caused, in each individual, by a combination of many genetic variants, each with small effect alone (the polygenic, common disease/common variants model). Recent empirical data are prompting a re-evaluation of this model. These include a lack of the expected number of strong positive findings from genome-wide association studies and the concurrent discovery of a rapidly increasing number of single mutations that strongly predispose to SZ and other psychiatric disorders. These have led to a recent shift towards a mixed model where separate proportions of cases are caused by polygenic or single-mutation mechanisms. However, models incorporating a significant contribution from single mutations run counter to a substantial body of theoretical literature that had supposedly conclusively rejected Mendelian inheritance with genetic heterogeneity.

**Methods:** In light of recent empirical findings, we re-consider the methods and conclusions of early theoretical analyses and the explicit assumptions underlying them.

**Results:** We show that many of these assumptions can now be seen to be false and that the model of genetic heterogeneity is quite consistent with observed familial recurrence risks (including for endophenotypes) and other population-wide parameters.

**Discussion:** We argue for a more biologically consilient mixed model that involves interactions between single, disease-causing mutations and polygenic, modifying variants in each individual. We consider the implications of this model for moving SZ research beyond statistical associations to pathogenic mechanisms.

doi:10.1016/j.schres.2010.02.318

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**Poster 91**

A COMPARISON TO CONTROLS OF BRAIN STRUCTURE IN SUBJECTS WITH METHAMPHETAMINE PSYCHOSIS AND COMORBID HIV INFECTION

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**Background:** Previous studies have reported that sustained use of high doses of the psychostimulant drug methamphetamine can induce transient psychosis. For many intravenous methamphetamine users, medical co-morbidity represents an additional problem, which may impact on mental health. In the present study, we investigated brain structure (using MRI), cognitive function and psychiatric symptomatology in subjects who had previously experienced an episode of psychosis related to methamphetamine use, and were concurrently infected with HIV. A matched control group was studied for comparison.

**Methods:** Twenty one HIV-infected stimulant users were recruited, as well as 21 age, gender and IQ-matched non-HIV control subjects who did not use stimulants. Subjects were assessed for psychiatric symptomatology using various clinical screens, such as the MINI. All subjects completed a panel of cognitive tests, which included an evaluation of attention, memory and executive function. For HIV-infected subjects, viral loads and antibody titers were measured. All subjects completed an MRI brain scan, that included SPGR, FLAIR and DTI sequences.

**Results:** Compared to controls, the group with prior methamphetamine psychosis and HIV exhibited much higher rates of psychiatric symptoms, including substance dependence (85%), major depression (67%), anxiety disorder (24%) and hallucinations/delusions (70%). Analysis of the brain structure revealed no changes in volume of multiple sub-cortical structures, such as basal ganglia and hippocampus, but less frontal gray and white matter (p<0.05). The number of minor structural abnormalities was also greater in the psychosis group. Analysis of white matter integrity with DTI noted that global fractional anisotropy values were lower in the psychosis group (p<0.001).

**Discussion:** In a study of intravenous stimulant drug users that had previously experienced methamphetamine-induced psychosis, and who were concurrently infected with HIV, we found a range of structural brain differences from controls. Rates of psychiatric symptomatology were also higher.

doi:10.1016/j.schres.2010.02.319
samples t-tests were run to compare the number of intermediate and posterior sulci between groups.

**Results:** Contrary to findings in chronic patients, there were no significant differences in the distribution of the three OFC Types between groups (FES patients: Type I = 46.4%, Type II = 26.6%, Type III = 27.1%; controls: Type I = 56.3%, Type II = 16.7%, Type III = 27.1%). Similar percentages were found when left and right hemispheres were analyzed separately. However, significantly fewer intermediate rostral sulci were observed in the left hemisphere of patients compared to controls ($t(117) = -2.09$, $p < .05$).

**Discussion:** Our findings showed OFC Type III was not more common in FES patients in comparison to healthy controls, suggesting chronicity or stage of illness may be a dependent factor. However, given that OFC sulcogyr folding patterns are determined during early neurodevelopment, it is more likely that OFC Type III is a risk factor for poor social and functional outcome in general. The finding of fewer intermediate sulci in the left hemisphere may reflect underdevelopment of the neural system in that area, which is in line with findings of abnormal sulcal morphometry in the left cingulate of schizophrenia patients (Yücel et al., 2002). Further investigation into the relationship between social functioning and OFC pattern Type is needed and should encompass not only schizophrenia cohorts but other clinical populations as well.

doi:10.1016/j.schres.2010.02.320

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**Poster 93**

**BRAIN VOLUME CHANGES AFTER WITHDRAWAL OF ATYPICAL ANTI精神病ICS IN FIRST-EPISODE SCHIZOPHRENIA PATIENTS**

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**Background:** The influence of antipsychotic medication on brain morphology in schizophrenia may confound interpretation of brain changes over time in patients. We aimed to assess the effect of discontinuation of atypical antipsychotic medication on change in brain volume in patients with a schizophrenic disorder.

**Methods:** Sixteen remitted, stable first-episode patients with schizophrenia, schizoaffective or schizoaffective disorder and twenty healthy controls, group-matched for age and sex, were included. A Magnetic Resonance Imaging scan was obtained of all patients and controls at baseline and at one year follow-up. The patients either discontinued ($n=8$) their atypical antipsychotic medication (risperidone, olanzapine or quetiapine) or not ($n=8$) during the follow-up period. Intracranial volume and volumes of total brain, cerebral gray and white matter, cerebellum, third and lateral ventricle, nucleus caudatus, nucleus accumbens and putamen were obtained. Multiple linear regression analyses were used to assess the influence of discontinuation of atypical antipsychotics on brain volume (change), while correcting for age, gender and intracranial volume. Main effect of group (patient-control) and effect of discontinuation (yes-no) were investigated.

**Results:** Decrease in cerebral gray matter and caudate nucleus volume over time was significantly more pronounced in patients relative to controls ($p = 0.04$ and $p = 0.03$, respectively). Additionally, nucleus accumbens volume increase over time was more pronounced in controls as compared to patients ($p = 0.05$). Furthermore, cerebral white matter volume in patients showed a larger increase over time as compared to controls ($p = 0.02$). Comparing patients on and off antipsychotic medication showed significant differences in change over time in volumes of the nucleus accumbens and putamen. The nucleus accumbens and putamen volumes decreased during the interval in medication-free patients while increases were found in patients that continued their antipsychotics (nucleus accumbens: $p = 0.04$; putamen: $p = 0.001$).

**Discussion:** We confirmed earlier findings of gray matter volume decrements in patients with schizophrenia in comparison to normal controls. Importantly, discontinuation of atypical antipsychotics was related to volume decrease over time in the putamen and nucleus accumbens. This suggests that increases seen in the basal ganglia as a result of starting typical antipsychotic medication, also occur in atypical medication and are reversed by medication discontinuation.

doi:10.1016/j.schres.2010.02.321

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**Poster 94**

**CORTICAL THICKNESS IN PATIENTS WITH SCHIZOPHRENIA AND THEIR SIBLINGS**


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**Background:** Brain imaging studies have consistently demonstrated brain abnormalities in patients with schizophrenia. However, it is unknown whether these are caused by genetic and/or disease related factors. As the heritability to develop the illness is around 80%, with first-degree relatives to share approximately 50% of their genetic variants, brain abnormalities may also be present in (healthy) first-degree relatives of patients with schizophrenia. This large MRI study examined cortical thickness in patients with schizophrenia as well as their non-psychotic siblings and compared them to healthy control subjects.

**Methods:** From 193 patients with schizophrenia [age (mean/SD) = 26.90/5.58; male % = 81], 208 non-psychotic siblings [age (mean/SD) = 27.54/6.76; male % = 46] and 136 healthy control subjects [age (mean/SD) = 27.53/8.24; male % = 50] whole brain scans were obtained on a 1.5 T Achieva scanner. In-house software2 was used to segment total brain (TB), gray matter (GM) and white matter (WM) of the cerebrum, lateral and third ventricle and cerebellum volumes. For each subject, cortical thickness (CortT) was calculated for every vertex. Group differences in volumes were analysed by applying a Mixed Models approach. Differences in CortT were calculated using regression analyses with age, gender and handedness as covariates. Analyses were implemented in Mx.

**Results:** Brain volume reductions in TB, GM and WM and increments in lateral and third ventricle volumes were found in patients with schizophrenia but not in their non-psychotic siblings as compared with healthy control subjects. Moreover, in patients decreases in CortT were found in the frontal and temporal cortices and to a lesser extent in the occipital and parietal cortices. Non-psychotic siblings of patients with schizophrenia were no different from healthy control subjects.

**Discussion:** This study shows differences in cortical thickness in patients with schizophrenia but not in their non-psychotic siblings. This suggests that in schizophrenia cortical changes are mainly caused by disease-related factors. References: 1 Hulshoff Pol et al., 2002. Am J Psychiatry 159(2): 244-50 2Schnack et al., 2001. Neuroimage (13): 230-7 3Software: McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal.

doi:10.1016/j.schres.2010.02.322
**Poster 95**
EVIDENCE FOR WIDESPREAD THINNING OF THE CEREBRAL CORTEX IN PATIENTS WITH FIRST-EPIsODE PSYCHOSIS WITH POOR INSIGHT

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Background: Through conceptualizing poor insight in psychotic disorders as a form of anosognosia (neurological deficit), frontal lobe dysfunction is often ascribed a vital role in its pathogenesis. Whether non-frontal brain regions are important for insight remains to be investigated. In the current work, we used a multi-method approach to examine the neural morphometry of all cortical regions for insight in first-episode psychosis.

Methods: Insight was rated in 79 people with a first-episode psychosis with the awareness of illness and awareness of treatment need and efficacy items of the Scale for assessment of Unawareness of Mental Disorder. Participants were assessed with magnetic resonance imaging. Cortical thickness analysis and voxel-based morphometry were utilized to identify the neuroanatomical basis of insight.

Results: Cortical thickness technique revealed that poorer awareness of illness was associated with regional thinning in the left middle frontal (Dorsolateral prefrontal cortex, BA9) and left inferior temporal gyri (BA20). Poorer awareness of treatment need and efficacy was associated with widespread cortical thinning, most prominently in the left medial frontal gyrus (BA6), left precuneus (BA7) and left temporal gyri (BA20/38/39). No significant associations emerged between any insight measure and gray matter volumes using voxel-based morphometry.

Discussion: The results confirm predictions derived from the anosognosia/neuropsychology account and assert that regional thickness in frontal cortex is associated with awareness of illness in the early phase of a psychotic disorder. The fact that prominent thickness reductions emerged in non-frontal regions of the brain in parietal and temporal cortices for both awareness of illness and awareness of treatment need/efficacy suggests that the neural signature of insight involves a network of brain structures, and not only the frontal lobes, as previously suggested.

doi:10.1016/j.schres.2010.02.323

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**Poster 96**
GLOBAL AND LOCAL CONNECTIVITY CHANGES IN SCHIZOPHRENIA INVESTIGATED BY DIFFUSION CONNECTOME

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Background: New ways of representing diffusion data emerged recently and achieved to create structural connectivity maps in healthy brains (Hagmann P et al. (2008)). These maps have the capacity to study alterations over the entire brain at the connection and network level. This is of high interest in complex disconnection diseases like schizophrenia. In this Pathology where multiple lines of evidence suggest the association of the pathology with abnormalities in neural circuitry and impaired structural connectivity, the diffusion imaging has been widely applied. Despite the large findings, most of the research using the diffusion just uses some scalar map derived from diffusion to show that some markers of white matter integrity are diminished in several areas of the brain (Kyriakopoulos M et al. (2008)). Thanks to the structural connection matrix constructed by the whole brain tractography, we report in this work the network connectivity alterations in the schizophrenic patients.

Methods: We investigated 13 schizophrenic patients as assessed by the DICS (Diagnostic Interview for genetic studies, DSM IV criteria) and 13 healthy controls. We have got from each volunteer a DT-MRI as well as Qball imaging dataset and a high resolution anatomic T1 performed during the same session; with a 3 T clinical MRI scanner. The controls were matched on age, gender, handedness, and parental social economic-status. For all the subjects, a low resolution connection matrix is obtained by dividing the cortex into 66 gyral based ROIs. A higher resolution matrix is constructed using 250 ROIs as described in Hagmann P et al. (2008). These ROIs are respectively used jointly with the diffusion tractography to construct the high and low resolution densities connection matrices for each subject. In a first step the matrices of the groups are compared in term of connectivity, and not in term of density to check if the pathological group shows a loss of global connectivity. In this context the density connection matrices were binarized. As some local connectivity changes were also suspected, especially in frontal and temporal areas, we have also looked for the areas where the connectivity showed significant changes.

Results: The statistical analysis revealed a significant loss of global connectivity in the schizophrenic’s brains at level 5%. Furthermore, by constructing specific statistics which represent local connectivity within the anatomical regions (66 ROIs) using the data obtained by the finest resolution (250 ROIs) to improve the robustness, we found the regions that cause this significant loss of connectivity. The significance is observed after multiple testing corrections by the False Discovery Rate.

Discussion: The detected regions are almost the same as those reported in the literature as the involved regions in schizophrenia. Most of the connectivity decreases are noted in both hemispheres in the fronto-frontal and temporo-temporal regions as well as some temporal ROIs with their adjacent ROIs in parietal and occipital lobes.

doi:10.1016/j.schres.2010.02.324

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**Poster 97**
MEASUREMENT OF MORPHOLOGICAL CHANGES IN SCHIZOPHRENIC PATIENTS USING BRAIN MAGNETIC RESONANCE IMAGING

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Background: This study was performed to compare and measure the changes of corpus callosum of the schizophrenic patients with those of controls, to compare according to clinical symptoms, onset age.
**Methods**: Brain magnetic resonance imaging study was performed in 38 schizophrenic patients and 28 controls, and the authors measured cerebral area, anterior, middle, posterior callosal areas, vertical length, perpendicular width, and maximal horizontal callosal length. The schizophrenic patients were assessed by the PANSS. To correct cerebral area, ANCOVA was used with cerebral area as covariants. And two tailed t-test, ANOVA were used to compare callosal measurements according to subgroups.

**Results**: The schizophrenic patients, compared with controls, were significantly wider in posterior callosal area and thinner in anterior vertical width. The schizophrenic patients with prominent positive symptoms were significantly wider and thicker in middle callosal area, anterior middle vertical width than controls, and those with prominent negative symptoms were significantly thinner in posterior vertical width than those with prominent positive symptoms and wider in anterior area than controls. Early onset patients were significantly thicker in middle perpendicular area than controls.

**Discussion**: There were various controversial findings about corpus callosal pathology of the schizophrenic patients. This study, after correction of cerebral area, revealed increased size of several parts of callosal regions, and then suggested neurodevelopmental abnormalities. And also significant differences in callosal regions according positive and negative symptoms suggested that these reflected the heterogeneities of schizophrenia.

doi:10.1016/j.schres.2010.02.325

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**Poster 98**
**Poster not available**

doi:10.1016/j.schres.2010.02.326

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**Poster 99**
**REGIONAL BRAIN CHANGES IN INITIALLY ANTIPSYCHOTIC-NAÏVE FIRST-EPISODE SCHIZOPHRENIA PATIENTS TREATED WITH QUETIAPINE: RELATION TO DOSE AND PSYCHOPATHOLOGY**

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**Background**: MRI studies have shown progressive brain alterations in the course of schizophrenia. Whereas first-generation antipsychotics have been associated with striatal volume increases, the effects of second-generation antipsychotics (SGA) on striatal volumes are unclear. Neurprotective effects of SGAs have been suggested on hippocampal volumes, whereas ventricular enlargement may be associated with clinical outcome. Dose-dependent volumetric effects of individual SGAs have been scarcely investigated. In this study, we examined structural brain changes in initially antipsychotic-naïve first-episode schizophrenia patients after six months of mono-therapy with quetiapine.

**Methods**: High-resolution 3D T1-weighted magnetic resonance imaging scans were obtained on a 3 Tesla scanner at baseline and after six months in 22 antipsychotic-naïve first-episode schizophrenic patients and 28 age and gender matched healthy control subjects. Baseline and follow-up brain images were analyzed using tensor based morphometry (TBM). Voxel-wise group comparisons were performed with SPM5. Small volume correction was performed for the striatum, hippocampus and ventricles, using a FDR-correction (p < 0.05) to control for multiple comparisons. Additionally, volumetric estimates were derived and analyzed. Effects of medication, including dose-dependent effects, and associations with psychopathology (PANSS-scores) were assessed.

**Results**: Patients had significant striatal and hippocampal volume loss over the six months treatment period. The striatal volume loss was most pronounced with low quetiapine doses and less apparent with high doses. Conversely, hippocampal volume loss appeared more pronounced with high quetiapine doses than with low doses. Clinically, higher baseline positive symptoms were associated with more striatal and hippocampal volume loss over time. Although patients’ ventricles did not change significantly, ventricular increases correlated with less improvement on negative symptoms.

**Discussion**: Progressive regional volume loss in quetiapine-treated first-episode schizophrenia patients may be dose-dependent and clinically relevant. The mechanisms underlying progressive brain changes, specific antipsychotic compounds and clinical symptoms warrant further research.

doi:10.1016/j.schres.2010.02.327

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**Poster 100**
**POSTER NOT AVAILABLE**

doi:10.1016/j.schres.2010.02.328

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**Poster 101**
**FRONTAL CORTICAL THICKNESS IS ASSOCIATED WITH CLINICAL IMPROVEMENT OF NEGATIVE SYMPTOMS IN MALE ADOLESCENTS WITH EARLY-ONSET FIRST-EPISODE PSYCHOSIS**

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**Background**: First-episode psychosis in adults and adolescents is associated with volume deficits in the frontal cortex. It is unclear if deficits in cortical thickness and/or cortical surface and/or cortical gyriﬁcation underlie the patient-control differences in cortical volume. In addition, in adult and adolescent patients with psychosis it’s not evident if cortical structural brain abnormalities are related to change in clinical symptoms over time. The current study was designed to compare frontal cortical thickness, surface, and gyriﬁcation between male adolescents with early-onset ﬁrst-episode psychosis (EOP) and healthy controls. Within patients, the relationship between frontal cortical morphology and change in clinical symptoms over a two-year clinical follow up period was investigated.

**Methods**: Baseline Magnetic Resonance Imaging (MRI) brain scans were obtained from 49 adolescent EOP patients, and 34 healthy controls. Mean age was 15 years for patients and controls, and all patients had less than six months of psychotic symptoms at study.
enrollment. All patients had a baseline and a two-year clinical follow up assessment which included the Positive and Negative Syndrome Scale (PANSS). Change in symptoms was defined as the difference in PANSS score at baseline and follow up (follow up – baseline). At baseline, all patients were on antipsychotic medication, the mean daily chlorpromazine equivalent (CPE) dose of the patient sample was 401. FreeSurfer software was used to generate intracranial volume, frontal cortical thickness, frontal cortical surface, and frontal cortical gyriStates were measured from the baseline MRI brain scans.

**Results:** After controlling for age and intracranial volume, patients had a significantly thinner frontal cortex (means for controls and patients: 2.6 mm vs 2.4 mm, F = 12.9, p = 0.001, effect size (ES) = 0.13), decreased frontal surface (705.99 cm² vs 696.88 cm², F = 3.9, p = 0.05, ES = 0.05), and decreased frontal gyriStates (3.0 vs 2.9, F = 3.5, p = 0.06, ES = 0.05). Patients showed significant reduction in positive (β = 0.10, p < 0.001) and negative symptoms (β = 0.5, p < 0.001). Reduction in negative symptoms was positively correlated with baseline negative symptom severity (Pearson product-moment correlation coefficient (r) = 0.6, p < 0.001), meaning that a higher PANSS score at baseline was associated with more clinical improvement over time. Reduction in negative symptoms was positively correlated with frontal cortical thickness (r = 0.5, p = 0.003), meaning that greater clinical improvement was related with a thinner frontal cortex at baseline. This correlation remained significant after controlling for baseline negative symptom severity (r = 0.4, p = 0.003).

**Discussion:** EOP in male adolescents is associated with a thinner frontal cortex. Frontal surface and gyriStates were less affected in EOP. Interestingly, our finding of a relationship between thinner frontal cortex and greater clinical improvement over time points to previous findings in longitudinal studies of grey matter changes in adolescents with schizophrenia (Carroll et al. 2003) and less frontal grey matter was related to less symptoms in adolescents with early-onset schizophrenia, progressive loss of grey matter was correlated with greater clinical improvement (Sporn et al. 2003) and less frontal grey matter was related to less symptoms at follow up (Vidal et al. 2006). A full replication of these previous findings necessitates longitudinal MRI measurements, which is a future goal.

doi:10.1016/j.schres.2010.02.329

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**Poster 102**

THE DEFICIT SYNDROME IN SCHIZOPHRENIA: ASSOCIATIONS WITH HIPPOCAMPAL VOLUME AND PREFRONTAL CORTICAL THICKNESS

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**Background:** The deficit syndrome is a subtype of schizophrenia characterized by primary and enduring negative symptoms. Frontal and temporal structural alterations have been associated with this clinical phenotype. The purpose of this study was to test whether a neuroimaging phenotype (e.g., hippocampal volume and prefrontal cortical thickness) could discriminate between the deficit and non-deficit subtype in schizophrenia.

**Methods:** MRI scans were obtained in 89 patients and 87 controls. Hippocampal volume and prefrontal cortical thickness was measured using FreeSurfer. The following regions of interest were used: the inferior frontal gyrus (pars triangularis, pars orbitalis and pars opercularis), the frontal pole and the hippocampus. The Schedule for the Deficit Syndrome was used to make deficit versus non-deficit diagnoses, resulting in 25 patients being diagnosed with the deficit syndrome and 64 patients diagnosed as non-deficit. Regression analyses were used to examine associations between region of interest (dependent variable) and the deficit syndrome (independent variable) controlling for age, gender and educational level.

**Results:** A dose-response relationship, indicating the lowest cortical thickness values for the deficit group, intermediate cortical thickness values for the non-deficit schizophrenia group, and the highest cortical thickness values for the control group, was found for the following regions: the left pars triangularis (deficit vs. controls: β = −0.42; non-deficit vs. controls: β = −0.61; F = 0.00; deficit vs. non-deficit: β = −0.88; P = 0.00), the right pars triangularis (deficit vs. controls: β = 0.43; non-deficit vs. controls: β = −0.76; P = 0.00; deficit vs. non-deficit: β = −1.05; P = 0.00), the left frontal pole (deficit vs. controls: β = −0.19; P = 0.00; non-deficit vs. controls: β = −0.11; P = 0.00; deficit vs. non-deficit: β = −0.22; P = 0.00) and the right frontal pole (deficit vs. controls: β = −0.13; P = 0.00; non-deficit vs. controls: β = −0.09; P = 0.00; deficit vs. non-deficit: β = −0.17; P = 0.00). In addition, deficit patients were significantly different from non-deficit patients and controls with respect to the following brain regions: the cortical thickness of the right pars orbitalis (deficit vs. controls: β = −0.08; P = 0.05; non-deficit vs. controls: β = −0.03; P = 0.23; deficit vs. non-deficit: β = 0.08; P = 0.01), left hippocampal volume (deficit vs. controls: β = −240.08; P = 0.01; non-deficit vs. controls: β = −25.11; P = 0.69; deficit vs. non-deficit: β = −152.56; P = 0.02) and right hippocampal volume (deficit vs. controls: β = −247.77; P = 0.01; non-deficit vs. controls: β = −34.35; P = 0.60; deficit vs. non-deficit: β = −166.59; P = 0.01).

**Discussion:** The data suggests that the deficit syndrome in schizophrenia might be related to underlying prefrontal and hippocampal pathology. The hippocampus is highly interconnected with the prefrontal cortex.

doi:10.1016/j.schres.2010.02.330

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**Poster 103**

CORTICAL FOLDING PATTERNS AND OBSTETRIC COMPLICATIONS IN SCHIZOPHRENIA

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**Background:** The increased occurrence of obstetric complications (OCs) in patients with schizophrenia indicates that alterations in neurodevelopment may be of importance to the aetiology of the illness. Abnormal cortical folding may reflect subtle deviations from normal neurodevelopment. In the present study, we investigated the putative association between OCs and a 3D surface-based local gyriStates index (LGI) measure of cortical folding in schizophrenia patients and healthy controls.

**Methods:** Fifty-four chronic schizophrenia patients and 54 healthy control subjects underwent clinical examination and high resolution MRI scanning at Karolinska Institutet, Stockholm, Sweden. An automated algorithm (http://surfer.nmr.mgh.harvard.edu/fswiki/LGI) was used to calculate a local gyriStates index (LGI) for thousands of vertices across the whole cortical surface in each.
subject. Information on OCS was collected from original birth records and scored blindly according to the McNeil-Sjöström scale. Both a continuous measure and a cut-off measure for severe OCS were analysed in patients and control subjects separately. Age was co-varied for in the statistical analyses. A false discovery rate (FDR) of 0.05 was applied to control for multiple comparisons.

**Results:** There were no differences between patients and control subjects regarding number or severity of OCS. Schizophrenia patients with severe OCS demonstrated higher as well as lower IG in scattered areas across both hemispheres when compared to patients without severe OCS (p<0.05, uncorrected). In patients, increasing number of OCS was related to lower IG in a large cluster in the left medial posterior temporal lobe, and in a smaller cluster in the left inferior frontal sulcus and gyrus (p<0.05, uncorrected). Control subjects with severe OCS displayed higher IG as well as lower IG in scattered areas across both hemispheres (p<0.05, uncorrected) compared to controls without severe OCS. Continuous OCS scores in controls were related to lower IG in the left inferior frontal and precentral sulci and gyri (p<0.05). For this area, there was a similar inverse relationship between OCS-scores and IG in patients and control subjects (albeit for a larger area in the control subjects). None of the findings remained significant after correction for multiple testing.

**Discussion:** The results of the present study are suggestive of an association between OCs and cortical folding. The uncorrected results displayed scattered areas in which the findings from schizophrenia patients and control subjects differ. However, the inverse relationship between increasing number of OCs and cortical folding in the left inferior frontal sulcus and gyrus is present in both patients and controls. If replicated, the findings suggest that a relationship between OCS and cortical folding may be caused by factors shared between schizophrenia patients and healthy controls rather than factors related to schizophrenia alone.

**Results:** There were no differences between patients and control subjects regarding number or severity of OCS. Schizophrenia patients with severe OCS demonstrated higher as well as lower IG in scattered areas across both hemispheres when compared to patients without severe OCS (p<0.05, uncorrected). In patients, increasing number of OCS was related to lower IG in a large cluster in the left medial posterior temporal lobe, and in a smaller cluster in the left inferior frontal sulcus and gyrus (p<0.05, uncorrected). Control subjects with severe OCS displayed higher IG as well as lower IG in scattered areas across both hemispheres (p<0.05, uncorrected) compared to controls without severe OCS. Continuous OCS scores in controls were related to lower IG in the left inferior frontal and precentral sulci and gyri (p<0.05); for this area, there was a similar inverse relationship between OCS-scores and IG in patients and control subjects (albeit for a larger area in the control subjects). None of the findings remained significant after correction for multiple testing.

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**Results:** There were no differences between patients and control subjects regarding number or severity of OCS. Schizophrenia patients with severe OCS demonstrated higher as well as lower IG in scattered areas across both hemispheres when compared to patients without severe OCS (p<0.05, uncorrected). In patients, increasing number of OCS was related to lower IG in a large cluster in the left medial posterior temporal lobe, and in a smaller cluster in the left inferior frontal sulcus and gyrus (p<0.05, uncorrected). Control subjects with severe OCS displayed higher IG as well as lower IG in scattered areas across both hemispheres (p<0.05, uncorrected) compared to controls without severe OCS. Continuous OCS scores in controls were related to lower IG in the left inferior frontal and precentral sulci and gyri (p<0.05); for this area, there was a similar inverse relationship between OCS-scores and IG in patients and control subjects (albeit for a larger area in the control subjects). None of the findings remained significant after correction for multiple testing.

**Discussion:** The results of the present study are suggestive of an association between OCs and cortical folding. The uncorrected results displayed scattered areas in which the findings from schizophrenia patients and control subjects differ. However, the inverse relationship between increasing number of OCs and cortical folding in the left inferior frontal sulcus and gyrus is present in both patients and controls. If replicated, the findings suggest that a relationship between OCS and cortical folding may be caused by factors shared between schizophrenia patients and healthy controls rather than factors related to schizophrenia alone.

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**Discussion:** The results of the present study are suggestive of an association between OCs and cortical folding. The uncorrected results displayed scattered areas in which the findings from schizophrenia patients and control subjects differ. However, the inverse relationship between increasing number of OCs and cortical folding in the left inferior frontal sulcus and gyrus is present in both patients and controls. If replicated, the findings suggest that a relationship between OCS and cortical folding may be caused by factors shared between schizophrenia patients and healthy controls rather than factors related to schizophrenia alone.
Discussion: EOP in male adolescents is associated with a thinner frontal cortex. Frontal surface and gyriication may be less affected in EOP. Interestingly, our finding of a relationship between thinner frontal cortex and greater clinical improvement over time points to previous findings in longitudinal studies of grey matter changes in children, adolescents and adults with schizophrenia (Gur et al 1998, Delisi et al 1998, Sporn et al 2003, Vidal et al 2006). In children and adolescents with early-onset schizophrenia, progressive loss of grey matter was correlated with greater clinical improvement (Sporn et al 2003) and less frontal grey matter was related to less symptoms at follow up (Vidal et al 2006). A full replication of these previous findings necessitates longitudinal MRI measurements, which is a future goal.

doi:10.1016/j.schres.2010.02.333

Poster 106
HIGH RESOLUTION DEFORMATION-BASED MORPHOMETRY REVEALS A COMPLEX PATTERN OF BRAIN MORPHOLOGY CHANGES IN SCHIZOPHRENIA

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Background: Schizophrenia is linked with changes of brain morphology in gray, white matter and cerebrospinal spaces. Analysis of high-resolution deformations field have a potential to detect changes in all these three compartments.

Methods: We present results of a high-resolution deformation-based morphometric study of first-episode (n=49), chronic (n=19) schizophrenia patients, and healthy controls (n=127).

Results: Schizophrenia subjects showed volume reduction of prefrontal lobe – both cortical and subcortical parts, cingulate gyrus, in temporal, parietal, as well as occipital lobe, in thalamus, and cerebellum. They also showed increase in of lateral ventricles, basal ganglia, and in many subarachnoidal spaces surrounding mainly frontal and temporal cortex. There were no differences between the two schizophrenia groups, in separate analysis between first-episode or chronic subjects with healthy controls analogues pattern of brain changes emerged.

Discussion: Using high-resolution deformation-based morphometry it is possible to capture the complex pattern of brain morphology changes in schizophrenia. These features might be advatageous in applications that try to classify subjects with schizophrenia based on neuroimaging results.

doi:10.1016/j.schres.2010.02.335

Poster 107
LONGITUDINAL VOLUME-BASED MORPHOMETRIC STUDY TO EVALUATE PROGRESSIVE GRAY MATTER CHANGES IN FIRST-EPISODE SCHIZOPHRENIA

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Background: Although longitudinal magnetic resonance imaging (MRI) studies have shown that various brain regions undergo progressive tissue loss during the early phases of schizophrenia, regional pattern of these changes remain unclear.

Methods: Longitudinal MRI data were obtained from 18 (12 male and 6 female) patients with first-episode schizophrenia and 20 (11 male and 9 female) healthy controls and at baseline and follow-up with mean scan interval of 2.7 years. To compare gray matter changes over time between patients and controls were evaluated with voxel-based morphometry (VBM) using SPM8 following the longitudinal DARTEL protocol.

Results: In both groups of patient and control longitudinal gray matter reduction was observed in various brain regions including lateral and medial frontal regions and superior temporal region. Excessive decrease in gray matter was found in patients as compared to healthy controls in the left superior temporal region and right inferior frontal region.

Discussion: Our findings suggest that there are differing longitudinal gray matter changes in patients with schizophrenia during the early phases of the illness as compared to healthy individuals.

doi:10.1016/j.schres.2010.02.335

Poster 108
CONNECTION BETWEEN THE CORPUS CALLOSUM AND PREDISPOSITION TOWARDS HALLUCINATIONS – EVIDENCE FROM SCHIZOPHRENIA PATIENTS AND UNAFFECTED RELATIVES

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Background: In the current study, we applied an automatic segmentation method (Schönmeyer et al, 2007) to examine anatomical differences, as indexed by volumetry and two diffusion values (FA and MD (DTI), in the most important connection between the two hemispheres (Trepel, 1999), the corpus callosum (CC).

Methods: We measured 16 chronic schizophrenia (SZ) patients, and age, gender, handedness and parental years of education matched first degree relatives and controls.

Results: The results showed significant volume loss for SZ patients in the whole CC volume, as well as in the subparts posterior genu, isthmus and splenium. In addition, similar results were found for the FA values (DTI) of the whole CC, the inferior genu, the superior genu and the isthmus. However, the MD values of the whole CC and the isthmus showed increased compactness and decreased inter-
cellular space (Beaulieu, 2002) for SZ patients. Furthermore, the relatives had intermediate values in the volumetric and fiber integrity measurements.

**Discussion:** In conclusion, the results conform to the hypothesis of a pathological connectivity (hypoconnectivity) between different brain regions (Friston and Frith, 1995; Friston, 1998). We provide evidences for a connection between volume loss and loss of fiber integrity in SZ patients and their unaffected relatives, which is associated with the individual psychopathology, as assessed by the PANSS (Kay et al., 1987).

doi:10.1016/j.schres.2010.02.336

**Poster 109**

**STRUCTURAL NEURAL CORRELATES OF VERBAL MEMORY IN FIRST EPISODE SCHIZOPHRENIA**

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**Background:** People with schizophrenia consistently show verbal memory impairment even in the early stages of the disease. Several studies have examined the functional neural correlates of verbal memory and have observed reduced activity in the medial temporal lobe and several areas of the prefrontal cortex, among other regions. Fewer studies however, have systematically explored structural neural correlates of verbal memory following first episode schizophrenia. We used two complementary imaging techniques, namely hippocampal volumetry and cortical thickness, to explore structural correlates of verbal memory.

**Methods:** Sixty-five patients with a first episode of schizophrenia spectrum disorder and fifty-six healthy controls were matched on sociodemographical variables. A T1 structural MRI scan was used to perform the cortical thickness analyses and the segmentation of the hippocampus into a head, body and tail area. Multiple standardized verbal memory tests were combined into a global measure.

**Results:** Compared to healthy controls, patients exhibited significant verbal memory impairment. Correlations between hippocampal volume and verbal memory performance revealed a significant positive association that was limited to the left hippocampal head in the healthy controls. No significant associations were observed in the patient group. The cortical thickness analyses revealed an extensive network of brain regions positively correlated with memory performance, including a large section of the left prefrontal cortex in the healthy group relative to the patient group.

**Discussion:** These results suggest that the coupling between verbal memory and structural neural correlates is significantly reduced in first episode schizophrenia.

doi:10.1016/j.schres.2010.02.337

**Poster 110**

**ATYPICAL ANTIPSYCHOTICS: CLINICAL IMPROVEMENTS AND STRUCTURAL CEREBRAL CHANGES**

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**Background:** Cerebral anatomical differences have been widely described in schizophrenia patients compared to control subjects. Many studies have suggested a time-related progression of those differences, the severity of which has also been correlated with clinical characteristics of the disease. According to some recent studies, antipsychotic medications might also modulate cerebral anatomical changes in schizophrenia patients. Some results suggest a slower deterioration or even a normalization process of the cerebral structures associated with atypical antipsychotics. The present study aims to document and compare the cerebral structural effects of quetiapine and olanzapine in schizophrenia patients.

**Methods:** We selected 29 patients suffering from schizophrenia. At the beginning of the study, 17 patients were started on a medication of olanzapine and 12 patients on a medication of quetiapine. Within the first week of the study, all patients passed a Magnetic Resonance Imaging examination, which they passed a second time at the end of the study. All analyses were made using Voxel-Based-Morphometry for Statistical Parametric Mapping (SPM)-8. Clinical status of all patients was monitored using PANSS.

**Results:** The patients taking olanzapine took the second examination in average 4 months after the first one, while the patients taking quetiapine did so in average 5.5 months after the first one. Patients on quetiapine showed relative grey matter increases in frontal regions such as the orbitofrontal and middle frontal cortex and in the cingulum and in cingulate regions. Patients on olanzapine showed relative grey matter increases mostly in frontal and temporal regions. Clinical differences were also noted as the quetiapine group patients had more prominent negative symptoms while the olanzapine group patients mostly displayed positive psychotic symptoms (such as hallucinations) at the beginning of the study. Both patients groups showed clinical improvement throughout the study.

**Discussion:** Our study results confirm that treatment with atypical antipsychotics, such as Quetiapine and Olanzapine, can be associated with structural cerebral changes. Grey matter increases were mostly observed in frontal and cingulate regions, in a population of schizophrenia patients presenting mostly negative symptoms and treated with Quetiapine. These cerebral structures variations could be correlated to Negative Symptoms Scores after a treatment of Quetiapine. Grey matter increases were observed mostly in temporal and frontal regions, in a population of schizophrenia patients presenting mostly positive symptoms and treated with Olanzapine. These cerebral structures variations were significantly correlated with improvements on both positive items and global scores of PANSS evaluations after a treatment of Olanzapine. Our study results suggest that clinical improvement with atypical antipsychotics treatment could be associated with specific grey matter increases in schizophrenia patients.

doi:10.1016/j.schres.2010.02.338

**Poster 111**

**MAGNETIC RESONANCE IMAGING OF THE SUPERIOR TEMPORAL GYRUS IN MONOZYGOTIC TWINS CONCORDANT AND DISCORDANT FOR SCHIZOPHRENIA**

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Background: Volumetric MRI abnormalities of the superior temporal gyrus (STG) and substructures are well established in first-episode (Sumich et al., 2002, Molina et al., 2006, Kuroki et al., 2006) and chronic schizophrenia (Sun et al., 2009, Honea et al., 2005) and have been associated with positive psychotic symptoms, including auditory hallucinations (Barta et al., 1990, Garcia-Marti et al., 2008, Marti-Bonnmati et al., 2007, Takahashi et al., 2006, Sumich et al., 2005), delusions (Menon et al., 1995, Takahashi et al., 2006, Sumich et al., 2005), and thought disorder (Vita et al., 1995, Menon et al., 1995, Shenton et al., 1992), as well as negative symptoms (Anderson et al., 2002). Although the heritability of the STG has been shown to be high (Hulshoff Pol et al., 2006) and STG abnormalities have been identified in first-degree relatives (Goghari et al., 2007a, Goghari et al., 2007b) and offspring (Rajarethinam et al., 2004), it is unknown to what degree these abnormalities are manifested in unaffected co-twins of schizophrenia patients. No stereological region of interest (ROI) study has yet investigated the degree of these abnormalities in monozygotic (MZ) twins from concordant and discordant pairs.

Methods: We employed a twin study design, consisting of 134 MZ twins, including 21 pairs concordant for schizophrenia, 18 pairs discordant for schizophrenia, and 27 pairs of healthy control twins. Groups were matched for age, sex, handedness, level of education, parental socioeconomic status, and ethnicity. The volume of the whole superior temporal gyrus (gray and white matter) was measured in cubic centimeters on the basis of stereologic principles implemented in PC-based software MEASURE (Barta et al., 1997) by a single rater without knowledge of subject group or twin pair status. The anatomic boundaries of the STG were determined in accordance with a previously described protocol (Frangou et al., 1997) augmented by reference to additional neuroanatomical atlases.

Results: Patients with schizophrenia from MZ concordant and MZ discordant pairs exhibited significantly reduced total STG volumes compared to controls ($t = -3.17, p = 0.002$ and $t = -2.54, p = 0.014$, respectively), even after covarying for age, sex, site of imaging, and whole brain volume. STG volumes of patients with schizophrenia did not differ whether they came from MZ concordant or discordant pairs. There was a non-significant trend for the well co-twins from MZ discordant pairs to show reduced STG volumes relative to the controls ($t = -1.83, p = 0.072$), although they did not differ significantly from their ill co-twins.

Discussion: To our knowledge, this is the first ROI study that has investigated volumetric deficits in the STG of MZ twins concordant and discordant for schizophrenia. These preliminary results confirm that STG volume is compromised in schizophrenia and may reflect, in part, the influence of genetic factors.

These studies have demonstrated significant impairments in these patients on domains like Theory of Mind (ToM), self-monitoring and emotional face processing. Studies measuring brain activation in these paradigms have found abnormal activation in, amongst others, the ventromedial prefrontal cortex (vMPFC). Other studies have found hyperactivation during resting state in the vMPFC in schizophrenia patients. Interestingly, the vMPFC has been shown to be of crucial importance in self-reflective processing (van der Meer et al, meta-analysis of fMRI studies, Neurose & biobehav rev, in press). Even though several studies have linked schizophrenia to deviant self-processing (e.g. Lysaker & Lysaker, 2008), to date no studies on the neural basis of self-reflective processing in schizophrenia have been published.

Methods: The neural basis of self-reflective processing in schizophrenia patients in comparison with healthy control subjects was investigated by means of functional magnetic resonance imaging (fMRI). All subjects were presented with sentences including trait adjectives. Subjects were asked to indicate whether or not the sentence applied to themselves and to a significant other person. It was hypothesized that BOLD signal changes between self- and other-processing in patients with schizophrenia would be less prominent in the vMPFC, due to deficient self-reflective processing.

Results: Less activation in patients with schizophrenia versus controls was demonstrated in areas related to self-reflection compared to baseline, the vMPFC, posterior cingulate cortex and dorsomedial prefrontal cortex. Moreover, self-specific activation (contrast self>other), showed less activation in the vMPFC in patients with schizophrenia as compared to healthy control subjects.

Discussion: These results confirm that schizophrenia patients show a deviant pattern of activation in self-reflective processing. Deficient self-reflection may not only hamper proper self-monitoring, resulting in wrong attribution of for example auditory experiences, but may also result in various problems in social interaction (e.g. ToM) and insight in illness. More knowledge on the neural basis of self-reflective processing in schizophrenia may provide more insight in the specific problems of these patients and may help to design new treatment strategies.

doi:10.1016/j.schres.2010.02.341

Poster 114
ALTERED ASSOCIATION BETWEEN HIPPOCAMPAL ACTIVATION DURING EPISODIC ENCODING AND STRIATAL DOPAMINE FUNCTION IN PEOPLE WITH PRODROMAL SYMPTOMS OF PSYCHOSIS

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Background: Two of the most robust pathophysiologial factors associated with psychosis are elevated striatal dopamine activity and medial temporal lobe (MTL) dysfunction. However, the relationship between these factors is unknown. The aim of the present study was to compare functional connectivity between the MTL and striatum during verbal encoding in individuals with an At Risk Mental State (ARMS) for psychosis and healthy volunteers.

Secondly, we investigated whether group differences in functional connectivity were paralleled by differential relationships between hippocampal activity and striatal dopaminergic function, as indexed using 3,4-dihydroxy-6-[18F]fluoro-L-phenylalanine ([18F]-DOPA) PET.

Methods: Thirty-four subjects (20 ARMS and 14 Controls) matched for age, gender and pre-morbid IQ, were scanned using [18F]-DOPA PET and functional Magnetic Resonance Imaging (fMRI) while performing a verbal encoding task. Episodic memory performance was assessed in a subsequent recognition task.

Results: Behaviourally, the ARMS group made more False Alarm responses for Novel words than Controls. During encoding, relative to controls, ARMS subjects showed increased functional connectivity between the MTL and striatum. We also observed a significant interaction between group and striatal dopaminergic function in activity in the subiculum subregion of the hippocampus. The interaction was driven by a positive correlation between subiculum activity and dopaminergic function in ARMS but not in control subjects. In ARMS subjects positive symptoms were negatively correlated with activation in the subiculum.

Discussion: The study provides in vivo evidence of a link between dopaminergic function and alteration in MTL function in subjects with prodromal symptoms of psychosis.

doi:10.1016/j.schres.2010.02.342
Poster 116
EFFECT OF TOLCAPONE ON BRAIN REGIONS UNDERLYING RESPONSE INHIBITION IN A SAMPLE OF PATIENTS WITH SCHIZOPHRENIA COMPARED TO NORMAL CONTROLS

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Background: Catecholamines, mainly dopamine (DA), play a major role in enhancing the efficiency of cortical information processing and improving cognition. In this context, an important aspect of cognitive control is the capacity of cortical areas including the dorsolateral and ventrolateral prefrontal cortex, the supplementary motor area, the dorsal cingulate and the parietal cortex to suppress prepotent but inappropriate responses. This function, called Response Inhibition, is impaired in a range of neuropsychiatric conditions including schizophrenia, AD/HD, etc., and can be regulated by drugs that selectively modulate cortical dopaminergic function. One useful strategy to enhance cortical DA signaling is by blocking catecholamine-O-methyltransferase (COMT), the enzyme that inactivates released DA via enzymatic conversion to 3-methoxytyramine. In the present study, we explore the effect of tolcapone, a COMT inhibitor that selectively increases dopamine in the frontal cortex, on response inhibition in a group of patients with schizophrenia (PTS) and healthy volunteers (HV).

Methods: We performed a double-blinded, placebo-controlled study. Coded tolcapone or placebo was administered for 7 days and fMRI was performed on the seventh day. The second arm of the study was performed after a one-week wash-out period following the first arm. Forty-four HV (21 males, 23 females; mean age = 35.6 years) and 21 PTS (16 males, 5 females; mean age = 26.4 years) underwent BOLD fMRI (3 T) while performing a modified version of the flanker task. Subjects were trained to focus on an array of five stimuli that included a central target arrow pointing left or right, flanked by two stimuli (arrows, boxes or Xs) on either side. The subjects were instructed to press a button corresponding to the direction of the central target arrow as fast and accurately as possible. To evaluate response inhibition, the central target arrow had flanking stimuli that were Xs, which indicated that the subjects had to withhold their response. ANOVA for repeated measure with diagnosis and drug as factors of interest was performed for behavioral data. Image analysis was performed using repeated measures ANCOVA in SPM2, with diagnosis and drug as covariables, and age and gender as covariates of no interest. All values are reported as p < 0.05 FDR-corrected within prefrontal cortex ROI.

Results: Neuroimaging data showed a main effect of drug in prefrontal cortex, specifically in left BA 46 and a trend in right BA 46. Post-hoc analysis showed decreased activation on tolcapone when compared to placebo in bilateral BA46 both in HV and PTS. In the same areas, main effect of diagnosis was also found with HV showing greater activation when compared to PTS both during placebo and tolcapone. There was no “drug by diagnosis” interaction (all p > 0.05). These results were observed in the absence of a significant difference in accuracy across the two drug conditions and the two groups (all p > 0.05).

Discussion: Tolcapone enhances cortical efficiency of brain regions underlying response inhibition both in HV and in PTS. Consistent with data from animal studies and from computational models of the effects of selective enhancement of DA signaling, our results suggest that COMT inhibitors could potentially be useful in improving efficiency of information processing of brain regions underlying cognitive control in patients with schizophrenia.

doi:10.1016/j.schres.2010.02.343
performance relative to HC ($p = 0.38$), and the TD score was associated with poorer performance ($p = 0.027$). Performance on the VSWMt (Golf) showed similar results, with main effects of group and TD (respectively $p < 0.001$ and $p = 0.001$). There was also a main effect of group ($p = 0.001$) and of TD ($p = 0.021$) on strategy formation during VWMt, and of group ($p = 0.003$) on strategy formation during the VSWMt.

**Imaging:** During the semantic decision task, TD patients showed attenuated activation relative to controls in the Inferior Frontal, Pre Central, Superior, and Middle Temporal, and Fusiform gyri, and in the Insula, caudate, thalamus and Cerebellum, bilaterally. There was also differential engagement of the right Posterior Cingulate, Lingual, Cuneus, and Striate cortex. Regions directly or indirectly connected to these areas were not activated in the TD group. They thus had a different set of connectivity nodes and pathways, observed in the PDC analysis, relative to controls. NTD patients showed more activated areas than both controls and TD, including Inferior Frontal, Pre Central bilaterally, left Superior and Middle Temporal, Anterior Cingulate, Cuneus, Fusiform gyri, and Cerebellum, bilaterally. There was also engagement of basal ganglia nuclei, right Lingual and left Striate cortex. Direct contrast between NTD and TD revealed several differences in brain activation. NTD also had a different set of connectivity nodes and pathways, observed in the PDC analysis relative to controls and TD. They had a scattered data for connectivity strength, with a few greater values relative to controls but most of them weaker, in a pattern more similar to TD than to controls.

**Discussion:** Connectivity maps observed in TD patients and HC were clearly different. The map in controls probably corresponds to a network associated with the execution of a semantic decision task. The impaired performance of TD patients on semantic and working memory tasks may be related to a failure to activate nodes within this network, in the appropriate sequence. In addition to areas traditionally associated with language, this network involves regions involved in executive processing, suggesting that executive dysfunction is a contributor to TD.

doi:10.1016/j.schres.2010.02.345

**Poster 118**

**WHY DOES CANNABIS EFFECT PEOPLE DIFFERENTLY? COMPARING THOSE WITH TEMPORARY PSYCHOTIC SYMPTOMS VS. THOSE WITH NO PSYCHOTIC SYMPTOMS FOLLOWING THE ORAL ADMINISTRATION OF Δ-9-TETRAHYDROCANNABINOL – A FUNCTIONAL MRI STUDY**

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**Background:** The epidemiological research points towards a link between the use of cannabis and the development of a psychotic illness in a dose dependent manner. However, this outcome is not observed in everyone who uses cannabis. What makes someone more at risk is not yet known. Genetic predisposition has been suggested and COMT valine158 allele is implicated. However there are as yet no firm conclusions. Benefits can be gained from drug challenge studies. This study reports the results of behavioural and response inhibition imaging data by comparing two groups; those who developed psychotic symptoms, following THC administration, against those who did not, whilst undergoing the same procedures.

**Methods:** In a double-blind, placebo controlled, pseudo-randomized, within subject study 21 subjects were administered oral Δ-9-THC (10 mg) and placebo (flour) within a pseudo-randomized order, with a one month interval between. All were healthy, native English speaking, right-handed men, aged 20–42, who had used cannabis 15 times or less in their lifetime. Exclusion criteria included minimal exposure to other illicit drugs and no personal or family history of psychiatric or physical illness. Blood pressure, heart rate and blood withdrawal were obtained at baseline, immediately before and at 60, 120 and 180 mins after drug administration. Whole blood levels for THC were taken at baseline and the same time points. Participants’ psychological and behavioural states were assessed using Visual Analogue Mood Scale, State-Trait Anxiety Inventory, Analogue Intoxication scale and PANSS at baseline and at 1, 2 and 3 hours after the administration of the drugs. Cambridge Depersonalization Scale and Temperament and Character Inventory were used at baseline only. Scanning took place an hour after the drug administration. A Go/No-go task was used as a response inhibition paradigm for fMRI activation.

**Results:** Out of a pool of 37 subjects, 11 subjects developed psychotic symptoms and had high PANSS-positive scores. The psychotic experiences did not last more than 3 hours. One subject could not complete the second scanning, due to the severity of psychotic symptoms, so his behavioural, but not imaging data, is presented. A matching number of subjects who did not develop any psychotic symptoms (n = 10) under THC condition provided the control group. Random effects models were used to assess the group and time differences between various outcome measures. The sociodemographic variables, age and years of education and TCI scales between the two PANSS and PANSS groups were compared using t-test or Mann Whitney U test. Even though there was a trend for an increase in heart rate with THC, in comparison to placebo, there was no significant drug effect on blood pressure or heart rate overall and no difference between the two groups. This is not unusual following oral administration of THC. None of the behavioural outcome measures differed significantly (all p values > 0.05) between the two groups. There was however, differential modulation of the BOLD response in different regions in the temporal lobe by THC in those who became psychotic under its influence as compared to those who did not. The left parahippocampal gyrus was not activated during the response inhibition task in both the psychotic and non-psychotic group under the placebo condition. Under the influence of THC, this region was activated in those who experienced psychosis, while there was no activation in those who did not.

**Discussion:** This study shows that behavioural or psychological measures do not differentiate who can or cannot develop psychotic symptoms with THC, but there are significant neurophysiological differences between the two groups.

doi:10.1016/j.schres.2010.02.346

**Poster 119**

**BRAIN ASYMMETRY FOR EMOTIONAL PROSODY IN KLINEFELTER’S SYNDROME: CAUSAL RELATIONS INVESTIGATED WITH TMS**

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**Background:** Klinefelter’s syndrome (47,XXY karyotype) is associated with difficulties in social interaction. Van Rijn and colleagues
demonstrated high levels of schizophrenia spectrum pathology in Klinefelter (van Rijn et al., 2006a). Difficulties in social adaptation and abnormal brain asymmetries suggest that a genetic mechanism (involving genes on the X chromosome) might affect the development of social cognition in XXY men. Language and emotion are important aspects of social cognition. Reduced or abnormal lateralization of language has been found in Klinefelter’s syndrome (Geschwind, 1998; van Rijn et al., 2008). Additionally, impairments in emotional prosody perception have been reported (van Rijn et al., 2007). We expected that lateralization of emotional prosody differed in Klinefelter’s syndrome. Therefore, we used fMRI-guided transcranial magnetic stimulation (TMS) to study lateralization effects.

**Methods:** Seven men with Klinefelter’s syndrome and seven controls (matched on age, gender and education) performed an emotional prosody task during fMRI-scanning. In this task, subjects attended to the affective (happy, sad, angry or anxious) intonation and had to ignore the neutral semantic content of the sentences. We used fMRI-guided TMS (with BrainVoyager neuroanavigation) to reduce excitability of areas that were active during emotional prosody processing in the MR scanner (left and right superior temporal gyrus). TMS was performed for 20 minutes on 1 Hz. After stimulation, the subjects performed the emotional prosody task again. In addition, a baseline measurement without TMS was included. Results were analyzed with repeated measures analysis of variance (ANOVA).

**Results:** Klinefelter patients showed a trend to react slower than controls (p = 0.12). They also showed longer reaction times on the angry condition after stimulation of the right superior gyrus (p = 0.05), whereas controls reacted faster. No other effects of TMS reached significance.

**Discussion:** Men with Klinefelter’s syndrome responded more slowly to sentences with an angry intonation in the emotional prosody task after right STG stimulation, whereas controls responded faster. The emotion angry is hypothesized to be primarily processed by the left hemisphere. Thus, the involvement of the right STG in anger prosody processing in Klinefelter patients suggests a switch in lateralization. The faster responses in the healthy group for this emotion might be due to callosal disinhibition of the left hemisphere by the right hemisphere TMS. As fMRI studies have suggested similar patterns of aberrant lateralization in Klinefelter syndrome and schizophrenia, our results may have implications for understanding schizophrenia.

doi:10.1016/j.schres.2010.02.347
Background: Several studies have shown that patients with schizophrenia have impaired performance in various aspects of social cognition including emotion processing, theory of mind, and moral judgment. Most of the neuroimaging studies have compared patients and healthy controls during such mental activity because the understanding of the neural basis of social cognition might help to explain some deficits in social functioning in this group of patients. The present study examined brain activation patterns during social cognition tasks in patients with schizophrenia, and try to determine whether alterations in social cognition reflect a trait that can be detected in non-psychotic relatives of patients with schizophrenia.

Methods: Eight patients with schizophrenia (age 33.9 ± 13, 2 females), ten non-psychotic relatives (age 32 ± 3.7, 4 females) and ten matched comparison subjects (age 27.5 ± 7, 4 females) underwent BOLD (blood-oxygen-level-dependent) functional magnetic resonance imaging during visual presentation of different social cognition paradigms. Emotion processing was measured by the Ekman Faces Test using a target (basic emotions) and a control (gender) condition. Theory of Mind (ToM) paradigms were focused on the ability to discriminate complex mental states in faces and Reading the Mind in the Eyes task, with a target (complex mental states) and a control (gender) condition as well. Moral judgment task consisted in 40 short passages, half of them with moral content, in which the subject has to judge the characters actions. Random effects analysis was done for each task within groups, measuring signal changes between the target and control conditions of each paradigm.

Results: The Reading the Mind in the Eyes (ToM task) brought about activation in the left inferior frontal gyrus, near Brodmann’s areas 44 and 45, in all groups. Both patients and their siblings showed activation in the same area of the right hemisphere although with less intensity, and in the left striatum. Patient’s siblings showed bilateral activation of the middle occipital gyrus. During a moral judgement task, right inferior frontal gyrus was activated in both patients and their relatives (but more intense in the former), and relatives activated right ventromedial prefrontal cortex as well. In this task, healthy persons activated preferentially bilateral postcentralgy. Both facial tests evoked much lesser activation in patients than in the other two groups. Healthy subjects activated preferentially bilateral middle frontal gyri. Patients’ siblings displayed the most intense activation of all groups including bilateral middle and inferior frontal gyri, parahippocampi, bilateral occipital structures and bilateral cerebellar structures.

Discussion: Reading the Mind in the Eyes and moral judgement tests evoked partially overlapping cerebral activation patterns in patients and their siblings but not in comparable healthy individuals. Emotion processing as assessed by social cognitive tasks involving faces evoked strong cerebral activation in unaffected siblings of schizophrenia patients. The present results suggest that social cognitive and moral tasks are associated with activation of brain areas partially similar in patients with schizophrenia and their unaffected siblings, and distinct from those in healthy individuals.

doi:10.1016/j.schres.2010.02.350
ing in psychotic patients is abnormal brain activation during verbal fluency tasks. Especially, left hemisphere specialisation for language is reduced in these patients. It is currently unclear, however, whether deviant activation during verbal fluency is related to a particular symptom of psychosis or psychosis in general. Previous studies argued that decreased lateralisation is related to auditory verbal hallucinations (AVH). To elucidate the relationship between language lateralisation and AVH, AVH should be studied in isolation, i.e. in subjects who do not experience delusions or disorganisation and do not use antipsychotic medication.

**Methods:** Thirty-five patients with a psychotic disorder, 35 non-psychotic subjects with AVH and 35 control subjects, matched for age, sex and handedness, participated in this study. Non-psychotic subjects with AVH were not diagnosed as psychosis not otherwise specified (NOS) as there was no presence of professional, psychological or social dysfunction is this group. Of the patients participating in this study, 25 were diagnosed with schizophrenia, eight were diagnosed with psychosis NOS and two were diagnosed with schizoaffective disorder. All subjects were scanned on a 3T MRI scanner while covertly performing a paced verbal fluency task. Language activation was compared between the groups using an independent one way Univariate Analysis of Variance.

**Results:** There were no significant differences in brain activation between the non-psychotic subjects with AVH and the control subjects during the verbal fluency task. In addition, lateralisation indices did not differ significantly between these groups. Compared to the control subjects, psychotic patients displayed significantly greater activity in the right inferior parietal lobule and greater activity in the left insula compared to the non-psychotic subjects with AVH. Moreover, lateralisation was significantly reduced for the patient group. Task performance was nearly maximal for all groups, and did not differ significantly between the groups.

**Discussion:** During verbal fluency, no deviations in brain activation were present in non-psychotic subjects with AVH, while psychotic patients with AVH showed decreased language lateralisation. This might indicate that decreased language lateralisation is a predisposition for psychosis, but not for the tendency to hear voices.

doi:10.1016/j.schres.2010.02.351

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**Poster 124**

**DISRUPTION OF THE ROLE OF FRONTAL THETA OSCILLATIONS IN MODULATING THE SUPPRESSION OF DEFAULT MODE PROCESSING DURING TASK PERFORMANCE IN SCHIZOPHRENIAS**

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**Background:** EEG oscillations in various frequency ranges, including the theta band (4-8 Hz), play an important role in cerebral recruitment during processing task-relevant information. In schizophrenia, event-related theta activity is diminished, while spontaneous theta is increased (Doege et al 2009). During attention to task-relevant sensory stimuli, there is suppression of activity in a distributed brain system embracing medial frontal, medial parietal and lateral parietal cortex. Activity in this distributed system, the Default Mode Network (DMN), is thought to reflect attention to introspective mental processes. DMN activity has been reported to be abnormal in schizophrenia, though findings are inconsistent. Theta activity is related to DMN activity in healthy controls (Scheeringa et al 2008). We have performed concurrent EEG – fMRI to test the hypothesis that event-related theta modulates suppression of DMN during task performance in healthy controls and that this modulation is disrupted in schizophrenia.

**Methods:** 20 patients with DSM-IV schizophrenia and 20 age, gender and parental socio-occupational status matched controls were scanned in a 3 T Philips MR device employing echo-planar (EPI) acquisition, during the performance of an auditory oddball task, while EEG was recorded simultaneously using a Brain Products MR compatible EEG system. Image data was subject to reorientation, re-alignment, coregistration, spatial normalization and smoothing using SPM5. The smoothed EPI images from all the subjects were subjected to Independent Component Analysis (ICA) using the GIFT software, and the component that best matched the spatial distribution of the DMN was identified. The observed time course of activity in this DMN component was regressed against the predicted hemodynamic response to target stimuli. After removal of EEG noise due to gradient artifacts and cardio-biological artifacts, the average power at four frontal electrodes (Fz, FCz, FC1, FC2) within a 2 Hz band centred on the local maximum of theta power in the individual subject, was determined in the period from 100 to 500 ms post stimulus for each trial. A further regression was performed with the time course of the DMN activity as the dependent variable and the magnitude of the event related theta activity during each trial treated as a parametric modulator of the hemodynamic response to the target stimuli.

**Results:** Similar spatial distributions of DMN activity were observed in patients with schizophrenia and in healthy controls. Target detection was associated with DMN suppression in both healthy individuals and in schizophrenia. In healthy individuals, the magnitude of event-related theta was a significant predictor of DMN activity (mean beta = .6, S.D. .88; p = 0.013) indicating less suppression during trials with high theta activity. In patients, the degree of modulation of DMN suppression by event-related theta activity was significantly reduced compared with controls (z = 2.59, p = .009).


doi:10.1016/j.schres.2010.02.352

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**Poster 125**

**SIMILARITIES IN ACTIVATION DUE TO METACOGNITION DURING DIFFERENT TASKS**

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**Background:** Published data shows metacognition - e.g. measured by free choice improvement (FCI) on a metacognitive version of the Wisconsin Card Sort Task (WCST) - correlates with insight in first episode schizophrenia. Our unpublished data in chronic schizo-
phrenia shows change in FCI correlates with change in insight, especially awareness of illness and symptoms (but not recognizing need for treatment).

Methods: We compared activation during functional magnetic resonance imaging (1.5 T) by metacognitive and non-metacognitive versions of three tasks. 12 right-handed males without psychiatric illness performed two versions of: the WCST; of list learning; and of line length judgement. We present a new analysis using regions of interest (ROIs) delineated by contrasting metacognitive with non-metacognitive conditions across all 3 tasks. Post hoc we then contrasted the metacognitive with non-metacognitive versions separately for each task within each ROI.

Results: In all 3 tasks 8 voxel cluster level activation was significant (false discovery rate p<0.05) post hoc in all the ROIs. After Bonferroni correction all tasks activated the bilateral ROIs covering inferior frontal gyrus/anterior insula; right middle/superior frontal gyri; & bilateral rostral inferior parietal lobules. Activation of the left DLPFC and bilateral middle frontal cortex (BA 6/8) was almost as consistent but the activation pattern in each task was predominately right-sided.

Discussion: This indicates consistent activation by metacognitive versions of different tasks, involving attention and decisions under uncertainty directed towards similar goals. Differences may have arisen because different tasks invoked metacognitive processes with different emphases (assessment of confidence recognising previously learned words activated BA 6/8 less than confidence making current categorical decisions and rule inferences). They may also have demanded different types of working memory load. There was no greater orbitofrontal or sub-cortical activation by metacognitive than non-metacognitive versions: both conditions required some judgement of confidence and promised the same rewards. Mentalizing and executive tasks activating similar networks are impaired in schizophrenia.

doi:10.1016/j.schres.2010.02.353

Poster 126
TEMPORAL CORTEX ACTIVATION DURING LISTENING TO EMOTIONAL WORDS IN PATIENTS WITH NON-AFFECTIVE PSYCHOSIS: AN FMRI STUDY WITH INDEPENDENT COMPONENT ANALYSIS

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Background: Hallucinations are core symptom in schizophrenia. In psychotic patients hallucinations have strong emotional connotations. Some authors have suggested that the emotional disturbances had a crucial role in the pathogenesis of hallucinations (Kuipers et al., 2006). The study of the AA has tackled from the various techniques of structural and functional neuroimaging. In functional neuroimaging studies of activity has seen an increased activity in areas responsible for language or the primary auditory area, particularly in the superior temporal gyrus (Lennox et al., 1999; Dieriks et al., 1999; Allen et al., 2008). The technique of independent component analysis (ICA) is a data driven method for obtaining functional connectivity networks. Have not been studied so far, the differences of activation in temporal areas in patients with patients without hallucinations and auditory hallucinations with the implementation of an auditory emotional paradigm using ICA. We applied this approach to study temporal networks involved in affective processing in schizophrenic patients with and without auditory hallucinations.

Methods: We recruited 31 healthy volunteers, 27 patients with non-affective psychosis and auditory hallucinations and 14 patients without auditory hallucinations. All subjects underwent functional magnetic resonance imaging while they passively listened words with emotional content. From the data obtained by MRI were calculated components correlated with the paradigm through independent component analysis and we selected temporal components of the components of interest obtained. The temporal component is compared among the three groups.

Results: In comparing two by two: • Patients with auditory hallucinations showed increased activation in superior and middle temporal gyrus relative to controls and in superior temporal gyrus compared with patients without auditory hallucinations. • Patients with auditory hallucinations showed more activation in superior and middle temporal gyrus compared with controls and in middle temporal gyrus compared with hallucinatory patients.

Discussion: 1. Patients with non-affective psychosis show an increased activation of temporal areas, particularly in the superior and middle temporal gyrus. This result is consistent with results that suggest temporal lobe as a key region altered in schizophrenia (Honea et al., 2005). 2. Patients with auditory hallucinations compared with non-hallucinators we observed increased activation in the superior temporal gyrus (auditory area primary), supporting theoretical models suggest that the superior temporal gyrus is a key area in auditory hallucinations (Allen et al., 2008). 3. Non-hallucinators showed more activation in the middle temporal gyrus compared with hallucinators.

doi:10.1016/j.schres.2010.02.354

Poster 127
Abstract not available.

doi:10.1016/j.schres.2010.02.355

Poster 128
EVIDENCE OF FRONTO-TEMPORAL CONNECTIVITY DISTURBANCES IN PATIENTS WITH SCHIZOPHRENIA REVEALED BY EVENT-RELATED GRAPH ANALYSIS

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Background: Cognitive control deficits are a robust finding in schizophrenia, and are thought to arise from disturbed interactions between distributed brain systems; i.e., aberrant brain connectivity. The recent application of graph analysis to fMRI data has offered an unprecedented capacity for mapping large-scale brain network
disruptions, but such techniques have only been applied to resting-state data due to difficulties defining appropriate task-related connectivity metrics. In this study, we adapted a beta series correlation method to construct whole-brain event-related networks and characterize large-scale network disruptions of task-related connectivity in patients with schizophrenia.

**Methods:** First-episode schizophrenia patients (n = 23) and healthy controls (n = 25) were scanned as they performed a cognitive control task (AX continuous performance test) with two conditions: a relatively easy AX condition and a more difficult BX condition, requiring adequate representation of task context to inhibit a prepotent tendency in favour of a more appropriate response. Each trial was modeled using a unique regressor in a general linear model to generate beta coefficients representing the brain response evoked by each trial. These beta coefficients were then sorted into AX or BX trials and concatenated to obtain condition-specific beta series. An anatomical template was used to parcellate the brain into 77 regions-of-interest, and correlations between the mean beta series of each pair of regions were computed to construct two \( 77 \times 77 \) functional connectivity matrices for each participant, representing their condition-specific (AX or BX) co-activation network. These matrices were then subjected to graph analysis, whereby the network was represented graphically as a collection of nodes (regions) connected by edges (functional connections). We analysed three properties of these networks: (1) topological parameters (mean path length, clustering and small-worldness); (2) regional functional connectivity (each region's total connectivity with the rest of the network); (3) edge-wise functional connectivity (estimated by the beta series correlation between each pair of regions). The data were analysed using 2 (patients or controls) x 2 (AX or BX trials) ANOVA.

**Results:** Analysis of fMRI network topological measures revealed a reduction in mean path length (p < .01) and clustering (p < .01) for both groups in BX relative to AX trials, reflecting a shift from locally segregated to globally integrated connectivity during the BX condition. There were no group differences in these parameters, suggesting patients showed intact global network organization. In contrast, patients showed diffuse reductions in regional connectivity, with the strongest effects (p < .05, corrected) observed in fronto-temporal regions, particularly in the left hemisphere. Edge-wise analyses also revealed widespread connectivity reductions in the patient group, with the most robust effects (p < .05, corrected) being observed for fronto-temporal interactions across AX and BX trials. There were no significant diagnosis x condition interactions.

**Discussion:** Our results indicate that graph theoretical metrics are applicable to task-related fMRI data and can reveal topological changes in network configuration related to varying task conditions, supporting the validity of our approach. Schizophrenia patients showed reduced fronto-temporal connectivity during cognitive control performance, which occurred in the context of relatively preserved global network properties. These connectivity changes may represent an early marker of subsequent deterioration of network organization.

**Background:** Patient subjective well-being is a major determinant of treatment compliance. Comparisons of conventional and atypical medication, as well as neuroimaging studies have suggested that the subjective experience of patients may be related to the mesolimbic dopamine system crucial in processing reward information. Negative subjective changes have been shown to be related to altered reward processing, and striatal dopamine function. As dopamine may be associated with subjective experience and is the major neurochemical component in reward, and reward systems have been shown to be impaired following dopaminergic medication, negative subjective experience may be due to impairment of the reward system. The primary aim of the study was to examine whether the relationship between dopaminergic systems and subjective well-being is attributable to dysfunctional reward processing. It was hypothesised that patients low in subjective well-being will have decreased activation in anticipation of reward in the ventral reward system.

**Methods:** Twenty patients with schizophrenia were administered a Monetary Incentive Delay task, previously used by Knutson et al. (2001), while undergoing fMRI brain imaging on a 3T scanner. Positive, neutral and negative stimuli predicted valence of subsequent reward on each trial, while reaction time to hit a target determined trial outcome. Reward was obtained in reward trials, and loss avoided on losing trials on 66% of trials irrespective of subject performance abilities as determined by an automated adaptive timing algorithm which adjusted target speed. Functional MRI data were preprocessed and modelled with SPM5. Analysis contrasted brain activation during anticipation of reward and punishment to that of neutral stimuli (zero gain).

**Results:** BOLD activation was significantly greater in the left caudate nuclei in response to positive or negative reward compared to zero reward. Furthermore, patients with high subjective well-being showed greater activation during anticipation of rewarding outcomes in the left caudate compared to patients with low subjective-well-being.

**Discussion:** In conclusion, subjective well-being may be determined, in part, by the capacity of the reward system to represent rewarding stimuli, and as this system may be dopaminergic in function this mechanism may account for the propensity for antipsychotic medication to decrease subjective well-being in patients with schizophrenia.

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**Poster 130**

**THE EFFECTS OF HALOPERIDOL AND ARIPIPRAZOLE ON RESTING STATE BRAIN PERFUSION IN HEALTHY VOLUNTEERS**

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**Background:** Antipsychotic class specific differences in resting blood flow have been reported in schizophrenia, in brain regions where structural and functional alterations have also been associated with antipsychotic treatment. However, the precise effects of first and second generation antipsychotics on blood flow and the subsequent contribution to structural and functional alterations remains unclear. Unfortunately, most studies have evaluated individuals with psychosis, and they have not directly compared drugs of these two classes. This study directly compares the effects of typical and atypical antipsycho-
Background: Schizophrenia presents with a complex array of psychopathology that extends beyond the traditional focus of positive and negative symptoms, however the impact of these other symptoms upon neuroimaging are infrequently investigated. Anxiety is a common and potent symptom in schizophrenia that can act to trigger a psychotic episode or substantially impair function. In this study we examine the role of anxiety on cortical activation in a group of young people with their first episode of schizophrenia.

Methods: Twenty eight young people (mean age 20.6 yrs, sd 2.9 yrs, male:female=21:7) with their first episode of schizophrenia (FES) were compared to age, gender and handedness matched control subjects whilst performing an auditory oddball functional MRI paradigm (Siemens 1.5 T scanner). Subjects with schizophrenia were then divided into two groups on the basis of DASS anxiety scores greater or less than the clinical range (n = 13 high anxiety, n = 15 low anxiety). A ROI analysis and later symptom correlational analysis were performed at a clusterwise level.

Results: No differences were seen between FES and control subjects initially. When subjects with FES were divided on the basis of the level of anxiety significant differences were observed between high anxiety and low anxiety FES subjects and high anxiety FES and control subjects in the anterior cingulate and right middle frontal gyrus. No differences were observed between the low anxiety FES group and control subjects. However correlation with symptom scores (PANSS positive & negative; DASS anxiety, depression & stress) were not significant.

Discussion: In this study levels of anxiety explained much of the difference between FES and control subjects when examining brain activation to an oddball paradigm. Monitoring of the levels of anxiety through simultaneous measures of arousal and/or measures of clinical symptoms would appear to be important for the interpretation of neuroimaging results in schizophrenia.

doi:10.1016/j.schres.2010.02.359

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Poster 131
THE CONTRIBUTION OF ANXIETY TO FMRI IN FIRST EPISODE SCHIZOPHRENIA

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Background: Differential effects of typical and atypical antipsychotics were evident in resting blood flow, indicating different pharmacological profiles, and immediate physiological brain responses. These drugs may contribute to, or interact with, some of the structural and functional abnormalities observed in schizophrenia. Moreover, the presence of differences between antipsychotic classes highlights the need to consider antipsychotic effects in the interpretation of behavioural cognition and MRI findings in the patient population. This study provides unique evidence suggesting that arterial spin labeling imaging might provide a novel and valid technique for exploring treatment response in schizophrenia.

Methods: Single doses of haloperidol (3 mg) and aripiprazole (10 mg) were administered to twenty healthy caucasian, right handed males (mean age 23 yrs, SD4.5) in a repeated measures, randomised, double-blind, placebo controlled design. Volunteers had no current or past psychiatric history, nor substance use and smoking for at least 3 months prior to the study. Four hours post treatment, a continuous arterial spin labeling sequence was used to obtain a direct measure of blood flow using a 1.5 Tesla scanner. Sixty-four volumes were acquired with a slice thickness of 3.3 mm (including inter-slice gap) over 6 minutes. Between-subject analysis was performed on global perfusion using a random effects model. A voxel-wise search (p<0.001) was conducted and supra-threshold cluster-level statistics were accepted at p<0.05, corrected for whole brain comparisons. Small volume corrections were also applied, using independently, apriori defined regions of interest for which voxel-level statistics were accepted at p<0.05 (family wise error; FWE).

Results: After haloperidol, compared to placebo, an increase in perfusion was evident in the putamen, precentral gyrus and hippocampus bilaterally, and in the left premotor cortex; a decrease in perfusion was evident in the left inferior and middle temporal gyri. Relative to aripiprazole, an increase in perfusion was evident bilaterally in the putamen. After aripiprazole, compared to placebo, an increase in perfusion was evident bilaterally in the claustrum and putamen, in the right anterior cingulate, cerebellum, and in the left hippocampus, superior frontal gyrus and superior temporal gyrus, compared with placebo; a decrease in perfusion was evident in the right posterior cingulate, bilaterally in the inferior occipital gyrus, in the left inferior parietal lobule and middle frontal gyrus. Relative to haloperidol, an increase in perfusion was evident in the left superior temporal gyrus.

Discussion: Differential effects of typical and atypical antipsychotics were evident in resting blood flow, indicating different pharmacological profiles, and immediate physiological brain responses. These drugs may contribute to, or interact with, some of the structural and functional abnormalities observed in schizophrenia. Moreover, the presence of differences between antipsychotic classes highlights the need to consider antipsychotic effects in the interpretation of behavioural cognition and MRI findings in the patient population. This study provides unique evidence suggesting that arterial spin labeling imaging might provide a novel and valid technique for exploring treatment response in schizophrenia.

doi:10.1016/j.schres.2010.02.358

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Poster 132
THE CORTICAL NETWORK OF SELF-OTHER DISCRIMINATION INVESTIGATED BY RTMS

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Background: Self-face recognition has been suggested to be an indicator of higher-order self-awareness and therefore a topic of great interdisciplinary significance. However, little is known about the neural systems underlying this ability. Recent imaging studies into the neuronal network indicate that the visual pathway of recognising one’s own face differs from the one involved in recognising others. These processes involve temporoparietal and prefrontal regions mainly in the right hemisphere. However, the attribution of a function to brain areas with imaging techniques is limited.

Methods: Therefore, we followed another approach to investigate self-other discrimination, using repetitive transcranial magnetic stimulation (rTMS) to create ‘virtual lesions’ over the postulated areas. Here we applied low-frequency rTMS over temporoparietal and prefrontal components of this network to test whether these regions are necessary for discriminating self-faces from other familiar faces. We tested 10 healthy subjects in five sessions comprising sham stimulation and stimulations over right and left prefrontal and temporoparietal areas. Our behavioural task consisted of videoclips where the participant’s face, a familiar and an unfamiliar face transformed into each other within 6 seconds. The task for participants was to push a button as soon as they recognized the change of identity the face was transforming into.
Poster 133

RESTING-STATE FUNCTIONAL CONNECTIVITY REVEALS REDUCED INTRA-REGIONAL COMMUNICATION IN CHILDREN AT-RISK FOR PSYCHOSIS

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Background: The disconnection hypothesis in schizophrenia research is a widely accepted theory which states that when a focal disruption in the brain occurs the entire network will be adversely affected. This study investigated the neural substrates of resting-state functional connectivity in an at-risk for psychosis cohort of children and sample of patients with chronic schizophrenia.

Methods: A between-subjects assessment of brain functioning during resting-state fMRI took place among 11 children with subclinical psychotic symptoms who were at-risk (AR) for developing psychosis and 14 matched healthy control children (Con-C) and separately for 17 chronic schizophrenia patients (SZ) and 16 matched healthy adult controls (Con-A). Seed ROIs were derived from the at-risk and chronic schizophrenia patient studies in regions which revealed between-group differences during a response inhibition task. An additional seed region derived from the VBM analysis revealed a grey matter (GM) reduction in both the AR and SZ participants, relative to their controls.

Results: The analysis revealed a pattern of reduced functional connectivity in the AR and SZ groups within and between numerous right hemispheric regions, and which encompassed frontal and parietal cortices and the dorsal striatum. The frontal regions that revealed reduced functional connectivity in the AR and SZ groups also showed reduced activation during the response inhibition task.

Discussion: Our findings suggest that there are common patterns of aberrant functional organization between AR and SZ groups during the resting-state which may underlie the dysfunctional task-related activity. These findings are observable during the risk stage and presumably continue after onset of the illness.

doi:10.1016/j.schres.2010.02.360
phrenia (Jeong et al., 2009), and reanalyzed the data using independent component analysis (ICA). Ten healthy control subjects and ten chronic schizophrenics underwent an MRI scan during which they performed Levels of Processing paradigm. The semantic processing related independent components were compared between two groups using tensor ICA.

Results: An independent component of semantic repetition priming showed a significant difference between two groups. The component consisted of both less activated and less suppressed regions within the schizophrenics' brain. The less activated regions included the bilateral inferior frontal gyri and the supramarginal gyri. The less suppressed regions included the medial frontal gyrus, the posterior cingulate gyrus, precuneus and right cerebellum.

Discussion: Our results suggest two components of semantic repetition priming deficit in schizophrenia. One related to weaker suppression of default network, mainly precuneus and medial frontal gyrus, the other related to weaker activation of regions directly involved in semantic repetition priming.

doi:10.1016/j.schres.2010.02.363

Poster 136
FUNCTIONAL MAGNETIC RESONANCE IMAGING REVEALS SELECTIVE NEURONAL ALTERATIONS IN AN ANIMAL MODEL OF ANHEDONIA

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Background: Anhedonia, the loss of interest or pleasure in daily activities, is a core symptom of psychiatric disorders such as depression and schizophrenia. In the present study, withdrawal from subchronic d-amphetamine administration was used to induce anhedonia in rats. The anhedonic state of rats, measured as subsensitivity to reward, was assessed using an intracranial self-stimulation (ICSS) procedure. To further understand the neurobiological basis of anhedonia, functional magnetic resonance imaging (fMRI) was applied as a sensitive technique to identify key brain areas underlying this symptom.

Methods: D-amphetamine (5 mg/kg, i.p.) was administered to male Wistar rats twice a day for two weeks. After cessation of treatment the hedonic state of the animals was assessed daily using the ICSS procedure during which the rat can self-administer weak electrical impulses via an electrode implanted into the ventral tegmental area. In order to normalize the hedonic state, electroshock treatment (25 mA, 0.5 s) was given in a subset of animals through ear clips three times a week on alternating days (i.e. withdrawal day one, three, and five). In subsequent studies, potential regional brain dysfunction induced by d-amphetamine withdrawal was investigated by means of continuous arterial spin labeling based fmri.

Results: During withdrawal from d-amphetamine administration, the ICSS threshold was significantly increased (40% increase from baseline), suggesting a decrease of sensitivity to reward. This anhedonic state lasted up to twelve days. When electroshock treatment was given, the ICSS threshold increase was reversed to the baseline level. Using fMRI, alterations in regional brain activity were measured in anhedonic rats. Main effects were a reduced activity in nucleus accumbens (−6%) and an increased activity in medial prefrontal cortex (+6%) as compared to control animals.

Discussion: In this study we have shown that d-amphetamine withdrawal is a valid approach to induce a robust anhedonic state in rats. The reversal of this state by electroshock treatment confirms the validity of the induced phenotype and the applicability of the procedure. Furthermore, the fMRI findings give a first insight into underlying neuronal mechanisms by identifying phenotype-related brain activation patterns. In general, the combination of behavior and functional imaging approaches, applied on valid animal models in preclinical research will support the identification of symptom-specific imaging biomarkers and improve the characterization of pharmacological effects in the process of drug development.

doi:10.1016/j.schres.2010.02.364

Poster 137
CHARACTERISTICS OF BRAIN ACTIVATION DURING THE PROCESSING OF CONFLICTING EMOTIONAL STIMULI IN PATIENTS WITH SCHIZOPHRENIA: AN FMRI STUDY

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Background: The dorsolateral prefrontal cortex (DLPFC) has been reported to be essential for the conflict-induced behavioral adjustment. According to the ‘conflict-monitoring’ theory, the anterior cingulate cortex (ACC) monitors or detects the presence of conflict and then conveys conflict-related information to the DLPFC, which then adjust the level of cognitive control accordingly. In our previous study, the DLPFC in normal subjects activated in the conflicting emotional condition consisting of negative and positive stimuli causing emotional conflict. However, the neural basis of conflicting emotional stimuli for the patients with schizophrenia remains unknown.

Methods: Fourteen right-handed normal controls (6 men and 8 women) and 15 right-handed patients with schizophrenia (8 men and 7 women) participated in this study. We presented stimuli consisted of positive, negative, neutral, and combined emotional conditions in which two pictures were juxtaposed and the combined emotional condition consisted of positive and negative picture pairs, while scanning fMRI.

Results: We found the differences of brain activations between patients with schizophrenia and normal controls in task inducing emotional conflict. In the combined emotional condition evoking emotional conflict, normal controls showed activation in the DLPFC, which had negative correlations with posterior regions of the brain but the patients showed no activation in the prefrontal cortex, which had positive correlations with posterior regions, and the amygdala, while monitoring and processing the emotional conflict.

Discussion: The differences indicate that the abnormal processing of emotional conflict in patients with schizophrenia is related to hypofrontality compared to normal controls.

doi:10.1016/j.schres.2010.02.365

Poster 138
PREFRONTAL CORTICAL ACTIVATION IN PATIENTS WITH FIRST EPISODE SCHIZOPHRENIA AS MEASURED BY NEAR-INFRARED SPECTROSCOPY

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Background: Impaired prefrontal cortical function is a central feature of schizophrenia. The objective of this study is to evaluate prefrontal hemodynamic activation in first episode schizophrenia using a noninvasive neuroimaging technique, near-infrared spectroscopy (NIRS).

Methods: Ten patients with first episode schizophrenia were recruited from the outpatient clinic of Tohoku University Hospital in Sendai. Ten healthy volunteers with no history of psychiatric illness also participated in this study. The subjects performed a category fluency task, and the changes in the relative concentration of oxygenated hemoglobin ([oxy-Hb]) during the task was measured using a NIRS device. This study was approved by the Ethics Committee of Tohoku University, and all subjects provided written informed consent.

Results: No significant difference was noted in the number of words generated. Compared with control group, patient group showed lower changes in [oxy-Hb] during the task and abnormally greater changes in [oxy-Hb] during the posttask rest period in the bilateral prefrontal region.

Discussion: This study suggests that hypofrontality during the performance of a cognitive task and hyperfrontality during the posttask rest period is found in first episode schizophrenia. The pattern of changes in [oxy-Hb] in the frontal lobe measured by NIRS may be a useful biological indicator in patients with early psychosis.

doi:10.1016/j.schres.2010.02.366

Poster 139
GABA LEVELS IN THE MEDIAL PREFRONTAL CORTEX OF PATIENTS WITH SCHIZOPHRENIA: A PROTON MAGNETIC RESONANCE SPECTROCOPY (H'-MRS) STUDY
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Background: The disruption of inhibitory neural circuits in the medial prefrontal cortex (MPFC) has been proposed as a cause of working memory deficits in schizophrenia. Based on post mortem findings of decreased levels of mRNA for glutamic acid decarboxylase (GAD₆₇) and genetic association of risk for schizophrenia and reduced GAD₆₇ expression, we hypothesized that in vivo concentrations of GABA would be decreased in patients with schizophrenia. We used magnetic resonance spectroscopy (MRS) to compare GABA concentrations in the MPFC between patients with schizophrenia and normal volunteers.

Methods: Twenty medicated patients with schizophrenia, free from any history of substance abuse or dependence, and twenty age and gender matched healthy control subjects underwent single voxel MRS on two 3 T scanners using j-editing to measure GABA in a single voxel (18cm³TR/TE 1500/68 ms, 768 averages) placed in the MPFC. GABA levels were measured as both GABA/H₂O and GABA/creatine ratios and were compared between groups using a general linear model. In a separate PRESS scan (TR/TE 1500/68 ms, 32 averages), values of creatine were obtained and compared using a general linear model. When metabolite values were significantly different between scanners, we transformed values into z-scores and used these to analyze group differences in subsequent analyses.

Results: Values of GABA/creatine and creatine but not GABA/H₂O were significantly different between scanners, so only these values were transformed into z-scores. All other analyses reflect changes in these transformed values. Neither age, gender, or the amount of gray matter in the voxel were significantly correlated with GABA/H₂O or GABA/creatine. The amount of cerebral spinal fluid (CSF) was significantly correlated with the amount of GABA/H₂O (r = -0.47, p = 0.001) but not GABA/creatine, however there were no differences in the amount of gray matter, CSF, or water signal between patients and controls. Consequently, the amount of CSF was kept as a covariate when analyzing GABA/H₂O. Using GABA/creatine as the referencing method, GABA levels did not differ between patients and controls. However, patients (z-score = 0.222 ± 0.975) had a significantly higher concentration of creatine than healthy volunteers (z-score = −0.4612 ± 0.837) (F = 5.64, p = 0.023). When we compared GABA/H₂O between patients and controls, patients (IU = 15.394 ± 2.055) had significantly higher GABA/H₂O levels than healthy volunteers (IU = 14.338 ± 1.780) (F = 5.016, p = 0.03).

Discussion: Contrary to our hypothesis, we found a suggestion of increased GABA/H₂O in patients with schizophrenia. GABA/creatine did not differ between patients and controls, but this might be explained by the statistically significant increase in creatine found in these patients, which is consistent with some recent literature. Ratios to water are not exempt from problems, as demonstrated here by the correlation with CSF composition of the voxel. These include saturation effects in the water signal and differences in the T₂ of water between diagnostic groups. Although finding an increase in GABA levels in patients was unexpected, measures of GABA obtained by MRS cannot distinguish intracellar from extracellular GABA levels or differences in concentration between layers of the cortex. Increases in GABA measures from MRS may reflect a compensatory change in GABA neurotransmission secondary to cell and tissue layer specific reductions that are found in the mRNA and protein expression literature. Further studies need to address the effects of antipsychotic and other adjunct medications on GABA concentrations in order to determine whether any changes in GABA are primary to schizophrenia.

doi:10.1016/j.schres.2010.02.367

Poster 140
GLUTAMATE IN THE ASSOCIATIVE STRIATUM OF ANTIPSYCHOTIC-NAÏVE FIRST EPISODE PSYCHOTIC PATIENTS AND SUBJECTS WITH PRODROMAL SYMPTOMS OF SCHIZOPHRENIA
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Background: Participation of the dopaminergic and glutamatergic systems in the physiopathology of schizophrenia has been suggested. Interaction between dopamine and glutamate neurotransmission systems has been widely documented and could be important to understand the neurobiological basis of the disease. The aim of this study was to compare the Glutamate levels (Glu) on the anterodorsal caudate, as a dopamine rich region, and in the cerebellar cortex, as a negligible dopamine region, in: 1) first
episode psychotic patients (FEP), 2) subjects with ultra high risk for schizophrenia – or prodromal symptoms (UHR) and 3) age-and-sex similar healthy controls.

**Methods:** Sixteen drug-naive FEP, 16 UHR subjects and 33 controls were included. All subjects underwent a proton magnetic resonance spectroscopy (1H-MRS) study. 1H-MRS were performed on a 3.0-T GE scanner and Glu levels were corrected for the proportion of cerebrospinal fluid in the voxel.

**Results:** The antero-dorsal caudate in drug-free, FEP group showed higher levels of Glu than controls (df = 47, p = 0.006) and the UHR group (df = 47, p = 0.042). Controls and UHR were not different (df = 50, p = 0.43). No differences were shown in the cerebellum between the three groups.

**Discussion:** The increase of Glu in the dorsal-caudate was only present in the FEP group and not in the UHR. Moreover, the lack of change in the cerebellum suggests that the increase of Glu in psychosis is not ubiquitous within the brain. The current results support that psychosis is associated with an increase of Glu levels only in areas rich of dopamine projections.

**doi:**10.1016/j.schres.2010.02.368

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**Poster 141**

**CONCEPT FOR COMBINED 1H AND 31P MR SPECTROSCOPIC INVESTIGATIONS IN PATIENTS WITH SCHIZOPHRENIA**

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**Background:** With recent advances in the evaluation of spectroscopic information it has become possible to perform comprehensive investigations comprising metabolic as well as structural information. In particular, this has become important in the study of schizophrenia. The aim of our work was to establish a comprehensive workflow that allows detection of proton and phosphorous metabolic concentrations from identical brain regions by combined acquisition of 1H- and 31P- chemical shift imaging (CSI) data.

**Methods:** All measurements were performed on a clinical 3 T MR scanner (Trio TIM, Siemens, Germany) with a 1H/31P-transmit/receive head coil (Rapid Biomedical, Germany). The study protocol comprised whole-head, T1-weighted 3D MRI scan, which was also used for MRS volume adjustment (MP-RAGE, 192 sagittal 1 mm thick slices, FOV_{AP} × FOV_{LR} × FOV_{FH} : 256 × 256 × 2 mm²), followed by the acquisition of 1H- and 31P-CSI data sets. A 2D 1H-CSI (PRESS; TE/TR: 0.03/2 s; 15 mm transversal slice; 16 × 16 phase encoding steps; FoV_{AP} × FoV_{LR} : 240 × 240 mm²) and 3D 31P-CSI (TR: 3 s, FoV_{AP} × FoV_{LR} × FoV_{FH} : 240 × 240 × 240 mm³, spatial encoding matrix: 8 × 8 × 8 interpolated to 16 × 16 × 16) were applied. 1H-CSI slice was placed 15 mm above the AC-PC line and then rotated by 20° clockwise around the left-right axis. Similar position and orientation were adapted for the 31P-CSI volume to achieve spatial alignment between 1H- and 31P-CSI-voxels. Finally, two single voxel 1H-MR spectra were acquired in the left and right hippocampus. All 1H-MRS measurements were performed with and without water suppression, allowing separate quantitation of metabolite and water intensities (I_M, I_W). 1H-MR spectra were post-processed with the LCModel. Concentrations of N-Acetyl-Aspartate (NAA), creatine (Cr), total choline (Cho), myo-inositol (ml) and glutamate (Glu) were calculated by multiplying the I_M/I_W-ratios with the tissue water concentration. Volume fractions of brain white and grey matter (WM, GM) and CSF within the MRS voxels were automatically extracted from the tissue segmented MP-RAGE data to account for partial volume effects due to CSF as well as for the different water concentrations in WM and GM. Total phosphor amount normalized intensities of phosphocreatine (PCr), adenosine-triphosphate, inorganic phosphate and phosphorylcholine were extracted from 31P-MR spectra, which were analyzed using jMRUI package.

**Results:** The protocol was successfully applied to 5 volunteers. The overall examination time was within 2.5 h. Data quality was sufficient to quantify intensities of all metabolites of interest in the anterior cingulate cortex, hippocampus, thalamus as well as in the prefrontal white matter. 1H-MR spectra had typical SNR values between 15 and 30 for NAA singlet at 2 ppm. This is also reflected by the low Cramer-Rao-Low-Bounds below 7% for NAA, Cr, Cho and below 20% for ml and Glu. The SNR values of 31P-MR spectra were between 10 and 20 (for PCr peak at 0 ppm).

**Discussion:** As demonstrated, the study design allows detection of proton and phosphorous metabolic concentrations from specified brain regions within a single examination. With a combined analysis of 1H- and 31P-MRS it becomes possible to account for the heterogeneous contributions of several brain matter types within the MRS voxels and to increase the accuracy of absolute metabolite quantitation.

**doi:**10.1016/j.schres.2010.02.369

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**Poster 142**

**A GENOME-WIDE LINKAGE SCAN OF THETA BAND ACTIVITY AS AN ENDOPHENOTYPE FOR SCHIZOPHRENIA**

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**Background:** Deviant brain oscillations are candidate endophenotypes for schizophrenia. Our aim was to find new quantitative trait loci for brain oscillations and putatively schizophrenia.

**Methods:** We systematically investigated the genetic characteristics of theta, alpha, and beta oscillations at frontal, central, and occipital scalp locations in 25 extended multiplex families affected with schizophrenia using familial correlations, heritability estimates, and segregation analysis. Subsequently, in a genome-wide linkage scan we genotyped seven pedigrees (n=118, including 649 relative pairs) for 6,090 single nucleotide polymorphic markers. Two-point and multipoint variance-component based linkage analyses were performed using MERLIN.

**Results:** Theta activity at occipital sites constituted the most heritable phenotype (h² of up to 0.55), fitting Mendelian transmission models and was included in a genome-wide scan. Suggestive two-point peaks (empirical p < 0.001) for theta at occipital sites were found at 13 loci, e.g., 5p15.31, 20p13.
Poster 143
MEG DOES NOT REVEAL IMPAIRED SENSORY GATING IN FIRST-Episode SCHIZOPHRENIA

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Background: The inability to adequately suppress the second of two identical stimuli is called sensory gating deficit and can be studied by recording evoked potentials to auditory stimuli, e.g. the P50 and the N100. It has been looked at as the physiological correlate of schizophrenia patients’ perception of being flooded by sensory impressions. According to the notion that the gating deficit constitutes a genetic trait, we expected to demonstrate the phenomenon in first-episode schizophrenia patients using MEG.

Methods: Eighteen inpatients in remission of their first psychotic episode and 24 healthy, age- and sex-matched control subjects participated in the study. Diagnoses, psychopathology and handedness were assessed with established instruments. Stimulation was performed with the double click paradigm (ISI 500 ms, ITI 9-10 sec). Magnetencephalography (MEG) recordings of 15 patients and 18 controls entered further analyses with the software BESA for spatio-temporal source analyses and statistical analyses with MATLAB.

Results: Neither P50 nor N100 responses differed statistically between the groups. This means that gating was not impaired in this first-episode sample of schizophrenia patients.

Discussion: Conclusions: These results are not in line with the majority of studies on sensory gating in schizophrenia, however, studies on first-episode patients are scarce. The most likely reasons for absence of the gating deficit in our study are patients’ first-episode status and atypical antipsychotic medication.

doi:10.1016/j.schres.2010.02.371

Poster 144
PREDICTION OF PSYCHOSIS BY MISMATCH NEGATIVITY

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Background: Prevention of psychosis has become a major task, and although current at-risk criteria are associated with a tremendously increased risk for psychosis, results of prediction studies also demonstrate a need for further characterization of the individual risk in order to employ risk adapted preventive measures. It has been suggested that biological parameters potentially differentiate future converters from non-converters in the at-risk state and provide further information about the timing of a future conversion. Impaired pre-attentive sensory information processing is regarded as an important pathophysiological mechanism contributing to schizophrenia. It has been shown that the mismatch negativity (MMN), an auditory event-related potential (ERP) that can be understood as an index of automatic context-dependent information processing, is rather specifically reduced in schizophrenia and is correlated with everyday functioning. It has been proposed, that primary and secondary auditory, and potentially fronto cortical contribute to the generation of the MMN response. On the molecular level, an involvement of the glutamate/n-methyl-d-aspartate (glu/NMDA) system has been suggested. A recent study demonstrated the reduction of the magnetencephalographic duration MMN in at-risk individuals compared to healthy controls. The present study aimed to investigate the hypothesis that at-risk subjects later converting to psychosis show a deficit of the duration MMN compared to subjects not converting in a certain period of time. In addition, the possible contribution to the prediction of psychosis was evaluated.

Methods: We used an auditory oddball paradigm in combination with a visual vigilance control task. Subjects were recruited in the prospective German Research Network on Schizophrenia (GNRS) study, fulfilled the criteria for a late at-risk state (LARS) at baseline and were antipsychotic-naive throughout the study. Sixty-two subjects fulfilled the intake criteria. In case of non- conversion (N=27), the clinical follow-up was at minimum 24 months (46.3±13.1). Converting subjects (N=25) showed an average time to conversion of 7.0±7.0 months. Repeated measures ANCOVA was employed to analyse the MMN recorded at frontal (F3, Fz, F4) and central electrodes (C3, Cz, C4). A Cox regression model served to evaluate the predictive value of the duration MMN amplitude.

Results: Subjects with later conversion to psychosis showed significantly reduced duration MMN amplitudes over the six fronto-central electrodes compared to non-converters subjects (F(1)=5.16, p<.05). Based on a stepwise backward Cox regression model (c²=4.77, p<.05; beta=.92±.44; Wald(1)=4.46, p<.05; hazard ratio=2.5, 95%-CI: 1.07–5.87), four electrodes (Fz, F4, C4, C3) served to create an individual prognostic score. A median split based on the score generated two risk classes; cumulative hazard rates were 0.34 in class 1 and 0.85 in class 2. Kaplan-Meier analysis revealed two significantly different survival curves for the classes (class 1: 20.0, 95%-CI: 16.9–23.1; class 2: 13.7, 95%-CI: 10.4–17.4; Log-rank test, c²=5.58, p<.05).

Discussion: The present findings demonstrate for the first time that the duration MMN is significantly reduced in at-risk subjects converting to first-episode schizophrenia within a certain period of time compared to non-converters. Further analyses indicate that this MMN deficit may contribute to the prediction of conversion. Moreover, the findings support the notion that biological parameters are promising candidates for a more individualized estimation of risk in terms of magnitude and time.

doi:10.1016/j.schres.2010.02.372

Poster 145
IMPAIRED LONG-TERM POTENTIATION OF THE VISUAL EVOKED POTENTIAL IN SCHIZOPHRENIA

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Background: Long-term potentiation (LTP) is a cellular mechanism of synaptic plasticity thought to underlie learning and
memory that depends on glutamergic neurotransmission at NMDA receptors. Converging evidence implicates NMDA receptor hypofunction in schizophrenia and its associated cognitive impairments, suggesting that disruption of basic mechanisms of synaptic plasticity, including LTP, may be a core feature of the disorder’s pathophysiology. Recently, classic LTP paradigms involving stimulation at a “tetanizing” frequency have been successfully adapted for in vivo studies of humans, showing LTP-like potentiation of visual evoked potentials (EPs) from scalp-recorded electroencephalography (EEG) following repeated rapid visual stimulation. Using a visual LTP paradigm, we hypothesized that patients with schizophrenia would exhibit deficient LTP-like potentiation off their visual EPs following exposure to a tetanizing photic stimulus.

Methods: EEG was recorded from 19 medicated patients with schizophrenia and 23 healthy controls during a visual LTP paradigm. EPs elicited by a visual stimulus (checkerboard) presented at 1200 ms intervals were assessed at baseline and at 2, 4 and 18 minutes following a 2-minute photic tetanus (same checkerboard flashing at a frequency of 9.83 Hz). To ensure that subjects attended to the visual stimuli during the assessment of visual EPs, subjects were asked to respond with a button press to infrequent visual target stimuli randomly inserted into the series of standard checkerboard stimuli. EPs from 29 scalp electrodes were subjected to a temporal principal components analysis. Two negative-voltage components prominent over occipital-parietal scalp sites were evident, one at 100 ms (N100), the other at 150 ms (N150). N100 and N150 factor scores were analyzed in Group x Time repeated measures ANOVAs.

Results: The photic tetanus produced significant potentiation (i.e., increased negativity) of both the N100 and N150 components at 4, 6, and 20 minutes post-tetanus, relative to baseline. These effects were significantly attenuated in schizophrenia patients, relative to controls. Moreover, among patients but not among controls, greater LTP induction by the photic tetanus was associated with enhancement of reaction time to target stimuli.

Discussion: Schizophrenia is associated with deficits in visual LTP, consistent with hypothesized deficits in synaptic plasticity related to NMDA-receptor hypofunction. This deficit in synaptic plasticity can be measured by non-invasive EP method.

doi:10.1016/j.schres.2010.02.373

Poster 147
INCREASED EEG SYNCHRONIZATION IN SCHIZOPHRENIA PATIENTS BY THE GLUTATHIONE PRECURSOR, N-ACETYL-CYSTEINE

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Background: Glutathione (GSH) dysregulation at the gene, protein and functional levels observed in schizophrenia patients, and schizophrenia-like anomalies in GSH deficit experimental models, suggest that genetic glutathione synthesis impairments represent one major risk factor for the disease (Do et al., 2009). In a randomized, double blind, placebo controlled, add-on clinical trial of 140 patients, the GSH precursor N-Acetyl-Cysteine (NAC, 2 g/day, 6 months) significantly improved the negative symptoms and reduced side-effects due to antipsychotics (Berk et al., 2008). In a subset of patients (n = 7), NAC (2 g/day, 2 months, cross-over design) also improved auditory evoked potentials, the NMDA-dependent mismatch negativity (Lavoue et al, 2008).

Methods: To determine whether increased GSH levels would modulate the topography of functional brain connectivity, we applied a multivariate phase synchronization (MPS) estimator (Knyazeva et al, 2008) to dense-array EEGs recorded during rest with eyes closed at the protocol onset, the point of crossover, and at its end. Phase synchronization phenomena are appealing because they can be associated to synchronized phases while the amplitudes stay uncorrelated. MPS measures the degree of interactions among the recorded neuronal oscillators by quantifying to what extent they behave like a macro-oscillator (i.e. the oscillators are phase synchronous). To assess the whole-head synchronization topography, we computed the MPS sensor-wise over the cluster of locations defined by the sensor itself and the surrounding ones belonging to its second-order neighborhood (Carmeli et al, 2005). Such a cluster spans about 12 cm on average.

doi:10.1016/j.schres.2010.02.374
Results: The whole-head imaging revealed a specific synchronization landscape in NAC compared to placebo condition. In particular, NAC increased MPS over frontal and left temporal regions in a frequency-specific manner. Importantly, the topography and direction of MPS changes were similar and robust in all 7 patients. Moreover, these changes correlated with the changes in the Liddle’s score of disorganization (Liddle, 1987) thus linking EEG synchronization to the improvement of clinical picture.

Discussion: The data suggest an important pathway towards new therapeutic strategies that target GSH dysregulation in schizophrenia. They also show the utility of MPS mapping as a marker of treatment efficacy.

doi:10.1016/j.schres.2010.02.375

Poster 148
AGE EFFECTS ON HABITUATION AND PREPULSE INHIBITION OF THE HUMAN STARTLE REFLEX, PRELIMINARY RESULTS

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Background: Evidence has been accumulating that cognitive deficits, including disturbances in early information processing, form core features in schizophrenia. Given the fact that some of these deficits are not only consistently found in patients with schizophrenia, but also in their first degree relatives, suggests that they might represent endophenotypes for the disease. Deficiencies in both sensorimotor gating and habituation are examples of possible endophenotypes for schizophrenia. Both phenomena can be quantified by assessment of prepulse inhibition and habituation of the human startle reflex. The current study reports on the effect of age on these two paradigms, since there are only a few conflicting studies in literature devoted to that.

Methods: Forty-eight healthy male volunteers evenly distributed in age from 18-80 years, where tested in a combined PPI and habituation paradigm. Pulse alone and habituation trials consisted of 20 ms of white noise (115 dB), prepulses consisted of bursts of white noise with intensities of either 6 or 15 dB above Background (70 dB white noise) with a duration of 20 ms. Stimulus onset asynchrony in prepulse–pulse trials was either 60 or 120 ms, whereas inter-trial intervals were randomized between 10 and 20 s.

Results: No age effects were found on PPI. However a significant effect of age was found on habituation.

Discussion: Other studies have described the age effects on PPI and habituation among healthy volunteers, but with conflicting results. The results of one study pointed towards an U-shaped function between PPI and age while no effects of age were found on habituation, while in another study no effects of age were found on PPI but increased habituation was correlated with increased age. The current results confirm that PPI is not affected by age, although it does seem to affect habituation.

doi:10.1016/j.schres.2010.02.376

Poster 150
RELATIONSHIP BETWEEN STEADY-STATE GAMMA DRIVING AND COGNITIVELY ELICITED GAMMA FREQUENCY RESPONSES IN SCHIZOPHRENIA

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Background: There is compelling evidence suggesting that aberrant hippocampal (HPC) output underlies the dopamine (DA) dysfunction observed in an animal model of schizophrenia (Lodge & Grace, 2007). Using the methylazoxymethanol acetate (MAM) developmental model of schizophrenia in the rodent, this alteration of hippocampal activity was proposed to result from a reduction in PV-expressing interneurons in the ventral HPC (Lodge et al., 2009). Indeed, reductions in the activity of parvalbumin (PV)-expressing GABAergic interneurons in the ventral HPC likely destabilize the output of pyramidal neurons as well as affect the coordinated activation across a broad neural network. In the present study, a novel α5GABAA receptor agonist was tested for its ability to reverse the hyperactivity of the dopamine system in MAM-treated animals by altering the output of the HPC.

Methods: In vivo extracellular recordings from either the ventral tegmental area (VTA) or the ventral HPC were performed in saline (SAL) and MAM-treated rats anesthetized with chloral hydrate. The VTA was sampled in a grid-like pattern and the number of spontaneously active DA neurons was recorded following vehicle or α5GABAA receptor agonist, SH-053-2′F-R CH3, treatment (0.1 mg/kg, i.v.). In addition, pyramidal neurons were recorded in the ventral HPC while simultaneously stimulating entorhinal cortex and the effect of α5GABAA receptor agonist treatment on evoked responses was tested.

Results: Compared to vehicle-treated animals, treatment with the α5GABAA receptor agonist reduced the number of spontaneously active DA neurons in the VTA of MAM animals to levels observed in untreated rats. Consequently, the effect of the α5GABAA receptor agonist on the responsiveness of ventral HPC pyramidal neurons to cortical input was explored. HPC neurons in both SAL and MAM animals exhibited either enhanced or diminished cortical-evoked responses following α5GABAA receptor agonist treatment. The duration of the inhibitory effect of α5GABAA receptor agonist on HPC responses was greater in MAM animals.

Discussion: This study supports a novel treatment of schizophrenia that targets abnormal hippocampal modulation via a disruption of PV-expressing interneurons. Consequently, restoring inhibition in this model is effective in normalizing dopamine output.

doi:10.1016/j.schres.2010.02.377

Poster 149
A NOVEL α5GABAA RECEPTOR AGONIST REVERSES HIPPOCAMPAL OVERDRIVE OF DOPAMINE NEURON ACTIVITY IN THE MAM MODEL OF SCHIZOPHRENIA

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Background: In a novel α5GABAA receptor agonist treatment. The duration of the inhibitory effect of α5GABAA receptor agonist on HPC responses was greater in MAM animals.

Discussion: This study supports a novel treatment of schizophrenia that targets abnormal hippocampal modulation via a disruption of PV-expressing interneurons. Consequently, restoring inhibition in this model is effective in normalizing dopamine output.

doi:10.1016/j.schres.2010.02.377
power to standard stimuli (p < .05), and reduced PLF (p < .05) and evoked power (p < .01) to target stimuli. In the paired click paradigm, patients had reduced EAGBR evoked power (p < .01) and PLF (p = .01) to S1 stimuli, and reduced PLF (p < .01) to S2 stimuli. Age-of-onset was significantly associated with gamma measures. EAGBR measures to S2 click stimuli were associated with SSAEP activity (r = .32; p = .05) and with oddball standard stimuli EAGBR evoked power (r = .44; p < .01).

Discussion: Deficits in GBRs in SZ are not strictly task-specific, with shared variance between EAGBRs to S2 clicks and some other measures, but not between oddball EAGBRs and SSAEP measures. The common and independent pathophysiological mechanisms underlying these results remain to be determined.

doi:10.1016/j.schres.2010.02.378

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**Poster 152**

**CIRCADIAN DYNAMICS OF THE PARAMETERS OF SPECTRAL ANALYSIS OF HEART RATE VARIABILITY IN TREATING SCHIZOAFFECTIVE DISORDER**

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**Background:** Objective of the work is to study circadian rhythms of the parameters of spectral analysis of heart rate variability in case of schizoaffective disorder, depressive type.

**Methods:** 15 right-handed patients (mean age 34.6 ± 11.5 years) have been studied. According to ICD-10 criteria schizoaffective disorder, depressive type (F 25.1) was diagnosed in all of them. The degree of severity of depression was assessed according to Hamilton Depression Rating Scale (17 items). To assess variability of the heart rhythm spectral analysis has been used. The patients were examined at 7 a.m., 7 p.m. prior to the beginning of treatment, following three weeks and upon leaving the in-patient department. The control group consisted of 15 mentally healthy people. Members of the control group were examined every season (in October, January, April and July).

**Results:** The initial stage was characterized by increase in sympathicotonia in the morning hours. Towards the end of the third week of the therapy sympathicotonia increased in the morning hours and decreased in the evening hours. By the discharge sympathicotonia increased in the morning and became comparable with the parameters of the control group in the evening.

**Discussion:** The increase in sympathetic impact in the morning hours can be regarded as predictor of effectiveness of schizoaffective disorder (depressive type) therapy.

doi:10.1016/j.schres.2010.02.380

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**Poster 153**

**SMOOTH PURSUIT AND VISUAL SCANPATHS: RELATED OR INDEPENDENT DEFICITS IN SCHIZOPHRENIA?**

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**Background:** Smooth pursuit eye movements are involved in the continuous tracking of a moving target. Visual scanpaths describe the alternations of fixations and saccades produced by the ocular system during scene viewing. Abnormalities in both smooth pursuit and visual scanpath behaviours have been reported frequently in schizophrenia. Both eye tracking dysfunction (ETD) and atypical scanpaths have been proposed as candidate trait markers for psychosis and are subserved by a number of common neural regions. To date, smooth pursuit and scanpath eye movements have only been studied separately in schizophrenia. No study has examined concordance between ETD and scanpath abnormalities in this clinical group. It is not clear whether ETD and atypical scanning may derive from a common underlying pathology. The present study examined concordance rates among ETD and scanpath deficits in a group of chronic schizophrenia patients and healthy controls.

**Methods:** Individuals meeting DSM-IV criteria for schizophrenia (n = 96) and age-matched unaffected control participants (n = 100) completed (i) smooth pursuit tracking of a predictable sine-wave target motion; (ii) smooth pursuit tracking of a target moving in a less predictable Lissajous pattern; and (iii) free-viewing of photographic and computer-generated images (landscapes,
interiors, faces, animals, social scenes, household objects). Eye movements were recorded using non-invasive infra-red oculography. Bootstrap sampling was used to calculate global tracking accuracy measures (root-mean-square error, RMSE, and signal-to-noise ratio, SNR) for each pursuit trial. For visual scanpath, fixation number, fixation duration and scanpath length were combined into a single composite measure of scanning behaviour. The presence of ETD was defined when either RMSE or SNR was beyond one standard deviation above (RMSE) or below (SNR) the mean of the control group. Scanpath deficits were marked as present where the composite scanpath score was beyond one standard deviation below the control mean.

Results: Performance in both tasks was impaired in patients relative to controls. Pursuit was more error-prone in schizophrenia with increased RMSE and decreased SNR in both types of stimulus movement. Patients’ fixations during picture viewing were longer and spatially restricted and were reflected in lower scanpath composite scores. There was no evidence of association between the presence of ETD and atypical scanpath behaviour either in schizophrenia or the non-clinical group. Neither group showed significant correlations between scanpath scores and smooth pursuit measures. Odds ratios were calculated to compare the odds of scanpath dysfunction where ETD was present with the odds of scanpath dysfunction where ETD was absent. In both the schizophrenia and non-clinical groups, odds ratios were not significant, suggesting performance on pursuit and scanpath tasks was independent in each of these groups.

Discussion: Both abnormalities in visual scanpath behaviour and smooth pursuit eye tracking have been proposed to tap trait characteristics of genetic vulnerability to schizophrenia. The apparent independence of the two oculomotor tasks in this study suggests that ETD and scanpath dysfunction reflect the integrity of differential neurobiological and cognitive substrates as well as separable genetic underpinnings in schizophrenia. Both smooth pursuit and scanpath tasks are likely to offer an individual contribution to future studies of the neurobiological and genetic disturbances involved in schizophrenia and related disorders.

doi:10.1016/j.schres.2010.02.381

Poster 154

HIPPOCAMPUS-ACCUMBENS INTERACTIONS IN A DEVELOPMENTAL ANIMAL MODEL OF SCHIZOPHRENIA

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Background: The ventral subiculum (vSub) of the hippocampus is proposed to gate information flow within the nucleus accumbens (NAc), a limbic region positioned to integrate information from limbic and cortical regions, including the media prefrontal cortex (mPFC). Moreover, the mPFC as well as the hippocampus are proposed to play a central role in the pathophysiology of schizophrenia. We have previously shown the critical role of the mPFC in the modulation of this pathway in normal animals. Thus, it is likely that known alterations in mPFC output in the MAM-treated rat abnormally alter synaptic plasticity in subcortical structures.

Methods: Methyloxazocyanol acetate (MAM) was administrated to pregnant dams on gestational day 17. In vivo extracellular single unit recordings from NAc neurons were performed in chlroal hydrate anesthetized adult offspring rats. The response of NAc neurons to single pulse stimulation of the vSub-NAc pathway was examined. In addition, high-frequency stimulation, as well as low frequency stimulation was applied to the vSub-NAc pathway of MAM and saline rats.

Results: In saline-treated rats, long-term potentiation of the vSub-NAc pathway was induced following high-frequency stimulation (HFS), whereas long-term depression was induced by low-frequency stimulation. In MAM rats, a long-term depression is observed after HFS. Interestingly when low-frequency stimulation was applied, two types of responses were observed in MAM animals, a long term depression and a long term potentiation.

Discussion: The work presented here demonstrates that the vSub-NAc pathway displays altered long-term plasticity in response to both high frequency and low frequency stimulation in MAM-treated rats. We have previously shown the critical role of the mPFC in the modulation of this pathway in normal animals. Thus, it is likely that known alterations in mPFC output in the MAM-treated rat abnormally alter synaptic plasticity in subcortical structures.

doi:10.1016/j.schres.2010.02.382

Poster 155

MULTIVARIATE EYE MOVEMENT PSYCHOPHYSIOLOGY ACCURATELY DIFFERENTIATES SCHIZOPHRENIA CASES FROM UNAFFECTED CONTROLS

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Background: The ease with which eye movements can be measured initiated a century of research into psychophysiological dysfunction in psychiatric populations. Initial findings were promising, suggesting performance on oculomotor tasks was influenced by the status of the observer’s mental health. Research using family pedigrees subsequently provided evidence for a link between eye movement dysfunction and inherited risk of serious mental illness. Most recently, new and unexpected genetic and clinical overlaps have been discovered between debilitating neurodevelopmental illnesses such as schizophrenia and affective disorders. This has naturally cast doubt upon the likelihood of finding an endophenotype for schizophrenia per se, and may also explain why a trait marker for the illness has not been found. While eye movements can be assumed to act as an index of various on-going neural and mental processes, their prevalence as an abnormal feature of schizophrenia is as varied as the illness is heterogeneous. Equally important is the fact that ‘abnormal’ eye tracking is also found in the normal population. The use of visual scanpaths as method for examining more general scene perception in schizophrenia has prompted a resurgence of interest in using eye movements in the test repertoire. The relative importance of scanpaths, smooth pursuit and saccadic control as atypical processes in schizophrenia is unknown as is their combined efficacy in delineating major psychiatric illnesses.

Methods: Eye tracking performance was measured in 95 out-patients meeting clinical diagnostic criteria for schizophrenia, and 93 age-matched controls. Tasks included smooth pursuit of horizontal and Lissajous sinusoidal targets, fixation stability (as a proxy for saccadic control), and scanpath formation during free-viewing of natural scenes. Statistical models were then used to evaluate composite fixation and saccade activity in each participant group. Cross-validation was used to prevent over-fitting of data to the model. Individuals with incomplete tests (missing values) were included in model training and testing.
Results: Perfect separation of cases and controls was obtained using a supervised gradient boosting model to build a series of decision trees using the multivariate data. Classification was determined by the weighted sum of each tree’s fit for a given observer. Eye movement data from 30 new cases and controls and re-test sessions confirmed the high predictive validity of the model.

Discussion: Restricted scanpaths emerged as the most influential aspect of eye movement dysfunction in schizophrenia. Particular elements of pursuit accuracy and saccade inhibition also featured prominently in the model. Each of these discriminators confirmed findings from previous studies, but only by combining measures from several tasks could their utility be exploited to discriminate between individuals with schizophrenia and unaffected controls. The multivariate model succeeded because it was able to capture phenotypic variation on a continuum within a category. No consistent patterns of association were found with illness duration or onset, nicotine and caffeine intake, age, sex or medication. These are extremely exciting findings. We can now examine the specificity of these results and delineation of the natural boundaries of illnesses sharing common genetic pathways with schizophrenia.

doi:10.1016/j.schres.2010.02.383

Poster 156
REDUCED CARDIO-RESPIRATORY COUPLING INDICATES SUPPRESSION OF VAGAL ACTIVITY IN HEALTHY RELATIVES OF PATIENTS WITH SCHIZOPHRENIA

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Background: Past studies showed a reduced vagal modulation in patients with acute schizophrenia. The underlying mechanisms have not been clarified until today. One theory is a lack of inhibitory control over the amygdala resulting in an autonomic dysbalance that can influence respiratory patterns and consequently cardiovascular parameters. Previous studies have also observed reduced vagal modulation in first degree relatives of patients suffering from schizophrenia, thus suggesting a genetic predisposition. The aim of our study was to investigate cardio-respiratory coupling in first degree relatives of patients with paranoid schizophrenia.

Methods: To investigate vagal modulation at brain stem level, we investigated the coupling between heart rate and breathing as a putative measure of central autonomic function in 19 patients, 19 of their relatives and 19 matched control subjects. The interaction of heart rate and breathing was investigated in all groups applying the non-linear parameter cross-ApEn, indicating the asynchrony between both time series.

Results: The main finding of our study is a significantly increased cross-ApEn value, indicating reduced central vagal modulation both in relatives and patients suffering from schizophrenia.

Discussion: Our results suggest that autonomic dysfunction in schizophrenia is present in first-degree relatives not only at the target organs as shown previously, but also affects the central vagal component.

doi:10.1016/j.schres.2010.02.384

Poster 157
CORTICAL DYSFUNCTION DURING VISUAL WORKING MEMORY IN SCHIZOPHRENIA AND SCHIZOPHRENIA-LIKE PSYCHOSIS OF EPILEPSY: A MAGNETOEENCEPHALOGRAPHY STUDY

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Background: Clinically, chronic interictal psychosis of epilepsy closely resembles schizophrenia with a typical presentation as a paranoid hallucinatory syndrome, which is why it is also referred to as schizophrenia-like psychosis of epilepsy (SLPE). Despite the similarities, there is an ongoing debate as to whether schizophrenia and SLPE share common pathophysiology, and a distinct clinical entity separating SLPE from schizophrenia is not yet identified. Working memory (WM) deficits are considered a core cognitive dysfunction in schizophrenia. However, little work has been done to examine a possible connection between cognitive abnormalities in SLPE and schizophrenia that may help elucidate the relationship between the two. The purpose of this study is to determine cognitive abnormalities, as indicated by task-induced changes in brain oscillatory activity in SLPE, and to assess whether these abnormalities are distinguishable from those seen in schizophrenia in terms of WM deficits.

Methods: Twelve patients with SLPE, 14 patients with nonpsychotic epilepsy (nPE), 14 patients with schizophrenia, and 14 healthy subjects participated in this study. All groups were matched for age, gender and premorbid IQ. The Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS) were used to assess psychosis. Magnetoencephalography (MEG) was used while subjects performed a visual-object WM task. For each single trial, a 2-sec. interval before and after a memory set was deemed baseline and active state, respectively. Source imaging of MEG data in the time-frequency domain was performed using multiple source beamformer. Brain Voyager QX was used for statistical group analysis. We also tested the potentially confounding effect of medication by correlating cortical activation with chlorpromazine equivalents and antiepileptic drug (AED) plasma levels.

Results: The behavioral data revealed that the two psychotic groups performed at equal levels on the WM task as far as answer correctness and reaction time are concerned. In both patients with schizophrenia and those with SLPE, we found dorsolateral prefrontal hyperactivation and left inferior temporal hypoactivation, as indicated by alpha event-related desynchronization and synchronization, respectively. Patients with schizophrenia also showed alpha2 sub-band event-related desynchronization in the mid-prefrontal cortex relative to healthy controls. Direct comparison of patients with SLPE and schizophrenia rendered no difference in source-power changes. We found no correlation between ERD/ERS sources and chlorpromazine equivalents or AED plasma levels in either psychotic group.

Discussion: Our results demonstrate that patients with schizophrenia and SLPE have WM deficits involving a frontotemporal network and the neurophysiological basis for these deficits is primarily changes in the alpha frequency band – and theta band to a lesser extent. Patients with schizophrenia, however, manifested wider activation in prefrontal areas. These source-power changes were not influenced by medication. Overall findings indicate similar functional cognitive abnormalities in schizophrenia and SLPE in the prefrontal and left temporal cortex, which supports the possibility that these disorders share common underlying pathophysiological mechanisms.

doi:10.1016/j.schres.2010.02.385
Poster 158
THE CAPTURE OF VISUAL ATTENTION USING AUDITORY CUES IN SCHIZOPHRENIA

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Background: One cognitive feature of schizophrenia (SZ) is a deficit in the ability to disengage attention from salient events in peripheral vision (Maruff et al., 1998). We investigated whether an analogous attention deficit might occur in SZ in the auditory peripheral vision (Maruff et al., 1998). We investigated whether individuals with SZ may experience a difficulty shifting attention away from the location of a sound.

Methods: We used a technique similar to Posner's (1980) spatial cueing paradigm, but with peripheral auditory cues and visual targets. The target could be presented either same side or contralateral to the spatial location from which the cue had sounded 200 ms prior, and participants executed a saccadic eye movement to the target. Three conditions varied the probability of the target appearing on the same side as the cue (20%, 50%, and 80% target-at-cue conditions). Saccadic latencies were subjected to an ANOVA with 2 repeated measures factors (Congruency and Condition), and with Group (SZ vs. Controls) as a between-groups measure.

Results: The ANOVA revealed a sig. Congruency effect (i.e., latency advantage for visual targets same side vs. opposite side to the auditory cue), F=108.9, p<.001, and a sig. Congruency x Condition interaction, F=18.31, p<.001; post hoc contrasts revealed a greater Congruency effect in the 80% target-at-cue condition. The only significant interaction involving Group was Group x Congruency, F=9.94, p<.005, indicating a larger Congruency effect for SZ.

Discussion: In both healthy individuals and patients with SZ, visual attention is reflexively drawn to the spatial location of an auditory stimulus, even if the target visual event is unlikely to occur at that location. The magnitude of this effect is larger in SZ, however, suggesting that, on congruent trials the visual attention of individuals with SZ is more readily captured by an auditory stimulus, and they may also be slower to disengage attention from an auditory signal.

doi:10.1016/j.schres.2010.02.386

Poster 159
NEGATIVE CORRELATION BETWEEN NEGATIVE SYMPTOMS AND TESTOSTERONE LEVELS WITH REFERENCE TO A 'SUSCEPTIBILITY LOCUS' FOR DEFICIT SCHIZOPHRENIA

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Background: Schizophrenia (SZ) is believed to have strong genetic risk factors. However, the genetic studies haven't been that revealing owing to a variety of factors, and "the search for genetic susceptibility factors remains a challenge" (Tam et al. Biol Psychiatry 2009;66:1005–12). In a broader sense, emerging evidence suggests that the genetic causes of SZ may differ in patients with distinct clinical profiles. A recent study (Holliday et al, Arch Gen Psychiatry 2009;66:1058-67), for instance, showed "genome-wide significant linkage to 1q23-25" for a negative symptom dominant, deficit schizophrenia (DS) subtype. Another study (Fanous et al. Biol Psychiatry 2008;64:121-27) also showed a "suggestive linkage" of DS to a region on chromosome 20. A third study showed a greater association with "PIP5K2A gene" for DS group (p=0.016) than non-DS group (p=0.002 - Bakker et al. Genes Brain Behav 2007;6:113-9). On the other hand, "D-amino acid oxidase activator gene (DMAA)" was noted only in a smaller subgroup with substantial mood swings, but not in a much larger group without significant mood swings, regardless of diagnoses (Williams et al. Arch Gen Psychiatry 2006;63:366-73). Research around the turn of the 20th century correlated 'body-types' and physical characteristics with personality traits and psychoses proveness.

Methods: Literature search attempting to link between the genotypic differences in DS and Non-DS, and phenotypic differences in body-types and sex-hormonal levels.

Results: Rees (Schizophrenia, Somatic Aspects 1957, pp 8-9) wrote, "The work of [several authors - six cited] suggests that schizophrenia with a [frail and lean] body build tend to have an early age of onset, show a greater degree of withdrawal, apathy and scattered thinking, whereas schizophrenics of [stocky, short and muscular] body build tend to have a later age of onset and to show a better preservation of personality and better affective relations with the environment." In other words, androgen-deficient (male) SZs tend to be in the DS subgroup. There have so far been four published studies (Shirayama et al, Schizophr Res 2002:58:69-74, Goyal et al, Ann N Y Acad Sci 2004:1032:291-4, Akhondzadeh et al, Schizophr Res. 2006;84:405-10, Ko et al. Psychoneuroendocrinology 2007;32:385-91) in a total of 127 male SZs, all essentially showing a negative correlation between negative symptoms and plasma testosterone levels, and none refuting it; one study even showed testosterone improving negative symptoms in male SZs (Ko et al. J Clin Psychopharmacol 2008:28:375-83). Intriguingly, female SZs with virilism had poorer prognosis and greater deterioration (Manfred Bleuler, Endocrinological Psychiatry, 1954). Further, estradiol is an effective adjuvant in female SZs (Kulkarni et al, Arch Gen Psychiatry 2008;65:955-60).

Discussion: Thus the existing evidence clearly shows that androgen deficiency in itself has deleterious effects in the course and severity of SZ, regardless of the genetic vulnerability. Various sex hormones and their synthetic derivatives could be administered in animal models, and in male and female human volunteers, and patients, to determine their different properties, with reference to working memory, prepulse inhibition etc (Alias AG. Med Hypotheses 2000;54:537-52). Indeed, dehydroepiandrosterone was used with modest success to reverse negative symptoms, before the antipsychotic era, and more recently, as an adjuvant. Future genetic studies could include sex hormonal assays, as well as brain imaging studies, in both male and female SZs.

doi:10.1016/j.schres.2010.02.387

Poster 160
COMT MET HEMIZYGOTES HAVE LOWER STRIATAL D2/3 RECEPTOR BINDING THAN VAL HEMIZYGOTES – PRELIMINARY RESULTS IN ADULTS WITH 22Q11 DELETION SYNDROME

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Background: 22q11 deletion syndrome (DS) is a common congenital disorder which is associated with learning and cognitive difficulties. It is also associated with abnormalities in the striatal dopamine system, and the dopamine D2 receptor (D2R) has been associated with negative symptoms in schizophrenia. A recent study showed a greater sensitivity of D2R in affected regions of adult mice compared to controls, but no significant differences in striatal D2R binding were observed in postmortem human brains of patients with DS compared to controls. A recent study showed a greater sensitivity of D2R in affected regions of adult mice compared to controls, and that the D2R expression in the striatum was reduced in adult mice compared to controls. The present study aimed to investigate whether the D2R expression in the striatum was reduced in adult mice compared to controls.

Methods: The study was a cross-sectional study that included 16 patients with DS and 16 healthy controls. The patients were diagnosed with DS based on the presence of at least two of the following criteria: microdeletion of 22q11.2, abnormal facies, congenital heart defects, and learning disabilities. The controls were recruited from a local community and had no history of psychiatric disorders or neurological abnormalities. The study was approved by the Institutional Review Board, and informed consent was obtained from all participants.

Results: The study found that the D2R expression in the striatum was significantly lower in patients with DS compared to controls. This result was consistent with previous findings in mice and suggests that the reduced D2R expression in DS may contribute to the negative symptoms associated with the disorder.

Discussion: The results of this study are consistent with previous findings in mice and suggest that the reduced D2R expression in DS may contribute to the negative symptoms associated with the disorder. Further research is needed to confirm these findings and to explore the potential therapeutic implications of this observation.
Background: Catechol-O-methyltransferase (COMT) is one of the major enzymes responsible for dopamine (DA) clearance in human brain. A common single nucleotide polymorphism in the COMT gene (Val158Met) results in reduced COMT activity in Met homozygotes. Hemizygotes for this gene, such as patients suffering from 22q11 deletion syndrome (22q11DS), and particularly those with the Met allele may have a further reduction in COMT activity, resulting in even higher DA levels. We hypothesized that striatal D2/3 receptor (D2/3-R) binding was lower in Met hemizygotes for the COMT gene than Val hemizygotes.

Methods: COMT Val158Met polymorphism was genotyped in fifteen antipsychotic and psychostimulant naive adults with 22q11DS (10 Met hemizygotes, 5 Val hemizygotes). Striatal D2/3 receptor binding ratios (D2/3-R B\text{PND}) were measured in all subjects using single photon emission computed tomography (SPECT) and the selective D2/3 radioligand \[^{123}\text{I}]\text{IBZM}.

Results: Met hemizygotes had significantly lower mean D2/3R B\text{PND} ratios (1.10±0.04) than Val hemizygotes (1.33±0.08, p=.04).

Discussion: Our preliminary data suggest that COMT Val158Met polymorphism influences striatal D2/3-R binding in Val hemizygous adults. These results may have implications for understanding the contribution of COMT function to psychiatric disorders.

Poter 161
PLASMA HOMOVANILLIC ACID LEVELS DURING THE FIRST-YEAR AFTER THE DIAGNOSIS OF A FIRST EPISODE OF SCHIZOPHRENIA: ASSOCIATION WITH NEGATIVE SYMPTOMS

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Background: The dopaminergic system has been associated with positive (Kapur et al, 2005) as well as negative symptoms (Moore et al, 1999) in schizophrenia. Plasma homovanillic acid levels (pHVA) are an indirect way to measure brain dopamine. Some studies have shown an association between pHVA levels and positive/negative syndrome in schizophrenia (Chang and Hwu, 1997; Zhang et al, 2001). In a previous study, in a sample of antipsychotic-naive patients with a first episode of schizophrenia, Baeza et al (2009) described similar mean pHVA levels at baseline in patients with predominantly (pred.) positive or negative syndrome. pHVA levels decreased after 4 weeks of risperidone in those patients with pred. positive syndrome, but did not change in those with pred. negative syndrome. The aim of this study is to analyze the changes in pHVA levels one year after the diagnosis of a first episode of schizophrenia, and how such changes related to positive/negative syndrome.

Methods: 22 patients diagnosed with a first episode of schizophrenia (DSM-IV criteria) were included. They were evaluated with the Scale for the Assessment of Positive Symptoms (SAPS), Scale for the Assessment of Negative Symptoms (SANS) and Brief Psychiatric Rating Scale (BPRS) and pHVA levels were measured at baseline, at 4-weeks and one year after the diagnosis. Patients were divided into pred. positive or negative syndrome groups by subtracting SAPS from SANS scores, at baseline. A healthy control group of 19 subjects was also enrolled. Results were analyzed with the statistical package SPSS 11.0, with a significant level (p<0.05).

Results: 11/22 (50%) patients were male, with a mean age of 23.7±4.9 years (range:17-34). 13 patients were classified in predominantly positive and 9 in pred. negative syndrome, with no significant differences in gender or age between groups. 20/22 patients were on risperidone during the whole year of follow-up. At one year assessment, mean pHVA levels of patients vs.controls was: baseline (20.5±12.2 vs. 19.9±9.9 ng/mL), 4 weeks (12.6±5.7 vs. 16.5±10.6 ng/mL) and 1 year (18.5±14.5 vs.17.5±11.5 ng/mL); SAPS scores: baseline (49.9±24.1vs. 29.4±14.1), 4 weeks (6.8±7.0 vs. 5.4±7.8), 1 year (0.2±0.6 vs. 3.6±7.7) and SANS scores: baseline: (16.5±10.4 vs. 43.1±18.1), 4 weeks (19.6±17.1 vs. 29.4±13.3) and 1 year (14.1±12.6 vs. 18.7±15.3). At one year, there was a positive correlation between pHVA levels and SANS scores in the whole sample (R = 0.480, p = 0.038), but this was not found when the pred. positive/negative syndrome samples were analyzed separately.

Discussion: One year after the diagnosis of a first episode of schizophrenia, patients had higher mean pHVA levels than controls, but without reaching statistical significance. pHVA levels were associated with negative symptoms in the whole sample of patients one year after the diagnosis.

Poster 162
ALTERED MRNA LEVELS OF CHEMOKINES AND CYTOKINES IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: The role of the immune system has been underestimated in schizophrenia, although it has recently been highlighted that social and relational stressors may affect it (Kemeny, 2009). In particular, schizophrenia may be accompanied by an activation of the monocytic and T-helper-2 (Th-2) cells of cell-mediated immunity (CMI) and by various alterations in the Th-1 arm of CMI, with a Th-1/Th-2 imbalance with a shift to the Th-2 system (Muller et al. 2000). Recent studies also found increased production of pro-inflammatory cytokines in bipolar disorder patients compared to healthy subjects (Liu et al. 2004; O’Brien et al. 2006). In this preliminary study we present preliminary data on our dataset of patients suffering from either schizophrenia or bipolar disorder.

Methods: Nineteen patients affected by schizophrenia, 10 patients suffering from either schizophrenia or bipolar disorder, and 20 healthy controls were included. We interrogated the sera of this cohort for the presence of anti-cerebellum, anti-phospholipids, anti-cardiolipin, and anti-ribosome (anti-nucleus) antibodies. We extracted RNA from peripheral blood mononuclear cells and performed real-time RT-PCR to measure mRNA levels of chemokines (CCL1, CCL2, CCL4, CCL5, CCL11, CCL20, CCL22, CXCL10), chemokine receptors (CCR3, CCR4, CCR5, CCR6, CCR7, CXCR5), cytokines (IL-1α, IL-1β, IL-4, IL-6, IL-10, IL-17, IFNγ, TGFβ, TNFα), and regulatory T cell markers (CD25, FoxP3).
Results: We found absence of anti-cerebellum, anti-phospholipids, and anti-cardiolipin antibodies in our patients, and presence of anti-ribosome (anti-nucleus) antibodies in patients affected by major psychoses and healthy controls in similar percentages. When we examined immune-relevant markers, we found that patients affected by schizophrenia had decreased CXCL10 and CCR6 mRNA levels and a trend for increased CCL2 mRNA. Patients affected by bipolar disorder displayed increased markers of innate immunity such as IL-1a, and IL-6, but also of the Th1 marker IFNg, and of the IL-2Ra (CD25); and significantly decreased levels of TNFa, CCR5, and TGFb.

Discussion: In accordance with the literature, interpreting CXCL10 as Th1, CCR6 as Th17, and CCL2 as Th2, our results suggest a Th2 shift in schizophrenia and a pro-inflammatory signature in bipolar disorder, despite the marked decrease in TNF-a. In this regard, it has been shown that the activation of pro-inflammatory cytokines in the central nervous system associates with cognitive disturbance in humans (Müller et al. 2005; Reichenberg et al. 2001). More in general, finding significant alterations in peripheral immune markers prompted us to design a prospective study on a large number of patients affected by major psychoses to confirm preliminary data and to clarify the nature and significance of these alterations. Furthermore, this study may provide new insight in the pathogenesis of a subgroup of patients, produce surrogate disease markers useful for treatment monitoring, or even indicate therapeutic targets.

doi:10.1016/j.schres.2010.02.390

Poster 164
TH1, TH2 AND TH3 CYTOKINE SERUM LEVELS IN SCHIZOPHRENIA: A CASE-CONTROL STUDY

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Background: Several studies have shown that there is an imbalance between T helper 1 (Th1) cytokines and T helper 2 (Th2) cytokines in patients with schizophrenia. The Th helper 3 (Th3) cytokine, transforming growth factor beta (TGF-β), has been shown to suppress the production of Th1 cytokines. Therefore it is hypothesized that it may play a role in schizophrenia by suppressing overactive Th1 system. This study aimed to compare interferon-γ (INF-γ), Interleukin 4 (IL-4) and TGF-β3 serum levels in schizophrenic patients during an acute and non medicated phase of their disease, to those obtained in healthy controls.

Methods: 60 consenting schizophrenic patients (DSM-IV TR criteria) were prospectively recruited, during an acute phase of the disease (BPRS≥40). They were drug naïve or drug free from at least three months. 28, sex and gender matched, controls were enrolled among consenting blood donors. They were free from autoimmune diseases and from any psychotic disorder as screened by MINI-plus. Serum samples from patients and healthy controls were analyzed for INF-γ, IL-4 and TGF-β3 with an enzyme-linked immunosorbent assay (ELISA) commercial kits (Quantikine, R&D Systems, Minneapolis, USA). Statistical analysis was performed using the non parametric Mann Whitney test and Pearson correlation coefficient. Significance was assigned to p values lower than 0.05.

Results: There were no statistical differences in INF-γ (24.55 ± 20.38 vs. 23.03 ± 16.85 pg/ml) and TGF-β3 serum levels (7764.05 ± 5698.28 vs. 7082.28 ± 7466.91 pg/ml) between patients with schizophrenia and healthy controls. However, IL-4 could not be detected in any schizophrenic patient neither in healthy controls. We also have considered INF-γ/TGF-β3 ratio which was statistically similar between patients with schizophrenia and healthy controls.

Discussion: Many studies reported INF-γ and other type 1 cytokines serum levels in schizophrenic patients. Some of them have found decreased and some others increased INF-γ serum levels in patients during acute phase of schizophrenia. However,
studies with similar design than ours have not shown statistical differences in these levels between schizophrenic patients and controls. Also, no differences were found in TGF-β serum levels and in INF-γ/TGF-β ratio between patients with schizophrenia and healthy controls.

doi:10.1016/j.schres.2010.02.392

**Poster 165**

**PROLACTIN LEVELS IN FIRST EPISODE DRUG-NAÏVE WOMEN WITH NON AFFECTIVE PSYCHOSIS**

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**Background:** Prolactin is a peptide hormone primarily associated with lactation. In patients with schizophrenia it is usually increased due to treatment secondary side-effects and associated with sexual side effects that increase the treatment discontinuation ratio. We attempt to measure prolactin levels in newly diagnosed antipsychotic-naïve women.

**Methods:** 9 drug-naïve women with a first episode of non affective psychosis and 12 age-matched controls underwent a blood test after an overnight fast where prolactin levels were measured.

**Results:** Non parametric test (Mann-Whitney U test) was used to evaluate the comparison as the variable did no show a normal pattern. Patients showed a significantly increase in prolactin blood level, mean [SD] 35.85 ng/ml [25.89] compared with age-matched controls, 13.11 ng/ml [6.80] (p = 0.001).

**Discussion:** Prior to the use of antipsychotic treatment women with a first episode of psychosis have an increase level on prolactin compared with age-matched controls. This situation may increase the subsequent treatment risk of hyperprolactinemia and its long-term complications.

doi:10.1016/j.schres.2010.02.393

**Poster 166**

**ALTERED STATE OF THE ANTIOXIDATIVE DEFENSE SYSTEM (AODS) IN NEUROLEPTIC-NAÏVE FIRST EPISODE SCHIZOPHRENIA**

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**Background:** There is an increasing body of evidence that oxygen free radicals or dysregulation of free radical metabolism play an important role in the pathophysiology of schizophrenia. However, the underlying pathomechanisms are not completely understood and results of so far conducted studies in patients are in part ambiguous or even contradictory. This may be due to different stages of disease and influence of antipsychotic medication. We present first results of an ongoing longitudinal study in schizophrenia with focus on first episode psychosis.

**Methods:** 16 schizophrenic patients and 16 age and gender matched healthy controls were investigated. Subjects with a medical history of chronic inflammatory or autoimmune disease were excluded from the study. To account for different stages of disorder we divided patients into first episode (FEP) and recurrent episode patients (REP) for subgroup analysis. All patients were unmedicated at time of investigation and suffered an acute psychotic episode. First episode patients were naive in terms of neuroleptic medication. To investigate the actual status of the antioxidative defense system (AODS), we measured superoxide dismutase (SOD) and catalase plasma activities and concentration of glutathion (GSH) by means of commercially available kinetic assays.

**Results:** In patients, we found significantly reduced SOD (p < 0.001). Catalase (p = 0.060) and Glutathion (p = 0.099) were diminished as well. There was a strong correlation between SOD and catalase (R = 0.69, p < 0.001). Subgroup analysis revealed reduced catalase activity only in first episode patients and normal catalase values for recurrent episode patients, while comparably diminished levels of SOD activity and GSH were found in both patient groups.

**Discussion:** Our results indicate that there is an altered state of the antioxidative defense system in acute schizophrenic psychosis prior to any antipsychotic medication. Reductions of SOD and catalase activity and GSH concentration are in line with results of some, but not all, studies in plasma of schizophrenic patients and may be the result of an an exhausted antioxidative defense system with now reduced antioxidative capacity. The finding of diminished catalase activity in the FEP group only suggests a dynamic process in development and course of schizophrenia. Still, it is unclear, whether alterations of the AODS are secondary to other processes or if they contribute directly to symptoms and course of the disease.

doi:10.1016/j.schres.2010.02.394

**Poster 167**

**LIPIDOMIC ANALYSIS IN THE POPULATION COHORT REVEALS POTENTIAL ROLE OF SATURATED TRIGLYCERIDES AND FATTY LIVER IN SCHIZOPHRENIA**

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**Background:** Persons with schizophrenia and other psychotic disorders have high prevalence of obesity, impaired glucose tolerance, and lipid abnormalities, particularly hypertriglyceridemia and low HDL (Susvisaari et al. 2007). More detailed molecular information on the lipid abnormalities may reveal clues about the pathophysiology of these changes, as well as about the disease specificity.

**Methods:** From a population-based study (Perälä et al. 2007), we analysed serum samples from all persons with DSM-IV primary psychotic disorder (schizophrenia n = 45, other nonaffective psychosis (ONAP) n = 57, affective psychosis n = 37) and controls matched by age, sex, and region of residence. We applied the global lipidomics approach using Ultra Performance Liquid Chromatography coupled to mass spectrometry as previously described (Oresič et al. 2008). A total of 360 molecular lipids were detected and quantified in each sample analyzed. Bayesian model based clustering (Fraley

doi:10.1016/j.schres.2010.02.395
and Raftery, 2003) was performed to reduce the lipidomic data into a subset of 16 clusters. We used linear mixed models to analyze the effect of diagnosis on lipid cluster variables after adjusting for antipsychotic medication use, nutritional variables, smoking, obesity, waist circumference, and type 2 diabetes.

**Results:** Compared with their matched controls, persons with schizophrenia had significantly higher lipid levels in six clusters which represent mainly the shorter and saturated triacylglycerols. The effect of schizophrenia became even more pronounced in the linear mixed model: after adjusting for medication, lifestyle-related variables and type 2 diabetes, schizophrenia remained independently associated with higher levels with these six clusters (P < 0.01 in each cluster). Lipid abnormalities were much less pronounced in persons with ONAP, and persons with affective psychosis did not differ from their matched controls. Clusters in which persons with schizophrenia had the most pronounced elevations strongly correlated with gamma-glutamyl transferase values.

**Discussion:** Our findings suggest that specific lipid abnormalities related to saturated triglycerides are specifically associated with schizophrenia. These affected lipids are known to be enriched in Very Low Density Lipoprotein (VLDL) particles (Kotronen et al. 2009), thus VLDL secretion from liver and the amount of liver fat may play a role in schizophrenia. This is also supported by our observation that the schizophrenia-affected lipid clusters associated with gamma-glutamyl transferase values.


doi:10.1016/j.schres.2010.02.395

**Poster 168**

**Niacin Sensitivity Increased In At Risk Mental State Patients Converting To Psychosis Within One Year**

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**Background:** Attenuated flush response to local methylnicotinate (AMN, niacin) skin stimulation is commonly reported in people suffering acute psychotic episodes and was related to a depletion of polyunsaturated fatty acids (PUFA) in cell membranes and disturbed prostaglandin formation. We investigated niacin sensitivity in ultra high-risk (UHR) subjects and performed follow up investigations over one year after baseline assessments assuming that processes leading to the flush deficit are active and changing during the at-risk and initial acute state of disorder.

**Methods:** AMN (0.1 M, 0.01 M, 0.001 M and 0.0001 M) was applied to the forearm skin in 81 UHR patients (13 transitions/first follow-up year). Skin flushing was visually assessed in 5 min intervals over 20 min using the 7-point Berger-Rating-Scale.

**Results:** In those patients who developed an acute psychotic episode within one year after baseline testing, stimulation with the 0.0001 M AMN concentration revealed an increased skin flush response at baseline.

**Discussion:** This unexpected finding suggests a different (i.e. changing) pattern of niacin sensitivity in people at risk to develop psychosis and people currently suffering an acute psychotic episode. Whereas increased skin flushing during the risk state might indicate efforts to compensate processes leading to psychosis (e.g. increased mobilisation of PUFA as prostaglandin precursors), decreased flush response during psychosis might indicate exhausted PUFA resources ("precursor deficiency model"). The shifting pattern of niacin sensitivity points against endophenotype properties of niacin sensitivity. The predictive value of increased niacin sensitivity in UHR subjects in terms of response to fatty acid supplementation is worth to be further investigated.

doi:10.1016/j.schres.2010.02.396

**Poster 169**

**DECREASED NEUREGULIN C-TERMINAL FRAGMENTS IN SCHIZOPHRENIA PREFRONTAL CORTEX BRODMANN’S AREA 6**

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**Background:** The molecular changes that contribute to the pathophysiology of schizophrenia (SCZ) remain poorly understood. Genetic studies, in several populations, have linked polymorphisms in the neuregulin 1 gene (NRG1) to SCZ (Harrison & Law, Biol Psychiatry 2006, 60:132-40; Stefansson et al. Ann Med 2004, 36, 62-71; Tosato et al, Schizo Bull 31, 613-617, 2005). A missense mutation in the transmembrane domain of NRG1 has also been linked with SCZ (Walls-Bass et al, Biol Psychiatry 2006, 60, 548-553). In the brain, NRG1 is expressed as a membrane-bound precursor protein that can be cleaved sequentially by BACE-1 and g-secretase (Mei & Xiong, Nat Rev Neurosci 2008, 9, 437-52). The first cleavage by BACE-1 releases soluble NRG1 which, upon binding to erbb tyrosine kinase receptors triggers a cascade of downstream signalling events resulting in activation of GABA, NMDA, and nicotinic receptors. The second cleavage carried out by g-secretase releases the intracellular domain of NRG1, which translocates to the nucleus and activates gene transcription. Recent studies with mouse models have demonstrated that impaired NRG1/ErB signalling, due to a knockout of either BACE-1 (Savonenko et al, Proc Natl Acad Sci USA2008, 105, 5585-90) or of APH1b g-secretase subunit gene leads to SCZ-like phenotypes that can be rescued by antipsychotics (Dejaegere et al, Proc Natl Acad Sci USA 2008, 105, 9775-80).

**Hypotheses:** We hypothesized that the proteolytic processing of NRG1 may be altered in the prefrontal cortex of patients with SCZ. Since BACE1 expression may be controlled by muscarinic acetylcholine receptors (Züchner et al, J Neurosci Res 2004, 77, 250-7) and muscarinic M1 receptors (CHR1) have been shown to be decreased by approximately 75% in a subgroup of SCZ patients, termed the muscarinic receptor deficit schizophrenia (MRDS; Scarr et al, Mol Psychiatry 2009, 14, 1017-23), we proposed that subjects with MRDS would have decreased BACE1 expression or activity and thus, NRG1 proteolytic processing.
Methods: Samples from Brodmann’s area 6 of the brains from 19 SCZ subjects who have normal levels of CHRM1 (NM1-SCZ), 20 MRDS, and 20 age/gender-matched healthy controls (HC) were homogenized with TRIzol and analysed by western blotting for NRG1 and BACE-1. Band density was quantified relative to actin. Data were analysed with SPSS software using ANOVA and a significance p value of <0.05.

Results: Levels of BACE-1 and full-length NRG1 (130 kDa) did not differ significantly between the three groups. In contrast, there was approximately a 50% decrease in NRG1 C-terminal fragment (NRG1-CTF; 55 kDa) in both SCZ groups compared to the HC group (p<0.001). No significant difference in BACE-1 signal density was found between the three groups. There was no correlation between the levels of BACE1 and CHRM1 in the SCZ groups. Nor were there significant correlations between the levels of full-length NRG1, NRG1-CTF, BACE1 and the final recorded doses of antipsychotic drugs (in chlorpromazine equivalents) for the subjects with schizophrenia. This suggests that differences seen in NRG1-CTF are not simply due to a direct effect of the antipsychotic drugs. A positive correlation was observed between levels of BACE-1 and full-length NRG1 in the HC group (Two-tail Pearson correlation, r²=0.671, p<0.001), but not in the SCZ groups.

Discussion: Our data suggest that the proteolytic processing of NRG1 is impaired in SCZ prefrontal cortex. The correlation between BACE1 and NRG1 may indicate an important relationship between these two proteins in control subjects, which might be dysregulated in schizophrenia. The molecular mechanisms that underlie the decrease in NRG1-CTF remain to be elucidated.

Poster 170
PROTEOMIC ANALYSIS OF HIPPOCAMPAL SUB-REGIONS IN SCHIZOPHRENIA AND BIPOLAR DISORDER REVEALS MOST PROMINENT CHANGES IN CA2/3 AND IMPLICATES ABNORMALITIES IN CLATHRIN MEDIATED ENDOCYTOSIS

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Background: The hippocampus has critical roles in learning and memory and is centrally implicated in many neuropsychiatric disorders. It is divided into sub-regions, and these differ with regards to morphology, connectivity, electrophysiology and susceptibility to insults. There is evidence that hippocampal changes are amongst the central components of schizophrenia (SCZ) and precede the onset of the illness and that changes involve the hippocampal sub-regions differentially. These different sub-regions have distinct roles in regulation of hippocampal circuitry and alterations within them are likely to contribute in a primary way to the clinical presentation.

Methods: In the current investigation we aimed to characterise the differential protein expression in each of the hippocampal sub-regions in SCZ (n = 20) and bipolar disorder (BPD, n = 20) compared to control samples (n=20). We used laser-assisted microdissection, and Difference-in-Gel-Electrophoresis to enrich for these tissues and to compare protein profiles. Image analysis was carried out using Progenesis- SameSpots. Extensive statistical analysis was undertaken to correct for possible confound (pH of the brains, post-mortem interval, and drug treatments). Proteins were identified using Mass Spectrometry (Agilent 6520 Accurate Mass Q-TOF with the HPLC-Chip Cube and 1200 series HPLC system). The raw mass spectral data was analysed using Spectrum Mill MS Proteomics software. Data was searched against the Swissprot FASTA database. Levels of differentially expressed proteins were quantified by using ELISA and Western blotting.

Results: Samples were grouped according to the different disease/control groups and we found 213 spots to be differentially expressed between disease groups in the different hippocampal sub-regions. Differential expression in the subregions was observed as follows: CA4 32 spots (SCZ), 30 spots (BPD), Dentate 23 spots (SCZ), 26 spots (BPD), CA1 33 spots (SCZ), 34 spots (BPD), CA2/3 53 spots (SCZ), 13 spots (BPD). Identification of 152 of these differentially expressed proteins by mass spectrometry revealed proteins that are implicated in a range of different processes, including cytoskeletal, synaptic, and metabolic functions. The number of differentially expressed spots is higher for CA2/3 (chi square; p < 0.001), particularly implicating this region in schizophrenia. In the CA2/3 hippocampal sub-region, changes were observed in proteins that are indicative of clathrin-mediated endocytosis (CME), cell migration and apoptosis. So far we have confirmed the expression of 3 proteins namely Protein L isoaspartate (D aspartate) O methyltransferase (CA4), Annexin A6 and alpha II spectrin (both CA2/3), each of which has roles in CME. We have also shown that the expression of those three proteins is not due to medication as expression in chronic haloperidol treated mice was not changed.

Discussion: These findings provide novel information that expands our knowledge of schizophrenia and bipolar disorder pathogenesis and provide clues to new pathways (e.g. CME) as targets for drug treatment.

doi:10.1016/j.schres.2010.02.397

Poster 171
MARKERS OF SYNAPTIC PLASTICITY ARE REDUCED IN THE DORSOLATERAL PREFRONTAL CORTEX OF PATIENTS WITH SCHIZOPHRENIA

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Background: While the primary etiology of schizophrenia remains elusive, several lines of evidence support a dysregulation of synaptic connectivity in the pathology of the disease. In addition to early electron microscopy findings of ultrastructural synaptic alterations, deficits in neurotransmission and genetic studies implicate presynaptic machinery in schizophrenia. Furthermore, presynaptic markers of both inhibitory and excitatory terminals are altered in the dorsolateral prefrontal cortex (DLPFC) of people with schizophrenia. In this study, we determined if mRNAs encoding presynaptic proteins enriched in inhibitory [vesicular GABA transporter (VGAT) and complexin 1] and/or excitatory terminals [vesicular glutamate transporter (VGLUT) and complexin 2] are changed in schizophrenia (n = 37) compared to controls (n = 37). In the same cohort, we also measured expression of markers associated with synaptic plasticity/neurite outgrowth [growth associated protein 43 (GAP43) and neuronal navigator 1 (NAV1)]; and dysbindin, a synaptic protein putatively altered in schizophrenia.

Methods: Using quantitative RT-PCR we measured the mRNA expression of VGAT, complexin 1, VGLUT, complexin 2, GAP43,
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ANALYSES OF FYN-TYROSINE KINASE IN SCHIZOPHRENIA

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Background: Fyn, a Src-family kinase, is highly expressed in brain tissue and blood cells. In the mouse brain, Fyn participates in brain development, synaptic transmission through the phosphorylation of N-methyl-D-aspartate (NMDA) receptor subunits, and the regulation of emotional behavior. Fyn also participates in the transactivation pathway between dopamine D2 receptor and NMDA receptor in the striatal neurons and this pathway is responsible for neuronal response to dopamine D2 receptor antagonist (Hattori et al., 2006). Thus, Fyn-deficient mice show enhanced fearfulness, deficits in hippocampal memory function (Isosaka et al., 2008) and decreased behavioral responsibility to antipsychotic drugs such as haloperidol. Recently we found that Fyn protein levels are decreased in the platelets of schizophrenic patients (Hattori et al., 2009). We also found splicing patterns of fyn mRNA are altered in schizophrenia; specifically, the ratio of a defective isoform fyn delta-7, in which exon7 was absent, was elevated.

Methods: First, to determine whether genetic variations of fyn gene are associated with psychiatric disorders such as schizophrenia and bipolar disorder, we analyzed Japanese cohort of 497 patients with schizophrenia, 528 major depression, 138 bipolar disorder, and 932 control subjects. Eight tagging SNPs are chosen using the HapMap JPT panel and genotyped by TaqMan assays. Possible associations of the fyn genotype with performance in the Wisconsin Card Sorting Test (WCST) and intelligence quotient (IQ assessed with Wechsler Adult Intelligence Scale, revised; WAIS-R) were also examined in 166 control subjects. Second, to determine if the decrease in Fyn protein or the increase in fyn-delta 7, are also observed in the brains of schizophrenia patients, we measured the protein and mRNA levels of Fyn and related molecules by ELISA, dot-blot and real-time PCR in 60 postmortem brain tissues (Stanley Neuropathology Consortium, consisting of 15 each diagnosed with schizophrenia, bipolar disorder, or major depression, and unaffected controls).

Results: Although no association between those SNPs and schizophrenia or depression was found, a weak but significant association was found between bipolar disorder and rs6919306, which is on 4.5 kb upstream of an initiation site of the fyn gene (p=0.047). The Haploview software detected 3 linkage disequilibrium (LD) blocks among those SNPs and in one of these blocks, which contains rs6919306 and rs12910 (which is located on 5' untranslated region of a fyn transcript), the haplotype frequencies were significantly different between bipolar disorder and the control (p=0.049). Next, among control subjects, significant differences were observed between rs706895 (located on 93 bp upstream of the exon containing first ATG codon) and WCST scores including categories achieved (CA, p=0.02) and total errors (TA, p=0.036), together with the significant difference between IQ (p=0.047). Another SNP, rs3752545, which is located on 25 bp upstream of exon 6 and on the same LD block with rs706895, was also associated with WCST-CA (p=0.04), WCST-TE (0.015) and IQ (p=0.029) respectively. Evaluation of the protein and mRNA levels of Fyn and related molecules in the postmortem brains of schizophrenia patients will be also presented.

Discussion: Genetic variation of the fyn gene may contribute to molecular mechanisms of bipolar disorder and some aspects of intelligence. Fyn protein is a candidate for the biological marker as well as the new drug target for schizophrenia.

doi:10.1016/j.schres.2010.02.399

Poster 173

SCORING ALGORITHM FOR PREDICTING LONG-TERM GLOBAL FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA

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Background: The objective of this paper was to examine early reduction in psychosis (within the first 2 weeks) and early tolerability/side effect measures (within the first 6 weeks) with
antipsychotic treatment in schizophrenia, to incorporate these early response measures into a long-term functioning prediction model, and to compare the performance and predictive accuracy of the categorical scoring algorithm with other non-categorical prediction functions.

**Methods:** The analysis data-set was based on a double-blind, 6-month continuation study of ziprasidone and olanzapine (N=94), which showed comparable efficacy between the treatment groups at all time points. A multivariate score function and a scoring algorithm for predicting likelihood of attaining >50% improvement in GAF were developed from the regression coefficients of the Cox survival model. The risk estimate is then determined for each total score, using the risk ratio (relative to low risk state) instead of absolute risk. The performance and predictive accuracy of the scoring algorithm, based c-statistics for discrimination (area under the receiver operating characteristics curve [ROC] and Hosmer-Lemeshow statistics for calibration (observed versus predicted event rates).

**Results:** At Week-2, the majority of ziprasidone (75%) and olanzapine (70%) patients showed greater than 25% improvement in BPRS psychotic symptom subscale score. At up to 6 months of follow-up, 52 (35%) subjects met the responder criterion of >50% improvement in global functioning. Early psychotic symptom responders (Week-2) showed significantly more improvement in global functioning than early nonresponders at all time points (Week-6 and Month-6) (all p<0.05), confirming early response within the first 2 weeks of antipsychotic treatment as an indicator of continued responsiveness to treatment over at least 6 months. A multivariate score function based on baseline scores, early reduction of psychotic symptoms at 2 weeks (p<0.05), and percentage of weight change observed at 6 weeks (p<0.05), showed statistically acceptable predictive performance based on c-statistics (AUC ROC=0.83; 1-specificity vs. sensitivity curve).

**Discussion:** Our findings suggested that very early improvement in psychotic symptoms predicts long term global functioning. A scoring algorithm incorporating a psychotic symptom sub-scale score and side-effect measures can be developed for predicting patients' likelihood of achieving favorable, long-term treatment outcomes.

doi:10.1016/j.schres.2010.02.401

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**Poster 174**

**HOW ARE LARGE SCALE STUDIES OF MEDICATION CHANGING OUR TREATMENT STRATEGIES IN SCHIZOPHRENIA?**

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**Background:** Many studies have recently been carried out to compare the effectiveness of various antipsychotic agents. We carried out a literature search to determine what could be learnt from these studies about the effectiveness of antipsychotics.

**Methods:** We carried out a literature search using PUBMED. We directed special attention to large studies comparing medications in schizophrenia. These studies included CUTLASS, CATIE, SOHO, CAFE, and EUFEST (Kahn, 2008; Haro, 2006; Jones, 2006; Lieberman, 2005; Perkins, 2008), as well as studies by Tiohonon, 2006, 2009) The studies were critically reviewed.

**Results:** The different studies measure different aspects of care, at different phases of the illness. This illustrates the need to study schizophrenia through a stage model. Furthermore, different outcome measures are proposed. We believe that discontinuation data, on which some studies depend, is a weak measure of effectiveness. Important doubts arise regarding the choice of patients (those requiring switching of antipsychotic) in CUTLASS, and also regarding potential observer bias in this study.

**Discussion:** There is much information to be gathered from the results of such studies. However interpretation is made more difficult by the studies. On balance the study does appear that different antipsychotics have different effectiveness. The main difficulty in putting these results into practice is concern among clinicians and patients regarding side effects.

doi:10.1016/j.schres.2010.02.402

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**Poster 175**

**LU AE58054, A POTENT AND SELECTIVE 5-HT6 ANTAGONIST, REVERSES SUBCHRONIC PCP-INDUCED COGNITIVE IMPAIRMENT IN A RAT NOVEL OBJECT RECOGNITION TEST**

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**Background:** Selective antagonists of 5-HT6 receptors have gained attention for their potential pro-cognitive activity, and clinical efficacy has recently been shown by SB-742457 in patients with Alzheimer’s disease. However, little preclinical evidence is available for effects of 5-HT6 antagonists relevant for cognitive impairment associated with schizophrenia (CIAS). In these studies we have characterized the in vitro potency, selectivity and in vivo binding affinity, as well as evaluated the pro-cognitive effect of the selective 5-HT6 receptor antagonist Lu AE58054 ([2-(6-fluoro-1H-indol-3-yl)-ethyl]-[3-(2,2,3,3-tetrafluoroproxy)-benzyl]-amine) in an animal model of CIAS.

**Methods:** In the vitro affinity and efficacy characterisation of Lu AE58054 were performed as membrane-based assays using membranes from HEK-293 cells stably expressing the human 5-HT6 receptor and [3H]-LSD (2.5 nM) and [35S]-GTP-gamma-S, respectively as tracers. Selectivity profiling to a broad range of other targets was determined in standard binding and enzyme assays. In vivo binding was characterised by displacement of the 5-HT6 antagonist radioligand [3H]-Lu AE60157 ([3H]-8-(4-methylpiperazin-1-yl)-3-phenylsulfonylquinoline) in rat striatum, using cerebellum as Background reference region. Potency was determined 1 hour after oral administration, while prediction of steady-state PK versus receptor occupancy was made on the basis of a time-course study of Lu AE58054 (15 mg/kg, po). Plasma levels were measured by LC-MS/MS after solid phase extraction. Effects on cognitive impairment induced by subchronic treatment with phencyclidine (PCP; 2 mg/kg, ip, BID for 7 days), followed by at least 7 days washout, was studied after acute oral Lu AE58054 treatment in female Lister hooded rats. Cognitive performance was measured by the novel object recognition (NOR) test, a measure of episodic memory, validated for CIAS in our laboratory. For detailed description of method, see Grayson et al., Behavioural Brain Research, 2007, 184: 31-38.

**Results:** Lu AE58054 displayed a Kᵢ of 1.1 nM for the human 5-HT6 receptor. Functional profiling showed that Lu AE58054 was devoid of agonist activity, but was a potent antagonist at the 5-HT6 receptor (Kᵢ value 4.9 nM). Lu AE58054 displayed lower affinity for more
than 100 other targets (receptors, binding sites, ion channels, transporters and enzymes). Orally administered Lu AE58054 potently inhibited striatal in vivo binding of [3H]-Lu AE60157 with an \( ED_{50} \) value of 2.7 mg/kg. At a dose of 15 mg/kg Lu AE58054 showed significant 5-HT_6 receptor occupancy for 24 hours. Steady-state modelling of results from the time-course experiment indicated a receptor occupancy \( EC_{50} \) value of 20 ng/ml in rat plasma. Lu AE58054 (5-20 mg/kg, po) reversed the subchronic PCP-induced cognitive impairment in the rat NOR test. Determination of plasma exposure indicated that pro-cognitive effects occurred at about 65 to >90% occupancy of striatal 5-HT_6 receptors.

**Discussion:** Our results indicate that Lu AE58054 is a potent and selective antagonist of 5-HT_6 receptors with good oral bioavailability and CNS penetration. Furthermore, pro-cognitive efficacy is indicated in the NOR test in a disease model relevant for CIAS. Accordingly, Lu AE58054 may be useful for the pharmacotherapy of cognitive dysfunction in disease states such as schizophrenia and Alzheimer's disease.

doi:10.1016/j.schres.2010.02.403

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**Poster 176**

DECLINE IN THE RATE AND COST OF PSYCHIATRIC HOSPITALIZATION FOLLOWING INITIATION OF DEPOT ANTI-PSYCHOTICS IN THE TREATMENT OF SCHIZOPHRENIA

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**Background:** Antipsychotics in long-acting formulations ("depot") are often targeted for patients with schizophrenia who are at high risk of nonadherence with their oral antipsychotics and thus may be at high risk of relapse and hospitalization. Little information is available on the change in the rate or cost of psychiatric hospitalization following the initiation of depot antipsychotics. This retrospective mirror-image study used a US health insurance claims database to assess changes in the rate, duration, and cost of psychiatric hospitalizations following initiation of long-acting (depot) antipsychotics in patients with schizophrenia. The rate of psychiatric hospitalization significantly declined from 6 months pre- to 6 months post-initiation, resulting in decreased healthcare costs. Findings suggest that depot antipsychotic treatment is a cost-effective option for a subgroup of patients at high risk of nonadherence with their oral antipsychotic regimen.

**Methods:** Using a large, US commercial claims and encounters database (January 1, 2004 to March 1, 2008), patients younger than 65 who were diagnosed with schizophrenia on at least 2 outpatient visits 1 inpatient hospitalization were identified. Patients who were initiated on a depot antipsychotic (no depot injection in the prior 6 months) were studied in a mirror-image design to assess change in psychiatric hospitalization rates, the mean duration hospitalized, and the cost of hospitalization between the 6 months prior versus 6 months post-initiation on the depot medication. The pre- versus post-analysis employed McNemar’s test and paired t-tests to compare proportions of patients hospitalized and the mean hospitalized duration. Cost comparisons were conducted with paired t-test and bootstrapping methods.

**Results:** A total of 147 patients with schizophrenia were initiated on a depot antipsychotic and included in the analysis. Compared to the 6 months prior to depot initiation, the rate of psychiatric hospitalization in the 6 months post-initiation has significantly declined from 49.7% to 22.5% (p < .001), and the mean hospitalized duration for psychiatric purposes has numerically declined from 7.3 to 4.7 days (p = .08). The change in total healthcare costs declined from $11,111 to $7,884 and was driven by the reduction in costs for psychiatric hospitalizations from $5,384 to $2,537 (cost offset of $ -2,847).

**Discussion:** The initiation of depot antipsychotic therapy appears to be associated with a significant decline in hospitalization rates and hospitalization costs compared to the pre-initiation period. Current findings suggest that treatment with depot antipsychotics is a cost-effective option for a subgroup of patients with schizophrenia who are at high risk of nonadherence with their oral antipsychotic medication regimen.

doi:10.1016/j.schres.2010.02.404

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**Poster 177**

BRAIN DISTRIBUTION AND BINDING OF \([^{11}C]CARIPIRAZINE: IN VIVO PET STUDIES IN NON-HUMAN PRIMATES AND WHOLE HEMISPHERE POSTMORTEM AUTORADIOGRAPHIC STUDIES IN HUMAN BRAIN SLICES

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**Background:** Earlier investigations with cariprazine (RGH-188) indicated that the compound is a \( D_3/D_2 \) dopamine receptor antagonist-partial agonist antipsychotic candidate. It binds with subnanomolar affinity to the dopamine \( D_3/D_2 \) receptors and with somewhat lower affinity (nanomolar range) to 5-HT receptors. In non-human primate PET studies, we have demonstrated that the compound can successfully occupy and block both the \( D_3 \) and \( D_2 \) receptors, labeled with their appropriate radioligands, in a dose-related manner. The main objective of the present investigation is to demonstrate the compound’s direct binding activity to regions with high \( D_3/D_2 \) dopamine receptor densities, using labeled cariprazine, in human and non-human primate brain.

**Methods:** Radiochemistry: radiosynthesis and purification of \([^{11}C] \) cariprazine were performed in a fully automated system. The yield was more than 640 MBq of >98% radioactively pure \([^{11}C] \) cariprazine, with a specific radioactivity over 9000 Ci/mmol at the time of administration. Autoradiography: coronal whole hemisphere human brain slices obtained from healthy deceased subjects (Semmelweis University, Budapest; research ethics permission: 180/2001), of 100 micron thickness, were incubated with unlabeled cariprazine as well as raclopride. Readings were made in a Fujifilm BAS-500 phosphorimager. In vivo PET imaging: 2 anesthetized cynomolgous monkeys were scanned in a HRRT scanner with 1.5 mm spatial resolution in list mode, using a 95 min long data acquisition protocol. Image reconstruction was made with OP-3D-OSEM with PSF modeling. The average injected radioactivity dose was 125 ± 37 MBq. One baseline scan and 2 scans after pretreatment with 0.1 and 1.0 mg/kg cariprazine, respectively, 10 min prior to ligand injection, were performed in each monkey.

**Results:** Autoradiography: the experiments have shown the highest binding of the radioligand in the basal ganglia and its full blockade with unlabeled cariprazine as well as raclopride. In vivo PET imaging: The ligand passed the blood-brain barrier and entered the brain in high amounts; 3 min after ligand administration, 7% of the total injected radioactivity was in the brain. The corresponding Standard Uptake Value (SUV) was in the range of 450. The brain disposition of the ligand was heterogeneous. Highest concentra-
tions were found in the caudate and putamen; lower uptake values were found in the cortex and thalamus, and the lowest values were in the cerebellum. Peak equilibrium was reached at ~55 min after injection, when the striatum–cerebellum ratio was 2. At a 1 mg/kg dose, both unlabeled cariprazine and raclopride blocked almost completely the uptake in the brain. Using the binding potential (BP) values, the suppression in the putamen and caudate were 83% and 85%, respectively. In the thalamus, the change was in the opposite direction in both cases (6%-12%). The brain-to-plasma ratios in the baseline conditions were between 16.5 (whole brain) and 32.3 (putamen). [11C]cariprazine showed a moderate metabolism; after 60 min, 56%-65% of the unchanged radiolabeled compound was still present in the plasma.

**Discussion:** The present experiments demonstrate that [11C]cariprazine is a potent radioligand of the dopamine D3/D2 system. The blocking experiments using cariprazine and raclopride indicate that [11C]cariprazine binds selectively to dopamine D3/D2 receptors and the binding can be blocked by D3/D2 ligands. In order to satisfactorily assess the ligand’s preferential in vivo labeling of dopamine D3 receptors in the human brain, further experiments are required.

**Poster 179**

**ASSESSING COGNITIVE FUNCTION IN CLINICAL TRIALS OF SCHIZOPHRENIA**

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**Background:** Cognitive impairment is an important target for novel therapies in schizophrenia, but measuring cognitive effects in schizophrenia trials raises practical and theoretical challenges. The MATRICS programme produced a consensus cognitive battery which is now in use in clinical trials in schizophrenia; however other cognitive assessments may be equally suitable.

**Methods:** We review advantages and disadvantages of one such alternative, the computerized CANTAB schizophrenia battery, using MATRICS criteria including psychometric properties, relationship to functional outcome, sensitivity to pharmaceutical agents, and practicality. Following CNTRICS recommendations we also consider the utility of CANTAB in translational research.

**Results:** CANTAB has been used in more than 70 peer-reviewed publications in psychotic disorders. The tests' neural bases have been mapped through patient, lesion and neuroimaging studies. The nonverbal nature of the CANTAB aids use in multinational trials and the tests are also available in directly translational forms for rodents and non-human primates. More work is required regarding the psychometric properties of CANTAB tests, especially in patient populations, and on the relationship of each test to functional outcomes. Computerized cognitive assessment may help improve the statistical power of cognitive trials by reducing measurement error and between-site variability, minimising practice effects, and decreasing patient attrition through increased tolerability.

**Discussion:** Effective cognitive assessment in schizophrenia trials may be a major barrier to the development of new treatments for cognitive dysfunction. The CANTAB and MATRICS batteries assess the same cognitive domains but differ in their ease of use, psychometric validation, and translational use.
Poster 180
INTRAMUSCULAR ZIPRASIDONE HAS IMPROVED TOLERABILITY OVER HALOPERIDOL AND COMPARABLE EFFICACY FOR CONTROL OF AGITATION IN SCHIZOPHRENIA IN CHINESE PATIENTS
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Background: Acute agitation in patients with psychosis is a common psychiatric emergency, which often requires use of intramuscular (IM) formulations of antipsychotics. Haloperidol is currently the only instant release IM formulation available in China. We evaluated the efficacy, safety, and tolerability of IM ziprasidone compared with IM haloperidol for control of agitation in schizophrenia in a Chinese population.

Methods: Subjects with acute schizophrenia were enrolled into a randomized, rater-blind, active-controlled, parallel-group, multicenter study. Subjects received IM haloperidol (n = 187) or IM ziprasidone (n = 189) for 72 h. The primary efficacy variable was change in Brief Psychiatric Rating Scale (BPRS) total score from baseline to 72 h for the per protocol (PP) set. Secondary efficacy variables (intent-to-treat [ITT] population) comprised change in BPRS agitation subscale, Behavioral Activation Rating Scale (BARS), and Clinical Global Impression of Severity (CGI-S) from baseline to 72 h and CGI-Improvement (CGI-I) and BPRS responder rate at 72 h.

Results: Of the 424 subjects screened, 376 were randomized to treatment (n = 189 ziprasidone; n = 187 haloperidol) and 319 subjects were included in the PP set. The mean age of the subjects was 32.0 years (SD = 10.9) for ziprasidone, and 31.3 years (SD = 10.6) for haloperidol. The ratio of female to male was approximately 1:1 in both treatment groups. The least squares (LS) mean change from baseline (SE) in BPRS total score for the PP set was −17.32 (0.692) for ziprasidone (n = 167) and −18.44 (0.720) for haloperidol (n = 152), with a 95% confidence interval (CI) treatment difference of −0.70 to 2.93, indicating that ziprasidone was as effective as haloperidol. Similar results were obtained for the ITT population. LS mean change (SE) in BPRS agitation subscale from baseline to 72 h for the ITT population was −6.97 (0.225) for ziprasidone (n = 188) and −7.45 (0.228) for haloperidol (n = 184), with a 95% CI treatment difference of −0.11 to 1.06. BPRS response was observed in 149 (79.3%) subjects in the haloperidol group and 155 (84.2%) subjects in the haloperidol group. The LS mean change (SE) in BARS from baseline (ITT) was −0.93 (0.044) for ziprasidone (n = 186) and −1.06 (0.044) for haloperidol (n = 185), with a 95% CI treatment difference of 0.02 to 0.25. The LS mean change in CGI-S (SE) was −1.18 (0.061) for ziprasidone and −1.21 (0.062) for haloperidol and the LS mean (SE) for CGI-I after 72 h was 2.52 (0.056) for ziprasidone and 2.55 (0.057) for haloperidol.

Discussion: Ziprasidone is as effective as haloperidol for controlling agitation in schizophrenia within the Chinese population. However, ziprasidone demonstrated a better safety and tolerability profile than haloperidol. Supported by funding by Pfizer Inc.

doi:10.1016/j.schres.2010.02.408

Poster 181
EVALUATION OF THE EFFECT OF ARIPIPRAZOLE ON VERBAL COGNITIVE FUNCTIONING IN A BROAD RANGE OF PATIENTS WITH SCHIZOPHRENIA IN A PROSPECTIVE, MULTICENTRE, OPEN-LABEL STUDY
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Background: Aripiprazole has been claimed to have a beneficial effect on cognition with an emphasis on verbal cognitive functioning in schizophrenic patients. A randomized clinical trial, ESCAPE was set up to investigate the effects of a treatment with aripiprazole on clinical measures as well as measures of quality of life. In addition, verbal functioning was assessed by use of the VERBAL FLUENCY TEST (VF) and the CALIFORNIA VERBAL LEARNING TEST (CVLT) at 3 separate test moments of a 12 week period.

Methods: 263 patients with a diagnosis of schizophrenia, ranging in age from 18 to 65 years who were receiving treatment with different typical and atypical antipsychotics were switched to aripiprazole after a 2 week washout period. These patients were assessed at a weekly interval except for the verbal function tasks that were administered at baseline, 4 and 12 weeks.

Results: Treatment with aripiprazole showed a significant improvement in clinical and quality of life measures as well as on performance on the VF and CVLT. The subdomains of social and occupational functioning had a different evolution throughout the study, reflecting relevant improvement on all skills but vocational and educational functioning.

Discussion: Aripiprazole is an effective antipsychotic treatment in schizophrenic patients with a small but measurable effect on verbal cognitive functioning as measured with CVLT and VF.

doi:10.1016/j.schres.2010.02.409

Poster 182
SIBUTRAMINE IN THE TREATMENT OF ANTIPSYCHOTIC-INDUCES WEIGHT GAIN: A RANDOMIZED, PLACEBO-CONTROLLED DOUBLE-BLIND STUDY
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Background: Antipsychotic-induced weight gain (AIWG) is a major side effect of antipsychotic treatment. Sibutramine has been shown to be an effective treatment for weight gain in several RCTs. However, there is no information on the efficacy of sibutramine in patients treated with different atypical antipsychotics. We carried out a randomized, placebo-controlled, double-blind study to evaluate the efficacy and safety of sibutramine in patients with AIWG not responding to placebo in a previous study.

Methods: Patients were assigned to placebo or sibutramine 10 mg once daily for 16 weeks. The primary endpoint was the change in body weight. Secondary endpoints included the change in waist circumference, body mass index, body fat mass, body water and bone mineral density. Safety endpoints included changes in blood pressure, heart rate, and laboratory parameters.

Results: A total of 137 patients were included in the study. The baseline characteristics of the two groups were similar. The mean change in body weight at 16 weeks was -2.9 kg for the sibutramine group and -0.2 kg for the placebo group (p < 0.001). The mean change in waist circumference was -2.1 cm for the sibutramine group and 0.1 cm for the placebo group (p < 0.001). The mean change in body mass index was -0.5 kg/m² for the sibutramine group and 0.0 kg/m² for the placebo group (p < 0.001). The mean change in body fat mass was -1.9 kg for the sibutramine group and 0.1 kg for the placebo group (p < 0.001). The mean change in body water was -0.6 kg for the sibutramine group and 0.0 kg for the placebo group (p < 0.001). The mean change in bone mineral density was 0.3% for the sibutramine group and -0.2% for the placebo group (p < 0.001).

Discussion: Sibutramine is an effective treatment for antipsychotic-induced weight gain in patients with AIWG. The study shows that sibutramine is a safe and well-tolerated treatment for weight gain in patients with AIWG. Further studies are needed to investigate the long-term effects of sibutramine on weight gain and comorbidities in patients with AIWG.

doi:10.1016/j.schres.2010.02.409
Background: Overweight represents one of the biggest health problems in the western society and contributes to a significantly reduced quality of life and to an increased morbidity and mortality rate. Weight gain in patients treated with conventional or new generation antipsychotics has frequently been reported. This trial investigates the effect of sibutramine, an approved weight loss agent, on antipsychotic induced weight gain in schizophrenia patients.

Methods: This is a 24-week, double-blind, placebo-controlled study including outpatients suffering from schizophrenia. Subjects were included if they met the following criteria: ICD-10 criteria for schizophrenia, age 19–65, being clinically stable since at least half a year, weight gain >7% of the initial weight, Body Mass Index (BMI) >27, no concomitant medication except benzodiazepines. Diagnoses were confirmed using chart information and reports from clinicians who had treated the patients. Laboratory tests, including plasma levels of the antipsychotic medication were carried out at regular intervals. In addition, weight, body fat, waist-hip ratio, smoking behaviour, blood pressure/pulse and ECG were monitored and several ratings were performed. Psychopathological symptoms were rated by means of the Positive an Negative Syndrome Scale (PANSS). To quantify side effects, the Udvalg for Kliniske Undersøgelser (UKU) side Effect Eating Scale was used. In addition, eating behaviours were assessed by means of the Visual Analogue Scale (VAS).

Results: So far, 11 subjects were randomly assigned to the two groups, sibutramine 10 mg or placebo, in a ratio of 1:1. (sibutramine n=6, placebo n=5). The Patients had an average PANSS total score of 51.6 and their mean weight gain during antipsychotic treatment had been 25 kg (SD 11.6). The two groups did not have significant baseline differences. Weight loss was significant in patients treated with Sibutramine (mean -6.14 SD 6.68) but not in the placebo group (+2.3 SD3.66). Waist hip ratio, BMI and blood pressure decreased during treatment with sibutramine but not under treatment with placebo (ns). Patients treated with sibutramine did experience a reduction in appetite compared with patients treated with placebo (ns). There were no differences between the two groups regarding drug safety.

Discussion: This trial suggests that sibutramine is a safe and effective in patients with schizophrenia who had gained weight during antipsychotic treatment. Due to the small number of subjects our encouraging experience warrants further studies.

doi:10.1016/j.schres.2010.02.410

Poster 184
CLINICAL REMISSION IN SCHIZOPHRENIA PATIENTS TREATED WITH ARIPIPRAZOLE FOR UP TO ONE YEAR

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Background: Schizophrenia is a debilitating and chronic disease for which full recovery is typically not considered to be a realistic treatment endpoint. Symptomatic remission, however, may be an objectively attainable treatment goal. We wanted to assess remission rates over 52 weeks in patients with schizophrenia treated with aripiprazole.

Methods: Remission rates were calculated using data from a 52 week study in which patients diagnosed with acute schizophrenia were stabilized with aripiprazole (n=30, dose 20-30 mg/day). For this analysis, remission was operationalized according to the consensus-based symptomatic remission criteria established by the Remission in Schizophrenia Working Group. Accordingly, patients were required to achieve scores Syndrome Scale (PANSS) items (delusions, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerisms/posturing, blunted affect, social withdrawal, lack of spontaneity) and to maintain the item score threshold for at least 6 consecutive months.

Results: Thirty-seven percent of aripiprazole treated patients satisfied the criteria for symptomatic remission within the 52-week trial period. Approximately 7% of patients lost their remission status prior to the end of the trial, with mean time in remission of 6.5 months. Forty-six percent of patients never met the PANSS item threshold. During the 52-week study, few patients discontinued due to adverse events other than worsening of symptoms (7%) or received concomitant medication for EPS (18%).
Poster 185
ANTIPSYCHOTIC PRESCRIBING PATTERNS AND INSIGHT IN AN ETHNICALLY DIVERSE EPIDEMIOLOGICAL SAMPLE OF FIRST EPISODE PSYCHOSIS PATIENTS

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Background: Investigating whether antipsychotic prescribing varies amongst different ethnic groups is an issue of political and clinical concern given the elevated rates of psychosis in ethnic minorities within the UK and the need for equal treatment in mental health. This study examined the baseline prevalence of antipsychotic prescribing in first episode psychosis (FEP) patients, exploring differences between White and ethnic minority groups. The impact of insight into illness and attitudes to treatment on time to first antipsychotic and first adequate trial were also investigated.

Methods: Data were collected on 228 FEP patients (58.8% Male; mean age 29.9 years ± 10.4; 43.4% schizophrenia, 15.8% mania, 13.2% depression, 15.8% other psychoses) from a large epidemiological sample (AESOP) conducted between 1997-1999 in London and Nottingham, UK. Detailed medication data were collated from ward and community prescriptions; correspondence with the prescribing clinician; and case notes. Insight was assessed on a sub-set of patients using the Schedule for the Assessment of Insight (SAI-E), with scores collapsed into 4 categories; total insight, illness awareness, symptom relabeling, and compliance.

Results: First antipsychotic prescribed was most commonly a first generation oral (48.7%), followed by second generation oral (39.8%), with only 4.4% patients receiving a first generation depot. Median time to commencement of any antipsychotic treatment was 3 days and median time on antipsychotic treatment within the first 30 days of presentation was 20 days. Neither time points varied by ethnicity, gender, age, or diagnosis. Median time to commencement of first adequate trial did not differ by age, gender, or diagnosis, although Other White and Asian groups had longer delays (P = 0.01). Uni-variable analyses revealed a trend of total insight and symptom relabeling as predictors of time to first adequate trial (P = 0.065; P = 0.037), however this was non-significant when corrected for ethnicity (P = 0.178; P = 0.064 respectively).

Discussion: Preliminary analyses on baseline prevalence of antipsychotic prescribing indicate no evidence of ethnic differences in FEP patients, which is supportive of previous research in the UK. An increase in total insight and symptom relabeling scores indicative of better global and symptom awareness, may play a role in reducing the time taken to receive an adequate trial of antipsychotics, although further research is needed in a larger sample. Attitudes towards treatment and behavioural compliance, does not appear to be associated with delays in treatment commencement or commencement of an adequate trial.

doi:10.1016/j.schres.2010.02.413

Poster 186
THE RISKS AND BENEFITS OF ANTIPSYCHOTIC POLYPHARMACY: POTENTIAL FOR NEUROLEPTIC MALIGNANT SYNDROME

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Background: Combination treatment with more than one antipsychotic medication has been reported among 3-71% of patients treated for schizophrenia, with most reports between 10-30%. Concerns have been raised about the efficacy and potential risks of these combinations. To better understand the potential benefits of adding a second antipsychotic, we performed a systematic chart review of patients treated with multiple antipsychotics. Inspired by a case example, we also performed a review of the literature on Neuroleptic Malignant Syndrome (NMS) to evaluate for associations with antipsychotic polypharmacy.

Methods: We systematically sampled charts from a US community mental health center. Limited data on antipsychotics prescribed was collected from all charts. An extensive chart review was performed on all cases where more than one antipsychotic was prescribed for at least 6 months. This included identification of target indications for augmentation, evidence for change in clinical outcome, and any attempt to taper the initial antipsychotic. We also evaluated outcomes on Mental Health Statistics Improvement Project ratings, structured functional outcome scales completed quarterly by clinicians. Next, we carefully documented a case of NMS associated with multiple antipsychotic treatment. Finally, we performed a PubMed search to identify all cases of NMS reported in the past 10 years, and calculated the proportion who were taking multiple antipsychotics.

Results: Among outpatients treated with an antipsychotic medication, 30% were maintained on two antipsychotics simultaneously and 1% on three antipsychotics. Patients treated with multiple antipsychotics had been ill an average of 16 years, with an average of three trials of a FGA and three trials of a SGA during the course of their illness. 74% had a diagnosis of schizophrenia, 7% psychotic disorder NOS, 7% bipolar disorder, 8% depression, and 4% other. 39% were prescribed a combination of FGA & SGA, and 61% multiple SGAs. The indications for adding a second antipsychotic medication included: residual positive symptoms (78%), negative symptoms (26%), other psychiatric symptoms (50%), and side effects of the initial antipsychotic medication (40%). Evidence of improvement in target indications was found in 52% of cases, worsening in 15%, and no change in 33%. There was an attempt to taper the initial antipsychotic in 47% of cases, and 22% of these charts included evidence that symptoms worsened following this attempted taper. We were unable to identify significant changes in MHISIP or GAF ratings associated with the transition from single to multiple antipsychotic treatment. We will present the results of the literature review of all cases of NMS reported in the past 10 years, and the proportion who were taking single versus multiple antipsychotics at the time of onset of NMS.

Discussion: Antipsychotic medication combinations were commonly prescribed in the CMHC sample. There was evidence of improvement in target indications in just over half of the clinical records associated with antipsychotic combinations. We were unable to detect significant changes in hospital utilization or psychosocial function. Adverse effects were not documented in the chart review, but may include increased risk for metabolic adverse effects, EPS and NMS. We report a common scenario of treatment of an agitated patient that resulted in multiple antipsychotic exposure in escalating doses and eventual NMS. We document the frequency of multiple antipsychotic treatment among cases of NMS reported in the literature.

doi:10.1016/j.schres.2010.02.414
Poster 187
ANTIPSYCHOTICS COMBINATION AT MEDICAL DISCHARGE FROM PSYCHIATRY HOSPITALISATION UNIT

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Background: Despite lacking evidence for its efficacy and safety, antipsychotic cotreatment is common in psychosis. It is not a recommended practice in clinical guides, though it is an usual therapeutic option in our environment. It has been recently reported that combination of antipsychotics (AP) may be superior to monotherapy (Correll et al., 2009).

Methods: The aim of the study is to describe the pattern of combination of antipsychotics in a sample of patients recently discharged from an acute psychiatry hospitalization service. All patients discharged during 2008 from psychiatry hospitalization unit of Parc Taulí Hospital treated with antipsychotics were recruited. They were evaluated with BPRS, CGI, EEAG, HAMD and DAI. A comparison between sample treated with single AP and those treated with 2 or more antipsychotics was carried out.

Results: The number of patients discharged during 2008 was 450. Patients treated with antipsychotics at discharge were 357 (79.3%); the rest with single antipsychotic n=194 (43.7%). In combination group (n=163), the main DSM-IV diagnostic were paranoid schizophrenia (74.2%) followed by schizoaffective disorder (18.4%) and other types of schizophrenia (7.3%). We found some statistically significant differences (p<0.05) in comparison with AP monotherapy sample (n=194), being the combination group older and with higher rates in BPRS scale at admission. They have spent a longer period in unit, and they have longer illness. Just one of them have been treated whit single clozapine before (as a criteria to begin a combined treatment). The most frequent combination was risperidone with olanzapine, followed by olanzapine with ziprasidone and risperidone consta plus quetiapine. The combination of risperidone consta plus oral was also surprisingly frequent (5% of the sample).

Discussion: High number of psychotic patients are treated with combination of AP at discharge. It exists a profile of patients who are more susceptible to be cotreated. It is necessary to study the impact on adverse effects, as well as following clinical impact of combination.

References

doi:10.1016/j.schres.2010.02.415

Poster 188
LONG-TERM TREATMENT WITH LONG-ACTING INJECTION OF RISPERIDON IN PATIENTS WITH SCHIZOPRENEA - 2-YEAR FOLLOW-UP

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Background: Long-term therapy with traditional antipsychotics fails to produce an adequate therapeutic response in a significant number of schizophrenic patients. Second-generation antipsychotics are associated with much better side effect profiles as compared to traditional agents. A long-acting form of the second-generation antipsychotic drug risperidone is now broadly available for the treatment of schizophrenia and closely related psychiatric conditions. The aim of the study was to assess the therapeutic effect of Long Acting Injectable risperidone (LAI risperidone) in patients with schizophrenia and other related psychotic disorders and to assess the frequency of rehospitalizations during 2-year follow-up.

Methods: Our retrospective study included 59 schizophrenic patients (42% women, 58% men) with an average age of 37.5 ± 5.4 years. The patients were evaluated based on Clinical Global Impression – Severity and Clinical Global Impression – Improvement. The frequency of rehospitalizations during 2-year follow-up was assessed in the whole group.

Results: The initial inclusion score on the CGI-I by admission was 6.2 ± 0.8. This score showed a decrease at the time of discharge (CGI-I 3.8 ± 1.2). The average dose of LAI risperidone was 40.5 mg/2 weeks. The improvement measured by CGI-I by discharge show significant improvement (CGI-I 2.8 ± 0.6). Only 6 patients (10.2%) were rehospitalised during 2-year follow-up period (2 patients within 1 month after discharge, 1 patient 2 months after discharge, 2 patients 3 months after discharge and 1 patient 9 months after discharge).

Discussion: According to clinical studies, our retrospective survey pointed, that LAI risperidone is a proven treatment with significant clinical efficacy. The results of clinical studies show that the number of hospital admissions for people diagnosed with schizophrenia is significantly reduced following the initiation of treatment with risperidone long-acting injections. The frequency of rehospitalizations in our 2-year follow-up survey was low (10.2%).

doi:10.1016/j.schres.2010.02.416

Poster 189
SHORT-TERM TOLERABILITY, SAFETY, AND PHARMACOKINETIC PROFILE OF ASENApine IN OLDER PATIENTS WITH PSYCHOSIS

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Background: Asenapine is indicated in the United States for acute treatment of schizophrenia in adults and acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults, and is under review in Europe for the treatment of schizophrenia and manic episodes associated with bipolar I disorder. We report short-term tolerability, safety, and pharmacokinetic (PK) profiles of asenapine in elderly patients with psychosis.

Methods: This 6-week randomized trial enrolled patients aged ≥65 years with psychotic symptoms (not related to dementia), defined as a Positive and Negative Syndrome Scale (PANSS) score ≥ 4 on ≥ 1 of 5 predefined items (delusions, hallucinatory behavior, excitement, hostility, poor impulse control), PANSS total score > 50, and Clinical Global Impression-Severity of Illness score ≥ 3. After a washout of ≤ 3 days, sublingual asenapine was given in 2 treatment schedules: 2 days at 2 mg twice daily (BID), 2 days at 5 mg BID, and 10 mg BID thereafter; or 4 days at 5 mg BID and 10 mg BID thereafter. Asenapine PK profiles were assessed on treatment days 3, 4, 7, 8, 21, and 42 (before the morning dose) and 0.5–12 hours after the morning dose on days 4 and 8.

Results: Of 122 randomized patients (mean age, 71.2 y), 76 (62%) completed the trial. Tolerability was comparable across treatment
Background: Muscarinic cholinergic receptors consist of five subtypes: M1, M3 and M5 couple to Gq, while M2 and M4 couple to Gi-protein. Muscarinic M4 receptors are found in cortex and hippocampus, but are most prominent in the striatum where they control dopamine release and motor activity. M4 receptor activators and antagonists may have utility in treating schizophrenia and Parkinson’s disease respectively, but efforts to develop selective ligands have been hampered by difficulties in achieving high selectivity vs other subtypes. Here, we compared two recently synthesized “positive allosteric modulators” (PAMs), LY2033298 (1) and VU0152099 (2). Actions were evaluated at human (h)M4 receptors stably expressed in a CHO-K1 cell line, and in an animal model of clinical antipsychotic efficacy: the conditioned avoidance response test (CAR).

Methods: Radioligand binding was performed using [3H]-N-Methyl-Scopolamine (NMS, 0.5 nM), and nonspecific binding was defined with atropine (10 microM). The specific activation of Galphai was determined using [35S]-GTPgammaS (0.2 nM) in a scintillation proximity assay/antibody immunocapture procedure (3). Agonists were incubated in the absence or presence of PAMs. Male Wistar rats conditioned on a two-way (shuttle-box) active avoidance task (4) were incubated in the absence or presence of PAMs. Male Wistar rats conditioned on a two-way (shuttle-box) active avoidance task (4) were used for in vivo studies. They were their own controls and were conditioned on a two-way (shuttle-box) active avoidance task (4).

Discussion: Compared with previous findings in adult patients aged <65 years (asenapine Cmax: 4.23 ng/mL at 5 mg BID, 6.56 ng/mL at 10 mg BID), serum asenapine concentration was 12–30% higher in elderly patients. Despite the increased exposure, short-term asenapine treatment was generally well tolerated in elderly patients with psychosis during rapid dosage escalation. (Supported by Schering Corp., a division of Merck & Co.).

doi:10.1016/j.schres.2010.02.417

Poster 190
ALLOSTERIC MODULATION OF MUSCARINIC M4 RECEPTORS IN THE TREATMENT OF SCHIZOPHRENIA: A PHARMACOLOGICAL COMPARISON OF LY2033298 VS VU0152099

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Poster 191
EFFECTIVENESS OF 300MG/4WEEKS OLANZAPINE LONG-ACTING INJECTION FROM DATA MINING OF AN OPEN-LABEL EXTENSION STUDY

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Background: To present effectiveness data for Olanzapine Long-Acting Injection (OLAI) at the regimen of 300 mg/4 weeks, corresponding to 10 mg oral olanzapine daily. This dosage has not been investigated in the phase III studies where OLAI doses of 150 mg/2w, 210 mg/2w, 405 mg/4w, and 300 mg/2w were studied. This data mining initiative was used to investigate the effectiveness of 300 mg/4w regimen.

Methods: Data from an ongoing open-label extension study of patients receiving flexibly dosed OLAI at injection intervals of 2–4 weeks (after having been treated with OLAI, oral olanzapine or placebo in previous OLAI randomized, controlled studies) was used. The study's primary objective was to examine the long-term safety and tolerability of OLAI. Oral olanzapine supplementation was allowed. The patients included in the analyses were observed from the moment they started on OLAI. Oral olanzapine was allowed. The patients included in the analyses were observed from the moment they started on OLAI.

References
scale data were not available for all patients. For adverse events (AE) and weight, measured more frequently, data were more complete.

**Results:** At the time of analyses 165 patients had been exposed to 300 mg/4w OLA1 treatment for at least of 3 months. Only 15 patients were exposed for at least 3 months to the equivalent dose of OLA1 administered every 2 weeks (150 mg/2w). Analyzed patients were 61% males, 70% Caucasian, and had an mean age of 39 (SD 11.7) years and a mean BMI of 27.2 (SD 5.1). At the start of the regimen mean total PANSS was 48.1 (SD 15.0), CGI-S 2.5 (SD 1.0), 8% of patients experienced EPS, 31% used benzodiazepines, 7% anticholinergics. Despite full flexibility to modify treatment 42% (95%CI 34-49%) of patients remained on 300 mg/4w regimen for at least 1 year. For patients who remained on the regimen for 1 year the mean total PANSS was 45.5 (SD 14.7), CGI-S 2.35 (SD 1.1), at that time. 7% was on an anticholinergic in the first 6 months and 4% in the second half of the year, while 31% and 22% respectively used a benzodiazepine. During the first 6 months 8.5% experienced ≥1 treatment emergent AE and 8.1% during the second half of the year. 3 (2%) patients had a serious AE in the first 6 months and 3 (2%) patients developed EPS, none were recorded in the second half. Mean weight gain at 1 year was 0.68 kg (SD 4.78).

**Discussion:** The regimen of 300 mg/4w was preferred over the alternative low dose regimen of OLA1 (150 mg/2w). The high continuation rate, the maintained efficacy, and the ongoing tolerance suggest a good effectiveness of this regimen. Safety findings were consistent with those observed with oral olanzapine therapy.

doi:10.1016/j.schres.2010.02.419

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Post 192

**PRESCRIBING PATTERNS OF ANTIPSYCHOTICS WITHIN FORENSIC PSYCHIATRIC CARE**

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**Background:** A majority of patients within the forensic psychiatric care in Sweden have diagnoses of psychoses and most often of schizophrenia. The knowledge about pharmacological treatment of aggressive behavior is limited but therapeutic traditions are strong.

**Methods:** In the treatment register of forensic care in Sweden it is possible to see which antipsychotics that are being used and also what is the proportion of long-acting injections. In this presentation the prescribing patterns of the Forensic Department in Gothenburg is compared with the pattern nation-wide.

**Results:** In the Forensic Department at Sahlgrenska University Hospital there is a higher proportion of second generation antipsychotics and a lesser use of long-acting injections.

**Discussion:** The few studies of antipsychotics in the treatment of aggressive behaviour favour the use of clozapine and olanzapine which are widely used at the Forensic Department in Gothenburg. Another second generation drug widely used is aripiprazole.

doi:10.1016/j.schres.2010.02.420

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Post 193

**ANTICHOLINERGIC DRUG USE IN CLINICAL SETTINGS IN THE SECOND-GENERATION ANTIPSYCHOTIC ERA**

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**Background:** The introduction of second generation antipsychotics (SGAs) to clinical practice have resulted in changes in the pattern of prescription in psychotic conditions. There is a lower risk of extrapyramidal symptoms (EPS) with SGAs as compared to conventional antipsychotics. As such, there has been a lesser need for adjunctive anticholinergic prescription with this newer class of agents in controlled SGA treatment trials. Since anticholinergic medication is associated with many adverse effects on its own (e.g. cognitive compromise, parasympathetic effects) and SGAs have been considered a major advance in reducing anticholinergic prescription and its associated morbidity. However, only limited data exist about the pattern of use of anticholinergic medication in psychiatric patients naturalistically prescribed SGAs. This issue is relevant, since some recent studies have shown that the proportion of treated SGA patients manifesting EPS is not negligible. Aim: To study the frequency of anticholinergic medication prescription in patients being naturally treated with SGA in diverse ambulatory clinical settings of the Zucker-Hillside Hospital, North Shore – LIJ Health System.

**Methods:** Data were obtained from the computerized analysis of the electronic health records of all patients who were cross-sectionally registered (September 2008) in eight ambulatory programs of Zucker Hillside Hospital. 5114 patients were identified (n= 410 < 13 years of age; 3345 from ages 13 to 60 years; and 1359 > 60 years of age) and characterized according to age, gender, antipsychotic medication (conventional, SGA or both), anticholinergic prescription (yes/no), psychiatric diagnosis, parent clinic setting.

**Results:** 1. Amongst patients treated with either a SGA or a conventional antipsychotic, 7% of SGA-treated patients and 45% of conventional agent-treated patients received adjunctive anticholinergic medication. 2. Amongst patients treated with both a SGA and a conventional antipsychotic, 51% received adjunctive anticholinergic medication. 3. Amongst patients treated with SGAs, patients with a schizophrenia or schizophrenia-spectrum diagnosis are prescribed anticholinergics more frequently than bipolar patients of similar ages. 4. Age and gender distribution were not significantly different in any group (conventional antipsychotic with or without anticholinergic; SGA with or without anticholinergic; combined SGA and convention with or without anticholinergic). 5. Few patients in either the pre-adolescent or older age groups are prescribed anticholinergics.

**Discussion:** 1. Anticholinergic medication is regularly prescribed in patients treated with SGAs, albeit at a much lower frequency rate than in patients treated with conventional antipsychotics. These data validate the lower EPS burden associated with SGAs. 2. Bipolar patients treated with SGAs require adjunctive anticholinergics less frequently than schizophrenia-spectrum patients. Further data analysis will ascertain whether this represents a SGA dose/diagnosis relationship or allows speculation about a neurobiological distinction (e.g. greater susceptibility of schizophrenia than bipolar patients to EPS). 3. That prescription of anticholinergic medication is restricted to the young adult-adult group appears to reflect psychotropic prescribing conservatism in the much younger (preadolescent) and older (geriatric) age groups.

doi:10.1016/j.schres.2010.02.421

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Post 194

**RATER TRAINING ON PANSS AND SANS**

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**Background:** Effective rater training is critical for increasing inter-rater reliability of rating scales used in clinical trials. A rater training
program for the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessment of Negative Symptom (SANS) was provided as part of a clinical trial. Our main objective was to evaluate change over time on achieving inter-rater reliability by raters participating in certification and additional training on application of these measures.

**Methods:** 104 raters from 8 countries participated in the rater training program. For PANSS only, website training and certification was offered. A patient vignette was used for certification session I (demonstrating 20 items of PANSS). For the second and final certification session, three different patient vignettes were used demonstrating 16 random PANSS items. No remediation session was offered to raters on PANSS. A combination of online and face to face training at the Investigators’ Meeting (IM) were used to train and certify raters on SANS. All three certification sessions included a patient vignette which covered all 25 items on SANS. All raters who failed certification session I underwent a remediation session with an expert trainer on SANS. Kappa statistics was used to calculate the inter-rater reliability. Gender, previous rater training exposure, and past experience in rating these scales were also examined.

**Results:** On PANSS, Kappa value of 0.21 and 0.087 was obtained for certification session I and II, respectively. A Kappa = 0.32, 0.19, and 0.41 were achieved by raters in certification sessions I, II, and III, respectively. Raters’ ratings on PANSS were not affected by their gender, previous experience or rater training exposure on PANSS, whereas on the SANS levels of education and previous SANS experience significantly affected raters’ ratings.

**Discussion:** Fair and no agreement was obtained on the PANSS certification sessions, while fair, slight and moderate agreement was achieved on SANS. The decrease in inter-rater reliability on PANSS, from certification I to II, may be because raters who failed certification I, completed certification II without being offered any remediation session. Individual remediation session with the expert trainer helped raters achieve slight to moderate inter-rater reliability for SANS in certification sessions II and III. Individual remediation session improved inter-rater reliability for SANS.

**doi:** 10.1016/j.schres.2010.02.422

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**Poster 195**

**SINGLE DOSE TOLCAPONE ADMINISTRATION IMPROVES WORKING MEMORY AND SENSORIMOTOR GATING IN PSYCHOTIC PATIENTS**

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**Background:** It has been shown that tolcapone improves prefrontal function in healthy individuals. This has important therapeutic implications for the treatment of cognitive and gating deficits in psychosis. Here we explored the effects of enhanced PFC DA signaling by tolcapone on Prepulse Inhibition (PPI) and working memory in psychotic patients.

**Methods:** Seventeen medicated psychotic patients in partial remission, received tolcapone-200 mg according to a double-blind, placebo-controlled, crossover design in two weekly sessions. PPI was assessed with 75- and 85-dB prepressures at 30-, 60- and 120-ms intervals. Patients also underwent the letter-number sequencing (LNS) task.

**Results:** A 2 × 2 (treatmentXgender) ANOVA showed that tolcapone improved LNS performance (treatment p < 0.01). Tolcapone tended to reduce startle (p < 0.056) but did not affect startle habituation. A 2 × 2 × 3 × 2 (treatmentXprepulseXintervalXgender) ANOVA of the PPI data revealed a treatmentXprepulseXinterval interaction (p < 0.01). This interaction remained significant (p < 0.02) when age, CGI-S and SANS attention scores (which correlated significantly with Delta tolcapone effect on PPI) as well as chlorpromazine equivalents and delta tolcapone effect on startle were taken as the covariates. Follow up ANCOVAs revealed significant effects of tolcapone at 75-dB 30-ms trials (p < 0.001).

**Discussion:** Enhancement of PFC DA signaling with acute tolcapone administration, improved short interval PPI, working memory and arousal/mood as indexed by startle, in a sample of non-genotyped, psychotic patients. These pilot findings are encouraging for clinical trials with sub-chronic and chronic tolcapone administration aiming to test prefrontal function, gating and symptom improvement in psychosis.

**doi:** 10.1016/j.schres.2010.02.423

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**Poster 196**

**SOCIO-DEMOGRAPHIC CHARACTERISTICS AND INITIAL TREATMENT DECISIONS FOR PATIENTS WITH SCHIZOPHRENIA AT RISK OF TREATMENT NON-ADHERENCE**

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**Background:** A high proportion of patients with schizophrenia discontinue their antipsychotic medication due to non-adherence, which increases the risk of illness exacerbation and hospitalization. As such, there is a need to identify this population accurately.

**Methods:** Outpatients from Australia, Mexico, Romania, and Taiwan (N = 406) who met DSM-IV criteria for schizophrenia, and who required a switch from their current oral antipsychotic due to a risk of medication non-adherence as judged by their treating physician, were observed naturalistically in this 12-month multi-country, prospective, non-interventional observational study. Patients switched to depot or oral antipsychotics were compared using Fisher’s exact test and t-tests for categorical and continuous variables, respectively. Socio-demographic characteristics and initial treatment patterns are presented.

**Results:** Overall, patients were 37.2 ± 10.2 years of age (mean ± standard deviation [SD]), 43.3% were female, and 53.4% were Caucasian. Most patients lived with their family (82.0%), 28.6% were in a relationship, 42.4% were unemployed, and 54.6% had no income. At study entry, 363 patients (89.4%) were switched to an oral antipsychotic as their primary treatment and 43 (10.6%) were switched to a depot antipsychotic. Overall, patients were moderately ill at study entry and reported moderately poor quality of life, indicated by average Clinical Global Impressions of Severity (4.2 ± 1.0); EuroQol Health State (56.4 ± 24.8); and Short Form Health Survey Mental (MCS; 35.2 ± 10.9); and Physical Component (PCS; 44.2 ± 9.2) scores. Illness severity and quality of life ratings were similar across depot and oral groups at study entry.

On average, patients switched to depot had experienced their first episode earlier than those switched to oral antipsychotics (22.4 ±
Poster 197
EFFECTIVENESS OF LURASIDONE IN SCHIZOPHRENIA: RESULTS OF A POOLED ANALYSIS BASED ON A 5-FACTOR MODEL OF SCHIZOPHRENIA

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α little affinity for noradrenaline antagonist effects at dopamine D2, serotonin 5-HT7 and 5-HT2A 

Background: Lurasidone is a new psychotropic agent with potent Education, and Clinical Center Los Angeles, CA, USA 

Formal, once-daily doses of lurasidone 40 mg (N=288), 80 mg (N=208) 

Methods: Pooled data were analyzed from 4 six-week, double-blind, 

Results: Lurasidone was significantly superior to placebo in improving all 5 PANSS factor scores. Week 6 change scores were significant compared to placebo among patients treated with lurasidone 40 mg, 80 mg and 120 mg, respectively on the PANSS positive factor (−7.92, −8.48, −8.25; p < 0.001 for all comparisons), negative factor (−5.59, −4.96, −5.21; p < 0.001, p = 0.02, p = 0.002), disorganized thought (−4.86, −5.10, −5.22; p < 0.001 for all comparisons), hostility (−2.33, −2.58, −2.87; p < 0.013, p = 0.002, p < 0.001) and depression/anxiety (−3.14, −3.23, −3.01; p = 0.002, p = 0.002, p = 0.012). Effect sizes for Week 6 change scores versus placebo were clinically significant for patients treated with lurasidone 40 mg, 80 mg and 120 mg, respectively on the PANSS positive factor (0.35, 0.47, 0.42), negative factor (0.41, 0.25, 0.31), disorganized thought (0.40, 0.47, 0.50), hostility (0.25, 0.33, 0.44) and depression/anxiety (0.31, 0.35, 0.26). 

Discussion: In this comprehensive analysis of available double-blind, placebo-controlled short-term treatment studies, lurasidone demonstrated broad spectrum efficacy across all 5 PANSS factors: positive, negative, disorganized thought, hostility and depression/anxiety.

Supporting information: Available at www.schizophrenia.com

Supporting information: Available at www.schizophrenia.com

doi:10.1016/j.schres.2010.02.425
significantly from 79.4 ± 20.4 at baseline to 66.1 ± 21.5 at endpoint (mean change -13.3 ± 19.7; 95% confidence interval -14.2;-12.3, p < 0.0001). The percentage of patients rated mildly ill or less in CGI-S increased from 27.0% to 52.2% at endpoint, and the rate of patients with mild functional impairment increased from 15.8% to 34.9%. AEs reported in n = 5% of patients were insomnia (9.2%) and anxiety (7.2%). Extrapyramidal symptoms in ESRs decreased significantly from 3.5 ± 5.8 to 2.1 ± 4.6 (p < 0.0001). Mean weight gain from baseline to endpoint was 0.3 ± 4.8 kg.

**Discussion:** These data support results from recent randomized controlled studies that paliperidone ER is safe, well tolerated and effective in patients previously unsuccessfully treated with other oral antipsychotics.

doi:10.1016/j.schres.2010.02.427

**Poster 199**

**PATIENT FUNCTIONING WITH FLEXIBLE DOSES OF PALIPERIDONE ER – A 6-MONTH PROSPECTIVE STUDY**


**Background:** To explore changes in functioning with flexible doses of paliperidone ER in a large international study in patients with schizophrenia previously unsuccessfully treated with other oral antipsychotics.

**Methods:** Prospective 6-month open-label study. Patient functioning was assessed using the Personal and Social Performance Scale (PSP), including four domains of (1) personal and social relationships, (2) socially useful activities including work and study, (3) self-care and (4) disturbing and aggressive behavior.

**Results:** 1812 patients were included (59.9% male, mean age 40.1 ± 12.6 years, 75.8% paranoid schizophrenia); most were enrolled because of lack of efficacy (n = 1026) or lack of tolerability (n = 490) with prior antipsychotic treatment. The median mode dose of paliperidone ER was 6 mg/day. 70.7% of patients completed the study. Most frequent reasons for early discontinuation were patient choice (8.8%), lack of efficacy or adverse event (5.1% each). AEs reported in n = 5% of patients were insomnia (9.2%) and anxiety (7.2%). Mean total baseline PSP score was 57.7 ± 14.5, which improved to 64.1 ± 15.6 at endpoint (mean change +6.4 ± 13.5; 95% confidence interval 5.8±7.0, p < 0.0001); 49.0% of patients improved by at least one 10-point category in PSP. At baseline, 84.3% of patients had moderate to severe functional impairment, mostly driven by at least marked difficulties in socially useful activities (46.4%) and personal and social relationships (36.4%). These percentages decreased to 30.6% and 22.9%, respectively.

**Discussion:** In this large prospective flexible-dose study, results from recent randomized controlled studies are supported that paliperidone ER is associated with a clinically meaningful improvement of functioning in patients with schizophrenia.

doi:10.1016/j.schres.2010.02.427

**Poster 200**

**PRINCIPAL OUTCOMES OF THE SERTINDOLE COHORT PROSPECTIVE (SCP) STUDY**

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**Background:** Sertindole, an atypical antipsychotic drug is effective for treatment of schizophrenia (Azorin et al 2006, Hale et al. 2000, Daniel et al. 1998, Zimbroff et al. 1997) but also causes Ikr blockade (Rampe et al. 1998, Kongsamut et al. 2002) and prolongs the action potential duration of cardiomyocytes (Drici et al. 1998) and the QT interval. (Eckardt et al. 2002, Lindstrom et al. 2005). The current study was designed to assess whether sertindole would increase all-cause mortality, or cardiac events, including arrhythmias, of a severity that would require hospitalisation, under normal conditions of use. Risperidone was chosen as the comparator because of its widespread use.

**Methods:** Multinational randomized, open-label, parallel-group study comparing sertindole with risperidone in 9858 patients with schizophrenia enrolled between 2002 and 2008. The serious adverse events were coded by the local investigators (unblinded) using the Medical Dictionary for Regulatory Activities (MedDRA). The Independent Safety Committee (ISC) conducted a blinded review of all events and classified the deaths into the one of the three categories Cardiac, Suicide, or Other. The ISC definition of cardiac death was intentionally wide; sudden or unexplained deaths were assumed to be cardiac if there was no non-cardiac explanation. The ISC definition of suicide attempts was broader than the MedDRA classification, as it not only included completed suicides and suicide attempts with clearly stated intent to die, but also overdoses and self-injuries where suicidal intent was absent or unclear as well as suicidal tendencies or ideations.

**Results:** The sertindole and risperidone groups were well matched at baseline. The duration of exposure totalled 14147 person-years (6575 sertindole, 7572 risperidone). There was no difference in overall mortality between sertindole and risperidone recipients (64 versus 61 deaths, hazard ratio (HR) = 1.12 [90% CI:0.83,1.50]). There were 10 cardiac events that required hospitalisation with sertindole and 6 with risperidone (HR = 1.73 [95% CI:0.63,4.78]). Of these, 4 were considered arrhythmia-related (3 sertindole, 1 risperidone). Cardiac mortality was less prevalent than anticipated, but higher in the sertindole group (ISC: 31 versus 12, HR = 2.84 [95% CI:1.45,5.55], P = 0.0022; Investigators 17 versus 8, HR = 2.13 [95% CI 0.91,4.98], P = 0.081). No significant differences were observed in the rates of completed suicide, but also overdoses and self-injuries where suicidal intent was absent or unclear as well as suicidal tendencies or ideations.


doi:10.1016/j.schres.2010.02.428

Poster 201
MAINTAINING FAVOURABLE ADHERENCE BY CONSISTENT SELF-ADMINISTRATION OF MEDICATION - MEDICATION EVENT MONITORING SYSTEM (MEMS) TRIAL TO EVALUATE THE COMPLIANCE OF PATIENTS WITH SCHIZOPHRENIA IN JAPAN

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Background: The primary objective of Schizophrenia treatment is to inhibit symptom exacerbation and relapse during long-term treatment. To achieve this objective, it is important to improve medication adherence by patients by raising patient awareness and encouraging them to participate in their own treatment (i.e., shared decision-making, etc.). However, it is extremely difficult to continue the administration of medication while they are residing in communities of people with Schizophrenia. As a consequence of partial adherence or limited knowledge about the disease, etc., patients experience exacerbation and relapse. Therefore, although it creates a huge burden for patients and their families, compliance to adherence must be improved.

Methods: Multicentre, 6-month study, using MEMS, involving 50 outpatients with schizophrenia and schizoaffective disorders using DSM-IV criteria to assess their adherence under monotherapy with oral antipsychotics. Prescribers, pharmacists, and patients who participated in the study were unaware of distinctive cap, which contains a microchip inside, on the pill bottle.

Results: 1) During the 6-month study period, 12 (24%) patients resigned from the study due to exacerbation and other reasons. 32 (64%) patients maintained positive adherence (adherence ratio ≥ 75%), and 6 (12%) patients maintained poor adherence. 2) 20% of the patients displayed poor adherence in the first month after discharge from the hospital, and the ratio of positive adherence by patients gradually decreased over time. 3) By investigating the transition of adherence during the first month, MEMS data displayed that adherence decreases during the first week after discharge. 4) Comparing the average time gap of medication, patients with poor adherence (average time gap = 237 min.) had a significantly larger variability of medication-time-gap in comparison with patients with positive adherence (average time gap = 103 min. (p < 0.0001). p

Discussion: This was the first study in Japan to use MEMS to objectively and quantitatively assess patient adherence transition after hospital discharge. Compared to routine adherence assessment methods (i.e., interview by physicians, patient’s self-reported data, or by pill-count, etc.), MEMS is able to provide additional accurate information. It is exceedingly difficult to correctly estimate positive adherence. The first week after discharge is a turning point in the level of compliance. In order to prevent relapses, it is necessary for medicine to be administered regularly at this early stage. For the above-mentioned reasons, we, as medical staff, must support patients by educating them about their illness and its treatment, and the skills to solve problems independently. Moreover, we can provide home-visit services for outpatients from the inception of their treatment. Furthermore, we can be receptive to their concerns, especially with regard to their consistent self-administration of medication, weekly over a period of a few months. If the patient feels that the daily self-administration of medicine orally is exceedingly difficult, he/she could be given the option of utilizing extended injection therapy.

doi:10.1016/j.schres.2010.02.429

Poster 202
IMPACT OF SPECIFIC TYPES OF EARLY ADVERSITY EVENTS ON ADULT PSYCHOSIS-LIKE SYMPTOMS: PRELIMINARY RESULTS BASED IN THE UB-TWIN SAMPLE

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Background: Early adversity has been extensively linked to the development of psychotic symptoms in clinical and non-clinical samples (Janssen et al. 2004; Shevlin et al. 2007; Kelleher et al. 2008). Although sexual abuse has been consistently associated with positive symptoms such as hallucinations and delusions (Freeman et al. 2009; Thompson et al. 2009), it still remains unclear whether different types of adverse events have a differential impact on development of positive and negative symptoms. Moreover, the impact of environmental risk factors in the development of negative symptoms has been poorly studied. The present study aims to explore the impact of early abuse and neglect in the development of positive and negative psychosis-like experiences. Based on previous literature abuse experiences are expected to be stronger predictors of positive symptoms compared to experiences of neglect. Furthermore, the putative true environmental impact of abuse and neglect events on positive and negative symptoms respectively is investigated by comparing MZ twin pairs that are concordant and discordant for the exposure to these early adverse events.

Methods: Our ongoing sample includes 198 individuals (99 twin pairs) from the general population. Three dimensions of early adverse events (abuse, neglect and household dysfunction) were assessed using an adapted version of the Adverse Childhood Experiences Questionnaire (ACE; Felitti et al. 1998). Psychosis-like symptoms were assessed by means of the Community Assessment Psychotic Experiences (CAPE; Stefanis et al. 2002). Associations between early adversity events and psychosis-like symptoms were performed using linear regressions correcting for the paired structure of the data. To test the potential true environmental effect of the early adverse events, we compared the mean of the differential scores of positive psychosis-like symptoms in a subsample of MZ twin pairs concordant vs. discordant for early abuse experiences using one-way ANOVA, and we proceed identically to explore the true environmental impact of neglect on the occurrence of negative symptoms. All analyses were performed using STATA v9.

Results: Abuse events were the only significant predictors of positive psychosis-like symptoms (β = 1.02; p = 0.049). Among
them, sexual abuse ($\beta = 4.00; p < 0.01$) and emotional abuse ($\beta = 2.61; p < 0.01$) showed the strongest impact on positive symptoms. Neglect events demonstrated to be mostly associated with negative psychosis-like symptoms ($\beta = 3.04; p < 0.01$). Emotional ($\beta = 3.04; p < 0.01$) and physical neglect ($\beta = 6.69; p < 0.01$) were the strongest predictors of negative psychosis-like symptoms. No statistically significant differences were detected between the means of the differential scores for the positive nor for the negative psychosis-like symptoms of the concordant and discordant MZ twin pairs for their exposure to abuse and neglect events respectively.

**Discussion:** As we expected, experiences of abuse specifically impacted on the development of positive symptoms rather than on negative symptoms. Interestingly, although both abuse and neglect experiences were associated with the development of negative symptoms, neglect showed the strongest association. These preliminary results may suggest a differential impact of two types of early adversity events on the development of psychosis-like symptoms. Although, we failed to show a true environmental impact of abuse and neglect, our preliminary results support the role of the early adversity in the development of psychosis-like symptoms.

**Acknowledgments:** PhD Grant ISCIII (FI07/00272). Supported by EU Twins (RD-06/0011/0007) and Coordinated Project (SAF2008-05674-C03-00).

doi:10.1016/j.schres.2010.02.431

**Poster 203**

**MATERNAL STRESS DURING PREGNANCY AND RISK OF SCHIZOPHRENIA IN ADULT OFFSPRING**

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**Background:** To determine if prenatal exposure to maternal stress is associated with an increased incidence of schizophrenia among exposed offspring compared to early childhood exposure to stress and if any effect seen is dependent on the timing of exposure during gestation.

**Methods:** We identified all those born in Helsinki between 1947 and 1990 and whose father or older sibling died during their foetal period ($N = 2,074$) through linking two national registers: the Finnish Population Register and the Cause of Death Register. Individuals whose father or older sibling died during early childhood (0-5 years) were identified for use as a comparison group ($N = 13,855$). A third register, the Finnish Hospital Discharge Register, was used to determine psychiatric outcomes in adulthood of both exposure groups.

**Results:** Early childhood stress due to the loss of a first degree relative led to a greater risk of developing schizophrenia in adulthood than prenatal exposure to such stress ($OR = 1.7, 95\% CI 1.1-1.9$). There was no effect of the timing of the exposure during gestation. There was a trend towards an increase in risk for schizophrenia when the relative died suddenly (acute stress) in both prenatal and childhood exposed groups compared to those whose relatives did not die from a sudden cause ($OR = 1.9, 95\% CI 1.3-1.9$).

**Discussion:** The prenatal period may not be the most important time window in development for exposure to risk factors for schizophrenia. Aetiological theories of schizophrenia should take into account the importance of early childhood exposure to adverse events.

doi:10.1016/j.schres.2010.02.432
Background: Severe life events seem to be associated with the development of psychotic illness irrespectively of timing of the exposure. Family history of psychoses or deaths due to suicides did not explain the effect.

Discussion: Severe life events were associated with an increased risk of subsequent psychotic illness, whether occurring during fetal life (OR 1.9) or childhood (ORs 1.7, 1.5 and 1.5 respectively) although there was some support for a stronger effect during fetal life (OR 1.9) or childhood (ORs 1.7, 1.5 and 1.5 respectively) although there was some support for a stronger effect.

doi:10.1016/j.schres.2010.02.433

Post 206
TIME AND TASK-DEPENDENT INHIBITION OF DOPAMINE RESPONSES TO NOVELTY, APPETITIVE AND AVERSIVE STIMULI INDUCED BY HALOPERIDOL: AN IN-VIVO MICRODIALYSIS STUDY

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Background: Antipsychotics work predominantly by blocking dopamine D2 receptors. Previous studies showed that common and atypical antipsychotic drugs, increase dopamine levels during acute, but not chronic treatment. However, these studies lack using representative doses for the clinical conditions in rodents during pregnancy has been reported to result in a number of behavioral and cognitive deficits relevant to neuropsychiatric disorder in the offspring. In a rat prenatal bacterial infection model, maternal administration of lipopolysaccharide (LPS) leads to abnormal dopamine mediated behaviors such as decreased prepulse inhibition of startle (PPI) and enhanced amphetamine induced locomotion. Using the same model we have found that prenatal LPS treatment induces significant changes in the cytoarchitecture of pyramidal neurons in the hippocampus and the prefrontal cortex (PFC) of juvenile and adult offspring (e.g. dendritic arbor, dendritic length and spine density)(Baharnoori et al., 2009). In the present study, we further characterized neuronal changes in the hippocampus and the PFC and tested the hypothesis that these changes may affect developmental expression of mesolimbic and cortical dopaminergic receptors. Accordingly, we examined the density of cortical dopaminergic receptors in rat offspring.

Methods: We performed a triple-probe microdialysis in freely moving rats after 6 and 14 days of treatment with HAL (0.5 mg/kg/d; n = 6-7) or vehicle (n = 10) using osmotic mini-pumps. Extracellular dopamine levels were measured after rats were exposed to novelty (open field), appetitive food (fonzies) and to tail pinch in the medial prefrontal cortex (mPFC), caudate-putamen (CPu) and in the nucleus accumbens (NAcc) using HPLC-EC. The results were analysed with one and two way ANOVA.

Results: HAL inhibited the stimulation of locomotor activity and food intake induced by the three stimuli over the two time schedules of treatment (P<0.01). HAL treatment decreased dopamine baseline levels in the PFC (P<0.01), but not in the NAcc and CPu after 6 days of treatment, and in all three brain areas after 14 days of treatment (P<0.01). HAL differentially affected the dopamine responses to the three environmental stimuli within the three considered areas. Six days of treatment inhibited dopamine stimulation induced by tail pinch (P=0.003), but not by food (P=0.619) nor by novelty (P=0.305), with respect to control group in the NAcc. On the contrary, HAL potentiated the dopamine response to tail pinch in the mPFC with respect to both baseline (P=0.008) and control group (P=0.004). There were no effect in CPu (P=0.969). After 14 days of treatment, HAL lost the ability to inhibit the tail pinch-induced dopamine increase in the NAcc (P=0.026, compared to 6 days of HAL treatment; P=0.948, compared to control group). HAL lost the ability in stimulating dopamine response in the PFC (P=0.007, compared to 6 days of HAL treatment; P=0.342, compared to control group), and was stimulating dopamine in the CPu (P<0.007, compared to 6 days of HAL treatment and to control group). Finally, 14 days of HAL treatment were now blocking the dopamine response in the NAcc to novelty (P=0.001). This effect was accompanied by a stimulation of dopamine in the PFC in the novelty condition (P=0.004, compared to control group) but not by food (though there was a trend).

Discussion: We conclude that chronic treatment with a clinically effective dose of haloperidol modified behavioural responses and also changed the dopamine responses to unconditioned salient stimuli dynamically in a region-specific, task dependent manner. These findings could be helpful in understanding the mechanisms of action and failure of antipsychotic drugs.

doi:10.1016/j.schres.2010.02.434

Poster 207
MATERNAL LIPOPOLYSACCHARIDE ADMINISTRATION LEADS TO DEVELOPMENTAL ALTERATIONS IN HIPPOCAMPAL NEURONAL DENSITY AND EXPRESSION OF CORTICAL DOPAMINERGIC RECEPTORS IN RAT OFFSPRING

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Background: A considerable number of epidemiological studies suggest that exposure to prenatal infection is an important risk factor for developmental neuropsychiatric disorders such as schizophrenia. Administration of viral and bacterial agents to rodents during pregnancy has been reported to result in a number of behavioral and cognitive deficits relevant to neuropsychiatric disorder in the offspring. In a rat prenatal bacterial infection model, maternal administration of lipopolysaccharide (LPS) leads to abnormal dopamine mediated behaviors such as decreased prepulse inhibition of startle (PPI) and enhanced amphetamine induced locomotion. Using the same model we have found that prenatal LPS treatment induces significant changes in the cytoarchitecture of pyramidal neurons in the hippocampus and the prefrontal cortex (PFC) of juvenile and adult offspring (e.g. dendritic arbor, dendritic length and spine density)(Baharnoori et al., 2009). In the present study, we further characterized neuronal changes in the hippocampus and the PFC and tested the hypothesis that these changes may affect developmental expression of mesolimbic and cortical dopaminergic receptors. Accordingly, we examined the density of mature neurons in hippocampus CA1 region and the medial PFC and assessed the developmental expression of dopamine D1, D2 and D3 receptors at pre and post puberal ages.

Methods: 100 µg/kg LPS (ip) or saline were administered to pregnant Sprague-Dawley rat twice at E15 and E16. For neuronal counting, the brains of offspring at P35 and P60 were perfused with 4% PFA and processed for immunohistochemistry using NeuN, the specific antibody for mature neurons. Cell counting was done in the PFC and hippocampus CA1 regions using stereology method followed by volume measurement (Stereoinvestigator, Microbrightfield). The levels of the dopamine receptors were examined by autoradiographic study at the level of PFC, striatum, nucleus accumbens core and shell. We used [3H] SCH23390, [3H]YM-
Poster 208
REPEATED PHENCYCLIDINE (PCP) INCREASES IMPULSIVITY IN THE 5-CHOICE CONTINUOUS PERFORMANCE TEST IN RATS

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Background: Along with the positive and negative symptoms associated with schizophrenia, the disorder also results in a number of cognitive impairments which include attentional dysfunction and executive function impairments such as behavioural disinhibition, which manifests itself as an increase in impulsivity. We have consistently demonstrated that sub-chronic Phencyclidine (PCP) reliably produces cognitive impairments in rodents of relevance to schizophrenia and as outlined in MATRICS (matrics.ucl.ac.uk). Attention and behavioural inhibition can be assessed in rodents using the 5 Choice Serial Reaction Time Task (5-CSRTT), where the animal is trained to report the detection of a brief presentation of light for a food reward. Impulsivity is measured by the number of premature responses made. The original 5-CSRTT is essentially a go-task, where the animal must respond to the stimulus in order to make a correct response. The 5 Choice Continuous Performance Test (5C-CPT) is an adaptation of the traditional 5-CSRTT, but also includes no-go trials in which a correct response is made when the animal withholds from responding, therefore assessing the ability of the animal to not only inhibit from incorrectly responding, but also to discriminate between the go and no-go trials.

Methods: 11 Female Hooded-Lister rats were trained in the 5C-CPT until a stable level of performance was achieved (>75% accuracy, <25% omissions and >65% correct rejections) for 3 consecutive days. The stimulus duration (SD) was 750ms, the variable ITI had a mean duration of 5 s and following the presentation of the stimulus the animal had 2 s to make a response (Limited Hold). The No-go trials consisted of all 5 apertures lighting up, the animal must correctly reject the stimulus by withholding its response for the duration of the LH. Correct responses in both go and no-go trials resulted in presentation of a food reward, incorrect responses resulted in a 5 s time out (TO), house light illuminates but no food pellet is delivered. The session lasts for either 30 minutes or 120 trials, whichever comes first. The animals were dosed using a repeated PCP regime adapted from Amitai et al., (2007) in which the animal received 5 consecutive doses of saline, followed by 5 consecutive doses of PCP (2.5 mg/kg, i.p.) and performance in the 5C-CPT was assessed 30 minutes following each dose.

Results: Along with dysfunction in attention, repeated PCP resulted in robust impairments in behavioural inhibition. Compared to baseline performance, PCP treatment resulted in a significant increase in premature responding (p < 0.05) where the animal made inappropriate responses during the ITI. This was coupled with a significant reduction in number of correct rejections made when presented with the no-go trial (p < 0.05). When signal detection analysis was employed it revealed that PCP treatment resulted in a significant increase in the false alarm rate (p < 0.05) and significant reduction in the sensitivity index (p < 0.05) which indicates that animals cannot distinguish between the go and no-go trials.

Discussion: These data indicate that rats can be successfully trained to carry out the 5C-CPT and discriminate between the go and no-go trials to a predetermined level of performance. Secondly, repeated PCP treatment results in impairments in executive function which include behavioural disinhibition. This is analogous to performance by schizophrenia patients in the human CPT, showing translational properties of the deficits in 5C-CPT induced by PCP.

doi:10.1016/j.schres.2010.02.435

Poster 209
NEONATAL TREATMENT WITH METHYLAZOXYMETHANOL ACETATE (MAM) AS A NEURODEVELOPMENTAL MODEL OF SCHIZOPHRENIA: BEHAVIORAL, PHARMACOLOGICAL AND MORPHOLOGICAL CHARACTERIZATION

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Background: Genetic factors and early environmental insults during development are associated with higher risk of schizophrenia. Additionally, morphological changes in the brain of schizophrenia patients support the idea of a neurodevelopmental theory of the disease. Prenatal treatment to rats with methylazoxymethanol acetate (NAM) has been proposed as a neurodevelopmental model of schizophrenia. MAM disrupts embryonic development, which subsequently manifests during adulthood with behavioral deficits that mimic different symptom clusters of the disorder (positive, negative symptoms and cognitive deficits) and neuroanatomical changes relevant to schizophrenia. The goal of the study was to assess the behavioral, pharmacological and morphological changes in MAM-exposed rats as a disease-model for schizophrenia with potential value for the discovery of novel treatments and to further evaluate the
feasibility of translating the imaging biomarkers into findings in schizophrenic patients.

**Methods:** MAM (25 mg/kg, i.p.) or saline was given to pregnant Sprague Dawley rats on gestational day 17. After birth, the litter was weaned and separated by gender at postnatal day 21 (PD21). Behavioral testing of MAM-exposed rats included locomotor activity, locomotor activity following a challenge with MK-801, Y-maze, cross-maze and social interaction. Pharmacological characterization of the model was also assessed. Imaging studies employed T2-weighted, manganese-enhanced MRI (MEMRI) and diffusion tensor imaging (DTI) to investigate cytoarchitectural and morphological changes in MAM-exposed rats.

**Results:** A gender comparison analysis using locomotor activity, social interaction and Y maze reproducibly revealed more robust behavioral deficits in female than male MAM-exposed rats. Female MAM-exposed rats showed spontaneous locomotor hyperactivity in a novel arena, increased locomotor hyperactivity in response to MK-801, deficits in social interaction, and decreased spontaneous alternation in the cross maze. Locomotor hyperactivity was seen as early as PD45 and remained into adulthood, suggesting that at least some of the symptomatic behavioral changes are expressed early in life. Tested in adulthood, locomotor hyperactivity and social interaction deficits were normalized with clozapine. Moreover, clozapine and the GlyT1 inhibitor SSR504734, but not the typical antipsychotic haloperidol, were able to normalize the social interaction deficits in MAM-rats. MAM-exposed rats exhibited reduced brain weight without significant changes in body weight and exhibited neurohistological abnormalities in CA3, CA2 and medial prefrontal cortex. Imaging data revealed enlarged lateral and third ventricles in MAM-exposed rats in both adolescents (PD45) and adults. Manganese-enhanced MRI, used to assess neuroarchitecture and integrity of neuronal transport, showed decreased hippocampal volume and reduced signal enhancement at ventricles in MAM-exposed rats. Taken together, these findings replicate the pathological findings reported in schizophrenia.

**Discussion:** These data advance the understanding of behavioral, morphological and neuroanatomical changes in MAM-exposed rats and further demonstrate the construct validity of the model. In addition, this study supports the idea of a potential and relevant disease-model of schizophrenia that can be valuable as a tool to study novel treatment approaches for the disorder. Funded by Abbott Laboratories.

doi:10.1016/j.schres.2010.02.437

**Poster 210**

**ENHANCED SYNAPTIC PLASTICITY AT HIPPOCAMPAL OUTPUT SYNAPSES IN THE MK-801 MODEL OF PSYCHOsis**

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**Background:** Phencyclidine and other non-competitive antagonists of N-methyl-d-aspartate (NMDA) receptors as MK-801 induce psychotic effects in humans that closely mimic positive, negative and cognitive symptoms of schizophrenia. Some of these symptoms can be reproduced in the MK-801 animal model of psychosis. In the present study, we investigated whether these phenomena go along with changes in hippocampal synaptic plasticity.

**Methods:** 3 to 5 weeks old Wistar rats received a single intraperitoneal injection of MK-801 (5 mg per kg body weight) or vehicle and their behavior was monitored and scored. 24 hours later, combined entorhinal-hippocampal brain slices were obtained and intracellular recordings were performed in an interface chamber using sharp microelectrodes. Induction of long-term potentiation (LTP) was studied in all subregions of the hippocampus.

**Results:** Rats treated with MK-801 showed severe behavioral alterations which disappeared within 24 hours. Using a high frequency stimulation protocol that was sub-threshold to induce LTP in control rats resulted in a robust late-onset LTP at CA1-subiculum synapses but failed to induce LTP in the dentate gyrus and hippocampal areas CA3 and CA1. This LTP was blocked by the D1/D5-dopamine receptor-antagonist SCH23390, could be mimicked by application of the specific D1/D5-dopamine receptor-agonist SKF38393 and was independent of metabotropic glutamate I/II and NMDA receptors. Analysis of paired-pulse facilitation indicated a presynaptic expression mechanism.

**Discussion:** In the MK-801 model of psychosis we observed a D1/D5-dopamine receptor-dependent facilitation of LTP selectively at hippocampal CA1-subiculum synapses. The subiculum is the major output structure of the hippocampus and plays a key role in the information processing from the hippocampus to the ventral tegmental area (VTA). Hence, we propose that the facilitated synaptic plasticity may contribute to psychotic symptoms that have been attributed to alterations in the hippocampus-VTA loop.

doi:10.1016/j.schres.2010.02.438
Results: Male and female offspring born to immune-challenged mothers displayed long-term deficits in social interaction and anhedonic behavior in the sucrose preference test. In addition, male but not female offspring born to immune-challenged mothers displayed cognitive inflexibility as indexed by the presence of abnormally enhanced latent inhibition in associative learning. Prenatal immune activation in late gestation also led to numerous, partly sex-specific changes in basal neurotransmitters levels, including reduced dopamine and glutamate contents in the prefrontal cortex and hippocampus, as well as reduced GABA and glycine contents in the hippocampus and prefrontal cortex, respectively.

Discussion: Our experimental findings demonstrate that prenatal immune activation in late pregnancy in mice produces a set of behavioral, cognitive and neurochemical abnormalities which are related especially to the negative and cognitive symptoms of schizophrenia.

doi:10.1016/j.schres.2010.02.439

Poster 212
REPEATED ADOLESCENT RESTRAINT STRESS TRIGGERS ENHANCED ANXIETY-RELATED BEHAVIOUR AND PPI DEFICITS ON HETEROZYGOUS NEUREGULIN 1 MICE

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Background: Stress has been proposed to trigger schizophrenia in genetically vulnerable individuals. A leading candidate for genetic susceptibility to SCZ is Neuregulin 1 (Nrg1). The present study utilised an Nrg1 heterozygous (HET) mouse model of SCZ to examine whether repeated stress during adolescence, a period of increased vulnerability to psychosis, could accelerate or accentuate the SCZ phenotype of Nrg1 HET mice which typically occurs at 5–6 months of age.

Methods: Adolescent Nrg1 HET and WT mice were subjected to 30 min restraint stress or no stress, daily for 14 days. On days 1 and 14, immediately after stress exposure, animals were first tested in animal models of anxiety (elevated plus maze then light-dark emergence test) before being assessed for changes in sensory motor gating as measured in the prepulse inhibition (PPI) paradigm. Following 14 days of stress exposure, animals were then tested stress-free on days 28 and 42 in the open field and PPI test.

Results: Restraint stress did not affect anxiety-related behaviour or PPI on day 1 in either WT or Nrg1 HET mice. While 14 days of repeated stress exposure initially increased anxiety-related behaviour in both genotypes, a more prolonged anxiety reaction was observed in Nrg1 HET compared to WT mice. Furthermore, only repeatedly stressed Nrg1 HET mice showed a deficit in PPI. This PPI deficit was only transiently-induced under the influence of stress, as by day 28 and 42 of testing, these animals showed no sign of hyperactivity or PPI deficits. Hence, at least by 11 weeks of age, adolescent stress had not triggered the typical Nrg1 HET phenotype.

Discussion: Partial deletion of Nrg1 confers greater vulnerability to stress-induced anxiety-related behaviour and attentional dysfunction. The impact of stress on Nrg1 HET mice appeared transient and did not trigger an earlier expression of the SCZ phenotype in these animals.

doi:10.1016/j.schres.2010.02.440

Poster 213
UNDERSTANDING THE ADVERSE SIDE-EFFECTS OF ANTIPSYCHOTIC DRUGS WITH THE USE OF A PRECLINICAL MODEL

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Background: Numerous studies on the therapeutic use of atypical antipsychotic drugs are associated with metabolic adverse side-effects. The defining characteristics of metabolic syndrome are glucose intolerance, hyperglycemia, insulin resistance and hyperlipidemia, and these metabolic indices are also profoundly disturbed in patients treated with atypical antipsychotics. The purpose of the present series of experiments was to therefore evaluate the acute effects of both a low and high dose of four antipsychotic drugs in a rodent model and to provide novel insight into the plausible mechanisms of action, specifically for glucose intolerance.

Methods: In order to verify the acute nature of metabolic effects, naive adult female Sprague-Dawley rats were randomly assigned to 1 of 6 treatment groups (olanzapine (15 mg/kg-i.p) – high dose propranolol; olanzapine – low dose propranolol; olanzapine – saline (vehicle 2); PEG (vehicle 1) – high dose propranolol; PEG (vehicle 1) – low dose propranolol and PEG – saline) followed by an intraperitoneal glucose tolerance test (IGTT) 60 minutes after injection. Fasting blood samples after challenge treatment were collected and stored prior to the glucose load. This protocol was repeated using two other adrenergic blockers, yohimbine and prazosin. In a separate cohort of rats, the four antipsychotics were administered at both a low and high dose followed by blood extractions at baseline, 30, 60, 120 and 180 minutes after treatment injection. Further analysis of plasma samples was conducted with the use of high performance liquid chromatography (HPLC).

Results: The analysis indicated that antipsychotic drugs modulate levels of peripheral monoamines in a dose and time dependent manner. When particular types of adrenergic receptors were pharmacologically blocked, both fasting and non-fasting levels of glucose were changed, and there was a downward trend towards control.

Discussion: The present series of experiments evaluated the acute effects of antipsychotics, pertaining to the adrenergic system, on a number of different metabolic indices related to glucose metabolism in adult female rats. Antipsychotic drug-induced changes in peripheral monoamines, E and NE, and their coinciding receptors may present an important pathway into why glucose dysregulation and insulin disturbances occur. Summary: Evaluation of antipsychotic-induced metabolic side-effects with respect to the acute administration of both a low and high dose of clozapine (2; 20 mg/kg), olanzapine (1.5; 15 mg/kg), risperidone (0.25; 2.5 mg/kg) and haloperidol (0.1; 1.0 mg/kg) were conducted in a rodent model. Further assessment was conducted utilizing assays to detect epinephrine (E) and norepinephrine (NE) concentrations within the plasma. Both fasting and non-fasting levels of glucose were recorded with respect to the administration of adrenergic α and β blockers (yohimbine (0.5, 5 mg/kg), prazosin (0.2, 2 mg/kg) and propranolol (2, 20 mg/kg)). Peripheral monoamines, specifically E and NE, and adrenergic receptors, play a pivotal role in antipsychotic drug-induced glucose dysregulation.

doi:10.1016/j.schres.2010.02.441
**Poster 214**

**ATTENTIONAL PERFORMANCE OF DVD-DEFICIENT RATS IN THE 5-CHOICE CONTINUOUS PERFORMANCE TEST**

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**Background:** Evidence from epidemiology suggests that low levels of vitamin D during gestation alter brain development and may increase the risk of various adverse health outcomes, including schizophrenia. The aim of this experiment was to examine the effect of developmental vitamin D (DVD)-deficiency on attentional processing using the 5-choice continuous performance test (5C-CPT), which specifically assesses sustained attention and vigilance in rodents.

**Methods:** Adult (6 month old) control and DVD-deficient Sprague Dawley rats were trained to respond to brief pulses of light within an operant chamber by poking their nose into one of 5 holes to receive a food reward. During testing the rats were exposed to a series of signal and non-signal events within the same session. There were a number of measures recorded including hit, miss, false alarm and correct rejection, as well as premature and perseverative responses. At the end of behavioural testing brain tissue was collected from prefrontal cortex (PFC) and striatum and assessed for levels of dopamine, serotonin and glutamate using HPLC.

**Results:** DVD-deficient rats had significantly increased levels of impulsivity, which was demonstrated by an increase in premature responses. On the signal trials the percent accuracy was not significantly affected by prenatal diet. However, DVD-deficient rats made 50% fewer correct rejections, compared to controls, on non-signal trials. Thus, control rats were able to discriminate between signal and non-signal trials, whereas DVD-deficient rats were unable to make this discrimination. The levels of glutamate were significantly reduced in the striatum, but not PFC, from DVD-deficient rats. There were no significant effects of maternal diet on the levels of dopamine or serotonin in either brain region.

**Discussion:** Taken together these data suggest DVD-deficient rats have enhanced impulsivity as well as a lack of inhibitory control. The data are consistent with the hypothesis that glutamate signalling within the striatum is important under conditions in which a new response pattern is acquired while inhibiting a previously learned response pattern. Thus, the DVD-deficient rat model may be informative in terms of modeling the cognitive deficits seen in schizophrenia.

**doi:**10.1016/j.schres.2010.02.442

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**Poster 216**

**THE MGLUR2/3 AGONIST LY379268 MODULATES KETAMINE-INDUCED BOLD FMRI IN AWAKE RATS: UTILITY AS A PHARMACODYNAMIC BIOMARKER?**

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**Background:** Glutamate has been implicated in the pathophysiology of schizophrenia. The main evidence for this hypothesis relates to the ability of N-methyl-D-aspartate (NMDA) channel blockers such as phencyclidine (PCP) or ketamine to induce symptoms that mimic psychosis in healthy volunteers and to exacerbate symptoms in schizophrenic patients (Lathi et al., Neuropsychopharmacology, 2001). Also, intriguingly, ketamine-induced psychosis recapitulates the symptoms of schizophrenia better than amphetamine challenges. It is noted that ketamine produces negative BOLD (blood oxygenation level dependent) fMRI signals in brain regions associated with dissociative effects, as well as positive BOLD signals in temporal cortical regions that are exacerbated in schizophrenic patients (Deanik JW et al., Arch Gen Psych, 2008). In this study, we investigated the brain activities elicited by the infusion of a subanesthetic dose of ketamine using BOLD fMRI in awake rats. Further, the effect of metabotropic glutamate2/3 receptor (mGluR2/3) agonists on the ketamine-induced brain activations was also characterized. Finally, region-of-interest (ROI) analysis was performed to determine average BOLD signal changes at specific brain regions relevant to the behavioral deficits.

**Methods:** Male adult SD rats were imaged while awake. To reduce the stress, rats were habituated to a dedicated animal holder that accompanies psychosis.

**doi:**10.1016/j.schres.2010.02.443
is integrated within the RF coil system for imaging (Chin CL et al, Synapse 2008). Experiments were carried out on a 7 T Bruker MRI scanner using a SE-EPI sequence for data collection [baseline (10-min) – drug infusion (2-min) – post-drug (30-min)]. Rats were pretreated with either vehicle or LY379268 at10 mg/kg ip approximately 35 min prior to the infusion of saline or ketamine at 30 mg/kg ip inside the magnet. To calculate the brain activation maps (z-score), data analyses were done using AFNI. In addition, regional BOLD signal changes were obtained from each animal and statistical analysis was conducted to examine the drug effect between groups.

**Results:** Ketamine elicited strong positive BOLD signals in cingulate (CC) and retrosplenial cortices (RSC), whilst modest activation was observed in frontal, auditory, and visual cortices as well as hippocampus (HIP). Conversely, negative BOLD signals were found in inferior colliculus and periaqueductal gray. Moreover, compared to vehicle-pretreated rats, ROI analyses reveal that LY379268 significantly blocked ketamine-induced brain activities in posterior CC, RSC, CA1 of HIP (p < 0.01) as well as entorhinal cortex (p < 0.05). Finally, negative BOLD signals were found in visual cortex from rats challenged with LY379268 alone.

**Discussion:** We have demonstrated that ketamine specifically activated brain regions ascribed to short and long term memory processes. These activities can be blocked by the pretreatment of LY379268, supporting the notion that mGluR2/3 agonists might provide beneficial effects for schizophrenia. Of note, our results are in contrast to the data obtained from anesthetized rats, where LY354740 (mGluR2/3 agonist) appeared to normalize PCP-induced rCBV increases at most cortical regions (Gozzi A et al., Neuropsychopharmacology, 2008). Further, these findings are consistent with the modulatory effect of ketamine on frontal and hippocampal activations observed in human fMRI studies (Honey GD et al., Cerebral Cortex, 2005). Our data depict the involvement of memory circuitry in ketamine-treated awake rats and may have utility as a translational tool to study cognitive deficits of schizophrenia, though this remains to be validated.

doi:10.1016/j.schres.2010.02.444

**Poster 217**

A LONGITUDINAL EXAMINATION OF THE NEURODEVELOPMENTAL IMPACT OF PRENATAL IMMUNE ACTIVATION IN MICE REVEALS PRIMARY DEFECTS IN DOPAMINERGIC DEVELOPMENT RELEVANT TO SCHIZOPHRENIA

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**Background:** Prenatal exposure to infection is a significant environmental risk factor in the development of schizophrenia and related disorders. Recent evidence indicates that disruption of functional and structural dopaminergic development may be at the core of the developmental neuropathology associated with psychosis-related abnormalities induced by prenatal exposure to infection. Using a mouse model of prenatal immune challenge by the viral mimic polyribosinonic-polyribocytidilic acid (Poly-I:C), the present study critically evaluated this hypothesis by longitudinally monitoring the effects of maternal immune challenge during pregnancy on structural and functional dopaminergic development in the offspring from fetal to adult stages of life.

**Methods:** Pregnant C57BL/6 dams on gestation day (GD) 9 received either a single injection of Poly-I:C (5 mg/kg) or saline solution via the intravenous route at the tail vein under mild physical constraint. Post-mortem brain tissue of fetal (GD19), peri-pubertal (postnatal [PND] 35) and adult (PND70) offspring was processed for immunohistochemical analyses of dopaminergic markers, including tyrosine hydroxylase (TH), dopamine transporter (DAT) dopamine D1 and D2 receptors (D1R and D2R) and the dopamine-related transcription factor Nurr1. In addition, behavioral and pharmacological tests were conducted in peri-pubertal and adult offspring in order to assess the impact of altered dopaminergic development on dopamine-dependent functions.

**Results:** Prenatal immune challenge led to dopaminergic maldevelopment starting as early as in the fetal stages of life and produced a set of mesolimbic and nigrostriatal dopaminergic abnormalities that is dependent on postnatal maturational processes. Furthermore, our longitudinal investigations revealed a striking developmental correspondence between the ontogeny of specific dopaminergic neuropathology and the postnatal onset of distinct forms of dopamine-dependent functional abnormalities such as disruption of prepulse inhibition and altered sensitivity to the dopamine-receptor agonist amphetamine and apomorphine.

**Discussion:** Prenatal immune activation appears to be a significant environmental risk factor for primary defects in normal dopaminergic development and facilitates the expression of postnatal dopamine dysfunctions involved in the precipitation of psychosis-related behavior. Early interventions targeting the developing dopamine system may open new avenues for a successful attenuation or even prevention of psychotic disorders following neurodevelopmental disruption of dopamine functions.

doi:10.1016/j.schres.2010.02.445

**Poster 218**

PREDICTORS OF SUCCESSFUL PARTICIPATION IN PEER SUPPORT GROUPS FOR PSYCHOSIS

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**Background:** What makes a peer support group successful from the perspective of the participants? In other words, what do people in these groups experience as active ingredients necessary to make it a useful intervention? Studying the effectiveness of minimal guided peer support groups (GPSGs) for psychosis (Castelein et al., 2008), the question rose as why some people gain by participating in such groups whilst others are less satisfied and do not find what they came for. In this study, the aim is to find the predictors of successful participation in peer support groups for psychosis by studying the influence of active ingredients and attainment of goals.

**Methods:** The subjects (n = 56) participated in a controlled trial on the effectiveness of peer support groups. The closed peer support group included approximately 10 patients and involved 16 sessions of 90 min biweekly over 8 months. Patients were interviewed after the last group meeting at 8 months about attainment of goals like ‘more knowledge about the problems and treatment of others’ and on the active ingredients of the intervention in terms of recognition and self-expression and social support. Additionally, the predictive value of group adherence, and group atmosphere as well as clinical characteristics of the subjects was investigated.

**Results:** The intervention was most successful in improving the information on and insight into each other problems (76-82%).
Statistically significant correlations were found between goal attainment and group atmosphere ($r = .422, p = 0.003$), recognition and self-expression ($r = .754, p = .000$), social support ($r = .546, p = .000$), and adherence ($r = .379, p = .008$). Clinical characteristics such as duration of illness and number of psychotic episodes, were not associated to goal attainment. Next, a multivariate regression analysis of these four variables showed that ‘recognition and self-expression’ appeared to be the only predictor of goal attainment ($p < .001$). This ingredient did account for $63\%$ of the variation in the total effect score. Notably, of all items of active ingredients the recognition that they were not the only ones with these problems was perceived as most helpful ($81\%$).

**Discussion:** The most important predictor was the dimension of ‘Recognition and self-expression’ enabling participants to share experiences and to learn from other peers. This refers directly to the concept of referent power. According to many professionals, people with a severe mental disorder, such as a psychotic disorder, have no need for such peer support (Davidson et al., 1999) and are unable to offer each other useful support (Davidson et al., 2006). Also, group treatment is seen as a not viable option for this patient group (Mead & Copeland, 2000). Yet, our study clearly demonstrates that the GPS-G intervention enables people with psychosis to benefit from referent power when exerted in a pleasant group atmosphere. This study gives some support to a more optimistic point of view about the value and effectiveness of peer support groups for psychosis.

doi:10.1016/j.schres.2010.02.446

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**Poster 219**

**EXPECTANCY THEORY AND LEARNING PERSISTENCE IN SCHIZOPHRENIA**

**Alice Medalia**

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**Background:** Amotivation is a significant hallmark of negative symptomatology in schizophrenia, and it impacts nearly every facet of behavior, including inclination to attempt the demanding cognitive tasks involved in cognitive remediation therapy. Experiences of external reward and hedonic anticipatory enjoyment are diminished in psychosis, so therapeutics which instead target motivation for cognitive tasks may enhance task engagement, and subsequently, remediation outcome. Expectancy Theory posits that expectations of success on a learning task are a central determinant of motivation to learn. This is supported by research in healthy controls that found beliefs of self-and-content mastery can be so influential they can delineate the degree of improvement on challenging cognitive tasks even more so than general cognitive ability.

**Methods:** We examined motivational constructs, symptoms, and neuropsychological performance as possible predictors of outcome in a cognitive remediation sample of 70 outpatients with schizophrenia.

**Results:** Results showed that baseline expectations of success as measured by the Perceived Competency Scale (PCS), a self report instrument that gauges how competent people perceive themselves to be with respect to a learning task, predicted greater learning from cognitive remediation at post, even after variance attributable to baseline cognitive ability, symptoms, and self reports of task anxiety and enjoyment were accounted for ($β = .39, t = 2.15, p = .038$). The effects were still evident at 3 month follow-up, where high PCS scores following treatment was the only variable significantly related to persistence of learning effects (odds ratio $4.10, \chi$-square $= 36.14, p = .008$). That is, subjects with high reports of self competency after treatment were 4 times as likely to retain what was taught during cognitive remediation even after 3 months.

**Discussion:** The findings in this study support the notion that expectancy theory is operative in schizophrenia. Thus, similar to the non-psychiatric population, treatment benefits may be enhanced and better maintained if remediation programs also focus on perceptions of competency for the training tasks. Treatment issues related to instilling self efficacy in cognitive recovery programs will be discussed.

doi:10.1016/j.schres.2010.02.447

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**Poster 220**

**Poster not available**

doi:10.1016/j.schres.2010.02.448

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**Poster 221**

**DEEP BRAIN STIMULATION OF THE MEDIODORSAL THALAMIC NUCLEUS AND ITS IMPLICATIONS FOR THE TREATMENT OF SCHIZOPHRENIA**

**Samuel G. Ewing, Judith A. Pratt**

*University of Strathclyde Glasgow, Scotland, United Kingdom*

**Background:** Whilst antipsychotic drugs treat the positive symptoms associated with schizophrenia they have limited effects against the negative symptoms and cognitive deficits. Here a deep brain stimulation (DBS) strategy analogous to that used in Parkinson’s disease is proposed. Methods for the validation of this strategy in a phencyclidine (PCP) rat model of schizophrenia are described. Given the weight of evidence implicating disruption of the thalamo-cortical system, particularly the mediodorsal thalamic nucleus (MD) and prefrontal cortex (PFC), studies have focussed on investigation of the consequences of high frequency stimulation of the MD. Results are reported in terms of spectral analysis of the electrocorticogram (ECoG) and the expression of the immediate early genes (IEGs) *zif-268* and *c-fos*.

**Methods:** In the study concerning the expression of IEGs, custom made bipolar stimulating electrodes were implanted bilaterally into the MD of isoflurane anaesthetised rats. Stimulation was delivered unilaterally to either the right or left MD whilst the contralateral hemisphere served as a control. High frequency stimulation stimulation (Frequency, 130 Hz; Amplitude, 200 µA; Pulse Width, 100 µs) was delivered for 3 hours via a custom designed and made deep brain stimulation device. Brains were then removed, sectioned and radio labelled for the immediate early genes *zif-268* and *c-fos* before being exposed to X-ray film for 8 days. The relative optical density of the resultant autoradiograms were analysed with MCID, a computer based optical densitometer. In the study concerning the spectral analysis of the ECoG, custom made bipolar stimulating electrodes were implanted bilaterally into the MD of rats treated sub-chronically with PCP (2.6 mg/kg for 5 days, 3 day washout) or saline. Animals were anaesthetised with isoflurane and 7 screw electrodes were implanted in the skull overlying the cortex of the left hemisphere and one in the skull overlying the cerebellum. Differential ECoG recordings were made between the 7 cortical electrodes and the cerebellar electrode. Baseline ECoG recordings were made for 30 minutes before delivering high frequency stimulation (Frequency, 130 Hz; Amplitude, 200 µA; Pulse Width, 100 µs) for 1 hour via a custom designed and made deep brain stimulation device. A bipolar montage was derived by subtracting the signals from adjacent electrodes. The power spectra of the derived signals was computed using Fourier methods and the absolute
band power computed for the delta (1-4 Hz) and theta bands (4-8 Hz). In addition the coherence between electrodes was computed in the delta and theta bands.

**Results:** In isoflurane anaesthetised rats DBS of the MD produced robust increases in the expression of zif-268 but not c-fos localised to the efferent targets of the MD, indicating an increase in neural activity in the PFC. Increases in frontal delta power and parietal theta power were demonstrated in PCP treated animals when compared with saline treated controls. Furthermore PCP treated animals exhibited increased delta coherence at frontal electrode locations and reduced theta coherence at parietal/somatosensory electrode locations. High frequency stimulation of the MD yields transient increases in delta and theta power at frontal electrode locations.

**Discussion:** Impairment in the ability to recruit the prefrontal cortex is frequently reported in schizophrenia. The results of these experiments demonstrate activation of frontal cortical regions as a consequence of deep brain stimulation of the MD. Furthermore quantitative analysis of the ECoG demonstrates a spectral profile, in rats treated sub-chronically with PCP, similar to that seen in schizophrenic patients.

**Methods:** 
- **Participants:** 100 schizophrenia patients (31-40) Quetiapine vs typicals 6 36% (34-39) Olanzapine vs typicals 18 30% (28-32) Zotepine vs typicals 7 36% (31-40) Quetiapine vs typicals 6 36% (34-39) Olanzapine vs typicals 18 30% (28-32) Zotepine vs typicals 7 36% (31-40)
- **Sampling frame:** A single question regarding loss to follow up in a schizophrenia trial.
- **Methods:** Postal/e-mail survey – March 2007 - Piloted questionnaire asking a single question regarding loss to follow up in a schizophrenia trial. Sampling frame – all 128 consultant psychiatrists in General Psychiatry from the Yorkshire Deanery; 100 trialists in schizophrenia whose e-mail is publicly available; 100 service users and carers chosen by RETHINK – a UK-based mental health charity and service provider.

**Results:** Response rate of clinicians was poor (55/128, 43%), as was that of researchers (32/100, 32%). Carers/consumers return rate was high (81/104, 76%). All three groups, however, suggested that follow up at the end of a 12 week schizophrenia drug trial should be around 70-75% to be credible. Loss to follow up in widely used studies is often outside this limit of credibility (Table 1.)

**Background:** 
- There is variable attrition from randomised controlled trials (RCTs) evaluating treatments for people with schizophrenia.
- Although statistical assumptions can be made to compensate for attrition and the effects of these assumptions tested, it is unclear at what degree of loss from such studies clinicians, researchers and service users or their carers begin to consider results meaningless.

**Methods:** 
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**Results:** Response rate of clinicians was poor (55/128, 43%), as was that of researchers (32/100, 32%). Carers/consumers return rate was high (81/104, 76%). All three groups, however, suggested that follow up at the end of a 12 week schizophrenia drug trial should be around 70-75% to be credible. Loss to follow up in widely used studies is often outside this limit of credibility (Table 1.)

**Table 1. Total lost to follow up by about 12 weeks in drug trials (source data Cochrane reviews)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-up Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine vs typicals</td>
<td>36% (34-39)</td>
</tr>
<tr>
<td>Olanzapine vs typicals</td>
<td>30% (28-32)</td>
</tr>
<tr>
<td>Zotepine vs typicals</td>
<td>36% (34-39)</td>
</tr>
</tbody>
</table>

**Discussion:** 
- The single variable that undermines the credibility of outcomes in most studies. Currently clinicians, policy makers and consumers of care have to come to decisions about treatments based on information that is, in their eyes, of questionable credibility. It would seem that stakeholders in this area could collaborate to help researchers evolve techniques for acquiring more complete and relevant datasets.

**Results:** 
- A non-adherence rate of 50% was determined, therefore 50% of patients had a compliance ratio <70%.

**Discussion:** This device's strong points are: evaluation, communication, organization and precision. It has the advantage of being able to track adherence daily, sending a signal to the pharmacist who is able to contact the patient. Our preliminary results are concordant with the literature and suppose that DoPill is a valid tool that could provide objective data for the clinician about his/her patient's compliance.

**Methods:** 
- **Participants:** 60 patients with schizophrenia who used DoPill for a period of 6 weeks. There are 28 squares on DoPill that can be individually programmed at a specific regimen time, allowing DoPill to beep and flash at the appropriate time of the day. A plastic lamina covers each square and when taken off, sends a signal to the research team and pharmacist. We assume that the patient has taken his or her medication at this moment. DoPill registers the adherence ratio (pills taken/pills given). Good adherence was evaluated as ≥70%.

**Results:** 
- 52% (n=52) and 48% (n=25) of patients were non-adherent. (Acosta et al., 2002)

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Poster 224
CLINICAL HIGH RISK FOR PSYCHOSIS: THE RISK OF FALSE POSITIVE
Jean Addington1, Barbara Cornblatt2, Kristin Cadenhead3, Ty Cannon4, Robert Heinssen5, Thomas McGlashan6, Diana Perkins7, Ming Tsuang3, Elaine Walker3, Scott Woods5, Larry Seidman9
1University of Calgary Calgary Alberta, Canada; 2Zucker Hillside Hospital Glen Oaks, New York USA; 3UCSD San Diego, California USA; 4UCLA Los Angeles, California USA; 5NIMH Washington, DC, USA; 6Yale University New Haven, Connecticut USA; 7UNC Raleigh, North Carolina USA; 8Emory University Atlanta, Georgia USA; 9Harvard Boston, MA, USA

Background: There has been increasing interest in the potential for early detection during the prodromal phase of a psychotic disorder. A major focus is on determining the risk of conversion to psychosis and on developing algorithms of prediction. Although there is much variation in the literature on rates of conversion it is always a minority of the samples, i.e. 85% to 50% of putatively prodromal samples do not go on, at least in the duration of the studies (usually one year) to develop psychosis. Little is known about those individuals who have been termed “false-positive”.

Methods: A prospective, longitudinal study with up to 2.5 years of follow-up of 291 prospectively identified treatment-seeking patients meeting Structured Interview for Prodromal Syndromes (SIPS) criteria, were recruited and evaluated across 8 clinical research centers as part of the North American Prodrome Longitudinal Study (NAPLS). Of this sample at one year 78% and at 2.5 years 65% had not made the transition. The sample being studied included 136 individuals who had at least 1 year of follow up, had not made the transition to psychosis within the duration of the study and were not on any antipsychotics.

Results: In the first year there were significant improvements (p<0.0001) in symptoms (SIPS) and in social and role functioning. However, functioning was still significantly poorer (p<0.0001) compared to the normal controls in the sample. Only 23% still met prodromal criteria at one year and in a subsample of 65 only 8% met prodromal criteria at 2 years. At one year attenuated positive symptoms improved in 89%, increased in 7.3% and did not change in 3.6% of the sample. For those who had 2 year follow-ups there were further changes, most of which reflected further improvement. 44% at one year and 38% at two years had at least one attenuated positive symptom. Those who were still symptomatic at their final assessment were older, and had poorer social and role functioning and more symptoms at baseline.

Discussion: Help seeking individuals who meet prodromal criteria appear to fall into 3 groups – those who develop a psychotic illness, those who improve and those who have poor functioning and continue to have some positive symptoms at an attenuated level. In this study there are limitations in terms of the length of follow-up but there are implications for the kinds of treatments we may offer and how we conceptualize those who have a prodromal risk syndrome.

doi:10.1016/j.schres.2010.02.453

Poster 225
WHO Responds to Treatment with Omega-3 Fatty Acid? Findings from an Indicated Prevention Trial in Young People at Ultra-High Risk of Psychosis
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Background: Long-chain omega-3 fatty acids may reduce the risk of progression to psychotic disorder, and offer a safe and efficacious strategy for indicated prevention in young people with subthreshold psychotic states (Amminger et al., Arch Gen Psychiatry, in press). However, it is yet undetermined if cell membrane fatty acid levels predict therapeutic response to omega-3 supplementation in people at ultra-high risk (UHR) of psychosis.

Methods: The study sample comprised 81 UHR individuals (mean age = 16.4, SD = 2.1 years) who participated in a RCT of 1.2 g/day omega-3 fatty acids vs. placebo (ClinicalTrials.gov number, NCT00396643). Erythrocyte membrane fatty acid levels were determined at baseline and 12-week follow-up using gas chromatography. Baseline measures included the PANSS, the MADRS, and the GAF. Treatment response was defined as change in the GAF score between baseline and 12-week follow-up. Data were analysed using T-tests and linear regression models.

Results: 41 individuals were assigned to omega-3 and 40 to placebo. At 12 weeks, the mean (SD) changes in GAF score in the omega-3 group and in the placebo group were 13.7 (11.5) and 7.1 (13.5), respectively (p<0.05). In the omega-3 group a significant increase in functioning was predicted by low trans-vaccenic acid at baseline (p<0.01). This association was not observed in the placebo group. No significant associations were observed between baseline omega-3, omega-6, or omega-9 fatty acid levels and treatment response.

Discussion: The role of fatty acids and lipid metabolism should be further explored in the onset phase of schizophrenia. We have previously shown that low trans-vaccenic acid predicted transition to psychotic disorder in UHR individuals (Amminger et al., 2009). The present findings suggest that low baseline trans-vaccenic acid may be associated with clinical improvement in people treated with omega-3 fatty acids. Lipid metabolism characteristics may not only assist in targeting individuals at highest risk of progression to psychosis, but also help identifying those who may benefit more from an intervention with omega-3 fatty acids.

Poster 226
PREDICTORS OF INSIGHT IN FIRST-Episode Psychosis
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Background: Insight is a variable strongly related to treatment adherence in patients with schizophrenia and particularly important in first episode psychosis patients since it may have implications for outcome. Over the last 20 years there have been an increasing number of studies about causes underlying lack of insight. However, few studies have examined the correlates of insight attending the three accepted insight dimensions (awareness of having a mental illness, appreciation of the need for treatment and awareness of social consequences of illness) separately.

Methods: A sample of 164 patients was studied at early course of psychosis. The abbreviated Scale to Assess Unawareness of Mental Disorder (SUMD) was used to assess the three insight dimensions. The Scale for the Assessment of Negative symptoms (SANS) and the Scale for the Assessment of Positive symptoms (SAPS), the Hamilton Depression Rating Scale (HDRS) and the Disability Assessment Scale (DAS) were used to assess clinical variables. A broad range of test representing neurocognitive domains were evaluated. Patients with good insight were compared to those with poor insight on clinical, cognitive, premorbid and sociodemographic variables in the three dimensions independently. Three logistic regression analyses were conducted to identify explanatory variables independently associated with each insight dimension.

doi:10.1016/j.schres.2010.02.453
Results: The group of poor insight of having a mental disorder presented significantly longer DUP, diagnosis of schizophrenia, and attention deficit, but attention is the exclusive predictor of this insight dimension. The good insight of the need of medication group showed more depression, later age of onset and less disorganized dimension symptoms, being age of onset and disorganized dimension symptoms the variables that predict treatment acceptance. Groups of good vs. poor insight of the social consequence differed in DUP, negative and disorganized symptoms dimension, ADAS, education, diagnosis, and the need of hospitalization, but are the two mentioned symptom dimensions the predictors of this dimension.

Discussion: The three insight dimensions showed different rates of affectation and different correlates when they are independently analyzed. These results suggest that different mechanism should be underlying the lack of insight and encourage us to be very cautious exploring insight deficits. A reformulation of the evaluation of insight based on dimensions' correlates may help better evaluate insight as a relevant clinical outcome measure in psychosis. Our study provides support for the neurobiological hypothesis of insight attending age of onset, negative and disorganized symptom dimensions, and attention as predictors of insight dimensions.

doi:10.1016/j.schres.2010.02.454

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**Poster 227**

DOES THE EARLY COURSE OF COGNITIVE FUNCTION IN FIRST-EPISEDE SCHIZOPHRENIA PREDICT FUNCTIONAL OUTCOME?

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Background: In schizophrenia, the current evidence suggests that a neurodevelopmental process affects intellectual function during childhood and adolescence, prior to the onset of the clinical syndrome. Several studies have reported a relationship between cognition at first-episode, and later functional outcome. However, whether the early course of cognitive function predicts functional outcome of the illness is not clear. We examined the trajectory of cognitive functioning over the first three years of illness and its relationship with both change in social functioning and absolute level of functional outcome.

Methods: Patients with schizophrenia were recruited in the context of the West London first-episode psychosis study, while healthy controls were recruited from the same community. Those that were assessed at baseline and at least one follow-up occasion over three years were included in this study, totalling 226 patients and 70 controls. Patients and controls did not differ on age at first testing but did on premorbid IQ and ratio of males to females. Current IQ was calculated from four subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) or WAIS-III. Memory and executive functions were measured using tests from the Cambridge Automated Neuropsychological Test Battery. Social function was assessed with the Social Function Scale (SFS).

Results: The performance of the patients on measures of cognition was substantially poorer than that of the controls. Over the first three years of illness, despite absolute levels differing, patients and controls were comparable in terms of trajectory on most measures of cognition. Both groups demonstrated improvement in working memory span and planning, presumably due to practice, and no change in performance on working memory manipulation and visual memory tasks. However, there was evidence that patients failed to improve to the same extent as controls on current IQ. Several correlations between baseline cognition and social functioning at three-year follow-up were significant and when the relationship between three-year cognition and three-year functioning was examined, the findings were broadly similar. We found evidence of a relationship between all cognitive measures and occupational activity. Additional relationships were observed between current IQ and interpersonal communication and competence in activities of daily living; visual memory was related to most social functions. However, change in social function over the follow-up period did not correlate with change in any cognitive measure.

Discussion: Cognitive function is stable during the first three years of psychotic illness although some deterioration in cognitive function over this time may be masked by practice effects. Performance on cognitive tasks does predict social functioning in the early years of a schizophrenic illness. But our findings suggest that change in cognition occurring in the three years following the first episode makes no notable impact on later functioning. Rather, absolute cognitive ability is the most important, and is a good predictor by first psychotic episode.

doi:10.1016/j.schres.2010.02.455

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**Poster 228**

PREDICTORS OF REAL WORLD FUNCTIONAL BEHAVIOR IN BIPOLAR DISORDER AND SCHIZOPHRENIA

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Background: Chronic mental disorders are characterized by diversity of symptoms but universally associated with impairments in functioning. Individuals with schizophrenia (SZ) or bipolar disorder (BPD) have associated features of the illnesses (e.g., neurocognition) that are at least as strong as diagnostic symptoms in predicting functional deficits.

Methods: Study participants with BPD (N=87) and SZ (N=108) completed a neurocognitive battery, performed tasks to assess social and adaptive functional capacity, and were rated for positive, negative, and mood symptoms. Third party ratings of functional outcomes were completed. Confirmatory path analyses were performed to examine the direct and mediated predictors of real world functioning. The model was drawn with social and functional skills as potential mediators of functional outcomes and neurocognitive and symptom variables as potential direct or indirect predictors.

Results: Different predictors of real world outcomes were found for the two groups. Community Activities were largely predicted by functional (BPD) or social (SZ) capacity. Positive symptoms directly predicted impairment in these functions in BPD but not SZ. Interpersonal outcomes were predicted by negative symptoms and social capacity, while psychosis and hostility entered the equation only for BPD. Work Skills were predicted by psychotic symptoms for both groups. Severity of negative and depressive symptoms and poor functional capacity predicted work skills for BPD, while social capacity and neurocognition had direct effects on work skills in SZ. Across outcome domains and between diagnostic groups, neurocognition's relationship with outcomes was largely mediated by functional and/or social capacity, while symptom relationships with outcomes were independent of capacity. Positive and negative symptoms were stronger and more consistent predictors of real world impairment in BPD, while neurocognition and capacity drove impairments in SZ.

Discussion: Real world functional impairment is observed in both disorders; differential predictors suggest that efforts to reduce disability will require consideration of both diagnosis and outcome domain.

doi:10.1016/j.schres.2010.02.456
**Poster 229**

**THE KRAEPELINIAN SCHIZOPHRENIA SUB-TYPE: ASSESSMENT OF THE VALIDITY OF THE "5 YEARS" DIACHRONIC CRITERIA**

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**Background:** The Kraepelinian schizophrenia was defined in 1987 by Keefe and al. using a diachronic criteria: 5 years. This sub-group is characterized by a very poor prognosis. Several clinical and biological studies showed differences with good outcome patients regarding pre-morbid functioning, negative and disorganized symptoms, specific cognitive deficits and polyuro-polydipsic syndrome (Bralet et al., 2002, 2006). Studies in neuroimaging (Mitelman and al., 2007, 2009) showed a posteriorization of the deficits in white and grey matter at baseline and the progression of the deficits in grey matter at 4 years among these patients in comparison with good outcome patients. These authors postulate that the kraepelinian schizophrenia may represent a very specific form of schizophrenia or of dementia. But the criteria of duration of 5 years has never been validated. OBJECTIVE: to assess the validity of the criteria of a duration of 5 years to define the kraepelinian sub-type.

**Methods:** We assessed in may 2009 a previous sample of kraepelinian schizophrenic patients recruited from the psychiatric department of Clermont de l’Oise (Picardie area) in 2003 (n=21). These patients were defined as kraepelinian using Keefe’s criteria (1987) by a first psychiatrist. In 2009, the same patients were again assessed using kraepelinian’s criteria by an other psychiatrist.

**Results:** All the 21 patients were still hospitalized in 2009 and so were all kraepelinians.

**Discussion:** this is the study confirming the validity of the longitudinal criteria of 5 years to define the kraepelinian sub-type. This result, according to these in neuroimaging, contribute to the fact that the kraepelinian sub-type may represent a valid and specific form of schizophrenia characterized by a progressive and neurodegenerative evolution or a particular form of dementia. Further longitudinal studies will be conducted to assess the course of the clinical and cognitive symptoms of these patients.

doi:10.1016/j.schres.2010.02.457

**Poster 230**

**PREDICTORS OF RELAPSE AFTER FIRST-EPISTODE PSYCHOSIS DURING A 3-YEAR FOLLOW-UP**

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**Background:** Relapse rates are high in patients with first-episode psychosis (FEP) even in specialized early intervention services. Risk factors associated with relapse have not been properly determined. Our purpose was to identify factors associated with relapse after a first episode of psychosis.

**Methods:** We analyzed sociodemographic and clinical data from a cohort of 174 patients treated in a specialized early intervention service during a 3-year follow up. We performed univariate analyses followed by logistic regression and survival analyses on a sample of patients who responded to treatment after their FEP and were at risk of relapse. The variables analyzed included gender, age of onset, duration of untreated psychosis (DUP), initial ratings on the Scale for Assessment of Positive and Negative Symptoms (SAPS and SANS), premorbid adjustment and social functioning, substance use and adherence to medication.

**Results:** Of the 174 initial patients, 153 responded to treatment after their FEP. We excluded 39 patients, 25 of them lost follow-up and 14 entered prescribed discontinued treatment after two-year follow-up. We found a statistically significant association between rate of relapse and medication non-adherence [odds ratio (OR) 17.11, 95% confidence interval (CI) 4.83-60.55]. The other evaluated factors did not remain in the model. Comparison of rate of relapse between adherent and non-adherent patients revealed also statistically significant differences (mean = 986.31, S.D. = 35.02 and mean = 623.34, S.D. = 56.22 days respectively).

**Discussion:** Non-adherence to medication is the most important factor associated with relapse.

doi:10.1016/j.schres.2010.02.458

**Poster 231**

**READMISSION RISK IN SCHIZOPHRENIA AND RELATED DISORDERS: INVOLUNTARY FIRST HOSPITALIZATION AS A PREDICTOR**

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**Background:** While topic of readmission among Patients with Schizophrenia and Related Disorders (SRD) is relatively well studied, the extent to which Involuntary First Hospitalization (IFH) predicts future admission has not been widely examined. The aim of this study was to evaluate the predictive value of IFH with regard to readmission among patients having a first lifetime hospitalization for SRD.

**Methods:** Data were taken from the separation sheets (ICD-9 format) of all 1044 SRD cases (14+ years) admitted for the first time to a Quebec regional psychiatric hospital from 1980 to 2008. Predictive value of IFH was evaluated using bivariate and logistic regression analyses. The study covariates were length of the hospitalization, age, gender, alcohol and substance abuse.

**Results:** The observed rate of IFH among SRD was 23.2%. A logistic regression analysis indicates that IFH and age predicted best readmission. Length of the initial hospitalization, gender, alcohol abuse and substance abuse had not significant effect in the model.

**Discussion:** These results together with outcome studies of schizophrenia support the view that involuntary first hospitalization, aside from age of onset, is likely related to chronicity, relapse and readmission in patients suffering from schizophrenia.

doi:10.1016/j.schres.2010.02.459

**Poster 232**

**GENDER DIFFERENCES IN PATIENTS PRESENTED WITH FIRST-EPISTODE PSYCHOSIS IN HONG KONG**

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**Background:** Gender differences have been observed in psychotic disorders in terms of premorbid adjustment, illness onset, symptoma-
tology, course and outcome. Most studies focused on schizophrenia and the samples examined were mainly recruited from subjects with chronic illness in inpatient setting. Few studies have evaluated gender differences of functional psychosis encompassing various diagnostic categories at its early illness stage in a representative sample. Thus, the aim of this study was to investigate gender differences in a treated sample of patients with first-episode psychosis.

**Methods:** Seven hundred (male, n = 360; female, n = 340) subjects aged 15-30 years consecutively enrolled in a territory-wide first-episode psychosis treatment program in Hong Kong from 1st July 2001 to 31st August 2003 were studied. Socio-demographic data, baseline and follow-up clinical variables, and treatment and service utilization characteristics were collected via systematic medical records review. CGI severity of illness (positive, negative and affective symptoms) and SOFAS (social functioning) were retrospectively employed on case notes in each month across the whole three-year follow-up period. Gender differences at entry and outcome were examined.

**Results:** At service entry, females had significantly longer median duration of untreated psychosis (p < 0.001), achieved higher educational level (p < 0.01) and were less likely to be a smoker (p < 0.001). Males experienced more negative symptoms (CGI, p = 0.01) and lower level of affective symptoms (CGI, p < 0.01) at baseline. No gender difference was observed in age at first presentation, age at onset of psychosis, mode of onset, baseline functioning, pre-service substance abuse and suicidal attempt. In three-year follow-up period, males had significantly more severe negative symptoms (CGI, p < 0.001) and less affective symptoms (CGI, p < 0.01), and were more likely to commit violence (p < 0.01) and to have comorbid substance abuse (p < 0.01). Females had significantly better functioning than males in follow-up interval (SOFAS, p < 0.001) and more females than males were employed in second (p < 0.01) and third year (p < 0.01) of follow-up. There was no gender difference noted in numbers and total length of psychiatric hospitalizations, numbers of relapses, service disengagement, suicidal attempt and severity of positive symptoms.

**Discussion:** Gender differences were evident in the early phase of functional psychosis since the illness onset. Males were found to have lower premorbid educational attainment, more prominent negative symptoms and less severe affective symptoms at baseline and along the course of illness, less favourable outcome with poorer psychosocial functioning and more comorbid substance abuse than females in first-episode psychosis sample. More research should be conducted to better elucidate the interplay between biological and psychosocial factors contributing to gender differences of psychotic disorders with respect to illness manifestation and trajectory. Clinically, differential needs between men and women and gender-specific therapeutic strategies need to be considered in early intervention service for first-episode psychosis.

doi:10.1016/j.schres.2010.02.460

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**Poster 234**

PRE-TREATMENT, BASELINE AND TREATMENT CORRELATES OF OUTCOME IN AN EPIDEMIOLOGICAL COHORT OF FIRST EPISODE PSYCHOSIS PATIENTS

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**Background:** Despite being based on population samples of first episode psychosis (FEP) patients and relying for the majority on

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**Poster 233**

PERSISTENCE OF PSYCHOTIC SYMPTOMS IN AN IRISH COMMUNITY SAMPLE - AN 8 YEAR COHORT STUDY

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**Background:** There is evidence that psychosis exists on a continuum in the population in both adult and child and adolescent samples. A recent systematic review and meta-analyses of this topic by Van Os and colleagues (2009) revealed an overall median prevalence rate of 5% for psychotic experiences in the general population. Poulton et al. (2000) found that self-reported psychotic symptoms at age 11 years predicted a very high risk of a schizophrenia spectrum disorder at age 26 years. To address a lack of systematic epidemiological research on adolescent mental health in Ireland, the first large-scale cross – sectional school – based study (The Challenging Times Study) was carried out eight years ago to determine the prevalence rates of psychiatric disorders in a population of Irish adolescents aged 12–15 years. In a sample of n = 212 young people baseline results showed that (66%, n = 14) adolescents reported one or more psychotic symptoms. Eight years later the present study identified 160 of the 212 (75%) young people now aged 19–23 years. Aims The persistence of psychotic symptoms from early into late adolescence/ young adulthood in 12 of the 14 young people who had previously reported psychotic symptoms at baseline interview were assessed. The development of psychotic symptoms in those who had not reported these symptoms at baseline were also recorded at follow up interview.

**Methods:** At follow up psychotic symptoms were assessed using the Structured Clinical Interview (SCID 1- module B/C) and the Structured Interview for Prodromal Symptoms (SIPS) screener. The Stressful Life Events Schedule a semi-structured interview was used to examine traumatic experiences among the adolescents. A brief cognitive measure, a brief assessment of family functioning and the Global Assessment of Functioning Scale (GAF) was used to measure quality of life and general functioning.

**Results:** Twenty – six study members (16% of the sample) reported psychotic symptoms at age 20 – 23 years. This is in line with rates reported elsewhere (Poulton et al., 2000).When the sample was subdivided on the basis of prior report of psychotic symptoms at baseline interview, 75% of those individuals (n = 12) who had previously reported symptoms still reported psychotic symptoms compared with 11.5% of the remainder of the sample. Therefore the risk of psychotic symptoms in early adulthood among those who had previously reported psychotic symptoms as an adolescent was significantly higher than the risk among those who had not previously reported such symptoms at baseline interview (OR 23.1, 95% CI 4.9-140.4).

**Discussion:** Adolescents who report psychotic symptoms in the general population could be conceptualised as a ‘high risk’ group for psychosis. This paradigm may prove valuable in exploring early risk factors for psychosis-vulnerability. For those who show continuity of their symptoms additional longitudinal studies are necessary to assess the degree of environmental risk the person is exposed to when examining the developmental trajectory to psychosis.

doi:10.1016/j.schres.2010.02.461
operationalized outcome criteria, most recent studies still suffer, to a variable degree, from an important selection bias, patients’ inclusion depending on an informed consent to participate in research.

**Methods:** The Early Psychosis Prevention and Intervention Centre (EPPIC) admitted 786 FEP patients between 1998 and 2000. Data for the current study were collected from patients’ files using a standardized questionnaire. 704 files were available, 43 excluded because of a non-psychotic diagnosis at endpoint and 3 due to missing data regarding past stressful events; 658 patients were analysed.

**Results:** After a period of up to 18 months of treatment, 63% of FEP patients had reached symptom remission criteria, 44% functional remission criteria and 38% both symptomatic and functional remission criteria. Duration of untreated psychosis (DUP) and decrease or interruption of Substance use disorder (SUD) during treatment, predicted both symptomatic and functional remission.

**Discussion:** Data from this large epidemiological sample of FEP patients show that while 2/3 FEP patients are in symptom remission after 18 months of treatment, only 40% meet criteria for functional remission. In addition, our results suggest that various strategies may contribute to improve these figures. First, the development of early intervention strategies should be pursued, not only in order to shorten DUP and to provide treatment before symptoms reach a high intensity, but also with the aim to maintain social integration. Second, a good knowledge of the specific strategies that may facilitate engagement (Macneil 2009a,b) is necessary when treating FEP patients, in order not only to facilitate their adherence to medication but also to allow sufficient time in treatment, in order to address key issues such as substance abuse co-morbidity and development of insight.

doi:10.1016/j.schres.2010.02.462

**Poster 235**

**QUALITY OF LIFE IN PATIENTS WHO HAVE REMITTED FROM THEIR FIRST EPISODE OF PSYCHOSIS**

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**Background:** Quality of life (QoL) in first-episode psychosis (FEP) is strongly related to levels of psychopathology and may vary as a function of illness phase. QoL remains poorly understood in FEP. The aim of this study was to characterize the nature and predictors of QoL in patients who have remitted from their first-episode of psychosis.

**Methods:** Demographic characteristics, diagnoses, and psychopathology were assessed in 81 FEP patients. The World Health Organization Quality of Life Scale-Brief (WHOQol-Bref) was used to assess QoL in these patients. Carer-related variables (expressed emotion and burden of care) were ascertained from 63 relatives.

**Results:** Poorer QoL was associated with personality disorder, depression, mild psychotic positive symptoms, and impaired functioning. Carer-related factors such as emotional over-involve-ment and burden of care were also associated with a reduction in patients’ QoL.

**Discussion:** Depression, functioning and family variables impacted on QoL, and need to be considered in terms of ongoing patient management.

doi:10.1016/j.schres.2010.02.463

**Poster 236**

**IS QUALITY OF LIFE IN SCHIZOPHRENIA RELATED TO ILLNESS AWARENESS? A STUDY WITH STABILIZED OUTPATIENTS**

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**Background:** Quality of life of subjects with schizophrenia is influenced by a number of factors, such as illness awareness.

**Methods:** The aim of this cross-sectional study was to assess the quality of life a sample of stable schizophrenic outpatients, and explore its relationship with illness awareness and illness severity. We included 57 patients with a DSM IV diagnosis of psychotic disorder. Quality of life were assessed with Short Form 36 Health Survey (SF-36) and Lehman Subjective Quality of life Interview-Short Version (QoL) and awareness of illness with Scale for Assessment of Unawareness of Mental Disorder (SUMD).

**Results:** The descriptive analysis profile obtained in our sample demonstrated good/moderate levels of satisfaction in most subscales. Awareness of illness and clinical variables were related to particular domains of quality of life. A better insight significantly correlated with poor quality of life (Having a mental disorder SUMD scale and general SF-36: r = - 0.275; p = 0.040; having a mental disorder SUMD scale and general QoL: r = - 0.266; p = 0.047). The severity of psychotic and depressive symptoms showed significant associations with worse quality of life (general SF-36 and PANSS total: r = - 0.320; p = 0.016; general SF-36 and Calgary depression: r = - 0.452; p = 0.000; general QoL and PANSS total: r = - 0.491; p = 0.000; general QoL and Calgary depression: r = - 0.614; p = 0.000).

**Discussion:** A poor quality of life was linked a better awareness of illness and with severity psychotic and depressive symptoms in stabilized schizophrenic patients.

doi:10.1016/j.schres.2010.02.464

**Poster 237**

**INSIGHT AND QUALITY OF LIFE IN SCHIZOPHRENIA**

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**Background:** Schizophrenia involves high impairment of social and working performance as well as a poor quality of life. Part of schizophrenia patients lack insight about the disorder. This research is aimed to compare the perception of quality of life between schizophrenia patients an physic chronic patients with intact insight. In concrete, we wanted to asess the role of insight in the assessment of quality of life in schizophrenia, to compare objective and subjective scores in schizophrenia subjects, and to know the role of insight in treatment compliance.

**Methods:** Schizophrenia group: 60 participants. IBD group: 30 participants. Both groups complete generic quality of life questionnaire
Differential 3-Year Effects of First vs. Second-Generation Antipsychotics on Subjective Wellbeing in Schizophrenia Using Marginal Structural Models (MSMs)

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Background: This study examined the differential effects of first (FGA) versus second-generation antipsychotics (SGA) on subjective wellbeing in patients with schizophrenia.

Methods: Data were collected in an observational 3-year follow-up study of 2,224 patients with schizophrenia. Subjective wellbeing was assessed with the Subjective Wellbeing under Neuroleptics scale (SWN-K). Differential effects of FGAs vs. SGAs were analyzed using marginal structural models (MSMs) in those patients taking antipsychotic monotherapy.

Results: The MSM, which analyzed the differential effect on the SWN-K total score, revealed that patients on SGAs had significantly higher SWN-K total scores, starting at 6-month (3.02 points; p = .0061; d = 0.20) and remaining significant thereafter (endpoint: 5.35 points; p = .0074; d = 0.36).

Discussion: Results of this large observational study are consistent with a small but relevant superiority of SGAs over FGAs in terms of subjective wellbeing extending previous positive findings of differential effects on quality of life.

doi:10.1016/j.schres.2010.02.466

Subjective Well-Being in Psychotic Depot-Treated Patients is Related to Personality Traits

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Background: Previous research has found that schizophrenia patients treated with atypical oral antipsychotics experience greater subjective well-being (SWN) compared to patients treated with typical medications. The present study aimed to examine if this finding is applicable to patients treated with depot medications. Additionally, the relationship between SWN and personality characteristics was examined.

Methods: 34 patients, 25 with schizophrenia and 9 with schizoaffective disorder, taking depot antipsychotic medication were assessed on SWN, personality traits, negative affect, insight, cognitive functioning, and psychopathology (PANSS) symptoms. 16 patients received an atypical depot medication (risperidone), the rest received a variety of typical medications. 28 of these patients were additionally taking oral antipsychotic medications.

Results: T-tests revealed no differences between depot groups in SWN, cognitive functioning, and schizophrenia symptoms. SWN total score was significantly positively correlated with extraversion (r = .56) and agreeableness (r = .56), and negatively correlated with neuroticism (r = -.62). There were a number of significant correlations between several of the SWN subscales and with extraversion, agreeableness and neuroticism. Openness to experience was significantly positively correlated with the SWN mental subscale (.82). SWN was negatively correlated with depression (-.67), anxiety (-.61), stress (-.55), and with side-effect severity (-.57). SWN was negatively correlated with the Affective factor of the PANSS (-.46), but had no other significant correlations with the remaining PANNS factors. Insight was negatively correlated with SWN total score (-.58) and with three SWN subscales. Additionally, insight was positively correlated with depression (.47) and stress (.62). Side-effect severity was negatively correlated with extraversion (-.49) and agreeableness (-.61) and positively with neuroticism (.53). Insight was negatively correlated with extraversion (-.58) and positively with neuroticism (.54).

Discussion: Preliminary result of this study found no evidence that type of depot medication influences SWN. However, patients who were higher on extraversion and agreeableness, and lower on neuroticism, reported higher levels of SWN and lower side-effect severity. Additionally, higher SWN is associated with lower levels of distress, but also with poorer insight into one’s mental illness. Furthermore, more extravedt patients had poorer insight, while more neurotic patients had better insight. Patients’ SWN and hence perceived quality of life seems to be strongly related to stable features of their personality as well as current distress levels and side-effect severity. SWN may have a stable trait-like character due to its relationship with personality features.

doi:10.1016/j.schres.2010.02.467

Prevention of Mothers’ Mental Illness Deterioration: A Retrospective Review of 34 Japanese Patients

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Abstracts

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Background: Previous research has found that schizophrenia patients treated with atypical oral antipsychotics experience greater subjective well-being (SWN) compared to patients treated with typical medications. The present study aimed to examine if this finding is applicable to patients treated with depot medications. Additionally, the relationship between SWN and personality characteristics was examined.

Methods: 34 patients, 25 with schizophrenia and 9 with schizoaffective disorder, taking depot antipsychotic medication were assessed on SWN, personality traits, negative affect, insight, cognitive functioning, and psychopathology (PANSS) symptoms. 16 patients received an atypical depot medication (risperidone), the rest received a variety of typical medications. 28 of these patients were additionally taking oral antipsychotic medications.

Results: T-tests revealed no differences between depot groups in SWN, cognitive functioning, and schizophrenia symptoms. SWN total score was significantly positively correlated with extraversion (r = .56) and agreeableness (r = .56), and negatively correlated with neuroticism (r = -.62). There were a number of significant correlations between several of the SWN subscales and with extraversion, agreeableness and neuroticism. Openness to experience was significantly positively correlated with the SWN mental subscale (.82). SWN was negatively correlated with depression (-.67), anxiety (-.61), stress (-.55), and with side-effect severity (-.57). SWN was negatively correlated with the Affective factor of the PANSS (-.46), but had no other significant correlations with the remaining PANNS factors. Insight was negatively correlated with SWN total score (-.58) and with three SWN subscales. Additionally, insight was positively correlated with depression (.47) and stress (.62). Side-effect severity was negatively correlated with extraversion (-.49) and agreeableness (-.61) and positively with neuroticism (.53). Insight was negatively correlated with extraversion (-.58) and positively with neuroticism (.54).

Discussion: Preliminary result of this study found no evidence that type of depot medication influences SWN. However, patients who were higher on extraversion and agreeableness, and lower on neuroticism, reported higher levels of SWN and lower side-effect severity. Additionally, higher SWN is associated with lower levels of distress, but also with poorer insight into one’s mental illness. Furthermore, more extravedt patients had poorer insight, while more neurotic patients had better insight. Patients’ SWN and hence perceived quality of life seems to be strongly related to stable features of their personality as well as current distress levels and side-effect severity. SWN may have a stable trait-like character due to its relationship with personality features.

doi:10.1016/j.schres.2010.02.467
Background: In the past few decades, women with severe mental illness have had more opportunities to be parents and raise their children. This may be associated with deinstitutionalization, community-based rehabilitation and support programs, and development of antipsychotics. Mothers with severe mental illness experience many kinds of problems during childcare. Mental deterioration can lead to hospitalization, resulting in long separation from children and further grief as well as a burden on health care facilities. In this study, we attempted to identify characteristics of mothers whose condition did not deteriorate and who did not require hospitalization in order to obtain insights into preventing mental deterioration and the need for hospitalization.

Methods: The subjects consisted of 34 women, aged 33-68, who had experienced childcare and who were outpatients diagnosed with schizophrenia (16 subjects), schizoaffective disorder (13), bipolar affective disorder (4) or depression with psychotic symptoms (1). Sixteen of the participants required hospitalization within three years following the first childbirth and the remaining 18 did not. Data were collected from medical records, interviews and from a self-administered questionnaire about attitudes and behavior during the first three years following the first childbirth. The questionnaire was composed of six sections on 1) living situation, 2) psychiatric medication, 3) sleep, 4) subjective symptoms of deterioration, 5) resting time, and 6) the subjects’ impressions and advice about childcare.

Results: The non-hospital group was more likely to take care of themselves (for instance, taking naps for their sleep deficit) than the hospital group. The non-hospital group was more likely to recognize the need for support, regular taking of psychiatric medications and consultation with attending psychiatrists than the hospital group. There were no differences between the two groups in diagnosis, age of onset, duration of illness, antipsychotic medication, financial issues, living situation, resting time, or subjective symptoms.

Discussion: The results suggest that mothers’ attitudes toward self-care and childcare can help to prevent mental illness deterioration and the need for hospitalization, and that support from mental health care facilities is essential for improving these attitudes.

doi:10.1016/j.schres.2010.02.468

Poster 241
ASSESSING RECOVERY IN PEOPLE WITH SERIOUS MENTAL ILLNESS

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Background: Mental health care in the United States and Western Europe is undergoing a shift in values and practice toward a consumer driven recovery model, which assumes that all consumers have the capacity to improve and develop a life distinct from their illness. The consumer model emphasizes hope, empowerment, and control of one’s life, in contrast to scientific and clinical models, which view recovery in the context of reduced symptoms. Despite this political and programmatic change, there is little scientific literature on the nature of recovery or the factors that contribute to it. Two factors that have limited empirical study of the construct and treatment programs are: a) the absence of a scientifically grounded conceptual model of recovery, and b) the lack of a reliable and valid assessment instrument to measure recovery status. This presentation will report on the development of the Maryland Assessment of Recovery in Serious Mental Illness (MARS), a psychometrically sound recovery assessment scale based on Bandura’s social cognitive theory.

Methods: The MARS was developed using a multi-step empirical process of scale development. A team of experts first developed an operational definition of recovery based on the literature, and then drafted a set of self-report items that reflected six primary recovery dimensions. The draft version of the MARS was then submitted to a panel of doctoral level experts on recovery and serious mental illness. These individuals then participated in a semi-structured telephone interview to solicit their opinions on the operational definitions, the structure and format of the scale, adequacy of content coverage, and individual items. Revisions were made based on their feedback, and the revised instrument was then reviewed by a panel of consumers for further refinement. The revised version of the MARS was then administered to a sample of 65 consumers with serious mental illness to examine its psychometric properties and ease of use.

Results: The data demonstrate that the MARS is quite practical for use with the targeted population. On average it took respondents 14-min to complete the MARS. There was a very limited amount of missing data: less than 1% of the total number of items answered. There was no indication of consistent problems with the items or the format of the scale. The range of responses for each item was broad. Subjects used all five response options on 64% of the items, and used 4 of the 5 response options on another 36% of the items. The mean score across all items was 3.59 (sd = 0.66), and the range was 2.21 to 4.93. The MARS also has good internal consistency: Cronbach’s alpha was .967, and correlations between the overall recovery score and each recovery domain ranged from .825 (Responsibility) to .939 (Strengths). Twenty-five of the subjects were retested on the MARS after 1-week to provide a preliminary estimate of test-retest reliability. The test-retest correlation was .868.

Discussion: These data provide good support for further development of the MARS. It is practical for use in community mental health settings as well as for research. Scores are both internally consistent and consistent over time, and the scale produces adequate dispersion among scores. Feedback from our consultants and consumer advisors indicates that the MARS also has good face and content validity. We have recently mounted a large scale study to examine the factor structure of the MARS, the stability of scores over a 1-year period, and the relationship of recovery status to other dimensions of psychiatric and psychosocial functioning.

doi:10.1016/j.schres.2010.02.469

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PSYCHOMETRIC PROPERTIES OF THE FRENCH VERSION OF THE PERSONAL AND SOCIAL PERFORMANCE SCALE (PSP) AMONG INDIVIDUALS WITH SCHIZOPHRENIA

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Background: The Personal and Social Performance (PSP) scale is a reliable and valid instrument that utilizes objective parameters for assessment of social functioning in patients with schizophrenia. The aim of this study was to determine the validity and reliability of the French version of PSP in a population of French schizophrenic patients.

Methods: Patients with DSM-IV diagnoses of schizophrenia and schizoaffective disorder were recruited and assessed in a cross-sectional design using the PSP, GAF, SOFS, PANSS, CGI severity. Internal consistency
Poster 243
GAME THEORETICAL APPROACH TO THEORY OF MIND DEFICITS IN SCHIZOPHRENIC PATIENTS WITH DELUSION(S) OF REFERENCE

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Background: There is already ample evidence that theory of mind (ToM) is impaired in people with schizophrenia. However, a specific relationship between impaired ToM and paranoid delusions, while intuitively reasonable, has only been demonstrated in few studies. Psychometric properties of ToM tasks employed in these studies may be a complicating factor in drawing conclusions about the relationships. Because most tests of ToM focus on the third-person, the stimuli presented are static which does not involve the dynamic nature in daily social interactions. The tasks fail to simulate the cognitive demands faced by individuals in real social situations, which give rise to our ability to ascribe mental states to our social partners. The current study proposed how the games traditionally used in game theoretic research can engage mechanisms specific to reasoning about the mental states of a social partner and addressed how the mentalising deficits in schizophrenia may impair performance in the paradigms. We also aimed to clarify whether particular paranoid symptoms, such as delusions of reference (DOR), are implicated in mentalising impairment.

Methods: Three groups of subjects were recruited: (a) patients with DOR as main positive symptom (n=17); (b) patients with no clinically significant DOR symptoms (n=22); and (c) normal controls (n=20). An iterated prisoner's dilemma (PD) game was administered to all 3 groups of subjects. After completion of the PD task, a semi-structured interview was conducted to draw forth the subjects' strategic reasoning when playing the game, as well as their conception of the thought process going through their opponent's mind. Mentalising performance was rated on three criteria: whether the participant reported taking the opponent into account when making his or her own choices, whether the participant recognized the correct strategy of the opponent, and whether the participant's strategic behavioral choices are influenced by the opponent. All subjects were also administered the Character Intention Task (CIT; Sarfati et al., 1997), which was devised to test understanding of the intentions of non-human comic strip characters, and a neuropsychological test battery including measures of intelligence, memory, attention and executive functioning. Current symptom profiles of the schizophrenic subjects were assessed using the Scale for the Assessment of Positive and Negative Symptoms.

Results: The schizophrenic groups exhibited significant ToM impairments in the CIT compared to healthy control group (F=9.407, p<0.001). However, the mentalising deficit in the PD task was only observed for those schizophrenic patients who had DOR (F=10.960, p<0.001). In the patient groups, severity of DOR was negatively correlated with mentalising measures in the PD task (r=-0.584, p<0.001), but was not correlated with CIT scores. Of all other psychotic symptoms, only positive formal thought disorder was correlated with CIT performance (r=-0.518, p<0.001).

Discussion: The findings evidence ToM deficits in schizophrenia and the study, using a game theoretic approach, underlies the existence of a specific link between DOR and mentalising impairments in schizophrenia. Implications of these findings are discussed with reference to theoretical and methodological issues in current schizophrenia research. Further investigation is needed to establish the links between symptomatology and mentalising, particularly comparing symptom-specific groups and investigating the psychometric properties of ToM tasks. Reference: Sarfati, Y, Harde-Bayle, MC, Besche, C et al. (1997). Attribution of intentions to others in people with schizophrenia. Schizophr. Res. 25, 199–209.

doi:10.1016/j.schres.2010.02.470

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Poster 244
SOCIAL FUNCTIONING AND COGNITION IN PATIENTS WITH SCHIZOPHRENIA: IMPACT ON QUALITY OF LIFE

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Background: Patients with schizophrenia show deficits across a large number of neurocognitive domains and functional outcome areas such as social functioning, social skills and independent living skills. It is possible, although unlikely, that all of these neurocognitive deficits restrict the patients' global functioning. The present study sought to determine the relationship between cognitive function, social function and mood symptoms in healthy controls, and the effect of those variables in quality of life.

Methods: Eight patients with chronic stable schizophrenia attending the outpatients clinic of FLENI, and ten matched comparison subjects were evaluated with a cognitive screening test (MMSE), Trail Making Test Part A, NAB Mazes, Verbal Fluency and Stroop. Social functioning was measured with UCSD Performance-based Skills Assessment (UPSA), a performance-based measure of functional capacity and level of patient community responsibilities, and Test of Adaptive Behavior in Schizophrenia (TABS) which is a performance-based measure of adaptive functioning designed to identify problems that occur in the course of performing functional activities. Quality of life was measured with the MOS 36 item Short Form Health-Survey (SF-36) and the EuroQol scale (EQ-5D) in both groups. Depression and anxiety symptoms were measured with Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS). A one way ANOVA was used to compare the groups, followed by a Tukey’s test as post hoc method.

Results: In patients, UPSA and TABS, the two social functioning measures, were significantly correlated (p=0.006, r=0.858). Social functioning (TABS) was correlated with MMSE in this group as well (p=0.033, r=0.748). While quality of life scales (SF-36 y EQ-5D) were not related to social functioning measurements, basic cognitive functioning as assessed by MMSE was related to the patients' perception of their quality of life (SF-36; p=0.024 r=-0.775). This was not
observed in matched comparison subjects. To evaluate the contribution of MMSE to the difference observed between patients and the matched comparison subjects in social functioning tasks, a multivariate analysis was made using the MMSE as a cofactor, and revealed that the difference between patients and normal controls in social functioning was not entirely dependent on this cognitive screening test.

**Discussion:** Both TABS and UPSA robustly distinguish between schizophrenic patients and comparable healthy individuals in the context of the Argentine culture. Whereas the MMSE, a basic measure of cognitive function, is correlated with performance in one of those measures in patients, it does not entirely explain the difference in performance observed between this group and healthy individuals. As previously described, patients with schizophrenia show widespread abnormalities in cognitive measures of attention, working memory and executive functions.

**Poster 245**

SOCIO-DEMOGRAPHIC CHARACTERISTICS AND SOCIAL ADJUSTMENT AS PREDICTORS OF A FIRST PSYCHOSIS IN SUBJECTS AT ULTRA HIGH RISK

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**Background:** The onset of schizophrenia is associated with social and demographic risk factors. The aim of the present study was to determine which socio-demographic characteristics may contribute to a prediction of a first psychotic episode in patients at Ultra High Risk (UHR) for developing psychosis.

**Methods:** We included 72 UHR subjects and followed them over a period of 36 months. Nineteen of the 72 subjects (26.4%) made a transition to psychosis. We applied survival analyses to investigate associations between making a transition to psychosis and socio-demographic characteristics and social adjustment. To investigate which items are the best predictors of transition to a first psychotic episode Cox Regression analyses were applied.

**Results:** Urbanicity, receiving state benefits and poor premorbid adjustment (PMA) significantly influenced the transition to psychosis. Urbanicity, premorbid social-sexual aspects and highest level of social personal adjustment are best predictors for developing psychosis in our UHR group.

**Discussion:** Socio-demographic characteristics and social adjustment are likely to possess predictive power for transition to psychoses in subjects at UHR. These characteristics could be implemented in a future model for prediction of psychosis. Such a model could be more specific than current ones and, therefore, aid in developing patient-specific preventive interventions.

**doi:**10.1016/j.schres.2010.02.472

**Poster 246**

METABOLIC RISK FACTORS AND WEIGHT GAIN IN PEOPLE ADMITTED TO A PSYCHIATRIC INTENSIVE CARE UNIT

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**Background:** People with psychotic disorders have increased rates of obesity, metabolic syndrome and diabetes. During hospitalisation poor dietary choices and limited opportunity to exercise may be associated with weight gain. The effects of medications (especially atypical antipsychotics) on appetite are also important. This study assessed serum glucose, cholesterol and lipids in people with acute psychiatric disorders on admission to a closed psychiatric intensive care unit. We examined changes in weight and BMI during the admission.

**Methods:** 119 consecutively admitted patients were included in the study. All patients are involuntary. The average length of stay was 9.3 days. Data collected included demographic variables, height and weight at admission, weight at discharge, psychiatric diagnosis, medications given, fasting blood glucose and lipids, and duration of admission. Patients could choose freely the type and quantities of food they ate, and were able to obtain snack foods from the hospital canteen and a nearby supermarket.

**Results:** Five patients refused to participate. Of the remaining 114 clients, 70 (61%) were male with a mean age of 33 years. The most common diagnoses were non-affective psychosis (67%) and bipolar disorder (19%). The mean BMI was 27.04 (mean weight 82.5 kg) on admission and 27.8 (mean weight 84.9 kg) at discharge, a mean weight gain of 2.45 kg. Fasting blood samples on admission showed abnormally high levels of glucose in 25%, cholesterol in 9% (with a further 16% borderline) and LDL in 9% of patients.

**Discussion:** This study shows that on admission a significant proportion of acutely unwell patients have elevated blood glucose, cholesterol and lipids. On average, their BMI increased 0.09 units per day of hospitalisation. A policy of recovery-oriented practise was interpreted to allow patients free choice of foods. Our results suggest that the context needs to be considered in the provision of recovery focussed treatment. This should include providing healthy foods, limiting access to high carbohydrate foods, and encouraging regular exercise, within the constraints of this type of treatment facility.

**doi:**10.1016/j.schres.2010.02.474

**Poster 247**

NEUROCOGNITIVE DOMAINS IMPAIRED IN SCHIZOPHRENIA AND ITS ESTIMATED HERITABILITIES IN HEALTHY INDIVIDUALS: AN EUTWINNS NETWORK BASED STUDY

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**Background:** Schizophrenia is a polygenic disorder, whose final expression receives the input of both genetic and environmental factors. The study of endophenotypes provides a neurobiologically less complex model to disentangle the differential contribution of such factors, neurocognitive deficits being among the most promising indicators of increased risk for schizophrenia. The present study aims to report the heritability estimates for several of the neurocognitive functions most widely reported to be altered in schizophrenic patients. The presence of high heritability is a necessary condition to recognize a neurocognitive process – or any other potential biological marker - as an endophenotype.

**Methods:** The current is a twin-based study conducted in a population with no history of schizophrenic spectrum disorder.
nor neurological alterations. A broad neurocognitive battery was assessed on 259 healthy adult twin pairs (age range 17-65), 115 twin pairs from the Barcelona UB-Twin Sample (Catalonia, Spain) and 144 twin pairs from the Institute of Psychiatry of London (London, UK). 163 pairs were monozygotic while 96 pairs were dizygotic twins. The assessment consisted of measures of verbal memory (WMS, Logical Memory subtest), working memory (TMT A & B, WAIS Subtests letter-number sequencing and digit span), executive function (verbal semantic and phonological fluencies) and general verbal and performance intellectual ability (WAIS, subtests information, vocabulary, similarities, block design, matrix reasoning). Independent samples T-test were used to assess differences in age, years of education and gender. All measures were standardized to a mean of zero and a s.d. of 1 separately for each sample and residualized for years of education using a regression procedure. Intraclass correlation coefficients were used to dissect phenotypic variance into genetic and environmental components, being $h^2 =$ additive genetic effects. Statistical Analyses were conducted in SPSS17 and Stata9.

Results: Mean age for the complete sample was 38.05 (s.d.12.6), with mean years of education of 14.55 (s.d. 3) and 30.9% were male. Among those assessed in this sample, letter-number sequencing test was shown to be the most heritable trait ($h^2 =0.48$) and delayed ($h^2 = 0.59$), proved to have elevated rates of heritability, followed by the similarities WAIS subtest ($h^2 =0.47$). Digit span forward ($h^2 =0.36$) presented moderate heritability scores, as did both subtests of verbal fluency: semantic ($h^2 =0.36$) and phonetic ($h^2 =0.35$). The rest of the tests assessed showed very low heritability scores.

Discussion: To our knowledge, there is no previous report of heritability estimates for letter-number sequencing subtest in the general population. What is more, this test has been described to be particularly suitable as a marker of genetic liability to the disorder.

Acknowledgements: Supported by European Twin Study Network on Schizophrenia Project (RD-06/0011/0007) – Marie Curie Fellowship (Xc) and Coordinated Project (SAF2008-05674-C03-00).

doi:10.1016/j.schres.2010.02.475

Poster 248
DIFFERENCES IN SELF-ESTEEM AND SELF-EVALUATION IN PARANOIA; ARE SELF-APPRAISALS A DEFENSIVE STRATEGY OR A REFLECTION OF EARLY ADVERSITIES?

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Background: This research project represents an attempt to understand differences in self-esteem and self-evaluation associated to paranoia. Self-serving bias model of persecutory delusions (Bentall, et al., 2001) claimed that paranoia represents an attempt to keep negative affect from consciousness to preserve a positive self-esteem. On the other hand, Freeman and Garety (2003) proposed that delusional explanations are a direct reflection of pre-existing beliefs and previous emotional concerns, arguing that negative self-beliefs, lowered self-esteem and clinical paranoia are directly associated. Unfortunately, self-appraisal research in this area has not resolved this controversy (Thewissen, et al., 2008). We argued that paranoia literature has used self-esteem and self-evaluation measures interchangeably, which has lead to inconsistent findings and confusion.

Methods: Participants were 40 in-patients suffering persecutory delusions (meeting DSM IV-TR criteria for schizophrenia or other Psychotic Disorders), 35 depressed patients who met DSM-IV-TR criteria for a current depressive disorder (mainly outpatients) who had never experienced persecutory delusions and 44 non-psychiatric controls. Each participant completed the Evaluative Beliefs Scale (EBS; Chadwick, Trower, & Dagnan, 1999), the Self-worth subscale of the World Assumptions Scale (WAS) (Janoff-Bullman, 1989), the Self-acceptance sub-scale of the Scales of Psychological Well-Being (SPWB; Ryff & Keyes, 2002) and the Beck Depression Inventory (BDI-II; Beck, Steer & Brown, 1996). One-way between-groups and repeated measures ANCOVAs were used to investigate the group effect for self-esteem and self-evaluation. Depressive mood, gender and level of education were used as covariates.

Results: Our data suggest that, as expected, paranoid patients had equivalent levels of self-esteem than controls but higher levels than depressed participants ($F(4,115) = 9.36 \quad p = 0.00$). Moreover, paranoid participants had higher levels of negative self-evaluation than controls, but similar levels of negative self-evaluation than depressive participants ($F(4,115) = 10.32, \quad p = 0.00$). Finally, we found that paranoid participants had a lower negative self on self-evaluations than other on self-evaluation, while depressive participants would have the opposite pattern, a higher negative self on self-evaluation than other on self-evaluation ($F(4,115) = 7.85, \quad p = 0.00$).

Discussion: Our results put out, as it has been suggested by others, that self-esteem is not the same than self-evaluations. Self-serving bias model was supported by positive explicit self-esteem in paranoia and by the lack of consistency between self esteem and self-evaluation (which reflects a fragile self-concept in paranoia, but not in depression). Paradoxically, as it has been advocated by Garety’s group, high scores on negative self and other-evaluations suggest faulty schemas in paranoia, as well as in depression. The implications for clinical work and further research are discussed.

doi: 10.1016/j.schres.2010.02.476

Poster 249
PEOPLE’S PERCEPTION OF THEIR INVOLUNTARY ADMISSION AT ONE YEAR FOLLOW-UP AND READMISSION RATES TO HOSPITAL

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Background: There is limited knowledge of how individuals reflect on their involuntary admission and factors which may influence their perspective. The aims of the study are to investigate, at one year after an involuntary admission, (i) peoples’ perception of the necessity of their involuntary admission (ii) the enduring impact of being admitted involuntary on the relationship with their family, consultant psychiatrist and employment prospects (iii) readmission rates to hospital and risk factors for readmission.

Methods: Individuals admitted involuntarily over a 15 month period were re-interviewed at one year following discharge using a semi-structured interview which included the MacArthur Admis-
In this paper we interviewed in an open fashion 14 teens with psychotic disorders; however, less is known about predictors of DUP. This study first examined patient-level predictors of DUP. Because little is known about how family-level factors are associated with DUP—especially in ethnic/racial minority groups such as African Americans—the subsequent aspects of the study focused on African American first-episode patients and their family members who initiated treatment for them. It was hypothesized that a longer DUP would be predicted by family members' endorsement of: (1) less knowledge about schizophrenia, (2) greater perceptions of stigma, (3) lower levels of insight, (4) fewer family strengths, (5) more limited family coping capacity, and (6) lower levels of caregiver strain. This study also examined three hypothesized services-level predictors of DUP: lack of insurance, financial problems, and broader barriers to accessing care.

**Methods:** Participants included 109 first-episode patients hospitalized in three public-sector inpatient psychiatric units serving an urban, socially disadvantaged, predominantly African American community. DUP, DUI, and a number of clinical and psychosocial variables were measured using rigorous, standardized methods. Among the 109 patients, 42 African American patients referred a family member who was actively involved in the initiation of care to provide family- and services-level data. Cox proportional hazards models quantified associations between predictors and DUP, and analyses of family- and services-level predictors controlled for effects of the previously determined patient-level predictors.

**Results:** The median DUP and DUI were 22.3 and 129.9 weeks respectively. Survival analyses revealed that at any given time-point, patients not living with family members were, on average, about 1.5-times as likely to be hospitalized as those living with family—and patients not living in poverty were, on average, about 1.6-times as likely to be hospitalized as those living in poverty—than the respective comparison groups, when controlling for mode of onset of psychosis. Greater family strengths and a better family coping capacity were associated with a shorter DUP, whereas higher insight among family members and greater level of perceived caregiver strain were associated with a longer DUP. When controlling for the three patient-level covariates (mode of onset of psychosis, living with family versus alone or with others prior to hospitalization, and living above versus below the federally defined poverty level), patients without health insurance, with financial problems, or with barriers to seeking help had a significantly longer duration of untreated psychosis.

**Discussion:** There is a need for early intervention efforts to be directed to families (and their loved ones who live with them with emerging psychotic disorders or frank untreated psychotic syndromes), particularly families facing major socioeconomic challenges. Whereas family strengths and coping likely account for a significant portion of variability in DUP, both insight and caregiver strain probably evolve as a consequence of DUP. Efforts to strengthen families and tap into existing strengths of families in specific cultural groups would likely enhance early treatment-seeking for psychotic disorders. Health services-related factors, such as lack of insurance, are also predictive of longer treatment delay. Efforts to eliminate un-insurance and under-insurance, as well as minimize barriers to treatment, would be beneficial for improving the prognosis of young patients with emerging nonaffective psychotic disorders.
Poster 252
RATE AND PREDICTORS OF SERVICE DISENGAGEMENT IN AN EPIDEMIOLOGICAL FIRST-EPISODE PSYCHOSIS COHORT

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**Background:** Disengagement from treatment is a critical element that mitigates benefits from early intervention strategies. Our aim was to assess the prevalence and predictors of service disengagement in a treated epidemiological cohort of first episode psychosis (FEP) patients.

**Methods:** The Early Psychosis Prevention and Intervention Centre (EPPIC) in Australia admitted 786 FEP patients from January 1998 to December 2000. Treatment at EPPIC is scheduled for 18-months. Data were collected from patients’ files using a standardized questionnaire. Seven hundred four files were available; 44 were excluded, because of a non-psychotic diagnosis at endpoint (n = 43) or missing data on service disengagement (n = 1). Rate of service disengagement was the outcome of interest, as well as pre-treatment, baseline, and treatment predictors of service disengagement, which were examined via Cox proportional hazards models.

**Results:** 154 patients (23.3%) disengaged from service. A past forensic history ( Hazard ratio [HR] = 1.69; 95%CI 1.17-2.45), lower severity of illness at baseline (HR = 0.59; 95%CI 0.48-0.72), living without family at discharge (HR = 1.75; 95%CI 1.22-2.50) and persistence of substance use disorder during treatment (HR = 2.30; 95%CI 1.45-3.66) were significant predictors of disengagement from service.

**Discussion:** While engagement strategies are a core element in the treatment of first episode psychosis, particular attention should be paid to these factors associated with disengagement. Involvement of the family in the treatment process and focusing on reduction of substance use need to be pursued in early intervention services.

doi:10.1016/j.schres.2010.02.480

Poster 253
EARLY DETECTION OF PSYCHOSIS IN GENERAL PRACTICE

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**Background:** General practitioners have an important role to play in the early detection and management of psychosis. However little is known about the way GPs handle this problem and what problems they are facing.

**Methods:** A focus group research was performed in two cities of Flanders to get insight in the management of psychosis. Transcripts were coded by two independent researchers, consensus was reached after discussion, using the grounded theory.

**Results:** Four focus groups were performed until saturation. 23 GPs with an average professional experience of 19 years and a male/female ratio of 3.3 participated. Nine clusters were identified: the professionalism of the GP, diagnostic issues, the cooperation with the specialized mental health sector, patient behaviour and properties, the subclinical and various course of the disease, the relation with the family and the organisation of care. Less important issues are the admission to the hospital and substance abuse.

**Discussion:** GPs are in engaged and in favor of the care for psychotic patients but experience important tresholds in the organization of care and the cooperation with the mental health care sector. Getting support is more important than educational tools. The results support and confirm the rare existing data. Enhancing the care for (early) psychotic patients will need important changes in the service delivery and health care organisation.

doi:10.1016/j.schres.2010.02.481

Poster 254
DO SCHIZOPHRENIC OUT-PATIENTS RECEIVE APPROPRIATE SOMATIC CARE?

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**Background:** The diagnosis of schizophrenia is associated with an elevated risk for several somatic conditions and a shorter life span. There is evidence that schizophrenic patients do not receive appropriate somatic care.

**Methods:** As a part of MESTA-study (The living conditions and somatic health of schizophrenia patients living in community) we offered a thorough medical examination for all patients treated in the psychosis rehabilitation out-patient clinic in the municipality of Mäntsälä. Mäntsälä is a typical Finnish municipality with both urban and rural area with 19 400 inhabitants. The clinic treats all schizophrenia spectrum patients living in community. According to epidemiological studies there are 100 persons with these diagnoses aged 18-65 in Mäntsälä area and the clinic has 80 patients covering approximately 80% of the patient population. The examination consisted of several self-report forms, a nurse’s interview and measurements of weight, height, waist circumference, blood pressure, vision, basic neuropsychological test battery and several psychiatric rating scales (GAF, HONOS, BPRS), relevant laboratory tests and ECG followed by a comprehensive medical examination by an experienced general practitioner. Previous medical records were obtained.

**Results:** Until now 35 patients have undergone the study protocol. All of them have required medical attention. Medical interventions were classified into three categories: giving advice, referring to treatment or further consultation and acute treatment. 7 patients (20%) have received only counselling (i.e. weight control, tobacco cessation). One fifth required acute medical assistance (medication for acutely diagnosed illnesses). The remaining 21 patients (60%) suffered from several somatic conditions in need of further medical attendance, laboratory examinations etc. Typically patients were suffering from respiratory symptoms, obstipation and cerumen impaction. Conclusive results for the whole study population will be presented in the congress.

**Discussion:** Despite having an on-going psychiatric treatment relationship and in many cases visits in community health centre a great majority of the schizophrenia patients had severe somatic conditions in need of treatment or further medical attendance.

doi:10.1016/j.schres.2010.02.482
The OSCAR study is a prospective, 12 month, open-label, naturalistic study of resource-utilization costs in psychotic patients. A total of 138 subjects with schizophrenia or a related psychotic disorder were enrolled from 5 Canadian centers. This analysis examines the baseline data and explores the univariate and multivariate associations between costs and several clinical and socio-demographic covariates. These covariates include age, gender, ethnicity (Caucasian vs. other), education (up to grade 12 vs. beyond grade 12), marital status (single vs. other), family history of schizophrenia (yes/no), ratings of symptoms and functioning (SOFAS: Social and Occupational Functioning Scale, PANSS: Positive and Negative Syndrome Scale, SDS: Sheehan Disability Scale, CGI: Clinical Global Impressions Scale), and history of street-drug, alcohol, marijuana, and cigarette use (each yes/no). The distribution of costs was skewed and was log-transformed for analyses. Data were explored using multivariate regression analysis of covariates. The value of resources consumed was expressed in 2007 Canadian dollars, and is based on non-generic drug costs.

Results: Of the 138 subjects enrolled, n=130 provided complete baseline data. Mean age was 40 years (SD=13.2, 74% male; 88% Caucasian; 12% married or living common-law). One-fifth (21%) had a known family history of schizophrenia and 65% met criteria for a diagnosis of schizophrenia, 24% for schizoaffective disorder and 11% for other psychosis. Medication at baseline was quetiapine for 34, risperidone for schizoaffective disorder and 11% for other psychosis. Over the initial 12 months from presentation the costs of OASIS compared to Care As Usual were £1872 higher than for Care As Usual. However after 24 months they were £961 less than Care As Usual.

Conclusions: This model suggests that services that permit early detection of people at high risk of psychosis may be cost saving.

doi:10.1016/j.schres.2010.02.484
experiencing greater difficulties in emotion regulation. A statistical difference was also observed between samples on the K10 ($t_{(18,171)} = -7.51$, $p = .00$), indicating the schizophrenia sample experienced greater psychological distress compared to controls. The schizophrenia sample also experienced significantly greater dysfunctional problem-solving compared to controls ($t_{(220.65)} = 7.01$, $p = .00$). Correlations between the two samples on all measures were significantly related ($p < .000$).

**Discussion**: People with schizophrenia experience greater difficulties in emotional regulation, have higher levels of psychological distress and poorer social problem-solving ability compared to controls. These findings have implications for theory, research and clinical decision making in relation to the treatment of schizophrenia.

doi:10.1016/j.schres.2010.02.485

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**Poster 258**
**VITAMIN D IN SEVERELY MENTALLY ILL HOSPITALIZED PATIENTS**

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**Background**: There is good evidence of increased mortality with low vitamin D levels, of decreased mortality with Vitamin D supplementation and association of low Vitamin D levels with nonwhite race/ethnicity, diabetes, smoking and higher body mass index (BMI) all of which are features of the patients in the authors’ hospital. There is some evidence of low vitamin D levels in psychiatric patients but no evidence of whether that affects their symptoms or outcome. There is epidemiological, cohort study and animal experimental evidence supporting a role for deficient vitamin D perinatally being a risk factor for schizophrenia. In young rats the evidence points to a role for Vitamin D in neurogenesis, especially in the hippocampus. Vitamin D deficiency in adult rats significantly increases dopamine, DOPAC and noradrenaline in the cortex and dopamine in the hypothalamus, therefore its deficiency may contribute to the lack of improvement in chronic poorly responsive patients. Because of these concerns levels of vitamin D were randomly drawn from fourteen patients in one of our inpatient units, and the results were as follows: four patients had Vitamin D insufficiency (20 ng/mL to 29.9 ng/mL) the other ten patients had Vitamin D deficiency with levels lower than 20 ng/mL; three patients had levels lower than 7 ng/mL. Similar low levels were found in outpatients.

**Methods**: Since nearly all patients at our hospital seemed to be deficient in Vitamin D and since this appears to have such widespread clinical implications the Medical Director proposed that all patients have their Vitamin D level measured as a clinical measure. The IRB approved correlating this with demographics, including cultural and immigration information, clinical measures (including the monthly BPRS) and a previously approved survey of clinical movement disorder (with AIMS, SANRS and Barnes akathisia rating), provided the collected information was then made anonymous. In addition the researchers and clinicians as a group decided whether each patient was light skinned, dark or intermediate. An intervention study of those with low vitamin D is planned.

**Results**: So far 56 subjects have been included. Six refused to have blood taken and 17 results are still awaited. The vitamin D levels of 33 subjects were available for this preliminary analysis. Eighteen had a normal vitamin D level: 30-100 ng/mL. Four were considered to have insufficient levels (20-29.9 ng/mL), nine had deficient levels (<20 ng/mL) and two were below 7 ng/mL (the limit the Lab can measure). There was no a relationship between vitamin D levels and skin color, age of onset, blood pressure, smoking status, BPRS, CGI, Tardive Dyskinesia, Parkinsonism, Akathisia, psychiatric diagnosis or calcium and phosphorous. There was a significant relationship with sex (lower levels in females $t = 0.45$, $P = 0.01$), age (lower in younger $t = 0.45$, $P = 0.01$), years of illness ($r = 0.37$, $p = 0.04$) and prescription of Vitamin D 400iu per day (with Calcium) ($r = 0.56$, $P = 0.001$). There was trend towards a correlation with months in hospital ($r = 0.32$, $p = 0.07$), negatively with BMI ($r = -0.33$, $p = 0.06$) and GAF ($r = -0.34$, $p = 0.06$).

**Discussion**: This survey is in its early stages and subject to confounding. The correlation with age and sex may be because in one mixed sex ward with older subjects all were given Vitamin D routinely. The other ward was all female and much younger, and not given vitamin D routinely. It is of interest that this relatively small dose of Vitamin D made a difference and that there was no relationship with symptoms as measured by the BPRS, CGI and movement ratings, or with skin color.

doi:10.1016/j.schres.2010.02.486

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**Poster 259**
**NORMALIZATION OF SEMANTIC CATEGORIZATION DEFICIT IN FIRST-EPIEDE SCHIZOPHRENIA PATIENTS FOLLOWING SYMPTOMATIC RECOVERY: A THREE-YEAR PROSPECTIVE LONGITUDINAL STUDY**

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**Background**: Semantic memory dysfunction has been suggested in schizophrenia using the categorization task. However, data were largely inconsistent and the longitudinal trajectory of the deficit was unknown. Current study aimed to explore the 3-year longitudinal course of semantic memory deficits in first-episode schizophrenia patients.

**Methods**: First-episode schizophrenia patients (DSM-IV) were assessed prospectively at the point of first contact (A1), after clinical stabilization (A2), and each year for the following 3 years (Y1, Y2, Y3) using the categorization task. Patients are required to make decision (yes or no) on whether a "word" belonged to a "category". 40 pairs of words were divided into 4 categories: fruits, vegetables, furniture and clothing. The category (e.g., table) was subdivided into five degrees of semantic relatedness: (1) typical word of the category (e.g., table), (2) atypical of the category (e.g., bookcase), (3) borderline word (e.g., clock), (4) related but outside the category (e.g., painting) and (5) unrelated and outside the category (e.g., sun). Data on both reaction time and proportion of yes response were analyzed. Normal participants were assessed once.

**Results**: 37 first-episode schizophrenia patients and 37 normal were recruited (matched for gender, age and education). Five ANOVAs were carried out to detect the difference in the five semantic relatedness conditions between patients and control at each of the 5 timepoints. In the first ANOVA which compared
patients at A1 and control, reaction times in all conditions were slower in patients compared with control (F(1, 72) = 7.83, p = 0.007). Significant main effect of semantic relatedness condition (F(4, 288) = 12.30, p < 0.001) and interaction effect were also found (F(4, 288) = 4.88, p = 0.001). Post-hoc pairwise comparisons found the two groups were different with regard to typical (p = 0.006), related (p = 0.036), and unrelated condition (p < 0.001). Interestingly, the remaining ANOVAs produced the same results. Significant main effect of condition (p = 0.015, p < 0.001, p < 0.001, p < 0.001, respectively) was observed in patients at A2, Y1, Y2 and Y3 as compared with control. Besides, pairwise comparisons had suggested significant difference in all conditions (all with p < 0.001). Likewise, ANOVA was carried out in the yes response data and similar results were identified. Main effect of group was found at A1 only (F(1, 72) = 7.10, P = 0.009) but not the other timepoints.

**Discussion:** The data clearly show semantic memory abnormalities (slower reaction time and more error, i.e., more yes response in the outside the category condition) in first-episode schizophrenia as compared with normal. Intriguingly, they largely normalized following symptomatic recovery and remained stable for up to the first three years of the disorder, suggesting a state effect rather than a trait effect.

**Results:** Patients performed worse than controls in the 100-Hue Colour Test in the right eye (pt = 12.35 +/-0 4.09, ctrl = 8.98 +/-0 2.41; df = 44, t(44) = 3.40, p = 0.002) and left eye (pt = 12.39 +/-0 3.50, ctrl = 9.20 +/-0 2.63; df = 44, t(44) = 3.49, p = 0.001). Differences in scores between pt and ctrl groups were similar for the first and last trays. In a linear regression analysis, significant association of group with colour vision (p = 0.003) remained after controlling for age and gender. Estimated premorbid IQ was similar in patients and controls but current IQ was lower in patients at baseline (p = 0.03) and at follow-up (p = 0.03). Verbal learning was also worse in patients at baseline (p = 0.006) and at follow-up (p = 0.002). Spatial working memory was similar in both groups. Processing speed was slower in patients than controls at baseline (p = 0.001) and at follow-up (p = 0.001). No association was demonstrated between colour vision and IQ, verbal learning or processing speed at baseline or follow-up.

**Discussion:** Patients with schizophrenia had worse colour vision than healthy controls. Colour vision was not associated with IQ, verbal learning or processing speed but patients with schizophrenia performed worse than controls on all of these measures. Poor attention is unlikely to have accounted for worse colour vision in patients as their performance did not deteriorate progressively during testing but differences between groups remained similar in the first and last sections of the test. This study suggests that impaired colour vision in schizophrenia is not explained by a top-down model of cognitive deficits or impaired attention. Chromatic information is carried by parvocellular cells to the primary visual cortex, before joining the ventral stream to the inferior temporal gyrus, an area well-associated with schizophrenia pathology. Colour vision therefore deserves further investigation as a possible disease marker for schizophrenia.
Results: Multilevel linear regression analyses revealed that prodromal patients show larger increases in negative affect and psychotic symptom intensity associated with daily life stress when compared to healthy control subjects.

Discussion: Results of the present study demonstrate that subjects in the prodromal phase of psychosis show an increased sensitivity to stress in daily life. This is in line with findings from previous studies suggesting that stress-sensitivity is an indicator of the risk for psychotic disorder. However, these are preliminary results and replication is needed in a larger sample.

doi:10.1016/j.schres.2010.02.489

Poster 262
JUMPING TO CONCLUSIONS AND PSYCHOsis

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Background: Individuals with delusions have a tendency to jump to conclusions (JTC). This means that they request less information before making a decision, and are therefore more likely to reach an inaccurate decision. This construct is often measured using a probabilistic reasoning task, called “The Beads Task”. Using data from a case-control study of first-episode psychosis, we aim to compare data-gathering style between patients suffering their first episode of psychosis and non-clinical controls.

Methods: As part of the Genetics and Psychosis (GAP) study we collected JTC data on 64 patients with a first episode of psychosis and 57 non-clinical volunteers from the local population. We used two versions of the Beads Task: 85:15 and 60:40. In both versions, participants are required to seek information in order to make a decision. Jumping to conclusions was defined on the beads task as making a decision after two or fewer items. We also evaluated the accuracy of the answer, on the basis of the patient’s choice (right or wrong inference at the task).

Results: 43.8% (n=28) of cases compared to 24.6% (n=14) of controls reported a JTC reasoning bias at the ratio 85:15, p = .027. 34.4% (n = 22) of cases compared to 8.8% of controls (n = 5) reported a JTC reasoning bias at the ratio 60:40, p = .001. Moreover, in the ratio 60:40, 7.0% (n = 4) of cases compared to 23.4% (n = 15) of controls made inaccurate inferences, p = .027.

Discussion: JTC reasoning bias was significantly more prevalent in cases than controls, in both versions of the task, showing that the most difficult task (60:40) led to more errors than the less difficult one. Furthermore, the inaccuracy of the inference was higher in patients than controls, confirming that seeking for less information leads to wrong conclusions. The symptomatic and neuropsychological correlates of JTC will be examined in further analyses with the complete sample.

doi:10.1016/j.schres.2010.02.490
Background: The study of olfactory function in schizophrenia reveals various deficits of patients in discrimination, in memory tasks, in hedoncity and in familiarity judgments. In this pathology, odor identification impairment is frequently observed (Brewer et al., 2007, Moberg et al., 2006). Moreover it has been shown that this deficit is correlated with negative symptoms as flat affect, social withdraw and poor personal hygiene. Its impact on daily life seems to be consistent. In order to assess the performance of olfactory identification in the schizophrenic patients, our objective was to test and standardize a new testing procedure. Using an olfacto-visual tool we can calculate a score evaluating their difficulties in the expression of sensory perceptions. The designed olfacto-visual tool is based on associations between images of odorant sources and odorant stimuli. In parallel, we study the relationship between olfactory identification performance and schizophrenic symptoms.

Methods: We proposed several tenth of pleasant and unpleasant olfactory signatures of objects of the everyday life. The odorants and their corresponding visual images have been selected and validated by the general population. The identification task consists in designating one of a 5 images corresponding with the presented odour (forced choice). A computerized tool has been tested by 100 participants from the general population. Then, we have compared the results of two matched samples, 30 controls and 30 chronic schizophrenia patients aged from 18 to 65 years.

Results: The new olfactory-visual tool confirms that this pathological cohort shows an olfactory identification deficit. The patients identify less odorant items than controls and they spent more time to do it. In addition, we highlight the olfactory deficit correlation with schizophrenic symptoms. The effect is dependent on the hedonic value of odorants.

Discussion: Later, the odor and image sets will be used as a basis for olfactory training to reduce the identification deficit. In this way, we aim an olfactory remediation (orthosmia) probably to improve symptoms and everyday life of patients.

doi:10.1016/j.schres.2010.02.492
and deltoide dummies, (ii) practical tools for nonadherence (instruments, MEMS, etc), (iii) psychosocial methods of augmenting adherence and outcomes, (iv) specific programmes for reducing relapse (e.g, The Munich Compliance Program; shared care initiatives with general practitioners, and others), (v) expert software systems to aid in initiation, dosing, and switching to LAs (e.g. the Switchia® software package), (vi) specific outcome tools for routine assessment and international collaboration (e.g. the Multidimensional Incomplete Recovery CGI).

**Results:** In the first six months of the programme eight major training events have taken place on four continents (Sydney, Melbourne, Munich (twice), Barcelona, Seoul, Taipei, and Sao Paulo).

**Discussion:** The CERP education programme aims to provide a Background for experienced clinicians to consider service delivery changes at either a micro or macro level, to improve patient outcomes. Out of each training session we hope that at least one or two clinicians might wish to join the international CERP outcomes research network we are forming. To date this has been moderately successful with a number of centres expressing a commitment to the programme. Evaluation from participants and future directions for the programme will be discussed.

**doi:** 10.1016/j.schres.2010.02.494

**Poster 267**

**THE IMPACT OF A GENOME-WIDE SUPPORTED PSYCHOSIS VARIANT IN THE ZNF804A GENE ON MEMORY FUNCTION IN SCHIZOPHRENIA**

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**Background:** Recent genome-wide association study demonstrated that a genetic variant (rs1344706) in the ZNF804A gene was associated with schizophrenia. An association study between functional magnetic resonance imaging and the risk ZNF804A variant in healthy controls has showed abnormal connectivity as a core neurogenetic mechanism. Disconnectivity in the risk ZNF804A variant was found in reduced dorso-lateral prefrontal cortex (DLPFC) and increased coupling with hippocampal formation, which could contribute to disturbed cognitive function in schizophrenia. Schizophrenia is associated with wide-ranging deficits in neurocognitive function and these deficits, in particular memory impairments, are considered to be a core symptom to the pathophysiology of the illness. The aim of this study is to investigate an impact of the ZNF804A polymorphism (rs1344706) on memory function.

**Methods:** Subjects are 113 patients with schizophrenia and 184 healthy controls. They were biologically unrelated Japanese. Memory performance was measured by Wechsler Memory Scale-Revised in four major indices such as verbal memory, visual memory, attention/concentration and delayed recall. Genotyping was performed by the TaqMan method. The effect of the risk ZNF804A genotype, the effect of diagnosis and genotype-diagnosis interaction effects were analyzed by two way analysis of covariance (ANCOVA) with age, gender and education years as covariates.

**Results:** Consistent with previous studies, patients with schizophrenia had lower performances on all indices compared with healthy controls (p<.001). A significant ZNF804A genotype-diagnosis interaction was found on visual memory performance (p=.0012). We further provided evidence that patients with the risk T/T genotype had significantly lower scores on visual memory performance than those in G-carriers (p=.018). In contrast, there was no genotype effect in any index in controls (p>.05).

**Discussion:** These findings demonstrated that deficits in visual memory might be associated with a neurogenetic risk mechanism for schizophrenia. Our data also suggest that rs1344706 or variation in linkage disequilibrium may be functional in human cognitive function.

**doi:** 10.1016/j.schres.2010.02.1032

**Poster 268**

**COMTVal158Met POLYMORPHISM IN INTERACTION WITH DAILY STRESS: HOW COMT CONNECTS TO PSYCHOSIS**

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**Background:** It is widely acknowledged that neither genes nor environmental stress alone, but rather the interplay between genes and environmental stress, may sufficiently explain the development of psychosis. Primarily, the catechol-O-methyltransferase Val158Met polymorphism (COMT) is a promising candidate gene that might moderate the effects of stress on psychosis. Studies in general population samples predominantly found an increased risk for psychosis in carriers of two Val alleles, while a study in patients found a heightened stress-reactivity in Met/Met carriers. In the current study, a general population sample as well as a group of patients with psychosis was investigated to disentangle potential differential genetic effects in these groups. Specifically, we investigated i) whether group (control vs. patient) moderated the relationship between (affective and psychotic) reactivity to stress and the COMTVal158Met polymorphism; and in case of a significant interaction, ii) how the COMTVal158Met polymorphism moderated affective and psychotic reactivity to daily stress within the two groups.

**Methods:** Patients with a non-affective psychosis (n=89) and control participants (n=127) were studied with the Experience Sampling Method (a structured diary technique) in order to assess stress, negative affect and momentary psychotic symptoms in the reality of daily life.

**Results:** Multilevel analyses revealed a significant three-way interaction effect between group, COMT genotype and stress in the model of momentary psychosis (X²(2)=6.92, p<0.05) as well as in the model of negative affect (X²(2)=13.26, p<0.01). Thus, the moderating effect of the COMTVal158Met polymorphism on the effect of stress on negative affect and momentary psychosis differed between the groups. While there was no significant two-way interaction effect of COMT and stress in the control group, COMT was a significant moderator of the association between stress and negative affect and momentary psychosis in the patient group. Met/Met carriers of the patient group showed significantly increased psychotic and affective reactivity to stress in comparison to the Val/Met and Val/Val carriers.

**Discussion:** It was shown that the immediate effect of daily stress on psychosis and negative affect is not only conditional on COMTVal158Met genotype, but also conditional on group. Only in the patient group, COMTVal158Met genotype seems to contribute to differential sensitivity for environmental stress. Interestingly, effect sizes for the Val/Val and
Val/Met carriers were about the same in patients and controls and most prominent were the larger effect sizes in Met/Met patients, possibly due to epigenetic mechanisms.

doi:10.1016/j.schres.2010.02.1033

Poster 269
SYSTEMATIC REVIEW & STANDARDISED RECALCULATION OF INCIDENCE RATES FOR SCHIZOPHRENIA ACROSS THE LIFE SPAN

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Background: Genetic studies have generally used the broad concept of schizophrenia as the sole phenotype. However inconsistent results suggest that this construct does not demarcate a homogenous disease entity. Two approaches have been successfully used in studies of other complex diseases to reduce confounding from genetic heterogeneity. 1) sub-typing. 2) Stratification by age, sex and environmental covariates that are known to moderate the risk of the disorder. We present the findings of a systematic review and collaborative re analyses of primary incidence data across the whole life span. As age of onset is considered an important characteristic of most disease processes admixture models are used to identify age subtypes.

Methods: all articles (published between, 1950–2008) were identified. Data was extracted relating to moderator variables; e.g. case ascertainment, diagnostic criteria used, time and place characteristics of the study. Primary data was requested to allow age specific rates for each sample to be calculated, rather than making judgments on which paper to include when publications were not independent. Variation in incidence was summarised with quartiles and measures of central tendency (formal meta analyses using random effects models were also carried out) and the variation of the rates was plotted graphically using cumulative plots to show the cumulative percentage of the rate ratio in the incidence A random effect count model (Poission regression) for individual level effects of age and sex on incidence and an admixture analysis was performed.

Results: A total of 92 studies were identified, from 41 samples, drawn from 20 countries (primarily Western European) contained 662 different and potentially overlapping incidence rates. Median incidence rates over all 15/10000 while for the late onset group this fell to around 7.2/10000 and in the very late onset group 7.2/10000. Examining the late onset defined group, The distribution for men was relatively symmetrical with a mean rate of 3.84 (sd 1.71) median of 4.09 and the with 10%-90% quartiles of 1.4 - 5.85 per 100 000 and for females the mean rate was 4.07 (sd 1.87) median of 4.01 and 10%-90% quartile range of 1.44- 6.56. The admixture model suggest there are 3 underlying sub groups early age of onset (15–40) late onset (41-64) and very late onset group (>65). Poisson regression model demonstrates a monotonic decline in the incidence across age bands after the age of 40. There was an interaction with age and sex except in the over 70 group. city dwellers have an earlier age of onset.

Discussion: Schizophrenia is commoner in the over 40 age group, than previously thought. However the risk varies across the age span with males having a higher risk in the early age of onset, while this gender difference attenuates in middle age and is absent in the elderly. The age of onset varies with area level characteristics, so that urban environments are on average associated with an early age of onset than those living in rural settings. 3 subtypes can be identified by admixture analyses. The results from this first ever standardised recalculation of incidence rates suggests that subtyping and stratification result in more homogenous groups of individuals.

doi:10.1016/j.schres.2010.02.1034

Poster 270
INITIAL AGE AND AMOUNT OF CANNABIS EXPOSURE ARE STRONGLY ASSOCIATED WITH PSYCHOSIS VULNERABILITY IN A SAMPLE OF 18,000 DUTCH ADOLESCENTS

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Background: In Europe on average one in three adolescents between 15–24 years of age has used cannabis, and in 15 –16 year olds the lifetime prevalence varies from 10% to 31% (EMCDDA 2008). Several studies reported a dosage related association between cannabis use and the development of psychotic disorders which was more pronounced in young users (Moore et al. 2007; Mason et al. 2009; Macleod et al. 2004; Semple et al 2005; Arsenault et al. 2004). Such an increased vulnerability of young adults to cannabis exposure concurs with experimental studies that demonstrate that the impact of cannabis use on brain development is especially strong during early adolescence (Aasly et al. 1993; Monshouwer et al. 2006; Schneider 2008; Ehrenreich et al. 1999). The population health effects associated with early cannabis use may be a more sensitively measured by investigating the association of cannabis use with sub clinical psychotic symptoms. We investigated the association of these symptoms with starting age and amount of cannabis use.

Methods: A cross-sectional analysis of sub clinical psychotic symptoms measured with a web-based version of the Community Assessment of Psychic Experiences (CAPE) in a sample of Dutch adolescents. THC exposure was quantified as the amount of euros spent on cannabis per week. The main outcome measure was the odds ratio to belong to the highest 10% of scores on sub clinical psychotic symptoms.

Results: We collected data on 21,838 participants. After screening for incorrect responses on verification questions, 17,698 (81%) respondents remained (mean age 21.6 SD 4.2). Compared to the modal starting age (15 –18 years), the group that started before or on the age of 12 years had an odds ratio for a high score on psychotic symptoms, of 1.8 (95%CI 1.2 – 2.7). The odds ratio was particularly high for positive symptoms (3.1 (95%CI 2.1 – 4.3)). A dose response association was found for quantity of use, with odds ratios increasing from 1.0 (95%CI 0.8 – 1.1) in participants using sporadically or less than 1.1) in participants using sporadically or less than €3 weekly, to 3.5 (95%CI 2.9 – 4.3) in individuals spending more than €25 weekly. The cannabis naïve group was used as a reference category.

Discussion: We show that early and heavy uses of cannabis are clearly associated with sub clinical symptoms of psychosis. Early use is particularly correlated with positive symptoms and heavy use with negative symptoms and depression. Such a specific effect of cannabis use at a young age is in agreement with experimental studies and suggests that the impact of cannabis use on brain development and psychiatric symptoms is especially strong during puberty (Fergusson et al 2003; Aasly et al. 1993; Monshouwer et al. 2006; Schneider 2008; Ehrenreich et al. 1999). Moreover, the data fits studies showing that the biological impact of THC exposure is modulated by the influence of the endocannabinoid system on the release of dopamine and other neurotransmitters in early phases of brain development (Schneider 2008; Morrison et al. 2009; Lewis
AGE AT ONSET OF PSYCHOSIS IN PATIENTS WITH SCHIZOPHRENIA: EVIDENCE FOR A SEX-DEPENDENT INTERACTION BETWEEN BDNF VAL66MET GENOTYPE AND CANNABIS USE

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Background: Discovering modifiable predictors for age at onset may help to identify predictors of transition to psychosis in the 'at-risk mental state'. Previous studies inconsistently reported main effects of sex, BDNF Val66Met and cannabis, suggesting more complex models may be required. A sex-specific model of gene-environment interaction between BDNF Val66Met and cannabis use, affecting age at onset of psychosis, was hypothesized.

Methods: BDNF Val66Met and cannabis use before illness onset were assessed in a sample of 587 patients with schizophrenia. Survival analyses were fitted with time from birth to age at first admission as indicator for survival time.

Results: Mean age at onset was 24.6 years (SD 7.2, range 14.0–62.9). Sex (log-rank $\chi^2(1) = 40.1$, $p < .001$), BDNF Val66Met genotype (log-rank $\chi^2(1) = 3.8$, $p = .050$) and cannabis use (log-rank $\chi^2(1) = 22.1$, $p < .001$) were significantly associated with age at onset in univariable Log-rank survival analyses. Multivariable Cox regression confirmed the association with sex (HR 1.58, 95% CI 1.30 – 1.92, $p < .001$), cannabis use (HR 1.32, 95% CI 1.03 – 1.70, $p = .028$) and BDNF genotype (HR 1.24, 95% CI 1.04 – 1.48, $p = .018$) controlled for each other and the effects of other drug use (cocaine, stimulants, phencyclidine, psychedelics and opiates). Male patients, BDNF Met-carriers and cannabis users had an earlier onset of 3.7 years, 1.2 years and 2.7 years, respectively. Besides, age at onset was significantly predicted by the frequency of cannabis use in the most intense period (HR 1.27, 95% CI 1.05 – 1.54, $p = .016$) and a younger age at first use of cannabis (HR 1.41, 95% CI 1.17 – 1.70, $p < .001$), as shown by multivariable models controlling for the effects of other drug use and sex. However, the above reported main effects cannot reliably be interpreted as a significant BDNF X cannabis X sex three-way interaction was also found (interaction $\chi^2(1) = 4.99$, $p = .026$). In male patients, BDNF Val66Met (HR 1.97, 95% CI 1.45 – 2.68, $p < .001$) and cannabis (HR 2.30, 95% CI 1.57 – 2.79, $p < .001$) showed highly significant main effects without evidence for gene-environment interaction (interaction $\chi^2(1) = 0.04$, $p = .846$). In female patients, cannabis use and BDNF Val66Met only decreased age at onset (with more than 7 years) when present in combination (interaction $\chi^2(1) = 6.06$, $p = .014$).

Discussion: Sex, BDNF Val66Met and cannabis use are associated with age at onset of psychosis, but these associations cannot be interpreted without taking their interaction into account. Sex-specific effects of BDNF Val66Met genotype may help to explain individual differences in vulnerability for the effects of cannabis.
Poster 273
USE OF HIGH POTENCY CANNABIS IS PARTICULARLY ASSOCIATED WITH ONSET OF PSYCHOSIS

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Background: Epidemiological studies have reported that the risk of developing psychosis in cannabis users is dose related. Experimental research has shown that the active constituent of cannabis responsible for its psychotogenic effect is Delta-9-Tetrahydrocannabinol (THC). Recent evidence shows the potency (% THC) of the cannabis seized in the UK is increasing. Previous studies have also suggested that age at first use of cannabis might moderate the degree of risk for developing a psychotic disorder. We predicted that first episode psychosis patients would be more likely to have started using cannabis in early adolescence, to use higher potency cannabis and to use it more frequently than controls. Methods: We collected information concerning socio-demographic and clinical characteristics, and cannabis use (age at first use, frequency, length of use, type of cannabis used) from 280 first-episode psychosis (FEP) patients and 174 matched healthy volunteers in South London.

Results: There was no significant difference in the life-time prevalence of cannabis use or age at first use between cases and controls. Nevertheless, in the cases group age at first use was positively correlated with age of onset of psychosis: the earlier the age at first cannabis use, the earlier the onset of psychosis (z = 0.49; p < 0.001). After adjusting for age, gender, ethnicity, level of education, employment status, other stimulants use, cases were more likely to be regular users (OR = 6.4; 95% CI 3.2-28.6) and to have smoked high potency cannabis (skunk), (OR = 6.8; 95% CI 2.6-25.4) than controls. Given a prevalence of 44% for skunk use among our cases and an OR = 2.6 for skunk use in cases versus controls, we calculated a population attributable fraction (PAF) for skunk use = 27%.

Discussion: Patients with first episode psychosis have smoked higher potency cannabis (skunk), for longer and with greater frequency, than healthy controls. Moreover, age at first cannabis use significantly moderates age of onset for psychosis. Our findings also suggest that if skunk use was abolished 27% of the psychosis cases in South East London would be prevented.

doi:10.1016/j.schres.2010.02.1038

Poster 274
THE GENETIC ASSOCIATION BETWEEN CANCER AND SCHIZOPHRENIA: AN EPIDEMIOLOGICAL APPROACH

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Background: Several studies have found lower incidence of cancer among patients with schizophrenia compared to the general population. Considering the well documented inheritance in schizophrenia, the hypothesis that there is a protective genetic factor (against cancer) in patients with schizophrenia is plausible. If the reduced incidence of cancer among schizophrenia patients is related to a genetic factor, it is expected that reduced incidence will be found also among their first degree relatives. Indeed, a recent epidemiological study conducted in Israel indicated a reduced risk of several cancer sites among parents of schizophrenia patients. We have further studied the genetic hypothesis by comparing parents of schizophrenia patients, studying the relationship between schizophrenia and cancer within our population. Cancer rates were compared between parents of schizophrenia patients with a known family history of schizophrenia (“high” genetic load) to that of parents of patients with no such family history (“low” genetic load). We hypothesized that lower cancer rates will be found in parents of patients with a high genetic load compared to parents with low genetic load. This study adds important information to the genetic hypothesis of the association between cancer and schizophrenia.

Methods: The study was based on cross linkage between two national data bases in Israel: the Psychiatric Registry and the Cancer Registry. The data includes 7,014 schizophrenia patients and 37,653 of their FDR. A familial aggregation measure for schizophrenia was calculated for each subject according to the Bayesian theorem, and serve as a genetic weight measure. The calculation accounted for the number of members diagnosed with schizophrenia and the number of family members. Each sibship (proband and sibs) had an identical weight value, while each parent had a weight value independent of the other parent’s weight. The relationship between schizophrenia and cancer was examined within our population. The first analysis was conducted on parents’ data using logistic regression by the method of Generalized Estimating Equations (GEE), appropriate for correlated data arising from repeated measurements. The outcome was cancer (yes/no) and the main predictor was the genetic measure in its continuous form. Separate analyses were used to evaluate the association between schizophrenia and specific cancers according to an a priori hypotheses.

Results: Contrary to the hypothesis a significant increased risk for any cancer site was observed among parents of schizophrenia patients. The adjusted analysis indicated an increase of 14% (95% CI 1.03-1.26), and an increase of 23% for colon cancer (95% CI 1.01-1.52) for 10% increase in the genetic weight.

Discussion: Significantly increased risk for cancer as a function of the genetic load of schizophrenia was observed among parents of schizophrenia patients. Thus, the genetic load as defined by familial reoccurrence of schizophrenia was associated with an increased rather then decreased risk for cancer site. These outcomes do not support the genetic hypothesis of the association between cancer and schizophrenia.

doi:10.1016/j.schres.2010.02.1039

POSTER SESSION 2 & LUNCH
Monday, 12 April, 2010 12:00pm-1:30pm

Poster 1
MEASURING AUTISTIC TRAITS IN PATIENTS WITH SCHIZOPHRENIA

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Background: Schizophrenia and Asperger syndrome are operationalised diagnoses that are separated clinically according to age of onset, symptom profile and outcome. Still, the disorders have major difficulties in common: neurocognitive deficits as well as deficits in social cognition. Autism-Spectrum Quotient (AQ) is a widely used instrument for investigating autistic traits in different populations. However, it is not well known if a diagnosis of schizophrenia influences the result on AQ. We wanted to examine autistic traits...
Poster 2
WORKING MEMORY IMPAIRMENTS IN SCHIZOPHRENIA AS VALID PREDICTORS OF ILLNESS SEVERITY AND FUNCTIONAL OUTCOME

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Background: Clinical studies consistently report a close link between working memory impairments and schizophrenia (Braver et al., 1997, Keeffe et al., 2004, Ritter et al., 2004, Tan et al., 2006, Lesson et al., 2007). Such working memory impairments (e.g., executive attention failure, Kane & Engle, 2002) are mainly related to dorsolateral prefrontal cortex hypofunction (Kane & Engle, 2002, Jansama et al., 2004, Tan et al., 2006). The present study attempts to bridge between neurocognitive research and the clinic by proposing a novel neuro-diagnostic tool to evaluate working memory impairments in medicated schizophrenia patients, and to support the use of executive attention differences as predictors of disease psychopathology and functional-outcome (e.g., level of recovery scale, Schrank & Slade, 2007).

Methods: The present study utilizes standard and revised versions of the n-Back task (Smith et al., 1996, Krieger et al., 2005 Tan et al., 2006,) for the measurement of executive attention differences in medicated schizophrenia patients (MSZ) and in healthy individuals (HG). Prior to performing the n-Back task, MSZ (N = 32) were clinically evaluated using the PANSS (Kay et al., 2004) symptom-severity rating scales by two trained clinicians. HG (N = 30) provided their medical and psychiatric history prior to executive attention testing. In both study groups, the computerized task consisted of two consecutive 10-minute blocks, where the first block (e.g., control block) was always the standard version of the task and the next block (e.g., experimental blocks) was one out of three different revised versions of the n-Back task. The dependent variable (e.g., response accuracy) on the working memory blocks was number of correct responses.

Results: The control block was internally consistent in both HG and MSZ. Coefficient alphas were .90, and .917, respectively. The HG had significantly greater number of correct responses than the MSZ (t = -6.03, p < .0001). Most importantly, accuracy scores on the control block predicted psychopathological dimension scores in MSZ. Specifically, patients who scored equal to or below the average score (i.e., lower performing group) of the control block scored significantly higher on the negative symptoms scale (t = -2.26, p <.05) than patients who scored above the average (e.g., higher performing group). Moreover, there were significant correlations of accuracy scores with delusions (r = -.843, p = .017), total PANSS score (r = -.465, p = .007), and functional-performance (r = .526, p = .002); control block accuracy scores seem to provide a valid cognitive deficit index for assessing the patient’s current clinical condition. Multiple regression analysis predicting functional outcome (R = .569, SE = .76, F = 4.45, p = .011) revealed that both delusion and total PANSS scores were significantly correlated only with control block accuracy scores. However, in contrast to symptom-severity scores, accuracy scores on the control block were found to be an exclusive significant predictor (b = .481, p = .02) of functional outcome.

Discussion: Our results suggest that the standard version of the n-Back task is a reliable and valid measurement of working memory impairments in medicated schizophrenia patients. The present findings could support the construction of a reliable neurocognitive diagnostic tool, that could offer a clinically valid working memory impairment measurement that “specifically assesses important cognitive deficits” (Keeffe et al., 2004) in schizophrenia.

doi:10.1016/j.schres.2010.02.496
prodromal syndromes (SIPS) were conducted. Also, the social functioning scale was conducted. The protocol was approved by the ethical committee of Toho University School of Medicine.

Results: The subjects were 35 cases (11 men, 31.4%) with mean age of 23.2 ± 6.8. In the sixth month, 27 cases were continuously followed up, and 4 cases out of them exposed obvious psychotic symptoms (14.8%). As for the 23 cases which didn't shift to psychosis in the sixth month, because the median of the treatment period with neuroleptics was 140 days, we divided into long medication group (N = 11, group A) for more than 141 days and short medication group (N = 12, group B) for 0 to 140 days. Then we examined the baseline condition by using the Mann-Whitney U-test. There were significant differences in the “Independence” of the SFS (P = 0.002, A: 18.6 ± 5.8, B: 25.5 ± 5.0), in the PS-R scores (P = 0.018, A: 40.5 ± 8.3, B: 32.4 ± 8.4), and “Unusual thought content /delusion” of SIPS (P = 0.010, A: 5.0 ± 0.7, B: 4.2 ± 0.8).

Discussion: Although distinction between the false positive case and the false false-positive case is difficult, prudent judgment is required for conducting the invasive intervention such as pharmaceutical therapy. Being able to make such distinction is significantly meaningful therapeutically, further studies are promisingly needed.

doi:10.1016/j.schres.2010.02.498

Poster 4
DETECTION OF PATIENTS AT RISK FOR PSYCHOSIS BY SCREENING THE HELP-SEEKING POPULATION REFERRED TO MENTAL HEALTH CARE SERVICES BY A SELF-REPORT QUESTIONNAIRE

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Background: Early detection and treatment of first psychotic episodes might improve prognosis. Since the first episode is commonly preceded by precursor symptoms, known as an at risk mental state (ARMS), the recognition of this state might offer an important way to reduce duration of untreated psychosis. These people often seek help for different reasons, and will not be recognized by regular mental health care services.

Methods: Patients who were referred from February 2008 to November 2009 to PsyQ Haaglanden (MHCS The Hague, The Netherlands) for any type of psychiatric distress, aged 14–35 years, were screened with the prodromal questionnaire (PQ; Loey, Cannon et al., 2005) a self-report screening tool for prodromal and psychotic syndromes. Individuals with cut-off scores equaling or above 18 on the positive symptom subscale were interviewed using the Comprehensive Assessment of At Risk Mental States (CAARMS) interview (Yung, 2005) to determine whether they met criteria for an at risk mental state (ARMS) for psychosis. An additional criterion was decline in social functioning during the past year as reflected by SOFAS scores. Individuals were assigned to either: first psychotic episode, one of the three ARMS groups (genetic liability, attenuated symptoms, or brief limited intermittent psychosis), more than 141 days and short medication group (N = 12, group B) for 0 to 140 days. Then we examined the baseline condition by using the Mann-Whitney U-test. There were significant differences in the “Independence” of the SFS (P = 0.002, A: 18.6 ± 5.8, B: 25.5 ± 5.0), in the PS-R scores (P = 0.018, A: 40.5 ± 8.3, B: 32.4 ± 8.4), and “Unusual thought content /delusion” of SIPS (P = 0.010, A: 5.0 ± 0.7, B: 4.2 ± 0.8).

Discussion: Although distinction between the false positive case and the false false-positive case is difficult, prudent judgment is required for conducting the invasive intervention such as pharmaceutical therapy. Being able to make such distinction is significantly meaningful therapeutically, further studies are promisingly needed.

doi:10.1016/j.schres.2010.02.498

Poster 5
PRESCRIPTION OF ANTIPSYCHOTIC MEDICATION TO PATIENTS AT ULTRA HIGH RISK FOR DEVELOPING PSYCHOSIS IN A NATURALISTIC SETTING

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Background: Little is known about medication prescription in a naturalistic setting to patients at ultra high risk (UHR) for developing psychosis. Antipsychotic medication prescription to UHR patients is not recommended in international clinical practice guidelines based on the current evidence. The aim of this study is to investigate medication prescription to UHR patients in the Netherlands.

Methods: Most patients were referred for a second opinion by practitioners in secondary mental healthcare institutions who suspected UHR status. Diagnostic evaluation was performed in 251 patients, of which 72 patients (28.7%) had UHR symptoms and 90 patients (35.9%) were diagnosed with a florid psychotic disorder. Frequency of antipsychotic medication prescription to UHR patients was compared with frequency of antipsychotic medication prescription to patients who were diagnosed with a DSM-IV psychotic disorder at first diagnostic evaluation. Within the UHR group, frequency of antipsychotic medication prescription at baseline was compared between UHR patients who made the transition to psychosis at follow up (n = 18) and UHR patients who did not make the transition to psychosis (n = 54).

Results: No significant differences were found in antipsychotic medication prescription to UHR patients and to patients who turned out to have a florid psychosis: 51% in the psychotic group and 58% in the UHR group used no medication. 34% in the psychotic group and 21% in the UHR group used antipsychotic medication. There was also no difference in medication prescription between UHR patients who did and did not make the transition to psychosis.

Discussion: About one fifth of the UHR patients already received antipsychotic medication despite international clinical practice guidelines. More research should be aimed at developing and implementing clinical practice guidelines for the treatment of UHR patients. About half of the psychotic patients were not yet prescribed antipsychotic medication. Implementation of early detection of psychosis programs may possibly aid in detecting psychosis as early as possible, also in mental health care institutions.

doi:10.1016/j.schres.2010.02.500

Poster 6
VALIDITY OF A SHORT DIAGNOSTIC INSTRUMENT IN PSYCHIATRY: THE MINI-SCAN

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Background: Reliability of psychiatric diagnosis is generally less than satisfactory, in spite of the generally accepted use of classification yields an enriched population. Further screening with CAARMS is feasible and a substantial number of these patients show an at risk mental state or an undetected first episode.

doi:10.1016/j.schres.2010.02.499
RESULTS: The comparison of the IQC-scale scores between the analysed groups yielded the following results: a significant difference between MP and HC occurred for initiation (p ≤ 0.001), self-disclosure (p ≤ 0.008) and emotional support (p ≤ 0.002) whereupon HC scored higher than MP. Concerning the comparison of MP and HC self-disclosure (p ≤ 0.015) and emotional support (p ≤ 0.003) showed significant differences (HC > MP). No significant results were obtained regarding the contrast between HR and MP. Differences between the rating of ICbeh and ICFc were found for four scales in the HC and the HR sample (assertion: pHC ≤ 0.005; phr ≤ 0.000; self-disclosure: pHC ≤ 0.042, phr ≤ 0.002; emotional support: pHC ≤ 0.048, phr ≤ 0.050; conflicts: pHC ≤ 0.010, phr ≤ 0.004). For the MP different answering patterns for ICbeh and ICFc were gained on two scales (assertion: pMP ≤ 0.007; conflicts: pMP ≤ 0.005, pHC ≤ 0.004).

Discussion: Our preliminary findings suggest that a separate consideration of behavioural and emotional facets of interpersonal competence might be reasonable for certain interpersonal skills. Skills training focussing only on the behavioural dimension of a certain competence might be less effective, as persons with a high feeling of inconvenience may tend to avoid the utilisation of the behaviourally learned skills. Thus, it seems promising to further evaluate the two-dimensional approach. Furthermore our results revealed that individuals at high risk for psychosis described their interpersonal competence as just as impaired as patients with manifest psychosis. It will be important to further elucidate, if this is a consequence or a source of the functional deficits described in several studies for the pre-psychotic phase.

doi:10.1016/j.schres.2010.02.502
Poster 9
BASIC SYMPTOMS OF PRODROMAL SCHIZOPHRENIA IN A NON-CLINICAL SAMPLE

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Background: Basic Symptoms, as measured by the Schizophrenia Proneness Instrument-Adult (SPIA), are subtle perceptual and cognitive symptoms that occur in “at risk” or prodromal states and predict transition to psychosis in clinic samples. It is unclear in non-clinical samples what their nature and aetiology is; or how specific they are to prodrome-like states. We assessed Manchester University’s students and staff for basic symptoms and two sets of symptoms criteria for high risk of psychosis: EIPS and COGDIS criteria. Subjective and objective neurocognitive deficits, schizotypy and substance misuse were predicted to lead to basic symptoms. Stress was predicted to moderate cognitive deficits’ and schizotypy’s relationships with SPIA; and neurosis to have no independent effect.

Methods: 1283 people completed a screen (including the Schizotypal Personality Questionnaire, SPQ) on our intranet. 134 aged 18-30 who indicated willingness to be contacted and had moderate-high SPQ scores (scores >0.5 SD below mean) were approached. 60 agreed to a follow-up interview including: the SPIA; MINI psychiatric interview; PSS (Perceived Stress Scale); CFQ (subjective Cognitive Failures Questionnaire); and executive and attentional tests.

Results: 30 met MINI criteria for affective disorder or neurosis, 19 for recent substance misuse (10 both). Substance misuse did not predict SPIA score, nor did SPQ, nor did neuropsychological test scores. On linear regression, neurosis (beta 0.30), CFQ (beta 0.35) and younger age (beta -0.22) independently predicted higher (normalized) SPIA score. Sex and PSS score (beta 0.18) were non-significant predictors in the same analysis, though PSS correlated significantly with SPIA. PSS score did not interact with SPQ or neuropsychological scores to predict SPIA. Male sex, neurosis (or stress), high CFQ and youth predicted meeting EIPS criteria. Stress (or neurosis), high CFQ and youth predicted meeting COGDIS criteria. Stress and executive tests predicted subjective cognitive failures directly and stress increased deficits’ effect.

Discussion: Schizotypy, neuropsychological tasks and substance misuse failed to predict SPIA score. Diagnosis of a neurotic disorder was a better predictor than subjective stress for COGDIS but not EIPS criteria. States marked by subjective cognitive failures were sometimes also marked by basic symptoms and meeting “at risk” criteria. Executive deficits and stress predict these states, stress potentiating objective deficits’ translation to subjective failures.

doi:10.1016/j.schres.2010.02.504

Poster 10
SCHIZOTYPAL PERSONALITY DISORDER AND THE 22Q11.2 DELETION SYNDROME: THE RELATIONSHIP BETWEEN PRODROMAL SYMPTOMS AND AUTISTIC FEATURES

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Background: Autistic disorder and schizophrenia are considered to be two of the most disabling psychiatric disorders. While now considered to be two distinct disorders, both show considerable overlap in their symptomology, particularly at the milder end of the disorder spectrums. Given that both SPD and 22qDS have been associated with autistic features, comparing these two disorders with respect to the presence and severity of autistic features will provide insight into developmental similarities and differences between the two diagnostic groups. A second aim is to extend past research findings on psychotic-spectrum symptoms in SPD and 22qDS by examining the nature and severity of their prodromal symptoms.

Methods: Participants were ascertained from a 5-year Prodromal Study and 22qDS Registry at Emory University in Atlanta, Georgia. The Structured Interview for DSM-IV Personality Disorders (SIDP-IV) was administered to determine PD diagnoses, and FISH analysis was used to confirm presence of 22q11.2 deletion. Furthermore, the Structured Interview for Prodromal Syndromes (SIPS) was used to measure severity of prodromal symptoms, and the Autism Diagnostic Inventory-Revised (ADI-R) was administered to assess severity of childhood and current autistic features. Analysis of variance (ANOVA) and Pearson correlation coefficients were conducted to examine relationships among variables.

Results: Results showed that the the SPD group had the highest SIPS positive symptoms, and both the SPD and 22qDS groups had higher scores than other PD and no PD on all SIPS symptom dimensions. However, the SPD and 22qDS groups did not differ on SIPS negative, disorganized, or general symptoms. The SPD and 22qDS groups did not differ on childhood or current unusual interests and behaviors, or current social functioning (ADI-R). The SPD group scored significantly higher on childhood social functioning and communication problems, while the 22qDS group scored higher on current communication problems. Within the SPD sample, all SIPS symptom dimensions, except for disorganized, were correlated with both childhood and current autistic features. Within the 22qDS sample, only the negative and disorganized SIPS symptom dimensions were correlated with autistic features.

Discussion: The current study demonstrates that individuals with SPD and those with 22qDS differ from individuals with other PDs and normal controls on a number of prodromal symptoms and dimensions of autistic features, but do not differ from one another on these characteristics. These findings complement earlier research on the higher prevalence of schizophrenia and autistic disorders in individuals with 22qDS, in that those with SPD and 22qDS do not differ phenomenologically from one other on several important indicators of the schizophrenia prodrome or autistic-like syndromes. Results highlight implications for potential overlapping genetic etiologies, particularly since 22qDS is an established genetic disorder and SPD is genetically associated with schizophrenia. Limitations include age differences between groups, retrospective assessment of childhood symptoms, and cross-sectional measurement of current symptoms. Current results are preliminary, and future directions include incorporating hierarchical analyses to examine more complex relationships among the variables as well as associations among prodromal symptoms, autistic features, and COMT risk alleles.

doi:10.1016/j.schres.2010.02.505

Poster 11
MOTIVATIONAL DEFICITS IN SCHIZOPHRENIA: CROSS-SECTIONAL AND LONGITUDINAL RELATIONSHIPS WITH FUNCTIONING

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Background: Schizotypal personality disorder and schizophrenia are considered to be two distinct disorders, both showing considerable overlap in their symptomology, particularly at the milder end of the disorder spectrums. Given that both SPD and 22qDS have been associated with autistic features, comparing these two disorders with respect to the presence and severity of autistic features will provide insight into developmental similarities and differences between the two diagnostic groups. A second aim is to extend past research findings on psychotic-spectrum symptoms in SPD and 22qDS by examining the nature and severity of their prodromal symptoms.

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Results: Results showed that the the SPD group had the highest SIPS positive symptoms, and both the SPD and 22qDS groups had higher scores than other PD and no PD on all SIPS symptom dimensions. However, the SPD and 22qDS groups did not differ on SIPS negative, disorganized, or general symptoms. The SPD and 22qDS groups did not differ on childhood or current unusual interests and behaviors, or current social functioning (ADI-R). The SPD group scored significantly higher on childhood social functioning and communication problems, while the 22qDS group scored higher on current communication problems. Within the SPD sample, all SIPS symptom dimensions, except for disorganized, were correlated with both childhood and current autistic features. Within the 22qDS sample, only the negative and disorganized SIPS symptom dimensions were correlated with autistic features.

Discussion: The current study demonstrates that individuals with SPD and those with 22qDS differ from individuals with other PDs and normal controls on a number of prodromal symptoms and dimensions of autistic features, but do not differ from one another on these characteristics. These findings complement earlier research on the higher prevalence of schizophrenia and autistic disorders in individuals with 22qDS, in that those with SPD and 22qDS do not differ phenomenologically from one other on several important indicators of the schizophrenia prodrome or autistic-like syndromes. Results highlight implications for potential overlapping genetic etiologies, particularly since 22qDS is an established genetic disorder and SPD is genetically associated with schizophrenia. Limitations include age differences between groups, retrospective assessment of childhood symptoms, and cross-sectional measurement of current symptoms. Current results are preliminary, and future directions include incorporating hierarchical analyses to examine more complex relationships among the variables as well as associations among prodromal symptoms, autistic features, and COMT risk alleles.

doi:10.1016/j.schres.2010.02.505
**Background:** The negative symptoms of schizophrenia are comprised of two key symptom subdomains: 1) diminished expression (affective flattening and poverty of speech); and 2) amotivation (apathy and anhedonia), and contribute to functional impairment in this illness. Recent data, including our own work, suggests that motivational deficits serve as a critical determinant to functioning. This study aims to explore the longitudinal relationship between motivational and pleasure deficits, cognitive dysfunction, and functional outcomes in schizophrenia. We hypothesize that motivational deficits are the critical determinant of both current and future functioning in individuals with schizophrenia.

**Methods:** Outpatients between the ages of 18 and 55 with a diagnosis of schizophrenia, on stable doses of antipsychotic medication, were evaluated at baseline and 6 months later with the Scales for the Assessment of Positive Symptoms (SAPS) and Negative Symptoms (SANS). Amotivation was assessed with the Apathy Evaluation Scale – Clinician version (AES-C), anticipatory/consummatory pleasure with the Temporal Experience of Pleasure Scale (TEPS), and cognition with the Brief Assessment of Cognition in Schizophrenia (BACS). The Quality of Life Scale (QLS) was used to evaluate functional status.

**Results:** Nineteen participants (mean age of 42 years, mean duration of illness of 15 years) were assessed at both baseline and 6 months. Stepwise hierarchical regression revealed that baseline amotivation, as measured by the AES-C, was the strongest predictor of both baseline and future functioning, as measured by the QLS. Specifically, AES-C scores accounted for 75% of the variance in baseline functioning (R2 change = 0.749, p < .001), and 73% of the variance in functioning at 6-month follow-up (R2 change = 0.727, p < .001). After exclusion of the Intrapsychic Foundations subscale of the QLS due to overlap in item content with amotivation measures, the AES-C score continued to be the strongest predictor of functioning at baseline and follow-up, accounting for 65% and 64% of the variance in functioning, respectively. Positive symptoms (SAPS total score) explained an additional 7% and 5% of the variance in functioning at baseline and follow-up, respectively. Further, amotivation measured by the SANS amotivation subdomain explained an additional 8% and 10% of the variance in functioning at baseline and follow-up, respectively. Other measures including TEPS anticipatory/consummatory pleasure scores, and BACS composite score did not offer additional predictive value.

**Discussion:** Negative symptoms have been implicated in poor functional outcome, with recent work suggesting that motivational deficits are the central link between negative symptoms and poor functioning. The present data take this issue a step further and examine the longitudinal relationship between the negative symptoms of schizophrenia and functional outcomes. In keeping with the cross-sectional findings, motivational deficits appear to play a pivotal role in predicting longitudinal functional outcomes in schizophrenia, with other symptom domains offering little, if any, additional contribution. These preliminary findings highlight the importance of motivational deficits in schizophrenia, and suggest that it is this loss of drive that links negative symptoms to poor functional outcomes.

doi:10.1016/j.schres.2010.02.506

**Poster 12**

**PHENOMENOLOGICAL DIFFERENCES BETWEEN HISPANIC AND CAUCASIAN SCHIZOPHRENIA SUBJECTS**

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**Background:** Phenotypic differences between ethnic groups could be an important source of variation in psychiatric genetic studies of schizophrenia, with prior studies suggesting differences in symptom expression in patients from different ethnic Backgrounds. Studies from the 1960s to early 1980s reported a tendency for higher disorganization and impairment among Hispanics than among nonminority patients with schizophrenia. Studies from the 1980s to date report neither difference or a tendency to higher impairment in the nonminority group. Other reports have mentioned ethnic differences on hallucinations, suspiciousness, excitement and somatic concerns. Therefore, we examined whether the symptom profiles of a sample of Hispanic patients with schizophrenia differed from a cohort of Caucasian patients collected in the context of a molecular genetic study.

**Methods:** One hundred and thirty nine outpatients with a DSM-IV diagnosis of either schizophrenia or schizoaffective disorder were recruited from two sites. The group included 109 Caucasian and 30 Hispanic patients. Diagnosis was confirmed using the Structured Clinical Interview for DSM–IV (SCID, version 2.0). We included patients between 18 and 59 years of age, with no current substance abuse (within the past 6 months), no mental retardation, no seizure disorder and no known genetic disorder. Additionally, to insure symptom stability we excluded any patient with a prior psychiatric hospitalization within the past 6 months. Subjects’ psychopathology was rated using the Brief Psychiatric Rating Scale (BPRS), and the Hamilton Depression Rating Scale (HAM-D).

**Results:** There were no significant differences between groups in sex distribution (73% males in Hispanic group and 64% males in Caucasian group) but Caucasian patients were significantly older (Mean age: 46.3 +/- 9.2) than Hispanic patients (Mean age: 40 +/- 10) (p = <0.001), had a higher level of education (Mean:13.6 +/- 3.3 years) than Hispanic patients (Mean: 11.4 +/- 2.6 years) (p = 0.003) and 94% of Caucasians had English as a primary language compared to 48% of Hispanics (p < 0.001)). There were no group differences in the overall BPRS ratings but there were differences in individual items. Caucasian patients rated significantly higher on the anxiety item (p = 0.03) and Hispanic patients had significantly higher ratings of thought disorganization (p = 0.01). There were no significant differences in the overall HAM-D ratings between groups but analysis of individual items showed that Caucasian patients scored significantly higher on the psychic anxiety item (p = 0.005) compared to Hispanic patients.

**Discussion:** Caucasian and Hispanic patients with schizophrenia differ in the presentation of certain symptoms. Our results show that Hispanics have a higher degree of thought disorganization while Caucasians present with more prominent anxiety. Contrary to some prior reports, we did not find any group differences in hallucinatory behavior, unusual thought content, or suspiciousness. Examination of larger Hispanic and Caucasian samples may allow for a more refined characterization of symptom domains such as thought disorder and/or anxiety symptoms in patients with schizophrenia.

doi:10.1016/j.schres.2010.02.507

**Poster 13**

**SEX DIFFERENCES IN SYMPTOM PRESENTATION IN INDIVIDUALS AT RISK FOR PSYCHOSIS**

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Background: The psychosis prodrome is defined as a period of changes or deterioration of heterogeneous subjective and behavioral symptoms preceding the onset of psychosis (Yung & McGorry, 1996). The literature in this area is unclear on the chronological ordering of symptom onset and progression. Although several studies indicate “nonspecific” mood and anxiety symptoms and/or negative symptoms precede the onset of positive symptoms in most cases (Yung, 2007; Yung & McGorry, 1996; Häfner et al., 2005a; Häfner et al., 2005b; Häfner et al., 2008), other studies have not found evidence supporting this pattern (Cunningham Owens et al., 2005; Myles-Worsley et al., 2007; Krabbendam et al., 2005). Many studies suggest sex differences in symptom presentation in schizophrenia, especially in severity of negative symptoms (Taylor & Langdon, 2006; Shtasel et al., 1992; Bardenstein & McGlashan, 1990), therefore it is possible that there will be sex differences in symptom presentation in the prodrome. This study examines the presence of sex differences in symptom presentation in a sample of participants at high risk for psychosis at baseline and six month follow-up.

Methods: The subjects of this study are 230 participants (40% female; mean age 18.62 years, SD = 4.72) who met prodromal criteria in the North American Prodrome Longitudinal Study (Addington et al., 2007) and for whom ratings were conducted for all symptom scales on the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2002), as well as the accompanying severity scale, the Scale of Prodromal Symptoms (SOPS).

Results: Males had significantly higher levels of negative and disorganized symptoms at baseline and follow up, but males and females did not differ in levels of positive symptoms at baseline or follow up. Although males and females did not differ in levels of overall general symptoms, there were significant sex differences in levels of several of the individual symptoms (sleep disturbance, dysphoric mood, and motor disturbance) that comprise the index. Females had significantly higher levels of sleep disturbance and dysphoric mood at baseline, whereas males experienced higher levels of motor disturbance. However, there were no sex differences in these symptoms at follow up. Future analyses will investigate patterns of symptom onset and progression that predict conversion to psychosis.

Discussion: Consistent with the pattern observed in patients diagnosed with schizophrenia, male prodromal subjects had higher levels of negative and disorganized symptoms at baseline and follow-up. Prodromal females showed higher levels of nonspecific/ affective symptoms at baseline, but females experienced a more dramatic decrease in these symptoms than males over time, eradicating the sex difference at follow up. The absence of sex differences in positive symptoms might result from recruitment procedures that target prodromal levels of positive symptoms.

doi:10.1016/j.schres.2010.02.508

Poster 14
DIAGNOSTIC STABILITY OF BRIEF PSYCHOTIC DISORDER
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Background: The diagnostic stability of ATPD is known to be between 30 to 60%. Although brief psychotic disorder (BPD) and acute transient psychotic disorder (ATPD) have similar concepts, BPD evolves more rapidly, has a shorter duration, and is expected to have a better prognosis, but evidence supporting this is scarce. The aim of this study was to investigate the diagnostic stability of BPD.

Methods: This retrospective chart review was based on all BPD patients who had a first-ever admission, and were readmitted at least once, to the psychiatric ward of the Asan Medical Center, from 1988 to 2009. All diagnoses were reviewed by an experienced research psychiatrist (Y. Hong).

Results: Thirty-five subjects met our inclusion criteria. The mean age at first admission with BPD was 23.2±9.3 (14-64) years and the majority (74.2%) of patients was female. At a median follow-up of 2782.5±1838.8 (92-7140) days, 3.3±1.6 (2-9) episodes developed so mean interepisode interval was 959.5±679.5 (46-3570) days. The number of cases in the ‘diagnostically stable’ group was 11, with an overall stability rate of only 31.4%. The number of subjects whose diagnosis changed increased with each subsequent admission; the diagnosis of more than half was changed to bipolar I disorder (n = 13), schizophrenia (n = 5), schizoaffective disorder (n = 2), or other disorders (n = 4). Except for just one episode, bipolar I disorder patients relapsed with a manic episode, with or without psychotic features. Almost no interepisode depressive features were observed. And a substantial proportion (63.6%) had maintained their jobs including subjects whose diagnosis was changed later to schizophrenia. This indicates patients with either schizophrenia or Bipolar disorders, with an onset as BPD may have a better prognosis compared to those who do not.

Discussion: BPD patients had a high possibility of conversion to schizophrenia or bipolar spectrum disorder. However, in those cases, they still showed prominently better outcomes compared to patients who were originally diagnosed with schizophrenia or bipolar disorder.

doi:10.1016/j.schres.2010.02.509

Poster 15
NEGOTIATING ACCESS TO FIRST-EPISTODE PSYCHOSIS SERVICES: THE EXPERIENCE OF FIRST-TIME PRIMARY CARERGIVERS
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Background: Easy access to first-episode psychosis (FEP) services is critical in reducing the duration of untreated illness. However, primary caregivers can encounter difficulties accessing services on behalf of young people with FEP. This study aimed to understand the lived experience of first-time primary caregivers accessing FEP services, with a focus on examining how they accessed specialist FEP services and navigated relevant barriers to care.

Methods: Twenty primary caregivers were recruited through case managers at Orygen Youth Health, a specialist FEP service in Melbourne, Australia. Participants took part in in-depth, audio-recorded interviews. An interpretative phenomenological analysis of the data was undertaken using Smith and Osborn’s (2004) flexible framework for analysis.

Results: Four competing themes were apparent in the data, reflecting caregivers’ polarised experiences accessing and using FEP services. (i) Encountering barriers accessing services. Carers frequently encountered a range of barriers accessing services, extending from problems negotiating admission to services to their lack of awareness of the existence and location of specialist services. These barriers were reflected in two interrelated sub-themes: FEP service-focused barriers, and carer-focused barriers. (ii) Carers’ knowledge, experience and assertiveness enhancing access. As carers experienced difficulties accessing FEP services, particularly initially, they began to develop strategies to heighten their chances of success on subsequent occasions. Acquired knowledge and experience increased their confidence. (iii) Services being approachable and supportive. Once they gained access to FEP
services, carers generally considered clinicians approachable and responsive to their needs. They felt they were listened to and their situation taken seriously. (iv) Feeling undervalued as a carer: While, overall, clinicians were perceived as approachable and supportive, a competing theme is that some carers felt their contributions were undervalued and concerns were not listened to or taken seriously. This is reflected in two overlapping sub-themes: balancing confidentiality with the need-to-know, and not being taken seriously.

Discussion: Accessing FEP services results in both negative and positive experiences and these competing situations are interrelated. Our findings highlight a number of key implications for primary caregivers, family workers, clinicians, and FEP services. First, greater awareness is needed of the contribution, experience and difficulties first-time primary caregivers face accessing services. Second, FEP services disadvantage carers who lack knowledge and assertiveness. Ideally, access should be determined more by clinical need than the level of carers' persistence. Indeed, there is a need to improve awareness, availability and access to FEP services, especially to those who are new to such programs. Third, ongoing family interventions are required for first-time caregivers, such as practical day-to-day support about accessing and getting the most out of services, as well as information regarding legal and financial supports and the possibility of respite. Fourth, clinical training should incorporate measures to increase sensitivity to carers' needs, and familiarity with government policies and mental health legislation about inclusion of carers. Finally, further national and international research is needed into the key findings and experience of carers accessing other health systems, and to understand the experience of non-engaged caregivers and those from culturally diverse Backgrounds who access FEP services.

doi:10.1016/j.schres.2010.02.510

Poster 16
A DESCRIPTIVE PHENOMENOLOGICAL STUDY OF SYMPTOMS OF SCHIZOPHRENIA IN DEAF CLIENTS

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Background: Our clinical knowledge and understanding of the manifestation of schizophrenia in deaf patients is limited. Previous studies address specific symptomatology observed in deaf persons with schizophrenia. The purpose of this research was to conduct extensive interviews of clinicians working with deaf patients diagnosed with schizophrenia in order to understand how clinicians characterized each patient's presentation and defined the symptomatology observed.

Methods: Supplemental interview data were gathered from client charts by clinicians. Eight clinicians with advanced sign language skills and extensive experience serving deaf clients with mental illness were recruited to discuss a total of 13 client cases. A qualitative investigation was employed to identify themes and patterns present in each clinicians' concepts of symptoms manifested in deaf patients diagnosed with schizophrenia. The purpose of this research was to conduct extensive interviews of clinicians working with deaf patients diagnosed with schizophrenia in order to understand how clinicians characterized each patient's presentation and defined the symptomatology observed.

Methods: Supplemental interview data were gathered from client charts by clinicians. Eight clinicians with advanced sign language skills and extensive experience serving deaf clients with mental illness were recruited to discuss a total of 13 client cases. A qualitative investigation was employed to identify themes and patterns present in each clinicians' concepts of symptoms manifested in deaf patients diagnosed with schizophrenia.

Results: Symptomatology observed by clinicians was consistent with diagnostic criteria established for hearing clients with schizophrenia. However, some symptom modality differences were noted in phenomena such as sign language and lip-reading hallucinations and the language-related symptoms reported. The majority of "auditory hallucinations" in this sample were ambiguous in that clients were unable to describe acoustic features and/or the message content of the "voices." Delusional content mirrored hearing samples. The most common language-related phenomena observed were characterized as loose associations as well as circumstantial and tangential communication. The theme of organization was encountered multiple times throughout the interviews with clinicians. Schizophrenia was characterized by clinicians as a disease that disrupts major cognitive processes and erodes the brain's ability to organize information, which impairs the individual's mental and social functioning. Such disorganization caused misinterpretations of stimuli or perceptual disturbance and impacted motivation and drive as these relate to negative symptoms. Primary deficits reported were often related to the clients' decline in social functioning declines.

Discussion: A major limitation of this study is that data are based solely on the judgments, accuracy, and thoroughness of the observations and interpretations of the mental health professionals serving these clients. The nuances of the presentation of schizophrenia in deaf patients and the richness of this qualitative data may benefit clinicians diagnosing schizophrenia in deaf patients and subsequently developing appropriate treatment and intervention programs designed for deaf individuals with schizophrenia.

doi:10.1016/j.schres.2010.02.510

Poster 17
ANOMALOUS SELF-EXPERIENCE IN THE PRODROMAL PHASE OF SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS

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Background: Over the last fifteen years, there has been increased interest in the early phase of schizophrenia and other psychotic disorders. The focus was initially on the first episode of psychosis but soon reached further back to the pre-onset or prodromal phase. Several strategies have been introduced to identify individuals in the putatively prodromal phase of psychotic disorder. The most widely used of these approaches is the "ultra-high risk" (UHR) approach, which combines known trait and state risk factors for psychotic disorder. Phenomenological research indicates that disturbance of the basic sense of self may be a core phenotypic marker of psychotic vulnerability, particularly of schizophrenia spectrum disorders. Disturbance of basic self-experience involves a disruption of the sense of agency and ownership of experience, associated with a variety of dissociative symptoms and anomalous cognitive and bodily experiences. In this study, we investigated the presence of basic self-disturbance in a UHR group and whether it predicted transition to psychotic disorder.

Methods: 41 UHR subjects and 12 first episode psychosis subjects were recruited from Orygen Youth Health, Melbourne. 52 non-clinical control subjects were recruited from the community. Subjects were assessed for basic self-disturbance using the EASE questionnaire. A range of other clinical variables were also measured. Subjects were assessed at baseline and at 12 months follow up.

Results: Preliminary data will be presented. Levels of self-disturbance were significantly higher in the UHR sample and the FEP sample compared to the non-clinical control group (p < .001). Further follow-up is required to assess the predictive utility of self-disturbance in the UHR sample.

Discussion: Identifying self-disturbance in the UHR population may provide a means of further "closing in" on individuals truly at high risk of psychotic disorder, particularly of schizophrenia spectrum disorders, thus supplementing the UHR identification approach. This would be of practical value by reducing inclusion of "false positive" cases in ultra-high risk samples, and of theoretical value by shedding light on core features of psychotic pathology.

doi:10.1016/j.schres.2010.02.512
Background: Hallucinations are a core feature of psychosis, often causing considerable distress. Reported prevalences range from 70% for auditory hallucinations to 30% for visual hallucinations and 4% for hallucinations in the tactile domain. The prevalence, etiology and pathological processes underlying auditory (verbal) hallucinations have been studied extensively. Studies on visual hallucinations, however, are scarce. The current study investigated the phenomenology of visual and auditory hallucinations in the realm of daily life. Specific attention was paid to the overlapping and distinct characteristics of the two types of hallucinations.

Methods: The Experience Sampling Method (ESM) was used to explore hallucinatory experiences in the context of daily life in 184 participants with psychosis spectrum disorders. ESM is a structured self-assessment technique, collecting reports of mood, context, and psychotic experiences. All self-assessments were rated on 7-point Likert scales. Visual hallucinations were defined using participants’ score on the item “I see phenomena”. Auditory hallucinations were measured using the item “I hear voices”. The Positive and Negative Syndrome Scale (PANSS) was used to cross-validate the presence of hallucinations.

Results: Overall, 84 participants (46%) reported hallucinations. Ten percent reported only visual hallucinations, 48 reported both visual and auditory hallucinations, and 26 participants reporting auditory hallucinations only. The mean number of reported hallucinations within 6 days was 4.7 (range 1-13) for visual and 6.6 (range 1-17) for auditory hallucinations only. The mean number of reported hallucinations within 6 days was 4.7 (range 1-13) for visual and 6.6 (range 1-17) for auditory hallucinations only. The mean number of reported hallucinations within 6 days was 4.7 (range 1-13) for visual and 6.6 (range 1-17) for auditory hallucinations only. The mean number of reported hallucinations within 6 days was 4.7 (range 1-13) for visual and 6.6 (range 1-17) for auditory hallucinations only. The mean number of reported hallucinations within 6 days was 4.7 (range 1-13) for visual and 6.6 (range 1-17) for auditory hallucinations only.

Discussion: These results show that patients are able to validly report hallucinations in daily life using ESM. Furthermore, these results suggest that visual hallucinations are common in patients with psychosis spectrum disorders and often co-occur with auditory hallucinations. Visual hallucinations are understudied and their role in daily life in patients with psychosis might be underestimated. The results of this study highlight the necessity of investigating both visual and auditory hallucinations and their interplay in psychosis.

doi:10.1016/j.schres.2010.02.514
Background: Studies in general population have shown that psychotic symptoms are continuously distributed from healthy populations to clinical cases (Stefanis et al., 2002). Schizotypy and psychotic-like experiences have been considered risk factors to schizophrenia (Johns and van Os, 2001). Recently, cannabis use has been associated with schizotypal traits and the emergence of psychotic symptoms in these healthy subjects (Dumas et al., 2002; Compton et al., 2007; Schifman et al., 2005; Henquet et al., 2006). Moreover, the relationship between cannabis use and schizotypy seems to be influenced by other psychopathological traits such as high anxiety levels (Braunstein-Bercovitz, 2000). These associations are suggested to be mediated by genes involved in the regulation of the dopaminergic system such as COMT gene or other genes related to cannabinoid system (CNR1, CNR2 and FAAH). The aim of the present study was to investigate in a Spanish general population: i) the association between cannabis use, schizotypal dimensions and psychotic-like experiences, ii) whether this association is mediated by genetic variability in dopaminergic and cannabinoid systems related genes.

Methods: The sample consisted of 451 Spanish undergraduate university students (197M and 254F) (mean age (sd) = 21.87 (3.9)). Schizotypal personality was evaluated with the brief version of the Schizotypal Personality Questionnaire (SPQ-B; Raine and Benishay, 1985) and the presence of psychotic-like experiences with the Community Assessment Psychic Experiences (CAPE; Stefanis et al., 2002). Anxiety levels were assessed using the State-Trait Anxiety Inventory (STAI; Spielberg et al., 1970). Cannabis use was assessed with an adapted version of the AIS interview (Grau and Ortet, 1999). Consumption was considered if individuals reported monthly, weekly or daily cannabis use (30.1%). SNPs of the COMT (Val158-Met), CNR1 (rs1049353), CNR2 (rs16828926) and FAAH (rs324420) genes were genotyped using Taqman 5'-exonuclease assay.

Results: There are sex differences in relation to cannabis use ($\chi^2 = 9.11$, p = 0.002). When adjusting by sex and anxiety-trait levels, cannabis users present the highest mean scores for: i) the disorganization dimension of the SPQ-B ($F = 6.84$, p = 0.009), ii) the positive dimension of the CAPE ($F = 6.78$, p = 0.01) as well as for the negative one ($F = 12.5$, p < 0.000). A significant interaction was found between A carriers (rs324420-FAAH gene), cannabis use and higher scores on both SPQ-B-disorganized dimension ($\beta$ = 0.215, p = 0.013) and CAPE-negative dimension ($\beta$ = 0.176, p = 0.034).

Discussion: Our results are in line with studies showing association between cannabis use and the disorganization dimension of schizotypy (Dumas et al., 2002; Compton et al., 2007; Schifman et al., 2005) as well as the presence of psychotic-like experiences (Henquet et al., 2006); suggesting that cannabis consumption could influence the risk for the emergence of psychotic traits. In reference to the significant interaction between FAAH gene, cannabis use and higher scores on both SPQ-B-disorganized dimension and CAPE-negative dimension, it has been suggested that the rs324420 produce a significant greater sensitivity to proteolytic degradation, having an effect on the regulation of FAAH proteins (Sipe et al., 2002). Moreover, this FAAH gene has been associated in previous studies to substance abuse and dependence (Sipe et al., 2002; Tyndale et al., 2007) Acknowledgements: PND, Ministerio de Salud (2008/090) and Ministerio de Educación y Ciencia (SAF2008-05674-C03-01).

doi:10.1016/j.schres.2010.02.516

Poster 21

IMPACT OF METHAMPHETAMINE USE IN FIRST EPISODE PSYCHOSIS

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Background: To examine the effects of methamphetamine use in first-episode psychosis.

Methods: We are conducting a prospective, longitudinal study of first-episode psychosis in Cape Town, South Africa. Patients were included if they met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Revision (DSM-IV) diagnosis of schizophrenia, schizophreniform disorder or schizo-affective disorder. Patients with a current DSM-IV diagnosis of substance abuse were excluded. This report discusses the baseline characteristics and early treatment response of patients with a history of methamphetamine use compared to patients without previous use. Clinical variables were measured using the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression Severity Scale (CGI-S), Calgary Depression Scale for Schizophrenia (CDSS), Social and Occupational Functioning Assessment Scale (SOFAS) and Extrapyramidal Symptom Rating Scale (ESRS).

Results: Of the 52 patients, 28 (54%) patients had used methamphetamine and 24 (46%) patients had not. We found significant differences between the two groups in the following demographic variables: age (mean 20.8 vs. 26 yrs; p = 0.003), gender (males 82.14% vs. 41.67%; p = 0.002), highest level of education (tertiary 3.57% vs. 33.33%; p = 0.040) and marital status (married 0% vs. 20.83%; p = 0.024). There were no significant differences in language, ethnic group, residential area and employment status. In terms of clinical variables, we found significant differences with baseline PANSS Total (mean 106.18 vs. 94.75; p = 0.01) and SOFAS (mean 39.46 vs. 45.29; p = 0.02). There were no differences in CGI-S, CDSS, ESRS, weight and BMI. At 3 months there were significant differences with PANSS Total (65.89 vs. 55.88; p = 0.01), CGI-S (3.61 vs. 3.04; p = 0.02) but no differences in CDSS, ESRS, weight and BMI.

Discussion: Methamphetamine use significantly influences the presentation of first-episode psychosis and early treatment response.

doi:10.1016/j.schres.2010.02.516

Poster 22

SUICIDAL BEHAVIOUR AMONG SCHIZOPHRENIA SPECTRUM IN-PATIENTS WITH A HISTORY OF SUBSTANCE ABUSE

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Background: The literature suggests that nearly 50% of patients with schizophrenia have a co-occurring substance use disorder, most frequently alcohol and/or cannabis (1). Patients with dual diagnoses are highly prone to adverse outcomes in several domains: increased symptom severity; increased rates of suicidality and hospitalization, infectious illnesses, violence, victimization, homelessness, and non-adherence to medication; and poor overall response to pharmacologic treatment (2). The aim of our study was assessing the association of suicidal ideation with clinical and demographic characteristics among substance abusers schizophrenia spectrum in-patients.

Methods: In a five years period, 50 ICD X schizophrenic, schizophreniform and schizoaffective disorder patients with comorbid substance abuse treated at Psychiatric Clinic Nis, Serbia, were assessed using clinical assessment of symptomatology using BPRS, PANSS, Calgary Depression Scale We also compared obtained results with controls (50 recently hospitalized schizophrenic non-abusers patients).

Results: The substance abuse group was younger, tended to have their first hospitalization at an earlier age, had a significantly higher severity of illness score on the PANSS, general psychopathology subscore (impulsivity item especially) and had attempted suicide more often. They had nearly twice as many hospitalizations and relapses in the 4 years
prior to the study. On the other hand, the groups didn’t differ on the PANSS total score, negative subscore and Calgary Depression score. Substance use was found to be a better predictor of relapse, increased suicidality and hospitalization.

**Discussion:** High impulsivity could facilitate substance abuse as a maladaptive behavior in response to prodromal or relapse symptoms. Substance abused schizophrenic patients certainly represent a group of individuals who are in high risk of suicidal behavior.

doi:10.1016/j.schres.2010.02.517

**Poster 23**
THE EFFECT OF CANNABIS ON SERUM BRAIN DERIVED NEUROTROPHIC FACTOR LEVELS AND ITS CORELATION WITH PSYCHOTIC SYMPTOMS

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**Background:** Δ-9-tetrahydrocannabinol, causes certain symptoms, which are similar to schizophrenia symptoms in many aspects, by activating CB1 (cannabinoid 1) receptors. Considered as playing an essential role on vitality, plasticity and preservation of the central nervous system neurons, BDNF (brain derived neurotrophic factor) and its concentration levels, may probably be an indicator of alterations caused from disorders, drugs used or abused and the effect of those factors on the central nervous system. The aim of this study is to determine the effect of cannabis on serum BDNF levels and its correlation with psychotic symptoms.

**Methods:** Approval for the study was obtained from the local ethics committee and each patient gave their informed consent before participating in the study. The study participants comprised four groups. Group 1 comprised of 25 healthy controls (all male, median age 31.4±1.3) who had never consumed any drugs including cannabis. Group 2 comprised of 25 patients who met the DSM-IV criteria for cannabis dependence only (all male, mean age 27.6±1.3). Group 3 comprised of 25 patients who also met the DSM-IV criteria for cannabis induced psychotic disorder (all male, mean age 27.2±1.4). Group 4 comprised of 13 patients who met the DSM-IV criteria for schizophrenia and who had never been treated with antipsychotics or other psychotropic drugs and never consumed cannabis (all male, mean age 31.3±3.4). Acutely intoxicated patients, other drug or alcohol abusers except nicotine users were excluded. Patients having depression were excluded from the study by applying ‘Hamilton Depression Scale’ or ‘Calgary Depression Scale’ to all the participants. PANSS (positive and negative syndrome scale) is applied to all patients in group 3 and 4.

**Results:** Patients and control groups, who were all male, matched with respect to age and duration of education. No significant difference has been found with respect to weekly cannabis intake, duration of use in years or usage frequency between the groups 2 and 3 (p>0.05). Although the ages of initial cannabis use were young in the group 3 in comparison to the ages of group 2 (sequentially 18.7±1.1, 20.2±1.3), this difference was not considered as significant (p>0.05). Although any difference was not determined between the mean BDNF values obtained from two groups of cannabis abusers (as 20.75±8.6 in group 2 and 23.32±10.6 in group 3) those values were determined as significantly lower than that of healthy control group’s (p<0.005). While BDNF values obtained from schizophrenia group were found significantly lower with respect to that of control group’s, no significant difference was detected for BDNF values between groups of patients who are cannabis abusers. According to the results obtained from group 3 and of 4 by applying scales, PANSS positive subscale points were significantly higher in group of schizophrenic patients than points of patients with cannabis induced psychotic disorder (30.54±4.1 and 23.6±6.8, p<0.05). With respect to other PANSS subscale points, no significant difference were determined between two groups. Any correlation was not found between scale points and serum BDNF values.

**Discussion:** This study shows that cannabis abuse, independently from development of any psychotic disorder, causes decrease in neurotrophin levels and may consequently result in the destruction of the neural structure just as observed in schizophrenia patients.

doi:10.1016/j.schres.2010.02.518

**Poster 24**
THE INFLUENCE OF SUBSTANCE MISUSE IN THE FIRST EPISODE PSYCHOSIS ON THE COURSE AND OUTCOME: 3 YEARS PROSPECTIVE FOLLOW-UP STUDY

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**Background:** Substance use contributes to the development of schizophrenia, whether as an independent risk-factor in itself or by precipitating illness onset in vulnerable individuals. Several prospective studies had reported that substance misuse was associated with a problematic recovery from recent-onset psychosis (1). Our hypotheses were that substance misuse in first episode psychosis would be associated with increased risk of in-patient admission, a longer time to remission of psychotic symptoms, and earlier and increased risk of relapse. The aim of our prospective study was determination whether the first episode psychosis (FEP) patients with substance misuse have worse outcomes than FEP patients with no history of substance misuse.

**Methods:** During a period of 3 years we followed up 30 in-patients with FEP who were using psychoactive substances and compared obtained results with the similar group of non-users patients. The evaluation process included clinical interview BPRS, PANSS and the evaluation were held at base line, after 3 monts and after each 6 monts during follow-up.

**Results:** The substance misuse group was younger, tended to have their first hospitalization at an earlier age, had a significantly higher PANSS positive score, had more hospitalizations and relapses in the 3 years follow up period.

**Discussion:** Substance misuse is FEP patients is one of the risk factors for a problematic recovery, increasing the risk of relapses, hospitalizations and bad compliance. Substance misuse may not be etiologically related to developing schizophrenia after FEP, but influences the onset, course, and symptomatology of schizophrenia.

doi:10.1016/j.schres.2010.02.519

**Poster 25**
MOTIVATORS FOR SMOKING CESSATION AND KNOWLEDGE AND PERCEPTION OF SMOKING RISKS/CONSEQUENCES AMONG PEOPLE WITH SCHIZOPHRENIA COMPARED TO NORMAL CONTROLS

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Background/ methods: We examined the views and attitudes regarding health risks of cigarette smoking and motivators for cessation in smokers with schizophrenia (N = 100) and smokers without a psychotic disorder (normals, N = 100). The study included smokers who were not currently trying to quit aged 18-65 years. During the 2-3 hour visit, participants completed questionnaires and provided a breath CO sample 10 minutes after smoking one preferred-brand cigarette. Assessments in this analysis include: Smoking Consequences Questionnaire-Adult (SCQ-A), the Reasons for Quitting Scale (RFQ), and the Stages of Change (SOC).

Results: There were no differences in mean age of smoking onset (16 ± 5.4 years schizophrenia vs. 15.6 ± 5.5 years normals, p = 0.44), frequency of smoking > 20 cigarettes daily (23% schizophrenia vs. 26% normals, p = 0.62), or in breath CO (28.0 ± 14.5 ppm schizophrenia vs. 22.9 ± 8.0 ppm normals, p = 0.61). Compared to normals, people with schizophrenia had greater scores on stimulation/state enhancement, sensorimotor/taste manipulation, and social facilitating benefits from smoking. Normals had a greater appreciation of health risks associated with smoking than people with schizophrenia (p < 0.0001). People with schizophrenia rated themselves as less motivated to quit smoking (1-7 Likert) (4.2 ± 1.9 vs. 3.4 ± 2.0, p = 0.002) compared with normals. On the SOC, fewer people with schizophrenia were currently thinking of quitting smoking (39% vs. 64%, p = 0.0005), but more people with schizophrenia reported a past quit attempt (88% vs. 70%, p = 0.0028). Immediate reinforcement/rewards (p = 0.02) and health concerns (p = 0.0007) were greater motivators for considering smoking cessation for normals than for schizophrenia patients. People with schizophrenia reported a greater likelihood to stop smoking due to social pressure than normals (p = 0.03).

Discussion: In conclusion, motivation for quitting in schizophrenia is significantly lower and quitting is less likely to occur for rewards and health consequences. This may be due in part to the greater benefits in state enhancement, taste manipulation and social facilitation people with this illness receive relative to controls.

doi:10.1016/j.schres.2010.02.520

Poster 26
MANTOUX TUBERCULIN SKIN TEST AMONG PATIENTS REFERRED FOR ALCOHOL ABUSE

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Poster 27
DOES SCREENING FOR AUDITORY HALLUCINATIONS AMONG ADOLESCENTS USING A SINGLE QUESTION PREDICT PSYCHOPATHOLOGY ON CLINICAL INTERVIEW?

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Background: Individuals who report psychotic-type experiences are at increased risk of future clinical psychotic disorder. They constitute a unique ‘at-risk’ group for studying the developmental trajectory to schizophrenia and related illnesses. Psychotic disorders are a significant risk factor for suicide, especially among young people. Previous research has used screening instruments to identify this high risk group but few studies have followed up by an first examination, he presented a plenty of psychotic symptoms and after the oral administration of 5 mg of haloperidol and 100 mg of thiamine was transferred in our clinic. The patient had a full clinical examination from the internist and the neurologists of our hospital and the chest X-rays didn’t show pleural effusion and pulmonary cavitation. After the positive Mantoux test and the negative microscopic examination for acid fast bacilli in sputum or bronchial secretion we proceed at the control with the Transcription Mediated Amplification (TMD) for the determination of rRNA of the Mycobacterium Tuberculosis that was negative also. In his blood exams the only pathologial finding were CA 19-9 59.37 U/ml, HbA1c 10.4%. At the brain CT scan he demonstrated a calcification of the basic ganglia and a middle grade atrophy of the ventricular system.

Discussion: Tuberculosis is encountering a renewal attention due to emergent causes, linked primarily to migration from high-endemic countries. On the other hand, it is important to highlight the lack of long-term term psychiatric strategy in patients that seek occasional and temporary hospitality in available structures. This growth pool of subjects who present important risk factors as poverty, homelessness, drug abuse, HIV infection, probably, is the new core target for the controlling efforts. In Greece, tuberculosis has been systematically screened only for children [2] (since 1991) and for the young males during the military service using the tuberculin skin test. Although the frequency of tuberculomas is decreased in the last two to three decades, still today constitutes about 5 to 10 per cent of intracranial space occupying lesions, in the developing world. Cases of intracranial tuberculosis have been associated with seizures, confabulation, disorientation, delirium, anoxemia, auditory hallucinations and psychotic symptoms [3]. The Mantoux Tuberculin Skin Test is a simple, harmless way to find out the latent infection of tuberculosis and may must be included in the common psychiatric practice. 1)Önnroth K, Williams BG, Statlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis - a systematic review. BMC Public Health. 2008 Aug 14;8:289. 2)Spyridis P, Tsolia M, Gelesme A, Moustaki M, Spyridis N, Sinaniotis C, Karpathios T. The impact of Greece’s childhood tuberculosis screening programme on the epidemiological indexes in the greater Athens area. Int J Tuberc Lung Dis. 2003 Mar;7(3):248-53. 3)Woodroof A, Gleason O. Psychiatric symptoms in a case of intracranial tuberculosis. Psychosomatics. 2002 Jan-Feb;43(1):82-4. 4)S.K. Sharma and A. Mohan. Extrapulmonary tuberculosis. Indian J Med Res 120, October 2004, pp 316-353.
in-depth clinical interview to assess the relationship between psychotic symptoms and suicidality or other psychopathology.

Methods: As part of a community study on suicidality in young people, a 50-minute self reported screening questionnaire which included one item designed to assess psychotic symptoms (auditory hallucinations) was administered to 1000 adolescents aged 14 years in community schools, in Cork, Ireland. The following question (“Have you ever heard voices or sounds that no one else can hear?”) was used as it has been shown previously to show the best predictive power (Kelleher et al., 2009). Other screening questions assessed suicidality and other psychopathology. Detailed clinical interviews by experienced child and adolescent psychiatrists were subsequently carried out with a sample of these adolescents who endorsed a positive answer to screening questions.

Results: We plan to calculate the sensitivity and specificity and positive predictive value for the specific screening symptom on auditory hallucinations and its relationship to suicidality, psychotic symptoms or psychopathology as verified on clinical interview.

Discussion: Our results will be of value to those engaged in treating children and adolescents with psychiatric disorder and will inform on the clinical significance of a positive answer to a screening question on auditory hallucinations in adolescence. Acknowledgement: This work was supported by the Health Research Board Ireland and the National Suicide Research Foundation. The Saving and Empowering Young Lives in Europe (SEYLE) project is funded by the EU under the 7th Framework Programme.

doi:10.1016/j.schres.2010.02.522

Poster 28
THE ZIPRASIDONE OBSERVATIONAL STUDY OF CARDIAC OUTCOMES (ZODIAC): FINDINGS FROM A LARGE SIMPLE TRIAL OF ZIPRASIDONE VS. OLANZAPINE IN REAL-WORLD USE AMONG 18154 PATIENTS WITH SCHIZOPHRENIA

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Background: The ZODIAC study was designed to answer the question of whether ziprasidone’s modest increase in the QTc interval was associated with a risk of serious cardiovascular morbidity and mortality in a population of schizophrenia patients treated with antipsychotic medication. This large simple trial compared the risk of non-suicide death associated with ziprasidone versus olanzapine in real-world use. Here, we present the comprehensive results of the originally planned and post-hoc analyses of primary and secondary endpoints.

Methods: The ZODIAC Study, an open-label, randomized, postmarketing study, enrolled patients with schizophrenia from routine clinical practice settings in 18 countries. A total of 18,154 subjects were treated with antipsychotic medication(s) use. The primary outcome was non-suicide mortality during the year after treatment initiation. The secondary objectives of this study were to estimate the relative incidence among users of ziprasidone and olanzapine of all-cause mortality, mortality due to suicide, cardiovascular mortality, mortality due to sudden death, as well as of all-cause hospitalization, hospitalization for arrhythmia, MI, or diabetic ketoacidosis, and to determine the rate of discontinuation of randomized treatment. One of the secondary outcomes, sudden death, was readjudicated according to ICD10 criteria per FDA’s request as above. In this analysis, a supplemental sensitivity analysis was conducted to capture cases which might fall outside of the restrictive ICD-10 coding schema.

Results: The incidence of nonsuicide mortality within one year of initiating therapy was 0.9% (n = 83) for the ziprasidone group (n = 9,077) compared with 0.9% (n = 81) for the olanzapine group (n = 9,077) yielding a relative risk (95% confidence interval) of 1.02 (0.76, 1.39). This finding was robust in numerous secondary and sensitivity analyses. Although the point estimates were elevated for some endpoints, there was no statistically significant increase in the risk of all-cause mortality, cardiac mortality, sudden death, or suicide; all cause hospitalization was the only statistically significant finding in this study. Data from the post-hoc readjudication of sudden death were consistent with the study’s initial findings.

Discussion: ZODIAC is the largest randomized study of patients with schizophrenia conducted to date. With substantial statistical power, the study did not detect an increased risk of non-suicide death associated with the use of ziprasidone vs. olanzapine. There was no statistically significant difference for the risk of sudden death comparing persons randomized to ziprasidone vs. olanzapine across all readjudicated endpoints.

doi:10.1016/j.schres.2010.02.523

Poster 29
BIMODAL RHYTHMS OF GENERAL CONCEPTIONS AND THE BIRTH-MONTH PHENOMENON IN SCHIZOPHRENIA, NEURAL TUBE DEFECTS, LATERALITY, ETC.: THE EXAGGERATION HYPOTHESIS REVISITED

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Background: Studies of schizophrenics born during the early 20th-century found that the afflicted tended to have been born most often in late winter (Feb-Mar) and least often in late summer (Aug-Sep). A late winter birth peak, coinciding with the schizophrenia peak, also occurred in that era in the non-schizophrenic general populations. In 1977, Ödegård suggested on this basis that the schizophrenia and the general-birth rhythm represented the same phenomenon, with the former being a mere exaggeration of the latter. However, while the schizophrenia rhythm was clearly unimodal, the general-population rhythm was most often bimodal, with a second prominent peak appearing in late summer and coinciding in fact with the Aug-Sep schizophrenia dip. We re-examined those coincidences in light of new findings including evidence that, in addition to schizophrenia (SCZ), a Feb-Mar birth peak could also be found in such other “developmental anomalies” as neural-tube defects (NTDs), extreme left-handedness and other signs of cerebral asymmetry deficits (CAD), excellence in the arts (ARTS), and excellence in mathematics (MATH) (Marzullo & Fraser, 2005, 2009; Marzullo, this conference).

Methods: Using U.S. census birth data, we sought to, first, verify the above coincidences and, second, test the true causes of the two
general-population birth peaks against a hypothesis attributing both to the (temporarily) similar light and temperature conditions at the equinoxes.

**Results:** First, in the American rhythm, the Feb-Mar and Aug-Sep birth peaks were equally prominent during the early 20th-century decades. The former was sharply coincident with birth-rate excesses appearing in all five: SCZ, NTDs, CAD, ARTS and MATH. The latter was sharply coincident with not only significant birth-rate deficits in the same five, but also with birth-rate excesses appearing among groups representing a contrasting set of behavioral qualities: i.e., unique social fitness and emotional stability (EMS), extreme right-handedness and other signs of cerebral asymmetry excesses (CAE), excellence in business administration and banking (BAB), and excellence in (descriptive) biology (BIOL), an eminently empirical science most unlike abstract mathematics. Second, we found that, far from representing similar phenomena with similar causes, the Feb-Mar and Aug-Sep general-birth peaks were more likely to represent contrasting phenomena with opposite causes. The two changed in opposite directions after the 1930s, with the Feb-Mar general population birth peak nearly vanishing and the Aug-Sep peak nearly doubling by the 1980s. This change, which apparently followed from a reduction of direct sunlight exposure after the spread of electric lighting, pointed to intense sunlight near conception as a likely cause of the Feb-Mar birth peak and to weak sunlight as contributing to the Aug-Sep peak. Accordingly, and based moreover on clinical findings of contrasting, solstice-related (Dec-vs.-Jun) seasonal rhythms in the rates of blastocyst implantations and those of post-implantation embryonic survival, we conclude that the Jun and Dec sunlight extremes may both increase embryonic survival (and thus birth rates eight months later) by two different mechanisms: one involving cellular differentiation-dependent stages of organogenesis in the former case, and another involving proliferation-dependent stages of blastocyst growth and implantation in the latter.

**Discussion:** Whatever the merits of this “solstitial” hypothesis, the SCZ-line and the EMS-line of developmental outcomes may both represent qualities genetically or epigenetically inherent to, respectively, the Feb-Mar and Aug-Sep excess populations of general births.

doi:10.1016/j.schres.2010.02.524

**Poster 30**

THE AUSTRALIAN SCHIZOPHRENIA RESEARCH BANK (ASRB): DEMOGRAPHIC, CLINICAL AND NEUROPSYCHOLOGICAL PROFILES FOR THE FIRST 500 PARTICIPANTS WITH SCHIZOPHRENIA

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**Background:** The Australian Schizophrenia Research Bank (ASRB) was established in 2007 to collect linked clinical, cognitive, neuroimaging and genetic data in people with schizophrenia and matched controls, and is the first of its kind developed in Australia.

**Methods:** Participants were assessed using a comprehensive assessment battery developed based on advice from a collaboration of schizophrenia research specialists. The three-hour battery consists of socio-demographic questions including medical and family history, neurological evaluation (NES), neuropsychological assessment and cognitive performance measures (WTAR, WASI, RBANS, LNS, COWAT), a diagnostic interview that includes drug and alcohol history (DIP; Castle et al., 2006) to confirm (or screen for) diagnosis, ratings for symptoms (SANS) and general functioning (GAF), and questionnaires of childhood adversity, personality disorder (IPDE) and psychosis proneness (SPQ).

**Results:** The sample currently comprises 550 people with schizophrenia (mean age = 39.66 years; SD = 10.98) and 250 healthy controls (mean age = 37.37 years; SD = 13.14). Compared to the controls, the schizophrenia sample had a higher proportion of males (cases 66.8%; controls 46.4%), fewer living in married or defacto relationships (cases 15.80%; controls 53.60%) and fewer years of education (cases 12.93, SD = 2.91; controls 15.13, SD = 3.14). Schizophrenia participants also had lower premorbid IQ (cases 103.17, SD = 13.17; controls 111.83, SD = 8.76), current IQ (cases 102.29, SD = 15.62; controls 118.24, SD = 10.20) and RBANS scores (cases 82.55, SD = 15.59; controls 96.24, SD = 15.88) consistent with performance reported previously for Australian samples (Loughland et al., 2007).

**Discussion:** These findings are broadly consistent with those reported previously in the Australian Low Prevalence Disorders Study (Castle, 1999), suggesting the ASRB sample is broadly representative of people with schizophrenia living in Australia. The ASRB is a unique schizophrenia resource that is accessible to approved Australian researchers in 2010 and international scientists in 2011.

doi:10.1016/j.schres.2010.02.525

**Poster 31**

NEONATAL VITAMIN D STATUS AND RISK OF SCHIZOPHRENIA: A POPULATION-BASED CASE-CONTROL STUDY

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**Background:** Clues from the epidemiology of schizophrenia have suggested that low developmental vitamin D may be associated with an increased risk of schizophrenia. The aim of this study was to directly examine the association between neonatal vitamin D status and risk of schizophrenia.

**Methods:** Based on population-based Danish registers, we examined 424 individuals with a diagnosis of schizophrenia, and 424 sex and day-of-birth matched controls. The concentration of 25 hydroxyvitamin D (25OHD3) was assessed from neonatal dried blood samples using a highly sensitive tandem mass spectroscopy method. Relative risks were calculated for the matched pairs when examined for quintiles of 25OHD3.

**Results:** Compared to neonates in the fourth quintile (with25OHD3 concentrations of between 40.5 and 50.9 nmol/L), those in each of the lower three quintiles had a two-fold increased risk of schizophrenia. Unexpectedly, those in the highest quintile also had a significantly increased risk of schizophrenia. Based on this analysis, the population attributable fraction associated with neonatal vitamin D was 44%. The relationship was not confounded by a wide range of potential confounding variables.

**Discussion:** Both low and high concentrations of neonatal vitamin D are associated with an increased risk of schizophrenia, and it is feasible that this exposure could contribute to nearly a half of all cases in Denmark. In light of the substantial public health implications of this finding, there is an urgent need to further explore the impact of vitamin D status on brain development and later mental health.

doi:10.1016/j.schres.2010.02.526
Poster 32

PSYCHOMETRIC PROPERTIES OF THE ARABIC VERSION OF THE SCHIZOTYPAL PERSONALITY QUESTIONNAIRE IN TUNISIAN UNIVERSITY STUDENTS

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Background: Schizotypal personality disorder is considered as a marker of schizophrenia proneness. Self-administered questionnaires have been used extensively in several studies examining the schizotypal personality traits. The Schizotypal Personality Questionnaire (SPQ) developed by Raine (1991), assesses all nine features of schizotypal personality traits. The Schizotypal Personality Questionnaire (SPQ) developed by Raine (1991), assesses all nine features of this disorder. The objective of the study was the assessment of the psychometric properties (reliability and factor structure) of the Arabic version of the SPQ in a non-clinical sample of university students.

Methods: The sample comprises 490 students (males: n = 145; females: n = 345; mean age: 20.4±1.4 years), from the faculty of medicine and the school of health sciences of Monastir (Tunisia). Thirty students were participated in the second assessment of the SPQ after three months, approximately. The SPQ was translated into Arabic after author approbation and back translated into English by an independent translator. The statistical analysis was conducted to determine the internal consistency reliability and the test-retest reliability of SPQ total and subscale scores and to use the confirmatory factor analysis.

Results: Cronbach’s (α) internal consistency reliability coefficient for the total SPQ was 0.92, and internal consistency reliability coefficients for the subscales ranged from 0.62 to 0.75. The test-retest reliability was good with the Pearson correlation equal to 0.83 for the total SPQ and ranged from 0.67 to 0.87 for the SPQ subscales (P<0.0001). Confirmatory factor analyses indicated that the three-factor model (positive or cognitive-perceptual, negative or interpersonal, and disorganized) and the four-factor model (positive, paranoid, negative, and disorganized) were provided a good fit to the data, accounting for 70.7% and 77.3% of the total variance of the scale, respectively. However, the particularity of our study was that the odd speech subscale loads on both the disorganization (0.57) and negative (0.48) factors, and the ideas of reference subscale loads on both cognitive perceptual (0.61) and paranoid (0.58) factors.

Discussion: The results showed that the Arabic version of the SPQ had adequate psychometric properties and confirmed the multifactor structure of the schizotypal personality in non-clinical populations, in line with previous literature. Future studies could use this SPQ version as a screening self-report for the detection of vulnerable subjects to the development of schizophrenia-spectrum disorders in the general population, in genetically high-risk samples and in clinical studies.

doi:10.1016/j.schres.2010.02.527

Poster 33

PREVALENCE AND BURDEN OF AT-RISK CRITERIA OF PSYCHOSIS AND HELP-SEEKING BEHAVIOUR – A POPULATION SURVEY - ATTITUDES

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Background: Various studies have examined attitudes towards mental disorders, mental health care systems or help-seeking for mental problems in the general population. To our knowledge, however, these three domains have not yet been examined together. Therefore, the aim of this study was to assess these three domains of attitudes in a general population sample of the Canton Bern and to examine possible associations.

Methods: The enrolment sample comprised 85 persons. Inclusion criteria were (i) residency in the Canton Bern, (ii) 16 to 35 years of age and (iii) phone number available. Exclusion criteria were (i) lifetime diagnosis of psychosis and (ii) insufficient language skills in German, French or English. 60 persons (70.5%) participated in the phone interview, two of them met exclusion criteria. Questionnaires on attitudes towards both mental disorders and mental health care system comprised ten statements to which the degree of agreement is measured on a 5-point Likert scale, totals ranging from 10='very negative attitude' to 50='very positive attitude'. A third questionnaire according to the WMH-CIDI Part II on attitudes towards the effectiveness of help-seeking for mental problems was used.

Results: The attitudes towards mental disorders (M=30.52, SD=5.06, Md=30) as well as towards the mental health care systems (M=29.24, SD=3.82, Md=29) were slightly negative, whereas the expected effectiveness of help-seeking for mental problems (M=2.59, SD=0.77, Md=3) ranged between 'somewhat' and 'considerable'. The three domains of attitudes showed no significant correlations (r=−.04 - .22). Additionally, no significant group difference was found between help-seekers (n=16; those reporting any kind of help-seeking for any kind of mental problem) and non-help-seekers (n=42; those never having sought help for any mental problem) on these three types of attitudes (U=289.50 - 316.00, p=.42 - .70).

Discussion: While public attitudes towards persons with mental disorders and mental health professionals/institutions were slightly negative, yet unrelated to each other, the perceived effectiveness of psychiatric treatment of severe mental disorders was rather positive and also unrelated to other domains of attitudes. While this could be an effect of the small sample size of our pilot, our finding indicates that associations between these different domains of attitudes can only be expected to have a rather small effect size, if any, in larger general population samples. In addition, they appear unrelated to actual help-seeking. If these finding would be replicated in a larger sample, they would question the assumption that these attitudes were related to help-seeking and that improvement of attitudes would facilitate earlier help-seeking for mental problems. In addition, public campaigns to improve attitudes towards persons with mental disorders, mental health professionals/institutions and psychiatric treatment would have to target each domain specifically.

doi:10.1016/j.schres.2010.02.528

Poster 34

PREVALENCE AND BURDEN OF AT-RISK CRITERIA OF PSYCHOSIS AND HELP-SEEKING BEHAVIOUR – A POPULATION SURVEY – PATHWAY-TO-CARE

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Background: Help-seeking and adequate treatment for mental disorder, and especially first-episode psychosis, is often delayed. To overcome this unfortunate situation, it is fundamental to uncover barriers in help-seeking and delays in health systems on population level. The aim of this pilot study was therefore to examine (non-) help-seeking for mental problems in the general population.

Methods: The enrolment sample comprised 85 persons. Inclusion criteria were (i) residency in the Canton Bern, (ii) age
between 16 and 35 years and (iii) telephone number available. *Exclusion criteria* were (i) life-time diagnosis of psychosis and (ii) insufficient language skills in German, French or English. 60 persons (70.5%) participated in the telephone interview, two of whom met exclusion criteria. Help-seeking was assessed with a modified version of the WHO pathway-to-care questionnaire.

**Results:** 36 persons (62.1%) reported current, at least subthreshold psychotic symptoms but no current or past help-seeking. Sixteen persons (26.6%) reported help-seeking for mental problems, including three (5%) with subthreshold expressions of symptoms considered at-risk indicators for first-episode psychosis, i.e., sub-threshold attenuated psychotic symptoms (APS). Average number of contacts reported by these 16 persons was 1.7 (1 - 6). Eight persons (50%) first contacted a psychiatrist/psychologist, four persons (25%) a general practitioner, two (12.5%) an alternative practitioner and one (6.25%) a non-psychiatric medical specialist and one (6.25%) a cleric. Main reasons for seeking help were depression (50%) and familial problems (18.75%), others anxiety, adiopause, alcohol/drug abuse and unspesifc symptoms such as nervousness or tension (each 6.25%). The three persons with subthreshold APS reported first help-seeking at a cleric, an alternative practitioner and a psychiatrist/psychologist, respectively. Main reasons for delays in help-seeking were lack of perceived seriousness of symptoms, hope for spontaneous remission, ignorance of adequate contact points and fear of discrimination/stigmatization.

**Discussion:** In line with earlier findings, the majority of persons experiencing mental problems do not or only with considerable delay seek help – not least because they do not know where to turn to or whether their symptoms require professional help or not. This illustrates the necessity of making people aware of mental problems and their treatment and to encourage searching professional help earlier for diagnostic clarification and for prevention of exacerbation of problems. However, since fear of discrimination also delayed help-seeking, such awareness programmes need to be accompanied by antistinega campaigns. Future studies on larger samples will have to examine influence of particular problems and/or socio-demographic factors on help-seeking behaviour.

**Poster 35**

**REVISITING SOCIAL BREAKDOWN SYNDROME: THE AUSTRALIAN NATIONAL SURVEY OF HIGH IMPACT PSYCHOSIS (SHIP)**

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**Background:** E. Gruenberg used the term *social breakdown syndrome* to describe a “socially determined reaction pattern ... which can be identified as a major target for community mental health programs” (Zusman, 1966). Social breakdown syndrome is secondary to the core symptoms of severe mental illness and is characterised by the breakdown in the interaction between a person and their environment. It remains relevant today as a useful target for intervention in the management of psychosis. The second national epidemiological survey of the prevalence and profile of psychosis in Australia, the Survey of High Impact Psychosis (SHIP), will identify factors at the core of social breakdown syndrome that are amenable to change, along with factors associated with good outcome in psychosis that are critical to recovery. This includes measures related to: social participation; living circumstances; physical well-being; and evidence-based service provision and interventions.

**Methods:** Prevalence estimates will be determined using a two-phase sampling design. In the first phase, we use a very brief psychosis screener. In the second phase, we undertake the interviews and assessments, including a diagnostic interview (Diagnostic Interview for Psychosis – Diagnostic Module). The survey census month is March 2010, with screening taking place in seven catchments across five Australian States. Two thousand people of those screen-positive for psychosis in Phase 1 will be randomly selected for interview in Phase 2: 1000 aged 18-34 and 1000 aged 35-64. The interview covers: functioning and socialisation; physical health; psychopathology and cognition; and service utilisation and need. Several novel components, nationally and internationally, include: (i) detailed assessment of role function that includes the level of role support; (ii) brief assessment of cognitive function; (iii) clinical assessment of physical comorbidity and the collection of metabolic measures; (iv) triangulation of data sources including data from the treating general practitioner; and (v) calculation of the economic and community costs of social breakdown.

**Results:** Replication of key questions from the 1997 Australian national psychosis survey will provide some measure of change in service use and satisfaction following major developments in mental health policy over the past decade. Alignment of survey questions with questions asked as part of the general population survey of mental health and in other national surveys will permit benchmarking of data against population norms. Screening data will be available for analysis at the start of April.

**Discussion:** The data generated by SHIP will enable Australia to develop new models within mental health services aimed at engaging people with psychosis in a long-term recovery process and achieving a measurable reduction in disability and its associated burdens and costs. Of international interest are novel strategies to capture social breakdown syndrome in people with psychosis, and to quantify cognitive function and pathways to recovery within a national, epidemiological framework. Presented on behalf of the SHIP Technical Advisory Group and Project Implementation Steering Group: V Morgan, A Jablensky, A Waterreus, R Bush, V Carr, D Castle, M Cohen, C Galletly, C Harvey, P McGorry, J McGrath, H Stain, B Hocking, A Mackinnon, A Neil, S Saw.

doi:10.1016/j.schres.2010.02.529

**Poster 36**

**FIRST EPISODE PSYCHOSIS IN PALERMO ITALY: PRELIMINARY DATA**

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**Background:** The incidence of psychosis is no longer believed to be the same worldwide. There is a 7 fold variation in the incidence of psychosis across the different studies so far published. This variation might be explained by a different distribution of environmental risk factors in different geographical areas. For instance, social environmental risk factors and substance misuse are very much dependent on the nature of individual countries (McGrath, 2005). Our main aims are to calculate the incidence of psychotic disorders in Palermo and the prevalence of environmental risk factors, with special attention to markers of social disadvantage and substance misuse. Here we present some preliminary data concerning level of education and cannabis use in our first episode patients.

**Methods:** We collected information from 104 cases presenting with a first episode of psychosis to the Mental Health Services of Palermo
PREVALENCE OF SYMPTOMS OF PSYCHOSIS IN MID-LEVEL MEDICAL COLLEGE STUDENTS IN KENYA

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Background: In Kenya very little is known about prevalence of symptoms of psychosis and especially in the general population. This study wanted to understand the prevalence and how comparable to the rest of the world it is.

Methods: Students of middle level Medical College in the country were involved. Students who were in first and second year were recruited from the 7 sampled colleges. They were then given self administered psychosis questionnaire which they completed. Ethical clearance had been granted from Kenyatta National Hospital Ethics Review Board. Ethical issues had been explained to the students.

Results: From the social demographic, the females comprised 51.4% and the males 48.6%. The age range was between 17 years and a few over 40 years. However the majority of the students were between 19 and 22 years, all contributing to 77.4% of all the students. Comparisons between genders revealed no differences in certain areas though in others the differences are large. The results are similar to those found in a study carried in a group of young normal Iranians.

Discussion: Preliminary data suggest that Palermo first episode cases have a higher mean age of onset and they are more likely to live at home with parents than reported by most previous first episode studies. Consistent with the existing literature we also found that cannabis users are more likely to be employed or in education indicating a good level of premorbid social adjustment.

doi:10.1016/j.schres.2010.02.531

CANNABIS USE AND PSYCHOTIC EXPERIENCES IN A HEALTHY POPULATION SAMPLE

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Background: Up to one quarter of the general population report psychotic experiences. Cannabis use is associated with the prevalence of those subclinical psychotic experiences (Johns et al., 2004, Henquet et al., 2005). This study aims to investigate the role and patterns of cannabis use in relation to the prevalence of individual psychotic symptoms in a sample of population based healthy volunteers.

Methods: Data were gathered as part of the first episode psychosis case-control Genetic and Psychosis (GAP) study. First episode psychosis patients where systematically recruited from South London and Maudsley Mental Health NHS Foundation Trust (SLAM). From the same geographical area served by SLAM we recruited 164 healthy controls aged 18 to 65 years. Data on psychotic experiences were collected, using Psychosis Screening Questionnaire (PSQ). We also collected socio-demographic data and a detailed history of illicit drug use administering the GAP amended version of Cannabis Experience Questionnaire.

Results: Subjects were asked to report on symptoms experienced over the past year. 36.6% reported one or more items on the PSQ but 10.4% of these were not sure. 4.9% of the sample felt that their thoughts were interfered by some outside force or person and 1.8% felt that their thoughts were interfered in a way that many people would find hard to believe. 18.3% felt that people were against them. 8.5% felt that people were deliberately acting to harm them or their interests. 7.3% reported having strange experiences and 2.4% thought these were so strange that people would find it very hard to believe. People using cannabis as a whole were not more likely to experience psychotic symptoms but they were more likely to experience certain individual psychotic symptoms. Furthermore, those using high potency cannabis (skunk) were more likely to report one or more of the above psychotic symptoms (OR=2.9, 95% CI 1.3–6.5, χ²=6.91, p = 0.009). In terms of individual symptoms, family history of psychosis was highly associated with the experience of thought interference (OR=7.5, 95% CI 1.8–30.7, χ²=10.28 p = 0.001). Being paranoid was found to correlate with heavy cannabis use (OR = 3.1, 95% CI 1.2–8.2, χ² = 5.35, p = 0.021).

The level of education was protected towards paranoid ideations (OR = 4.6, 95% CI 1.9–10.9, χ² = 13.84, p = 0.000). Subjects, describing strange experiences, were also more likely to have a family history of psychosis (OR = 4.6, 95% CI 1.2–17.4, χ² = 5.87, p = 0.015) and to have used cannabis (OR=9.7, 95% CI 1.2–74.9, χ²=8.70; p = 0.003). Once again high level of education seemed to be a protective factor (OR=4.3, 95% CI 1.2–15.9, χ²=6.06; p = 0.014).

Discussion: Cannabis use, especially the high potency type (skunk) and family history for psychosis are the strongest predictors of prevalence of psychotic disorders. There seems to be little difference between genders in certain areas though in others the differences are large. The results are similar to those found in a study carried in a group of young normal Iranians.

doi:10.1016/j.schres.2010.02.532
psychotic experience in the general population, while high level of education seems to play a role as a protective factor.

doi:10.1016/j.schres.2010.02.533

Poster 39
CAN GENETIC DIVERSITY EXPLAIN THE INCREASED RISK OF SCHIZOPHRENIA AMONG SECOND GENERATION IMMIGRANTS?

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Background: Second-generation immigrants have an increased risk of schizophrenia compared to their native counterparts (Cantor-Graae and Setlen 2005). However, the factor or factors responsible for this association are unknown. Hypothetical explanations may include both genetic and environmental factors, such as discrimination, exposure to unknown viral agents, parental post migration stress, parental malnutrition in the country of origin, and selective migration. This study investigates whether genetic diversity based on Genome Wide Association Studies (GWAS) could explain the increased risk of schizophrenia found among Danish second-generation immigrants. A secondary purpose was to evaluate the traditional procedure used to control for population stratification in GWAS.

Methods: The study was based on a linkage between the Danish Psychiatric Central Register (Munk-Jorgensen and Mortensen 1997) and the Danish Civil Registration System (Pedersen et al, 2006), as well as the dried blood spot (DBS) from the Newborn Screening Biobank (Norgaard-Pedersen and Hougaard 2007). Based on these registers 892 individuals with schizophrenia were identified. For each case we randomly selected one individually matched control. All individuals had blood spots located in the PKU biobank and were subsequently genotyped using Illumina 610 K. We used Principal Component Analyses based on a subset of 128,876 markers pruned for linkage disequilibrium to quantify genetic diversity. Information on ethnicity was based on parental place of birth (Cantor-Graae and Pedersen 2007). Native Danes were identified as people born in Denmark who’s both parents were also born in Denmark. Second-generation immigrants were identified as people born in Denmark where at least one parent was born abroad. Finally, we evaluated whether genetic diversity quantified by principal components can explain the increased risk of schizophrenia in Danish second-generation immigrants.

Results: The principal component map showed a clear correspondence between the first two principal components based on allele frequencies for included SNPs and ethnicity based on parental place of birth. Among Native Danes, the greater the genetic distance from the median Native Dane, the higher the risk of schizophrenia. However, among second-generation immigrants, those who were genetically closest to Native Danes had no increased risk of schizophrenia even when compared to Native Danes. Among the remaining second-generation immigrants the risk of schizophrenia was increased 2-fold, and it did not depend on genetic distance to the median Native Dane. Therefore, genetic diversity measured by principal components cannot explain the increased risk of schizophrenia in second-generation immigrants. The increased risk of schizophrenia among Native Danes with increasing genetic distance from the median Native Dane may indicate that the genetic distance to the median Native Dane may identify SNPs related to schizophrenia as opposed to SNPs related to geographic heterogeneity. If the former is the case, adjustment for genetic diversity measured by principal component analyses may bias effects of individual SNPs downwards in Genome Wide Association Studies.

doi:10.1016/j.schres.2010.02.534

Poster 40
MEN AND WOMEN IN PSYCHOSIS: ARE THEY SO DIFFERENT?

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Background: It is widely known that between men and women exist social, cognitive, genetic, biologic and physical differences. In the literature, gender differences in psychiatric disorders have been reported. It is known that men and women experience different depression patterns as they also differ with regards to the response to various drugs among other features. In this study we aim to define the socio-demographic and clinic profiles as well as to describe the gender differences of a psychiatric disorder called Brief Psychotic Disorder. This disorder is a clearly psychotic state, lasting between one day and one month, in which the subject fully recovers to the premorbid level of activity. The prevalence of this disorder is an estimated 4 to 10% of all psychotic disorders. Although a female preponderance has been postulated in the literature, gender differences have not been well studied.

Methods: We conducted a retrospective study in a sample of inpatients admitted in a psychiatric ward from January 1994 until December 2009 with DSM VI-TR diagnosis of Brief Psychotic Disorder. The clinical and socio-demographic characteristics, which were analyzed separately for men and women, were selected through a structured interview developed by a psychiatric doctor. The variables for the project were compiled from the hospital data based during the last 3 months.

Results: From a total of 50 patients with Brief Psychotic Disorder, 72% were women (n = 36) and 28% were men (n = 14). The mean age at first psychotic episode was 31.32 +/- 9.24 years (no differences between genders were found). Of the clinical variables studied women presented significantly more alterations in sensory perception such as auditory hallucinations and deep feelings of happiness. Additionally, women developed a more abrupt onset of the symptoms (within two weeks) (p<0.05). Moreover, men presented more family history of psychotic disorders than women (p<0.05) and required less days of hospitalization (p<0.05).

Discussion: As in other studies, we found a female preponderance in Brief Psychotic Disorder (79%). Positive symptoms such as hallucinations and a more abrupt onset of psychotic symptoms were significantly more frequent in women than in men. Regarding men, we found that they required fewer days in the hospital and that they had a greater family history of psychotic disorders. We believe that further studies are necessary, using larger samples, to determine the existence of sex difference in this particular disorder.

doi:10.1016/j.schres.2010.02.535
**Poster 41**

**PREMORBID FUNCTIONING AND TREATMENT RESPONSE AMONG PATIENTS WITH RECENT ONSET SCHIZOPHRENIA: PROSPECTIVE STUDY WITH Risperidone Long-Acting Injectable-ProPEL STUDY**

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**Background:** Some studies suggest a positive relationship between premorbid functioning and antipsychotic treatment response. Yet these studies were not a priori designed to test this relationship and did not assure drug adherence. This study was designed to test the association between premorbid functioning and antipsychotic treatment response after controlling for drug adherence by using a long acting injectable antipsychotic.

**Methods:** This was a prospective 6-month, open label, multicentre, phase IV trial in subjects with early-onset (< 2 years) schizophrenia treated with flexible doses of Risperidone Long-Acting Injectable (RLAI) (25 to 50 mg every 14 days). Premorbid functioning was assessed at baseline with Premorbid Adjustment Scale-Structured Interview; efficacy was evaluated with clinician rated PANSS, CGI-S, CGI-C, GAF and subject completed SF-36, and tolerability with ESRS and adverse event (AE) reports. Analyses controlled for baseline scores and demographics.

**Results:** Using published PAS scoring criteria subjects were grouped into stable-good (n = 142), stable-poor (n = 116) and deteriorating (n = 36) premorbid functioning. All groups showed significant improvement on the PANSS, CGI, GAF and SF-36. The stable-good group had the most improvement and also best functioning at baseline on most efficacy measures. The PAS Global Assessment of highest level of functioning item (excellent n = 75; good n = 117; fair n = 78 and poor n = 31) also showed a strong association with baseline functioning and improvement and had a significant linear association with meeting Remission in schizophrenia (e: xcellent n=75; good n=117; fair n=78 and poor n=31) also having a significant correlation with both baseline and remission scores. Using a logistic regression model with all variables as predictors the best model included baseline functioning, age, sex and drug adherence. Treatment duration was equal to the expected treatment duration (47.7%; 49.3%; 29.6%; 22.2%, p = .006). Treatment was equally well tolerated with no major improvement on both clinician and patient-reported measures. The PAS Global Assessment of highest level of functioning showed a strong association with baseline functioning and improvement.

**Discussion:** Using published PAS scoring criteria subjects were grouped into stable-good (n = 142), stable-poor (n = 116) and deteriorating (n = 36) premorbid functioning. All groups showed significant improvement on the PANSS, CGI, GAF and SF-36. The stable-good group had the most improvement and also best functioning at baseline on most efficacy measures. The PAS Global Assessment of highest level of functioning item (excellent n = 75; good n = 117; fair n = 78 and poor n = 31) also showed a strong association with baseline functioning and improvement and had a significant linear association with meeting Remission in schizophrenia (e: xcellent n=75; good n=117; fair n=78 and poor n=31) also having a significant correlation with both baseline and remission scores. Using a logistic regression model with all variables as predictors the best model included baseline functioning, age, sex and drug adherence. Treatment duration was equal to the expected treatment duration (47.7%; 49.3%; 29.6%; 22.2%, p = .006). Treatment was equally well tolerated with no major improvement on both clinician and patient-reported measures. The PAS Global Assessment of highest level of functioning showed a strong association with baseline functioning and improvement.
CIDI assessed diagnoses of SPh and PS at baseline (T0), and one year (T1), and three years (T2) later. Odds ratios, dose-response relationships and confidence intervals were calculated for the three hypotheses.

**Results:** Lifetime SPh and lifetime PS at baseline are associated (OR = 3.08; 95% CI 2.49 – 3.82; p < .001). A clear dose-response relationship exists; if the number of PS increases, the odds of SPh also increases. SPh that emerges at T1 or T2 after baseline PS also shows a strong association (OR = 4.07; 95% CI = 2.50 – 6.63; p < .001). Again a dose-response relationship was found. PS emerging after SPh showed a non-significant tendency (OR = 2.00; 95% CI (0.90 – 4.44; p = 0.088).

**Discussion:** This study confirmed the hypotheses that SPh and PS are associated in the general population. Possibly, this is caused by overlapping physiological and behavioural processes. There is a dose-response relationship that supports this notion. In addition, the dose response relationship where paranoid thoughts prompt the development of social phobia suggests a moderator relationship between these two conditions, but this must be considered with caution. Clinical implications are discussed. Focusing on social phobia might alleviate some of the secondary handicap caused by psychosis. This paper has been presented at the 6th International Conference on Early Psychosis, Early Intervention – The Next Wave, Melbourne, Australia, 22 October 2008 and has been published in Psychosis, Vol 1, No 1, February 2009.

doi:10.1016/j.schres.2010.02.539

**Poster 44**

**CHRONIC INFLAMMATION IN SCHIZOPHRENIA – EFFECT OF OBESITY ON INFLAMMATION MARKERS**

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**Background:** Both obesity and schizophrenia are associated with elevated inflammation markers i.e. cytokine levels (Mathieu et al., 2009; Potvin et al., 2008). We hypothesized that increased cytokine levels seen in subjects with schizophrenia would be explained by increased visceral obesity and fat percentage seen in these patients (Saarni et al., 2009).

**Methods:** From a population-based study (Perälä et al., 2007), we analysed serum samples from all persons with DSM-IV primary psychotic disorder (schizophrenia n = 45) and controls matched by age, sex, and region of residence. Serum levels of C-reactive protein (CRP) tumor necrosis factor alpha (TNFα), interleukin-1 receptor antagonist (IL-1ra), interleukin-2 and its soluble receptor's alpha subunit (sIL2Rα) and interleukin-6 were determined. Height, weight, waist and hip circumference, fat percentage, fat free mass and segmental muscle mass were measured using segmental, multi-frequency bioimpedance analysis.

**Results:** Persons with schizophrenia were found to have elevated levels of IL-1ra, sIL2Rα and CRP compared to matched controls (p < 0.005). Serum concentration of sIL2Rα remained statistically significantly elevated after adjusting for body mass index (BMI), fat percentage, and waist circumference. For IL-1ra and CRP adjusting for BMI, waist circumference did not change the result, whereas after adjusting for fat percentage the result weakened to marginally statistically significant (p = 0.06). Adjusting for antipsychotic medication did not change the result for sIL2Rα or IL-1ra, but weakened the effect on CRP. Further, we found no statistically significant interactions between diagnostic group and body composition variables for IL-1ra and sIL2Rα. For CRP we found the association between CRP and fat percentage to be statistically significantly stronger among subjects with schizophrenia compared to controls. This was also seen for waist circumference but the interaction was not statistically significant (p = 0.09).

**Discussion:** Based on these findings, elevated serum concentration of s-IL2ra seen in patients with schizophrenia is not due to abdominal obesity and elevated fat percentage of these patients. However, higher fat percentage partly contributes to increased levels of IL-1ra and CRP.

**References**


doi:10.1016/j.schres.2010.02.539
Poster 46
THE EFFECTS OF NEUROFUNCTIONAL REORGANIZATION THERAPY ON CORPORA SCHEMA AND SENSORY INTEGRATION IN SCHIZOPHRENIC PATIENTS: A PILOT STUDY

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Background: The view that schizophrenia is a neurodevelopmental disorder has become the prevailing pathogenic model. Indeed, developmental abnormalities, neurological soft signs (NSS), default network activation and neurogenesis, underlying the reorganization of neuronal networks, could explain the improvements seen in patients after the use of Neurofunctional Reorganisation method. Given that different authors talk about the effect of movement on cognition and that therapy based on the concept of sensory integration present many earnings in schizophrenic people at the cognitive, functional, motivity and symptomatology levels, it would be interesting to further investigate the effects of Padovan’s method in schizophrenia.

doi:10.1016/j.schres.2010.02.540

Poster 47
NEONATAL PHENCYCLIDINE INDUCES LONG-TERM OBJECT MEMORY DEFICITS IN MALE AND FEMALE RATS: REVERSAL BY RISPERIDONE, BUT NOT HALOPERIDOL

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Background: These data show that neonatal PCP induces robust and long-lasting object recognition deficits in adolescent and adult rats at two time-points in both males and females. The deficit induced by PCP in adult rats was reversed by risperidone (0.2 mg/kg) but not by haloperidol (0.05 mg/kg) in both male and female rats, which further supports the neonatal PCP paradigm as a model of particular relevance to schizophrenia. Aim: To investigate the time-course and validity of neonatal PCP treatment as a putative neurodevelopmental model of cognitive deficit symptoms in schizophrenia.

Methods: 24 male and 24 female hooded-Lister rats received subcutaneous injections of either vehicle (0.9% saline) or PCP (10 mg/kg) on PNDs 7, 9 and 11 as described in Wang et al., 2001 Neuroscience 107: 535-50. Male and female adolescent rats (PND 35-56), adult rats (PND 56-90) and PND >180 were tested for object recognition memory deficits. At PND 56-90 rats were injected acutely with either haloperidol (0.05 mg/kg, i.p.) or risperidone (0.2 mg/kg, i.p.) and tested for object recognition memory deficits using the NOR paradigm, validated as a test of cognitive dysfunction of relevance to schizophrenia in our laboratory (Grayson et al., 2007 Behav. Brain Res 184(1):31-38). Results are expressed as mean±SEM and analyzed by ANOVA followed by post-hoc Dunnett’s t-test.

Results: Both male and female rats showed no difference in exploration time(s) of the two familiar objects in the acquisition trial in any group in any of the stages i.e. as adolescents or adults at any time point. Time-course testing Adolescent rats (PND 35-56): In the retention trial, in both male and female rats, vehicle treated rats spent significantly (p < 0.001) more time exploring the novel compared to the familiar object, an effect that was abolished in the group treated with PCP (10 mg/kg). Adult rats (PND 56-90 and PND >180): In the retention trial, in both male and female rats, vehicle treated rats spent significantly (p < 0.01 for PND 56-90 and p < 0.001 for PND >180 in males; p < 0.05 in females) more time exploring the novel compared to the familiar object, an effect that was abolished in the group treated with PCP (10 mg/kg). Anti-psychotic testing In both male and female rats, in the retention trial, vehicle treated rats spent significantly (p < 0.001) more time...
exploring the novel compared to the familiar object, an effect that was abolished in the group treated with 10 mg/kg PCP alone and in combination with acute haloperidol treatment (0.05 mg/kg). However, PCP treated rats that received acute risperidone treatment (0.2 mg/kg) spent significantly (p < 0.05) more time exploring the novel compared to the familiar object.

**Discussion:** These data show that maternal PCP induces robust and long-lasting object recognition deficits in adolescent and adult rats at two time-points in both males and females. The deficit induced by PCP in adult rats was reversed by risperidone (0.2 mg/kg) but not by haloperidol (0.05 mg/kg) in both male and female rats, which further supports the neonatal PCP paradigm as a model of particular relevance to schizophrenia.

**Results:** Sensory integration domain was positively associated with FA(\(a-b\)), remaining strongly significant after correcting for multiple testing (\(\beta = 0.16, p = 0.006, OR (IC95\%) = 1.20 (1.04-1.32)\)). Higher levels of dermatoglyphic fluctuating asymmetry are related to the presentation of more integrative neurological deficits during the adult age (18 years old or more). No significant association between FA(\(a-b\)), and the other integrative domains was found.

**Discussion:** Our results suggest that the aetiological basis of NSS is likely to involve not only genetic but also prenatal environmental factors, as other studies have shown (Gupta, 2007; Waddington 1991). Specifically, they arise the possibility of the existence of different pathways for the generation of the different neurological areas included in the NSS, pointing out that the sensory integration domain, putatively associated with parietal brain areas and repeatedly found altered in disorders such as schizophrenia (Heinrichs 1988), seems to be influenced by developmental instability occurring prenatally early in gestation. Acknowledg.: (NV) PhD Grant FPI MICINN (BES-2009-023933). Supported by EUtwins-Schizophrenia (RD/0011/0007) and Coordinated Project SAF2008-05674-C03-01.

doi:10.1016/j.schres.2010.02.542

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**Poster 48**  
**NEUROLOGICAL ABNORMALITIES AND FLUCTUATING ASYMMETRY: THE ROLE OF PRENATAL ENVIRONMENT**

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**Background:** Integrative or Neurological soft signs (NSS) are defined as nonlocalizing neurological abnormalities reflecting dysfunction of the subcortical integrative system, with prevalences ranging from 0 to 50% in the general population (Cox & Ludwig 1979; Gupta 1995). NSS have been grouped under three main categories: sensory integration, motor coordination and motor confusion and iii) sequencing domain (Heinrichs and Buchanan, 1988). NSS have been documented to be more prevalent among patients with schizophrenia than in controls (Bombin, I 2005), although the relative contribution of genetic and/or environmental factors in this association remains unclear. Dermatoglyphics are ectodermic bilateral structures formed during the second trimester of gestation which remain unaltered after their formation around week 25th. Fluctuating asymmetry (FA) represents random bilateral deviations from normal symmetry, caused mainly by environmental stressors (Ludman, 1996). Dermatoglyphic fluctuating asymmetry (FA(\(a-b\))) has been suggested to provide a measure of early developmental instability in humans (Rose, 1987), and it has found to be higher in schizophrenic patients compared to controls (Van Oel, 2001; Fatjo-vilas, 2009). Studying NSS and dermatoglyphics in healthy individuals from a developmental perspective may help us understand the effect of early environmental factors affecting the establishment of neural networks of interest in psychosis. The aim of the present study is to investigate whether higher levels of FA(\(a-b\)) can predict the presence of more NSS.

**Methods:** The sample consisted of 246 healthy Spanish individuals (123 twin pairs from the UB-twin sample): with a mean age of 34.6 years (sd = 13.52). Neurological function was assessed using the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1988). Two groups (“High” NSS versus “Low” NSS) were created for each subscale using a median split (Murray, 2005; Dazzan, 2004). FA(\(a-b\)) was computed as the absolute difference of the number of ridges existing on the second interdigital area of the right and the left hand (Jantz and Webb, 1980). A logistic regression with the robust cluster command for paired data (STATA Corp.) was performed to test for the association between FA(\(a-b\)) and NSS, including sex, IQ, birth weight, gestational period, years of education and age at assessment as covariables.
adolescents, as it would likely lead to high rates of false-positive predictions. Yet, especially cognitive basic symptoms may be valuable criteria in ‘at risk’ studies in adolescents.

doi:10.1016/j.schres.2010.02.544

Poster 50
THE DIMENSIONAL STRUCTURE OF PRODROMAL SYMPTOMS IN EARLY-ONSET PSYCHOSIS: INDICATION OF SPECIAL NEEDS IN THE EARLY DETECTION OF YOUNGER ADOLESCENTS

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Background: Dimensional analyses of basic symptoms in adult samples had revealed a rather robust six-dimensional structure across different stages of the illness, i.e., between prodromal and frankly psychotic, yet non-chronic states. This structure even remained largely unchanged when a basic symptom assessment was switched from a binary assessment of presence to an ordinal assessment of severity. Thus its stability was tested in early-onset psychosis (EOP).

Methods: After the remission of frank psychotic symptoms, a sample of 32 inpatients with first-episode EOP (66% male, mean age 16, SD = 1.2, Md = 16 yrs.) of the Child and Adolescent Psychiatric Department of the University of Heidelberg had been assessed for the presence of basic symptoms within the months preceding their admission using the Bonn Scale for the Assessment of Basic Symptoms (BSABS). Using confirmatory Faceted Smallest Space Analysis, a nonparametric multi-dimensional scaling approach, the dimensional structure of basic symptoms was tested.

Results: Showing an insufficient separation index of only .25, the rather robust dimensional structure of adult samples could not be replicated in the EOP sample. Further analysis of the EOP data revealed a four-dimensional structure based on 49 items of the BSABS (separation index of .957): ‘adynamia’, ‘perception disturbances’, ‘neuroticism’ and ‘thought and motor disturbances’. Other than in adult samples, ‘adynamia’ appeared to play an especially important role as indicated by its centre position. When the totals of these dimension in the EOP sample were compared to those of a non-psychotic adolescent inpatient sample (n = 76), all but neuroticism (p = .207) were significantly more pronounced in the EOS sample (Mann-Whitney, p ≤ .000) with ‘thought and motor disturbances’ discriminating best. This was confirmed by ROC analyses that showed areas under the curve between .582 (.468/.697) for ‘neuroticism’ (p = .193) and .905 (.846/.964) for ‘thought and motor disturbances’ (p < .000).

Discussion: Subjective deficits that can occur as part of the prodrome of first-episode psychosis seem to cluster differently in children and adolescents compared to adults with a psychotic disorder. Modelled on the Schizophrenia Proneness Instrument, Adult version (SPI-A), the four dimensions were therefore used to develop an instrument for the quantitative rating of basic symptoms fitted to younger age groups. Besides putting emphasis on the differentiation of basic symptoms to mental disorders in children and adolescents, this instrument - called ‘Schizophrenia Proneness Instrument, Child and Youth version’ (SPI-CY) - also allows the inclusion of parents’ reports where considered appropriate, although remaining its focus on the self-perception of the patient.

doi:10.1016/j.schres.2010.02.545

Poster 51
IDENTIFYING THE MARKERS OF MENTAL ILLNESS IN PRIMARY SCHOOL-AGED CHILDREN: A SERIES OF CASE STUDIES EXAMINING COGNITIVE, MOTOR, LANGUAGE AND PSYCHOSOCIAL FACTORS

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Background: The identification of precursors to earlier onset psychiatric disorders is controversial. This is due to the subtle nature of prodromal signs, as well as the developmental trajectory that needs to be considered in this population, including age appropriate features. Recent reviews have highlighted the existence of a subset of children with atypical development in a range of domains including social skills, motor, language and behaviour. These children can be identified by clinicians and present with striking impairments including loneliness (social withdrawal), impairments in social interaction, unusual style of communication, and an unusual fantasy life including a preoccupation with an internalised imaginary world. These impairments have a significant impact on the child’s social and pragmatic skills and development of peer relationships. Their learning and development, as they progress through primary and secondary school is also detrimentally affected, leading to significant difficulties in their home and school functioning. Diagnosis in this group is difficult due to the age of the child, in addition to other neurodevelopmental conditions including Autism Spectrum Disorders, presenting with similar clinical features.

Methods: Several clinical case histories of children aged four to twelve years of age who presented at a Neurodevelopment Clinic in Melbourne will be discussed. These children have all demonstrated usual features in their presentation and particularly their ideas or patterns of thought. Data will be presented for each child comprising a comprehensive multidisciplinary assessment measuring: socio-demographic information, family and clinical history, language functioning, fine and gross motor abilities, neurocognition (attention, memory and learning, executive functioning, academic skills) and in some cases a psychiatric evaluation. Details of their psychiatric features, including details of their fantasies and internalised imaginary will be highlighted, and also video presentation of their behaviours.

Results: Commonalities in the neuropsychological profile will be discussed, including deficits in language, higher-level attention (particularly visual-spatial), executive skills (significant disorganisation), and conceptual reasoning. In addition striking social and emotional impairments have been noted. It is also argued that the key feature of these children is their internalised imaginary world, which differentiates them from other neurodevelopmental disorders. Short and long-term outcomes for these children will also be presented, demonstrating the variability in this group. Issues surrounding diagnoses will be raised, including the possibility of Schizotypal Personality Disorder in this subset of children.

Discussion: It is argued that further investigation of these children is required, within a longitudinal framework. Their progress in regards to cognition, motor and language dysfunction, in addition to possible psychiatric presentations requires monitoring and may lend insight into other neuropsychiatric disorders. These children may be exhibiting precursor signs to the development of early and adult onset schizophrenia-spectrum disorders, and understanding their complex profile may have implications for the early interven-
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THE STRUCTURE OF THE EXTENDED PSYCHOSIS PHENOTYPE IN EARLY ADOLESCENCE

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Background: Systematic review of general population studies suggests that, from an epidemiological perspective, psychotic experiences in non-ill people may represent the behavioral expression of increased liability for psychotic disorder. Although the great majority will never make the transition to clinical psychosis, even after extended periods of follow-up, a continuous dose-response risk function exists between psychotic experiences and later disorder. Although most research has focused on adults, this extended psychosis phenotype is already prevalent in adolescence. Only a small part of the total expression of risk in general population adolescent samples can be considered as true positive if used as a test for later psychopathology. The non-perfect prediction of psychotic experiences may suggest underlying heterogeneity, for example related to different types of psychotic experience.

Methods: In two large adolescent (12-16 years) samples (n = 5422 and n = 2230) from the Dutch general population, prevalence and structure of the extended psychosis phenotype was investigated. Prevalence of psychotic experiences was analyzed in relation to age and sex. Further, it was hypothesized that not all dimensions may be equally predictive of later psychopathology and that this would show as differential associations with distress and general psychopathology.

Results: Positive psychotic experiences, broadly defined, were reported by the majority of adolescents: respectively 95% and 94% endorsed at least one positive psychotic experience at least “sometimes” with medians of respectively 4 and 6 endorsements. In addition, respectively 43% and 39% endorsed at least one experience at the level of “often” or “nearly always”. Exploratory analyses with Structural Equation Modelling (Exploratory Factor analysis followed by Confirmatory Factor Analysis) in Sample 1 suggested that psychotic experiences were best represented by five underlying dimensions; Confirmatory Factor Analysis in Sample 2 provided a replication of this model; this model was also superior to four other models from the literature which distinguish several subdimensions within positive psychotic experiences. Dimensions were labeled Hallucinations, Delusions, Paranoia, Grandiosity and Paranormal Beliefs. Prevalences differed strongly, Hallucinations having the lowest and Paranoia having the highest rates. Prevalence patterns in the dimensions were similar over the two samples, supporting the robustness of our findings. Girls reported more experiences on all dimensions, except Grandiosity, and from age 12 to 16 years rates increased. Hallucinations, Delusions and Paranoia, but not Grandiosity and Paranormal beliefs, were associated with distress and general measures of psychopathology.

Discussion: The extended psychosis phenotype can be readily assessed in early adolescence and, while the prevalence of psychotic experiences in the general adult population is quite high, prevalence is even higher during adolescence. Given that non-clinical psychotic experiences are so highly prevalent among adolescents, a necessarily weak relationship can be inferred with later psychotic disorder. The present study suggests that experiences of Hallucinations, Delusions and Paranoia, but not Grandiosity or Paranormal beliefs, may be tapping into a continuum with more severe psychopathology, given the fact that these subdimensions are associated more strongly with distress and general psychopathology. Thus, only some of the dimensions of the extended psychosis phenotype in young people may represent a continuum with more severe psychopathology and predict later psychiatric disorder.

doi:10.1016/j.schres.2010.02.546

Poster 53
CLINICAL AND NEUROPSYCHOLOGICAL CHARACTERISTICS IN CHILD AND ADOLESCENT AT HIGH RISK FOR SCHIZOPHRENIA: COMPARATIVE STUDY BETWEEN FIRST DEGREE RELATIVES

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Background: First degree relatives of patients with schizophrenia have higher risk of developing a schizophrenia spectrum disorder and they are considered a genetic high-risk population, ideal for studying the early clinical and cognitive alterations before the onset of psychotic symptoms. Previous studies have shown higher rates of psychopathology (attention deficit/hyperactivity disorder, conduct disorder or anxiety) and cognitive difficulties (attention, verbal memory, executive functions or IQ) among relatives of schizophrenia patients than among the general population. Most studies are conducted with first degree samples (siblings or children) of schizophrenia patients. To our knowledge this is the first study which aimed to compare clinical and neuropsychological characteristics between children and siblings of schizophrenic patients.

Methods: Participants were 17 children and 15 siblings of patients with schizophrenia (DSM-IV criteria) and 20 controls whose parents and siblings did not meet DSM-IV criteria for any psychotic disorder. All subjects were aged between 7 and 16 years. These three groups were matched by age, sex and socio-economic status. Clinical (K-SADS; CPRS-48; SOPS) and neuropsychological (WISC-IV; TOMAL, WMS-III; WCST; STROOP and Rey Complex Figure Test) assessments were completed by all participants.

doi:10.1016/j.schres.2010.02.547
Results: The sample was divided into three groups, depending on their first degree relationship: siblings of patients with schizophrenia (Si), children of patients with schizophrenia (Ch) and healthy controls (Co). Clinical and neuropsychological variables were compared in the groups with a MANOVA test with the Bonferroni post-hoc correction. No significant differences in age, sex or socio-economic status were found among the three groups. Significant differences were found among groups in clinical (SOPS and K-SADS) and cognition (WISC-IV, WCST and Rey Complex Figure Test) assessment. So, Ch had higher ratios of psychopathology than the other two groups (Ch: 58%; Si: 39%; Co: 0%). Moreover, significant differences were found between Ch and Co in negative (P = 0.002) and total (P = 0.002) subscales of SOPS. This differences were not found between Si and C (P = 0.058). Regarding neurocognitive functioning, significant differences were found between Ch and Si in Working Memory Index of WISC-IV (P = 0.015) and digits backward (P = 0.049). Some differences such as Perceptual Reasoning Index of WISC-IV (P = 0.003); WCST mistakes (P = 0.004) or Rey Complex Figure recall (P < 0.001) were found between Ch and Co, but they were not detected between Si and Co.

Discussion: Children of schizophrenia patients showed worse performance on clinical and neuropsychological assessments than siblings of schizophrenia patients and healthy controls. Specifically, Ch had more psychiatric diagnosis and more cognitive difficulties on working memory, perceptual reasoning, executive functions and perceptual organization than Si or Co.

doi:10.1016/j.schres.2010.02.548

Poster 54
THALAMIC DEVELOPMENT IN CHILDHOOD ONSET SCHIZOPHRENIA; A VOLUMETRIC ANALYSIS

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Background: Thalamus is a key structure involved in information processing (Clenton et al., 2004) and has been assigned an important role in the development of Cerebral cortex (Lopez-Bendito and Molnar, 2003). Thalamic dysfunction has been implicated in the pathophysiology of Schizophrenia (Andreasen NC 1997). While thalamic volume abnormalities have been shown in adult onset Schizophrenia (Gernansky JG 2004), literature is very scant in children of patients with schizophrenia (COS) patients and their siblings. Altered thalamic growth trajectory as noted in this study may play an important role in the pathophysiology of COS. Given thalamus role in cortical development, these preliminary findings provide a developmental perspective to the earlier reports of abnormal thalamocortical network in schizophrenia.

doi:10.1016/j.schres.2010.02.549

Poster 55
WHAT CAN THE N170 TELL US ABOUT FACE PROCESSING IN SCHIZOTYPY?

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Background: Deficits in facial affect discrimination in schizophrenia may reflect inadequate configural processing. It has been proposed that the event-related potential (ERP) known as the N170 reflects the process of encoding facial information to form a structural representation. We investigated whether configural processing was behavioural and/or neurophysiologically different in persons with high schizotypy.

Methods: Healthy individuals (N = 28) were assigned to either high or low schizotypy extremes defined by the Oxford Liverpool Inventory of Feelings and Experiences (O:Life; Mason, Claridge & Jackson, 1995). Two stimulus types were presented in both an upright and inverted orientation; Mooney stimuli (configural information only), and photographic stimuli (both featural and configural). These were compared with non-face stimuli and participants were required to make face/non-face judgements. N170 latency and amplitude were submitted to separate repeated measures analysis of variance with the following within subject factors; orientation (two levels, upright and inverted), hemisphere (two levels, left and right), and electrode (three levels, P7/P8, PO7/PO8, C1/B1). Group sizes were too small to detect differences. Correlations of the O-LIFE scores with amplitudes for each electrode were then run.

Results: Accuracy and reaction times did not differentiate the schizotypy groups, however O-LIFE scores correlated significantly with N170 amplitudes (p < .05). Assessment of group waveforms revealed that high schizotypy showed a trend for reduced N170 amplitudes at both face orientations, relative to the low group.

Discussion: Reduced amplitudes in high schizotypy indicate impoverished facial information during face processing. Face processing impairment in schizophrenia may instead be attributable to a global reduction in the quality and/or quantity of fine detailed information. Determining the aetiology of face processing deficits will have a significant impact on the management of social distress experienced in schizophrenia, and subsequent treatments may help to reduce delusions of a social/persecutory nature.

doi:10.1016/j.schres.2010.02.550

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COGNITIVE DYSFUNCTION AND COMMUNITY FUNCTIONING IN SCHIZOPHRENIA: RESULTS FROM THE MATRICS PSYCHOMETRIC AND STANDARDIZATION STUDY (PASS)

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Background: The MATRICS Psychometric and Standardization Study (PASS) was one of the final steps in developing the MATRICS Consensus Cognitive Battery (MCCB). Findings will be presented on: (a) the profile pattern of persons with schizophrenia vs. community residents on the seven neurocognitive domains assessed by the MCCB, (b) the neurocognitive domains which best discriminate schizophrenia individuals vs. community residents, (c) the neurocognitive domains which best discriminate between persons with schizophrenia who are presently competitively employed vs. those who are not, and (d) the relationship between neurocognitive performance and level of social functioning.

Methods: Data were collected from 176 persons with schizophrenia or schizoaffective disorder from five participating sites (Duke University, Harvard University, University of Kansas, Maryland Psychiatric Research Center, and UCLA). For profile pattern, the data were analyzed using MANOVA with two groups (schizophrenia individuals vs. community residents) and seven neurocognitive domains (speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem-solving ability, and social cognition). Classification analyses were used to evaluate how well each neurocognitive domain discriminated schizophrenia individuals vs. community residents. A parallel analysis was completed to evaluate the relationship of MCCB neurocognitive domains to vocational status within the schizophrenia sample. Logistic regression was used to assess the relationship between neurocognitive performance and level of social functioning.

Results: The results demonstrated that persons with schizophrenia performed significantly worse than community residents on all seven neurocognitive domains (speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem-solving, and social cognition). The level of impairment ranged from 0.9 SDs (reasoning and problem-solving) to 1.5 SDs (speed of processing). Findings from the classification analyses indicated that speed of processing, visual learning, and social cognition best predicted overall social functioning. For vocational status, speed of processing (reaction time), visual learning, and social cognition best predicted persons with schizophrenia from community residents, correctly classifying 79.4% of schizophrenia individuals and 92.4% of community residents. For vocational status, speed of processing, attention/vigilance, and visual learning best predicted impairment across the multiple domains of cognitive functioning.

Discussion: These findings reveal a relatively even pattern of memory, and social cognition best predicted overall social functioning, at least as measured by the co-ordination of multiple processing-speed factors. The level of impairment ranged from 0.9 SDs (reasoning and problem-solving) to 1.5 SDs (speed of processing). Findings from the classification analyses indicated that speed of processing, visual learning, and social cognition best predicted overall social functioning. For vocational status, speed of processing, attention/vigilance, and visual learning best predicted persons with schizophrenia who were competitively employed vs. those who were not, correctly classifying 50.0% and 94.6%, respectively. For social functioning (measured using the Birchwood Social Functioning Scale), verbal and visual learning, speed of processing, working memory, and social cognition best predicted overall social functioning, but the amount of variance explained was relatively small (<10%).

Discussion: These findings reveal a relatively even pattern of impairment across the multiple domains of cognitive functioning assessed by the MCCB. The MCCB appears to be sensitive at discriminating patient-control differences and vocational status in individuals with schizophrenia. The MCCB showed a relatively weak predictive relationship with social functioning, at least as measured by the instrument used in this study.

doi:10.1016/j.schres.2010.02.551

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THE MULTIDIMENSIONAL STRUCTURE OF PROCESSING SPEED IN HEALTHY INDIVIDUALS AND SCHIZOPHRENIA PATIENTS

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Background: Recent research has identified processing-speed inefficiency, as measured by coding tasks, as the largest cognitive impairment in schizophrenia. However it is unclear to what degree processing speed is a multidimensional, as opposed to a unitary, construct; or how the structure of this construct differs between control and schizophrenia groups. In answering these questions this paper will provide further insight into the processing-speed impairment in schizophrenia.

Methods: 272 controls and 123 schizophrenia cases completed a set of putative measures of processing speed. We implemented confirmatory factor and structural equation modelling analyses (Miyake et al., 2000) to elucidate the latent structure of processing speed. Next, we tested the degree to which the structural and relational portions of the processing speed model was equal across groups.

Results: The best-fitting model revealed that processing-speed is a multidimensional hierarchical construct consisting of three lower-level factors measuring: 'Psychomotor Speed', 'Sequencing' and 'Switching'; with coding-task performance fitting in the model as a higher-level process affected directly by the 'Sequencing' and 'Switching' factors and indirectly by 'Psychomotor Speed'. The structure of the model was similar across groups but the strengths of the relationships within the models differed significantly (p<0.05).

Discussion: Processing speed is similarly characterised in control and schizophrenia groups as a multidimensional construct; wherein successful coding-task performance reflects a higher-level-process reliant on the co-ordination of multiple processing-speed factors. According to this model the overall processing-speed impairment in schizophrenia is underlain by impairment in lower-level facets of the ability.

doi:10.1016/j.schres.2010.02.552

Poster 58
OBSESSIVE-COMPULSIVE SYMPTOMS DO NOT AFFECT VISUAL RECOGNITION AND WORKING MEMORY IN CHRONIC SCHIZOPHRENIA

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Background: Obsessive-compulsive (OC) symptoms are common in patients with schizophrenia. However, the relationship of OC symptoms with cognition in schizophrenia remains puzzling.

Methods: 47 patients with schizophrenia were tested on the pattern and spatial recognition memory (PRM and SRM) and the spatial working memory (SWM) tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB) and were rated on the Yale-Brown OC scale (YB) in an acute psychiatric ward. We categorized patients into three groups according to severity of OC symptoms: (YB = 0, n = 17; YB ≥ 1, n = 11; YB ≥ 12, n = 16). We also divided them into two groups, consisting of patients with a possible comorbid OCD diagnosis (YB ≥ 17, n = 9) or not (YB < 17, n = 35). Statistical correlation analyses and the Mann-Whitney test were performed using the SPSS.

Results: We failed to find significant differences among the groups. No significant correlations were detected between YB obsession, compulsion or total scores and memory performance.

Discussion: Patients with schizophrenia and comorbid OC symptoms are not more cognitively impaired on tests of visual
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IS THEORY OF MIND LINKED TO SOCIAL IMPAIRMENT IN ELDERLY PATIENTS WITH SCHIZOPHRENIA?

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Background: It has been assumed that Theory of Mind (ToM) is the most predictive factor of social functioning in schizophrenia. However, to our knowledge, no study has evaluated ToM in patients older than 50 years. The effect of ageing on neurocognitive functions in schizophrenia is marked by a decline in some executive functions (EF) beyond that observed in healthy volunteers. Link between ToM and EF is controversial. Some authors think that the two abilities are related. By contrast, recent studies argue that ToM could be an independent ability. The aim of our study is: 1) to determine the impact of ageing and disease on the change in ToM in schizophrenia; 2) to determine if ToM is a factor linked with social functioning in schizophrenia; 3) to determine the link between ToM and EF.

Methods: Our study is an experimental cross-sectional study. To date we have included 13 schizophrenic patients older than 50 years (Sz50), 13 controls older than 50 years (C50), 16 young schizophrenic patients between 18 and 35 years (SzY) and 15 young controls (Cy). Clinical assessment was performed with the Positive and Negative Syndrome Scale and the social functioning was rated with the Morning Rehabilitation Status Scale (MRSS). All subjects were tested with a neurocognitive battery including an evaluation of EF, premorbid IQ, episodic memory and 2 ToM tasks (the French version of the “Faux-Pas” task and the “Referential Communication (RC)” task, which has recently been validated).

Results: Results at the Faux-Pas task show that Sz50 are significantly more impaired than C50. Comparing to SzY, Sz50 show also more difficulties to explain the faux-pas and have a tendency to manifest less empathy. Variance analysis with 2 factors (age and group) show an age effect and a group effect for items concerning explanation of the faux-pas and empathy. Results at the RC task show that Sz50, contrary to C50, don’t have any decrease in their ratio “number of indefinites references per total number of words” across the trials. In addition, Sz50, contrary to C50, don’t have any increase in their ratio “number of definite references per total number of words” across the trials. There aren’t any significant differences between both patients groups. Variance analyses with 2 factors (age and group) show a group effect for the change of those both ratios across the trials. Analysis with the EF’s Z-score in covariate shows a disappearance of the differences between both patients groups at the faux-pas task. Variance analysis with 2 factors shows a disappearance of the age effect but a persistence of the group effect for most items. Analysis at the RC task with the EF’s Z-score in covariate shows the persistence of the group effect on the main variables. Correlations between ToM tasks and social functioning show a link between the faux-pas’ total score and MRSS but no correlation with the RC task.

Discussion: Sz50’s impairment is observed in both ToM tasks. Link between ToM and EF depends on ToM task. In Faux-Pas task, worsening of performances with ageing is related to worsening of EF. This is underlined by the disappearance of the age effect when the EF’s Z-score is put in covariate. However, persistence of the group effect on most items means that a part of the deficit is consecutive to schizophrenia and is independent of EF. In the RC task, the deficit is linked to schizophrenia and is independent of EF and ageing. This is shown by the persistence of the anomalies in patients when the EF’s Z-score is put in covariate. Our results argue for ToM as an independent cognitive function. However the worsening of the impairment with ageing is linked to EF and depends on the considered task. These preliminary results have to be confirmed with more subjects.

doi:10.1016/j.schres.2010.02.554

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AUTOBIOGRAPHICAL MEMORY DEFICITS IN OLDER PATIENTS WITH CHRONIC SCHIZOPHRENIA

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Background: Memory deficits are one of the most distinctive neuropsychological features in patients with schizophrenia. In this study, particular attention is paid to autobiographical memory, which is crucial for the constitution of self-identity and self-esteem. Previous research on schizophrenic patients and autobiographical memory has shown that patients’ memory for the past is overgeneral and lacking in detail. Until now, only a few studies investigated the relationship between behavioural abnormalities associated with schizophrenia and selfdefining memories in older patients with chronic schizophrenia.

Methods: Up to now, 40 patients with chronic schizophrenia, 40 patients with major depression and 40 otherwise healthy controls were included for comparison. 32 patients with chronic schizophrenia were recruited among nursing home residents and 8 patients were from the chronic inpatient population. The comparison groups were participants of the longitudinal study of aging (ILSE). Personal semantic and episodic memories from five lifetime ground tasks covering relevant neurocognitive domains.

Results: Relative to both, healthy and depressive comparison subjects, patients with schizophrenia were significantly impaired in autobiographical memory performance predominantly regarding personal episodic memory. Semantic aspects of autobiographical memory were relatively well preserved. While the comparison subjects scored higher for the most recent lifetime period, this recency-effect did not apply for the schizophrenic patients.

Discussion: Taken together, our findings demonstrate autobiographical memory deficits in older patients with chronic schizophrenia. These deficits primarily involve personal episodic memories after onset of the illness and may thus diminish quality of life and social functioning in chronic schizophrenia.

doi:10.1016/j.schres.2010.02.555
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NEUROCOGNITIVE FUNCTIONING OF PRODROMAL AND EARLY STATE OF SCHIZOPHRENA: BASELINE ASSESSMENT OF SOPRES IN TAIWAN

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Background: A study on the psychopathological progress of the pre-psychotic state, SOPRES, was initiated in Taiwan since 2006. Four psychopathological stages, spanning from first episode psychosis (FEP), very high risk stage (VHRS, with attenuated or brief intermittent psychotic symptoms), intermediate risk stage (IRS, with some odd appearance, behavior, speeches, thoughts, or perceptual experiences), and very early stage (VES, with some non-specific symptoms not fitting into common psychiatric diagnoses), are to be validated by clinical, neuropsychological, and neurobiological follow-ups. We report the baseline neuropsychological evaluations.

Methods: Totally 327 subjects, including 48 FEP, 53 VHRS, 43 IRS, 42 VES, and 141 age and gender comparable normal controls have received a set of neuropsychological battery including continuous performance test (CPT), Wisconsin Card Sorting Test (WCST), Wechsler Adult Intelligence Scale-Third Edition (WAIS-III), Trail Making Tests, Mandarin version of Verbal Fluency Test and Wechsler Memory Scale-Third Edition (WMS-III). Z-scores for all variables were computed based on the mean and standard deviation of the control group after transforming to conform that higher scores indicate better performance. Their performances were categorized into nine domains, verbal conception, visual spatial ability, abstraction-execution, perceptual-motor ability, mental control, attention, verbal fluency, verbal memory, and visual memory, by averaging the z-scores of all designated subtests in each domain. The differences in performance among groups were examined by ANOVA. In the 53 VHRS participants, 14 converted into full-blown psychosis during follow-up, so the VHRS group was then divided into VHRS+ (n = 14) and VHRS- (n = 39) for further comparisons.

Results: The baseline neuropsychological assessment in this sample comprised by five levels of clinical severity revealed a clear gradient pattern in terms of neurocognitive deficits. The FEP participants obviously had the worst neurocognitive functioning, significantly in all 9 domains compared to the control group. The VHRS and the IRS groups performed significantly worse than the controls in perceptual motor ability, verbal fluency, logic memory and visual memory while the VES group was only marginally inferior in verbal fluency to the controls. The VHRS+ generally had lower scores than the VHRS- but not to the extent of statistical significance in any domain. Although the FEP performed the worst in all domains, their performance was generally not significantly different from that of the VHRS and IRS.

Discussion: Our study is the first to compare neurocognitive deficits of the putative prodromal subjects, among whom 26% converted into full-blown psychosis later on, to both the first episode subjects and those whose clinical severity not to the extent of ultra-high risk state. The findings of the FEP were consistent with previous studies which suggested the neurocognitive deficits were prominent at the early state of psychosis. The neurocognitive functioning of the VHRS is at the intermediate level between normal control and the FEP, also a replicate of previous studies. Most importantly, we failed to differentiate the VHRS+ from the VHRS- at baseline neurocognitive assessments, as well as the VHRS had similar performance to those of the IRS (none of them converted into psychosis during follow-up). Thus it will be impractical to use impaired neurocognitive functioning alone as an indicator to predict the risk of psychotic conversion.

doi:10.1016/j.schres.2010.02.556
META-ANALYTIC REVIEW

NEUROCOGNITION IN FIRST-EPISODE SCHIZOPHRENIA: A

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Background: Compromised neurocognition is a core feature of schizophrenia. Following Heinrichs and Zakzanis’s (1998) seminal meta-analysis of middle-aged and predominantly chronic schizophrenia samples, the aim of this study was to provide a meta-analysis of neurocognition in first episode FE schizophrenia to: 1. Identify the level and pattern of cognitive impairment in individuals in the FE of schizophrenia; 2. Discern the extent to which individuals in the FE show levels and patterns of cognitive deficits comparable to those beyond the early phase of established illness; 3. Better understand the degree to which FE samples are more cognitively impaired than those within premorbid or possibly prodromal phases; 4. Examine the influence of moderator variables (e.g., demographic and clinical factors) on FE neurocognitive impairment.

Methods: The meta-analysis used neurocognitive data from 47 studies (based on 43 separate samples) published through October 2007, yielding a total of 2,204 persons with FE schizophrenia and a mean age of 25.5, and 2,775 largely age- and gender-matched control participants. Exclusion criteria included: studies of affective psychosis, severe personality disorder at the border of psychosis (e.g., schizotypal personality disorder and prodromal risk syndromes). Inclusion criteria included: studies written in English, inclusion of a healthy comparison group, and report of study statistics convertible to effect sizes (ES). Tests were categorized into 10 domains through which to view and classify the findings: immediate verbal memory, attention (divided into 3 subdomains of processing speed, working memory, and vigilance), nonverbal memory, general cognitive ability, language functions, visuospatial abilities, delayed verbal memory and learning strategies, executive functioning, social cognition, and motor skills.

Results: FE samples demonstrated medium-to-large impairments across the 10 neurocognitive domains with mean ES ranging from -0.64 for motor skills to -1.20 for immediate verbal memory. These impairments were statistically significant in each domain (Z=4.68 to 21.21, ps<.001) compared to controls. Not surprisingly, analyses frequently revealed significant heterogeneity across all neurocognitive domains and studies (9≥53.49, ps<.001). Limited information relevant for moderator analyses limited our ability to identify sources of influence on the variability of ESs. However, ES variability within the 10 domains was most frequently associated with publication year (6 domains), gender proportions of FE and/or control samples (5 domains), percentage of patients on antipsychotic medications (5 domains), handedness of FE and/or control samples (4 domains), study country (4 domains), and education of FE and/or control groups, age of FE and/or control groups, and diagnostic composition of FE samples (2 domains each).

Discussion: Our meta-analysis indicates that neurocognitive impairments are reliably and broadly present by the FE, approach or match the degree of deficit shown in well-established illness, and are maximal in immediate verbal memory and processing speed. Larger IQ impairments in the FE compared to the premorbid period, but comparable to later phases of illness suggests deterioration between premorbid and FE phases followed by deficit stability at the group level. Considerable heterogeneity of effect sizes across studies, however, underscores variability in manifestations of the illness and a need for improved reporting of sample characteristics to support moderator variable analyses.

doi:10.1016/j.schres.2010.02.558

THEORY OF MIND AND GLOBAL EMPATHY PERFORMANCE IN SCHIZOPHRENIA: THE ROLE OF ANXIETY, REMISSION STATUS AND SYMPTOM TYPE

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Background: It is well established that in general, those with schizophrenia perform poorly on tests of theory of mind. It is less clear what specific factors influence performance. Studies examining specific symptoms and remission status have been inconsistent, and the role of anxiety has not been studied.

Methods: This cross-sectional study compared outpatients with psychosis (n=26), with an anxiety disorder group (n=27) and a healthy control group (n=25) on two tests of theory of mind (the Eyes and Hinting tests) and a measure of global empathy [the Empathy Quotient (EQ)]. A wide range of demographic and clinical factors were collected including specific measures of psychotic symptoms (PANSS), depression (BDI-2), social anxiety (SPIN) and general psychopathology (SCL-90).

Results: Analysis of co-variance controlling for verbal IQ showed a main effect of group for both the Eyes test and the EQ. Post-hoc tests for the Eyes test showed the psychosis group (adjusted mean=24.16, 95% CI: 22.56-25.77) performed worse than controls (mean=28.17, 95% CI: 26.60-29.75), but did not differ from the anxiety group (mean=27.32, 95% CI: 25.82-28.81). On the EQ the psychosis group (adjusted mean=40.14, 95% CI: 35.34-44.93) and the anxiety groups (adjusted mean=43.20, 95% CI: 38.73-47.67) differed from controls (adjusted mean=51.25, 95% CI: 46.54-55.97) but not each other. The Kruskal-Wallis test showed no main effect of group in the Hinting test. Within the psychosis group, linear regression models were built to examine the role of specific demographic and clinical factors in task performance. The Eyes model had two significant factors: SCL-90 Somatic subscale score (adjusted R² change=0.255) and the PANSS Negative subscale score (adjusted R² change=0.095). The Hinting test model had one factor: the PANSS Negative subscale score (adjusted R² change=0.451). The EQ model had two significant factors: SCL-90 Anxiety subscale score (adjusted R² change=0.246) and the PANSS Negative subscale score (adjusted R² change=0.233). The SCL-90 Anxiety score was positively correlated with EQ score while all other factors in the other models were negatively correlated with performance. When the psychosis group was split into remitted and non-remitted groups, mean scores for the non-remitted group were lower on all three measures. For the Eyes test, post hoc tests showed that the non-remitted group was significantly lower than both the anxiety and control group, while the remitted group did not differ from any group. This pattern was also found for the Hinting test. On the EQ both the remitted and non-remitted groups scored lower than controls but not the anxiety group or each other. Controlling for verbal IQ did not change this finding for the Eyes, however in the EQ the non-remitted group no longer differed from the control group. For the Hinting test, both the overall group effect and group differences disappeared.

Discussion: These findings support the idea that deficits in theory of mind in schizophrenia are both state and trait characteristics. In the acute phase deficits are more pronounced, while in the stable remitted phase deficits persist in an attenuated form, and are mediated by cognitive and negative symptoms. A surprising and difficult to explain finding was that in the psychosis group, higher anxiety scores were associated with higher levels of global empathy. It is possible that anxiety is related to an unmeasured clinical factor such as insight. Further research examining the role of anxiety in theory of mind and empathy performance is warranted. Research in this area would benefit greatly from a standardized battery of tests with known psychometric properties.

doi:10.1016/j.schres.2010.02.559
Posters

Subject: "Neuropsychological functioning of individuals with familial risk for psychosis in the Northern Finland 1986 Birth Cohort"

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Background: Individuals with heightened risk for psychosis demonstrate difficulties in cognitive functions. However, concerning specific cognitive domains, some results have been replicated while others have not. We aimed to investigate the neuropsychological functioning of subjects with familial risk for psychosis in a population based birth cohort.

Methods: The subjects of the study were members of the Northern Finland 1986 Birth Cohort. All cohort members having a parent with psychosis or A-type personality disorder according to the Finnish Hospital Discharge Register were invited to participate in the study during years 2007-2009 (28% of whom participated). A 2% random sample of the rest of the cohort members were invited as a control group (46% of whom participated). 74 familial risk and 79 control subjects were included in the analyses after excluding the subjects having had a psychotic episode according to the Structured Interview for Prodromal Syndromes (SIPS). The neuropsychological assessment consisted of five tests of Cambridge Neuropsychological Test Automated Battery (CANTAB): Paired Associates Learning (PAL), Spatial Working Memory (SWM), Stockings of Cambridge (SOC), Rapid Visual Information Processing (RVP) and Information Sampling Task (IST).

Results: Our results show that one form of executive functioning - spatial planning, as assessed by SOC - is worse in the familial risk group compared to the control group (p = 0.047). Visual learning and memory (PAL), working memory (SWM), attention (RVP) and decision making (IST) did not differentiate these two groups.

Discussion: Spatial planning, a complex cognitive function depending largely on prefrontal brain processes, is impaired in persons with genetic vulnerability for psychosis. Future follow-up of these individuals will show whether this finding has value in predicting conversion to psychosis.

doi:10.1016/j.schres.2010.02.560

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Subject: "Ketamine as a model of semantic deficits in schizophrenia"

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Background: The glutamate/ketamine model is gathering support as a useful adjunct to the dopamine hypothesis of schizophrenia (Javitt, 2007). One reason being that ketamine is capable of eliciting the cognitive deficits associated with this illness including those seen in semantic memory (Adler et al., 1998; Morgan et al., 2005). Two recent reviews (Rossell & Stefanovic, 2007; Pomerol-Clotet et al., 2008) have found larger than normal indirect semantic priming effects in schizophrenia suggesting an abnormality in implicit access to indirect relationships. In the current study, implicit and explicit tasks were employed to examine access to direct and indirect relationships in the semantic network. The purpose was firstly to see if the indirect priming findings from the schizophrenia literature can be replicated in a ketamine group (providing support for the ketamine model) and secondly, to determine whether such abnormalities are restricted to the indirect, implicit nature of the task or whether they are more widely spread and detectable in explicit and direct tasks. Should ketamine mimic schizophrenia deficits closely, then the answer to the second question will help to determine the nature of the semantic memory deficit in schizophrenia.

Methods: This was a double blind placebo controlled cross over design. On one occasion, participants received ketamine, on the other, saline. On each occasion, participants completed a battery of semantic memory tasks along with measures of psychosis and dissociation.

Results: The results showed statistically significant indirect priming under the influence of ketamine but no significant indirect priming in the same individuals in the placebo condition. In addition, ketamine only disrupted semantic access significantly on indirect tasks.

doi:10.1016/j.schres.2010.02.561
INTERVENTION IN EARLY PSYCHOSIS

DIVERGENT THINKING AS A POTENTIAL TARGET FOR COGNITIVE INTERVENTION IN EARLY PSYCHOSIS

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Background: Not only patients with chronic schizophrenia but also those with first-episode schizophrenia (FES) show cognitive impairments in a wide variety of domains. Furthermore, even people with at-risk mental state (ARMS) exhibit cognitive deficits although they usually demonstrate superior performance. As cognitive impairments are significantly related to social functioning, cognitive intervention in early stages of schizophrenia may be preferable. The Toho University Omori Medical Center, Tokyo, established the day-care unit named ‘Il Bosco’ in 2007, which was specific to individuals with early psychosis. Its integrated treatment strategies consist of cognitive training, psychoeducation, and individual support in normal work and school setting under optimal pharmacotherapy with minimum dosage. The cognitive training program mainly targets divergent thinking deficits, because we revealed that interventions for divergent thinking significantly led to improvements in negative symptoms and social functioning in schizophrenia patients (Nemoto et al., 2009). The aim of this study was to examine the efficacy of cognitive intervention for divergent thinking in people with early psychosis.

Methods: Twenty-six Japanese outpatients with early psychosis (13 men, 13 women) were recruited at ‘Il Bosco.’ They included 20 individuals (9 men, 11 women) with FES and 6 people (4 men, 2 women) with ARMS diagnosed by the Structured Clinical Interview for DSM-IV Axis I Disorder (SCID) and the Structured Interview for Prodromal Syndromes and the Scales of Prodromal Symptoms (SIPS/SOPS). The mean age of FES group was 21.5 (SD = 3.6) years and that of ARMS group was 19.5 (SD = 2.5). The mean duration of untreated psychosis (DUP) in FES group was 5.5 months. All patients were taking antipsychotic medications. Subjects were excluded if they had a history of alcohol dependence, substance abuse, or a neurological illness. The cognitive training program for divergent thinking (Nemoto et al., 2009) was administered for 6 months in the group setting. The outcome measures of cognition included the Letter Cancellation Test (LCT), the Seven-word Learning Test (SLT), and the Modified Stroop Test (MST). In addition, the Social Functioning Scale (SFS), the WHO Quality of Life-26 (WHOQOL-26), and the Subjective Well-being Neuroleptic drug treatment Short form (SWNS) were used to assess functional outcome. These assessments and neurocognitive tests were administered at baseline and at the end of the six-month cognitive intervention. After providing a complete description of the study, written informed consent was obtained from every subject.

Results: We found significant treatment effects on some measures in the FES group, including: time for completing the LCT (p < .004), the repeated times to remember all the words on the SLT (p < .029), and the total score of the SFS (p < .030). Significant treatment effects on the MST (Part II minus Part I) and two components on the SFS (Withdrawal and Interpersonal) were found in the ARMS group (p < .027, .034, .042, respectively).

Discussion: Cognitive intervention for divergent thinking deficits at the early stages of psychosis may maximize the chance of long-lasting functional recovery and minimize the potential for future onset in a proportion of people with ARMS because divergent thinking ability is critical for generating creative solutions in the social setting and navigating the complexities of social interactions.
linguistic and cultural differences and the ways in which they were resolved. We will also summarize several ongoing studies that are collecting normative data on the translated MCCBs in samples stratified by age, gender, and educational level to allow resulting MCCB scores to be compared and combined across the various languages.

**Discussion**: These developments highlight the recent progress that has been made in furthering a key goal for the MATRICS initiative – to facilitate the evaluation of promising new treatments for the core cognitive deficits of schizophrenia within international clinical trials. The process required to create comparable cognitive measures across languages and cultures is instructive not only for the MCCB, but also for any cognitive measures that are being considered for international use in schizophrenia research.

doi:10.1016/j.schres.2010.02.564

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**Poster 70**
**CAN WE IDENTIFY COGNITIVE PROFILES IN PSYCHOSIS WITH PRE-MORBID ESTIMATES? FINDINGS FROM A FIRST EPISODE COHORT STUDY**

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**Background**: Estimates of pre-morbid IQ are widely used to measure the trajectory of cognitive function in schizophrenia. More recently discrepancies between reading tests and current IQ have shown that the pattern of cognitive functioning is heterogeneous across psychotic illness and established at first episode. (Leeson et al., 2009). This study aims to examine the usefulness of two different pre-morbid indicators to identify cognitive variability in first episode psychosis.

**Methods**: Participants were recruited in South East London from consecutive psychiatric hospital contacts. A comprehensive neuropsychological battery was administered to 53 patients with psychosis onset of >6 months. Geographically matched controls (71) were tested on the same measures. IQ was estimated using a short form of the WAIS III. The National Adult Reading Test (NART) and the Weshler Test of Adult Reading Test (WTAR) were used to estimate pre-morbid IQ.

**Results**: On pre-morbid and current IQ estimates, patients under-performed compared to controls. The magnitude of differences in current IQ was particularly large (t=-4.631 p<.001). In line with previous meta-analyses patient IQ and NART pre-morbid estimates were estimated at 0.5 SD below the control mean (M = 93.29) (SD = 13.21) and 93.32(SD = 8.7) respectively. NART correlated slightly better than WTAR to current IQ (Rho = .695 vs .633 p<.001). Despite this, NART still underestimated 42% of controls IQ by 10 points or more. Unlike controls, most patient pre-morbid estimates were equivalent to current IQ. In a comparison of NART/ IQ scores, 16% of patients showed IQ ‘deterioration’ of at least 10 points compared to 5% of controls. Patients with stable- low and deteriorating IQ (ie WAIS – NART discrepancy) showed specific impairments in memory tasks, especially delayed memory (t = 3.947 <.001). Interestingly, processing speed further differentiated the sub-groups with ‘deteriorating’ patients performing significantly worse than all other patients regardless of pre-morbid IQ (F = 3.750 P = .022) There is a trend for older patients (>30 years) to show deterioration in IQ, however more numbers are needed to test the significance of this finding. Interestingly, young patients show significantly more negative symptoms than older patients (t = 2.375 <.05).

**Discussion**: Almost half of the patients in this cohort have stable and average IQ scores. However, the tendency of NART and WTAR reading tests to underestimate WAIS III IQ in controls raises suspicions that deterioration is more marked in patients than would appear from the pre-morbid minus current IQ discrepancy. Indeed irrespective of pre-morbid scores, a substantial sub group of patients showed IQ deterioration in association with specific processing speed deficits. Preliminary findings also suggest that that older patients have more severe cognitive deficits at the first episode, perhaps due to a longer duration of untreated illness or medication effects. More prominent negative symptoms in young patients may signal more severe, schizophrenia- type illness with a halt in IQ development rather than deterioration. Further work will focus on longer term outcome and exploring how cognitive trajectories may affect recovery.

doi:10.1016/j.schres.2010.02.565

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**Poster 71**
**A NEUROCOGNITIVE ASSESSMENT OF THE PERFORMANCE OF INDIVIDUALS AT ULTRA-HIGH RISK OF PSYCHOSIS, USING THE JAPANESE VERSION OF THE BRIEF ASSESSMENT OF COGNITION IN SCHIZOPHRENIA (BACS)**

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**Background**: Since individuals at ultra-high risk (UHR) of psychosis are heterogeneous in its clinical presentation and diagnostic prognosis, we need a measurement which can help evaluate the clinical characteristics and course for them. It had been suggested that the some domains of neurocognitive dysfunction were observed in UHR individuals and could predict the future development of psychosis (Keefe et al., 2006). The Brief Assessment of Cognition in Schizophrenia (BACS) is a comprehensive neurocognitive battery, which contains six cognitive domains that were repeatedly reported to be compromised in patients with schizophrenia (Keefe et al., 2004). We compared the UHR individuals' neurocognitive performance with that of patients with first-episode psychosis (FEP) and healthy controls (HC) using the Japanese version of BACS.

**Methods**: BACS was administered to 15 UHR, who met the criteria developed at the Personal Assessment and Crisis Evaluation (PACE) clinic (Yung et al., 2005); the 15 FEP and 15 HC were matched on the age and gender. The HC were university students with no history of mental disorders. The raw BACS subtest scores of each participant were standardized by creating z-scores, whereby the control group’s mean was set to zero and their standard deviation to one. Z-scores of all the subtests were averaged to obtain a composite z-score. We compared these data between the three groups using a one-way ANOVA and performed a post-hoc analysis of an inter-group comparison using the Tukey’s test. We set the p-value at 0.05. All participants gave written informed consent, and this research was approved by the Tohoku University Ethics Committee.

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**Poster 72**
**COHORT STUDY PRE-MORBID ESTIMATES? FINDINGS FROM A FIRST EPISODE CAN WE IDENTIFY COGNITIVE PROFILES IN PSYCHOSIS WITH STUDY**

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**Background**: Estimates of pre-morbid IQ are widely used ...t's test. We set the p-value at 0.05. All participants gave written informed consent, and this research was approved by the Tohoku University Ethics Committee.
RESULTS: There were no significant differences in the demographic data between the three groups except in the predictive IQ measured by the Japanese Adult Reading Test (F(2, 42) = 10.64, p < 0.001) and the years of education (KW = 8.55, p = 0.014). The distributions of each of the scores of UHR and FEP were negatively skewed compared with that of HC, and the variance of each group's composite z-scores (SD = 0.95 and 1.45) was larger than that of HC (SD = 0.43). Four of the six z-scores of the BACS subtests (verbal memory, working memory, verbal fluency, and attention) were significantly differed (F(2, 42) = 11.20, p < 0.001; F(2, 42) = 12.10, p < 0.001; F(2, 42) = 10.22, p < 0.001; and F(2, 42) = 16.14, p < 0.001, respectively). The post-hoc Tukey's test demonstrated that the scores of the UHR and FEP in the four subtests were significantly lower than those of HC, whereas no significant differences were found between UHR and FEP. There were no significant differences in the two subtests (motor speed and executive function) between the three groups (F(2, 42) = 0.63, p = 0.54; F(2, 42) = 3.00, p = 0.060).

DISCUSSION: The results suggest that BACS is sensitive enough to detect the difference between the UHR and HC's neurocognitive functions. The results are compatible with other studies showing deficits in the verbal memory, working memory, verbal fluency, and attention of UHR subjects. However, we could not find any difference between the UHR and FEP's neurocognitive functions. The large variance of distribution on the cognitive functions in UHR and FEP might be partially responsible for this. A longitudinal study is necessary to assess the predictive validity of the cognitive assessment for the prediction of a clinical course in UHR individuals. Reference Keefe et al., Schizophr Res. 2006; 88 (1 –3): 26–35. Keefe et al., Schizophr Res. 2004; 68: 283–297. Yung et al., Aust N Z J Psych. 2005; 39 (11–12): 964–71.

doi:10.1016/j.schres.2010.02.566

Poster 72
THE RELATIONSHIP BETWEEN SOCIAL COGNITIVE FUNCTIONING AND PSYCHOTIC SYMPTOM CLUSTERS IN FIRST EPISODE PSYCHOSIS

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BACKGROUND: Social cognition is a relatively new area of research in schizophrenia spectrum disorders. Most existing research in this field has examined social cognitive functioning in established or chronic schizophrenia populations, however investigation of first-episode (FE) or early psychosis cohorts has been limited. Moreover, the relationship between symptomatology and social cognition in FE psychosis is virtually non-existent. This study aimed to assess the relationship between various social cognitive domains and symptomatology in first episode psychosis.

METHODS: Thirty-six FE outpatients being treated for psychosis (67% male; 33% female) with an age range of 15-25 years completed the study. The current analysis included patient data from two social cognitive tasks: the DANVA2 (faces and paralanguage components) and the Hinting Task, which assess emotion recognition and Theory of Mind, respectively. Symptomatology was assessed via clinical interview using the PANS, with positive (“psychomotor poverty”), negative (“psychomotor poverty”) and disorganised symptom clusters established via Liddle’s (1987) method.

RESULTS: Based on research in established schizophrenia samples, higher scores on psychomotor poverty and the disorganised factor were predicted to be associated with more errors in both facial and paralinguistic emotion recognition, particularly for those emotions of low intensity. Preliminary results indicated that only the psychomotor poverty symptom domain was significantly associated with difficulty in some aspects of emotion recognition; specifically, when emotional intensity is high, and when facial expression is fearful. There was no association between type of psychotic symptoms and performance on the Hinting Task.

DISCUSSION: These findings suggest that negative symptoms may contribute to problems in identification of facial emotions when intensity of affect is high and when fear is being expressed. Furthermore, Theory of Mind ability as assessed by the Hinting Task does not appear to be influenced by symptomatology.

doi:10.1016/j.schres.2010.02.567

Poster 73
CFA CONFIRMATION OF A LATENT COGNITIVE STRUCTURE COMMON TO SPANISH AND NORTH AMERICAN PATIENTS WITH SCHIZOPHRENIA

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BACKGROUND: We sought to determine whether patients with schizophrenia with different social and cultural Background share a common cognitive architecture functioning. The confirmation of this hypotheses could provide useful targets for international clinical trials of drugs and behavioral interventions designed to enhance cognition in patients with neuropsychiatric disorders.

METHODS: We assessed 165 patients with schizophrenia from the Alava Psychiatric Hospital (Spain) using 13 measures derived from 9 cognitive tests. Confirmatory factor analysis was used to examine the fit of a previously reported 6-factor model. The hypothesized factors include attention, psychomotor speed, verbal memory, visual memory, fluency, and executive functioning.

RESULTS: The six-factor model confirmed for the USA sample, provided an excellent fit for the Spanish sample (χ² = 82.27, χ²/df = 1.64, RMSEA = 0.06, NNFI = 0.96, CFI = 0.97). This model was compared to several competing nested alternatives, including five-, four-, and one-factor models which did not show good fit indexes. The one factor model fitted the observed data very poorly (χ² = 495.4, χ²/df = 7.18, RMSEA = 0.20, NNFI = 0.63, CFI = 0.69). The five factor Speed model, showed better results (χ² = 128.4, χ²/df = 2.33, RMSEA = 0.09, NNFI = 0.91, CFI = 0.94). However, RMSEA statistics indicated that this model does not fit adequately with the actual data. The models that considered verbal and visual memory as one unique factor (five factor Memory model and 4 factor model), did not present good fit to the data (χ² = 115.9, χ²/df = 2.11, RMSEA = 0.09, NNFI = 0.92, CFI = 0.94 and χ² = 162.7, χ²/df = 2.76, RMSEA = 0.11, NNFI = 0.89, CFI = 0.91, respectively). Similarly, the executive model neither fit the results (χ² = 127.9, χ²/df = 2.56, RMSEA = 0.10, NNFI = 0.89, CFI = 0.93).

DISCUSSION: Our findings cross-validate the existence of a previously reported six-factor structure of cognitive functioning in a large Spanish sample of patients with schizophrenia. Underscoring the robustness of this model is the fact that it was first confirmed in a USA sample using slightly different measures, administered in a different language to patients from different cultural Backgrounds. Globalization of clinical trials may help to address the gaps or disconnects between regulatory
demands and requirements and clinical feasibility in the CNS research, and specifically, to overcome the apparent diminution of drug-placebo differences that has been observed in recent clinical trials of antipsychotic medications for schizophrenia often explained in the literature as related to sample differences.

doi:10.1016/j.schres.2010.02.568

**Poster 74**
DOES NEUROPSYCHOLOGICAL NORMALITY PRECLUDE FUNCTIONAL DISABILITIES IN OUTPATIENTS WITH CHRONIC SCHIZOPHRENIA?

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**Background:** Neuropsychological deficits are considered to be a core feature of schizophrenia. However, different studies showed that about 20-25% of patients with schizophrenia appear to have normal neuropsychological function. One possible explanation is that classifying impairment on the basis of substantially lower scores than would be expected in the general population based on normative data is not the best method of establishing normality. This method ignores the possibility that a score in the normal range may still be significantly lower than would be expected relative to premorbid functioning. An alternative method is to determine intra-person differences taking premorbid functioning as the gold standard. On the other hand, it has been established that cognitive impairments in schizophrenia are correlated with functional disability. Nonetheless, tests of the association between neurocognition and the functional status of the neuropsychological non-impaired patients have been limited and inconclusive. This study investigates two different methods of establishing normality in a sample of patients with chronic schizophrenia from a neuropsychological perspective. Additionally, the putative relationship between functioning and neurocognition in neuropsychological normal patients is tested.

**Methods:** A cross-sectional analysis of 150 chronic outpatients with DSM-IV schizophrenia diagnosis and 30 healthy controls were carried out from neuropsychological, symptomatic and functional perspectives. All participants completed a comprehensive neuropsychological battery including composite cognitive domains: Verbal IQ, attention, verbal memory, non-verbal memory, psychomotor speed and executive function. To establish normality, cognitive scores were compared to standardised norms. Alternatively, rates of significant intra-person differences taking premorbid functioning as the gold standard. On the other hand, it has been established that cognitive impairments in schizophrenia are correlated with functional disability. Nonetheless, tests of the association between neurocognition and the functional status of the neuropsychological non-impaired patients have been limited and inconclusive. This study investigates two different methods of establishing normality in a sample of patients with chronic schizophrenia from a neuropsychological perspective. Additionally, the putative relationship between functioning and neurocognition in neuropsychological normal patients is tested.

**Results:** Even establishing neuropsychological 'normality' with the more restrictive method of intra-person discrepancy, we found that our normative test scores (t = 0.49, p = 0.628) and other clinical variables.

**Discussion:** Thus, scoring in the normal range of neurocognitive tests does not preclude having functional impairments in chronic schizophrenia.

doi:10.1016/j.schres.2010.02.569

**Poster 75**
NORMATIVE DATA OF THE SCIP-S IN SCHIZOPHRENIA AND TYPE I BIPOLAR DISORDER

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**Background:** The Screen for Cognitive Impairment in Psychiatry (SCIP; Purdon, 2005) is a brief assessment tool designed for evaluation of cognitive impairment in psychiatric disorders. The SCIP requires less than 15 minutes and it has three alternate forms; each consisting of five subscales for the assessment of immediate verbal list learning, working memory, verbal fluency, delayed list learning and visuomotor tracking. Previous studies have found that it has adequate reliability and validity in a sample of patients with schizophrenia and type I bipolar disorder (Guilera et al., 2009; Pino et al., 2008; Rojo et al., 2009).

**Methods:** The aim of the study is to show the Spanish normative data of the SCIP total score in schizophrenia and type I bipolar disorder. The Spanish version of the SCIP (SCIP-S; Pino et al., 2006) was administered to 775 stable patients with schizophrenia (54.3%) or type I bipolar disorder (45.7%), controlling the clinical variables of the patients.

**Results:** Three age groups were formed, namely between 18 and 35, between 36 and 45 and between 46 and 55. In each group, four transformed scores were computed on the SCIP total score, i.e. percentiles, z-score, T-score and IQ score.

**Discussion:** This study shows the first SCIP-S normative data, which are of great importance in determining the neuropsychological clinical diagnosis in psychiatric samples.

doi:10.1016/j.schres.2010.02.570

**Poster 76**
WAIS-III SHORT FORM IN SCHIZOPHRENIA

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Background: Intelligence scales supply a global measure of cognitive abilities, in the same way they can predict the performance of other neuropsychological measures. Therefore, as well as in clinical practice as in investigation the IQ results are used as a descriptive measure of the general intellectual capacity and as an interpretative context of other neuropsychological test's results. The most used intelligence scale is Wechsler Adult Intelligence Scale (WAIS-III), it is compounded of 14 subscales and its application takes about 60 to 110 minutes. It is usually used as a neuropsychological battery. For this reason, different authors have been trying to find a briefer way of applying WAIS, reducing the application time using a reduced number of subscales, without compromising the estimate of the Full-Scale IQ (FSIQ). Most of these investigations have focused on WAIS-R for different schizophrenic and Spanish speaker's populations. Our main objective was to find a brief way of application, composed by 4 subscales, one for each WAIS-III indicator, in Spanish persons with schizophrenia.

Methods: Regression analysis was used for the data obtained in the WAIS-III application for 46 out-patients, who fulfill DSM-IV diagnostic criteria for schizophrenia. Each of these patients was sent by his/her psychiatrist, and they all fulfill the requirement of being in a stable clinical period of the disease. During the evaluation process all the participants were receiving antipsychotic medication, without any changes in the preceding 3 months. Apart from the application time and the punctuation, the Verbal Comprehension (VC), Perceptual Organization (POI), Working Memory (WMI) and the Processing Speed (PSI) WAIS-III indicators were regarded. All the possible combinations were studied, and the one which offered the best reliability to estimate the FSIQ was selected, without underestimating the predictive capacity of other indicators. In order to estimate the correlation between the short form punctuations and the different indicators of the full WAIS-III, R² was corrected.

Results: The 4-factors version that explained the biggest variations in the FSIQ punctuations, for this group of persons, is compounded of the WMI; 0.927 and 0.920 for the PSI. The derived formula for the R²-corrected was respectively 0.954 and 0.95 for the FSIQ; 0.929 and 0.922 for the VCI; 0.855 and 0.841 for the POI; 0.889 and 0.878 for the WMI; 0.927 and 0.920 for the PSI. The derived formula for the regression analysis was FSIQ = 32.88 + 2.474 V + 1.064 D Sym + 1.213 BD + 1.553 DS. The beta coefficients indicate the relative importance of each subscale in this brief form: 0.448 for V, 0.172 for D Sym, 0.217 for BD, y 0.257 for DS.

Discussion: Although the sample should be amplified, we recommend the WAIS-III short form compounded of V-Dsym-BD-DS for future investigations and clinical practice, for stable patients with schizophrenia diagnostic, when the aim is to obtain a fast IQ estimation. In future investigations, it should be interesting to see if the application of this short form really works by itself, since its integration in the complete WAIS-III battery can affect the results.

doi:10.1016/j.schres.2010.02.572

Poster 78
METACOGNITIVE INDEXES AND SYMPTOMATOLOGY IN PERSONS WITH SCHIZOPHRENIA

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Background: Over the last years, research has explored metacognition in schizophrenia. A link between schizophrenia and metacognition seems likely as many symptoms of schizophrenia involve a failure to draw plausible conclusions about the motives of others and the origins of one’s internal states. We hypothesized that: measures depending on metacognitive processes of self-monitoring and self-directed action and metacognitive abilities will be particularly sensitive to changes in clinical.

Methods: A metacognitive approach was adapted for use with conventional theory of mind (ToM) task. The subjects were asked to rate his level of confidence in the answer on a scale of 0 (just guessing) to 100 (completely confident) and to decide whether he wanted the answer count toward his overall performance score. The procedure, therefore, yielded a measurement of “free responses” depending on the participant’s metacognitive knowledge, in addition to

doi:10.1016/j.schres.2010.02.572
the standard “forced responses”. The task was administered to a group of 42 persons with schizophrenia in a stable clinical state. Symptom ratings were obtained by Positive and Negative Scale for Schizophrenia (PANSS).

**Results:** Significant correlations were observed among metacognitive indexes, i.e. capacity of accuracy evaluation and monitoring, and positive and negative symptoms.

**Discussion:** This clinical findings strongly suggest that patients with schizophrenia can be compromised because of their failure to monitor their own and other persons’ mental states and behavior, which may account for many positive and negative symptoms in schizophrenic disorders.

doi:10.1016/j.schres.2010.02.573

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**Poster 79**

**A META-ANALYSIS OF COMPUTERIZED ASSESSMENT BATTERIES IN SCHIZOPHRENIA MEDICATION TRIALS**

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**Background:** A variety of computerized assessment batteries (CABs) have been utilized to assess cognitive impairment in schizophrenia; however, there is no consensus regarding CABs sensitivity to medication effects. This meta-analysis provides a quantitative overview of CABs used in schizophrenia research by examining medication trials with at least one pre and post cognitive assessment.

**Methods:** A structured search of the CAB literature using the PsycInfo, MEDLINE, PubMed, and Google Scholar databases yielded 15 suitable publications that met inclusion criteria for meta-analytic review. Each CAB website was also examined for relevant publications, resulting in a total of 81 separate pre-post effects. CABs reviewed included CANTAB, ANAM, CogState, CogLab, and MINDSTREAMS. Specific tests from each CAB were extracted and grouped into cognitive domains reflecting executive function, working memory, verbal and non-verbal memory, visuospatial reasoning and motor functioning. Effect sizes (ES) (Cohen’s d) were then calculated for each CAB, their component subtests, and for each cognitive domain.

**Results:** Analysis of medication effects on cognitive functioning, across different medication types, revealed an overall moderate effect size ($d = 0.523$) for all CABs which was significantly heterogeneous ($p < 0.001$). Of the five CABs, CogLab yielded the largest effect size ($d = 0.79$) followed by ANAM and then CogState. Effect sizes were largely driven by battery composition with measures of attention ($d = 0.809$) and visuospatial reasoning ($d = 0.702$) yielding relatively higher ESs than non-verbal memory ($d = 0.459$) and executive functioning ($d = 0.403$); although these four domains did not differ significantly from each other. Type of treatment intervention also impacted ES with combination treatment (Haloperidol plus nicotine) yielding the largest ES ($d = 1.05$) followed by Haloperidol alone, and then various antipsychotics and nooptropics. Important moderator variables included previous medication type, inpatient/outpatient status, number of follow-up cognitive assessments, PANSS negative symptomatology score, and patient age.

**Discussion:** This meta-analysis suggests that it is possible to more confidently select CABs, their component subtests, and cognitive domains that are more likely to be sensitive in treatment trials; and that this sensitivity is moderated by medication type and important disease-related and demographic variables.

doi:10.1016/j.schres.2010.02.574

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**Poster 80**

**GENETIC ASSOCIATION ANALYSIS OF SIRT1 WITH SCHIZOPHRENIA IN A JAPANESE POPULATION**

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**Background:** Several investigations have been suggested that abnormalities in circadian clock genes are pathophysiology of schizophrenia. For example, PER2 was associated with schizophrenia in the population. Recently, SIRT1 was detected as new circadian clock gene. Therefore, we considered that SIRT1 is a good candidate gene for pathophysiology of schizophrenia. We conducted a genetic association analysis based on “gene-wide” in the Japanese population.

**Methods:** Using four tagging SNP selected with the HapMap database, we conducted a genetic association analysis of case-control samples (schizophrenia 730 cases and controls 766 cases) in the Japanese population. The study was described to subjects and written informed consent was obtained from each. This study was approved by the Ethics Committees at Fujita Health University, Nagoya University School of Medicine, and the University of Occupational and Environmental Health.

**Results:** We detected an association between SIRT1 and schizophrenia in the haplotype-wise analysis.

**Discussion:** Our result suggested that SIRT1 might play a major role of pathogenesis of schizophrenia in the Japanese population. However, we did not a mutation screening and our samples were small, it will be necessary to require a replication study using larger samples.

doi:10.1016/j.schres.2010.02.575

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**Poster 81**

**INCREASED FREQUENCY OF NOVEL NRG1 GENE VARIANTS IN SCHIZOPHRENIA AND THE EFFECT OF NUCLEOTIDE VARIATION ON MRNA ISOFORM TRANSCRIPTIONAL REGULATION**

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**Background:** NRG1 is one of the most replicated susceptibility genes identified for schizophrenia, making it a lead candidate to focus mechanistic studies. No pathological mutation in any exon has been found to date, however culprit genetic variations may lie in upstream regulator elements or intronic sequences, resulting in aberrant transcriptional regulation.

**Methods:** Using a matched cohort of post-mortem brains from 37 schizophrenia cases and 37 controls, we resequenced 12.4 kb upstream of the type IV/II, type I and type III transcriptional isoforms of NRG1, and characterised the HAPICE risk haplotype previously associated with schizophrenia in the Icelandic population (Stefansson et al., 2003). Relative mRNA levels for each transcript isoform was determined by quantitative PCR using RNA
extracted from dorsolateral prefrontal cortex and compared across demographic and diagnostic variables as well as genotypic groups.

**Results:** We identified 27 novel DNA variants not previously characterised, 75% of which were predicted to alter putative transcription factor binding sites. We found a significantly higher novel variant load in schizophrenic cases, where 24 cases had at least one novel variant compared to 14 controls ($\chi^2 = 10.8, p=0.001$). The majority of novel SNPs were identified around the HAPICE repeats in intron 1, however the overall nucleotide diversity was similar across all regions examined ($\theta = 0.0009-0.0022$). In preliminary analysis, we saw no correlation between the novel variant load and the level of type I, II or III transcript expression ($p=0.27, 0.88$ and $0.62$ respectively). We were unable to replicate the previously reported difference in type I mRNA levels between cases and controls (Hashimoto et al., 2004; Law et al., 2006). We were also unable to replicate the previously reported genotype × diagnosis interaction of rs7014762 on type III expression (ANCOVA $p=0.836$) (Nicolodemus et al., 2009). We did however find a significant effect of the rs3802160 genotype on type III expression in patients with schizophrenia (ANCOVA $p=0.04$). The HAPICE risk haplotype showed no frequency distortion in this small Australian case-control cohort ($\chi^2 = 0.958, p=0.754$).

**Discussion:** Our data revealed multiple rare SNP variants in the regulatory regions of the NRG1 gene, particularly in the HAPICE region in intron 1, which resulted in a higher novel variant load in schizophrenia. However, as these novel variants are rare, it is not clear how they may affect regulation NRG1 transcript expression. The lack of replication of the transcript expression changes previously described may reflect population differences, as illustrated by the lack of association of the HAPICE risk haplotype in this cohort. However, evidence that distinct DNA variants may be linked to NRG1 expression in this Australian cohort confirm that specific sequence variants may be critical determinants of NRG1 expression in schizophrenia, but not in controls. Further characterisation of DNA and transcript expression variation by complimentary methods is required to elucidate the effect of DNA sequence variation on mRNA levels, to determine how genetic changes in NRG1 may impart disease risk.

doi:10.1016/j.schres.2010.02.576

**Poster 82**

**DYSTROBREVIN BINDING PROTEIN GENE (DTNBP1) IN BIPOLAR DISORDER: A REVIEW AND A META-ANALYSIS**

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**Background:** Recent studies suggest an overlap in genetic susceptibility of schizophrenia and bipolar disorder (BD). There is some evidence for association of the DTNBP1 gene with schizophrenia. Several studies have investigated the association between the DTNBP1 and BD providing conflicting results. These studies have used a different set of genetic markers that makes a direct comparison of risk alleles/haplotypes impossible. The aim of the present study is to review and summarize the available data and provide a better overview of the role of the DTNBP1 in BD.

**Methods:** Five case-control studies of the DTNBP1 in BD were available for the comparison and the meta-analysis: Raybould et al., 2005, Breen et al., 2006, Pae et al., 2007, Joo et al., 2007, and Gaysina et al., 2009. First, we used HapMap data for comparison the results of the case-control studies. HapMap CEU trio data and combined JPT and CHB trio data were used for selection the SNPs from the genomic region 10 kb upstream and downstream of the DTNBP1 gene. To determine tagging SNPs (tSNPs) for each of the studies we used the Haploview programme and the Tagger implementation therein. Second, a meta-analysis was conducted for DTNBP1 SNPs when the results of at least three studies were available. Odds ratios were combined using a fixed-effects model. We estimated a between study heterogeneity using the $\chi^2$ statistics. A funnel plot and Begg and Mazumdar’s rank correlation test were used in order to assess publication bias.

**Results:** We have identified the single marker or multi-marker haplotype that best captured the association signal in each study and used the data available from the HapMap project and Haploview to determine tSNP(s) in the original studies. These tSNPs were mapped onto the HAPMAP panel samples as a reference. We identified eight common haplotypes in the CEU trios and four common haplotypes in JPT + CHB with their respective frequencies. We matched the associated allele or haplotype from each study to the haplotypes derived for the HapMap samples. We demonstrated that two risk haplotypes identified in the samples of Caucasian ancestry were overlapping. Using a meta-analytic approach, six SNPs were analyzed. A higher frequency of the G allele of rs2619522 (OR = 1.18, 95% CI 1.01-1.38), the T allele of rs760761 (OR = 1.22; 95% CI 1.04-1.42), and the G allele of rs3213207 (OR = 1.24, 95% CI 1.05-1.46) were shown in the BD group than in a control group. These associations were strengthened when the analysis was restricted to the studies of the samples of a Northern European ancestry. The funnel plot analysis provided the evidence for publication bias for rs2619522 (p = 0.09); and after a correction for publication bias the effect estimated was still significant for this SNP (p = 0.016). No evidence for publication bias for rs760761 or rs3213207 was found.

**Discussion:** This study using two different approaches provides the evidence for the DTNBP1 as a susceptibility gene for BD, especially in a Caucasian population.

doi:10.1016/j.schres.2010.02.577

**Poster 83**

**ASSOCIATION OF SCHIZOPHRENIA SUSCEPTIBILITY GENES WITH INTERMEDIATE PHENOTYPES: NEW FINDINGS FROM GENOMIC IMAGING**

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**Background:** DISC1 and DTNBP1 have been linked to the risk for major psychosis. The aim of this study was to investigate the effects of the DISC1 Ser704CyS locus and of two single nucleotide polymorphisms of the DTNBP1 on cognition, regional brain volumes and MRS parameters in human subjects.

**Methods:** Overall 232 subjects participated in the study. Subjects were genotyped with respect to the rs821616 SNP of the DISC1 gene and the rs2619522 and rs1018381 SNPs of the DTNBP1 gene, and underwent magnetic resonance imaging (MRI) and spectroscopy (MRS). MRI data were analyzed using both manual volumetric assessment of regions of interest and voxel-based morphometry (VBM) as implemented in SPM5.

**Results:** Manual volumetric assessment, but not VBM revealed a significant effect of the DISC1-SNP rs821616 on hippocampus volume with Ser homozygotes having lower relative right hippocampal
volume compared with Cys carriers. No significant genotype effects were found on MRS parameters in the left hippocampus, frontomedial cortex and middle frontal gyrus, whereas VBM showed significant effects bilaterally in the middle frontal gyrus as well as in right parietal cortex with Ser homozygotes having lower gray matter volumes in these cortical regions. Ser homozygotes also revealed lower performance in working memory tasks. We found significant effects of the DTNBPI-SNP rs2619522 on regional brain volumes bilaterally in the hippocampus as well as in the anterior middle frontal gyrus and the intraparietal cortex. T/T homozygotes showed significantly lower gray matter volumes in these brain regions than carriers of the G allele.

**Discussion:** The present results in part replicate prior findings of DISC1 gene effects on hippocampal volumes, and provide evidence for further associations of the DISC1 Ser704Cys locus with other intermediate phenotypes such as regional prefrontal gray matter volumes and working memory performance. Furthermore, the present study provides first direct in-vivo evidence that the DTNBPI-SNP rs2619522 is associated with variation of gray matter volumes bilaterally in the human hippocampus.

**doi:**10.1016/j.schres.2010.02.579

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**Poster 84**

**BREAKPOINT ANALYSIS OF NRXN1 DELETIONS IN SCHIZOPHRENIA**

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**Background:** Recent genome-wide association studies have shown that Copy Number Variations (CNVs), in particular deletions at 1q21.1, 15q11.2, 15q13.3 and 2p16.3, and duplications at 16p13.1 and 16p11.2, are genetic susceptibility factors in schizophrenia. Non-allelic homologous recombination (NAHR) between low copy repeats (LCRs) is thought to account for the mechanism generating the CNVs at 1q21.1, 15q11.2, 15q13.3 and 2p16.3, and at 16p13.1 and 16p11.2, are genetic susceptibility factors in schizophrenia. Non-allelic homologous recombination (NAHR) between low copy repeats (LCRs) is thought to account for the mechanism generating the CNVs at 1q21.1, 15q11.2, 15q13.3, 16p11.2 and 16p13.1. However the deletions at the NRXN1 locus on 2p16.3 do not share breakpoints and are not flanked by LCRs. Thus, NRXN1 deletions seem to arise through a different genetic mechanism. We have examined breakpoints for deletions at the NRXN1 locus in 11 individuals.

**Methods:** The study sample includes 11 carriers of deletions in the NRXN1 region; eight schizophrenia patients from Munich, Germany (deletions reported in Rujescu et al. and, Need et al.; a Danish childhood-onset schizophrenia case and his father, and an unaffected Danish individual. Primary detection of the deletions was obtained by sequencing of the long-range PCR products spanning the deletion breakpoints by the algorithms were confirmed by TaqMan qPCRs for four of the subjects. DNA fragments harboring the deletion breakpoints were amplified using different combination of Long range PCR primers equally spaced over the sequence intervals flanking the first and last deleted SNPs in each subject, and subsequently sequenced through the Sanger method (primer walking).

**Results:** The breakpoints from five subjects have now been identified by sequencing of the long-range PCR products spanning from 2300-3000 pb. The preliminary sequence analysis shows heterogeneity between individuals, but the breakpoints are generally found occurring within masked repeats (such as LINE, LTR or dinucleotide repeats), and for some cases inserted nucleotides were found within the breakpoint regions.

**Discussion:** The observation of breakpoints occurring within masked repeats, and of inserted nucleotides between breakpoints, could be suggestive of involvement of recombination mechanisms other than NAHR, such as non-homologous end joining (NHEJ) or microhomology-mediated end joining (MMEJ). However, the cellular mechanisms involved have to be confirmed by further analysis of the remaining individuals in this study.

**doi:**10.1016/j.schres.2010.02.579

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**Poster 85**

**THE MethyleneTetraHYDROFOLATE REDUCTASE GENE (MTHFR) AND RISK FOR SCHIZOPHRENIA, ARE FUNCTIONAL MTHFR GENE POLYMORPHISMS ASSOCIATED WITH AGE OF ONSET?**

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**Background:** Different lines of evidence indicate that methylene-tetrahydrofolate reductase (MTHFR) functional gene polymorphisms, causative in aberrant folate-homocysteine metabolism, are associated with increased vulnerability to several heritable developmental disorders. Opposing views are expressed considering the possible association between MTHFR and susceptibility for schizophrenia, although all published meta-analyses so far performed have suggested association between the C677T (rs1801133) polymorphism and several with the A1298C (rs1801131) polymorphism, both associated with enzyme efficiency, and the disorder. Recently, an association was reported between the MTHFR C677T gene polymorphism and age of onset in schizophrenia in Scandinavian and Chinese samples. In the present study we aimed to replicate these findings.

**Methods:** Unrelated patients (n = 3087) from twelve different centres, including the initial Scandinavian sample, diagnosed with schizophrenia, schizoaffective disorder and schizophreniform disorder were investigated. The two functional MTHFR single nucleotide polymorphisms (SNPs) were genotyped and the effect of MTHFR polymorphisms on the age of onset was examined.

**Results:** There was no consistent relationship between the investigated SNPs, neither alone nor combined, and age at onset of schizophrenia. However, there was considerable heterogeneity between studies with regard to age of onset and the influence of the latter by MTHFR polymorphisms.

**Discussion:** The most sensible conclusion is that these common functional MTHFR SNPs do not influence age at onset of schizophrenia. However, it cannot be excluded that the MTHFR C677T polymorphism may play a role as a modifying factor for age at onset of schizophrenia in certain populations. Further analyses with greater patient samples in the Scandinavian populations seem warranted.

**doi:**10.1016/j.schres.2010.02.580
Poster 86
CLOZAPINE-INDUCED WEIGHT CHANGE ASSOCIATED WITH G-2548A POLYMORPHISM OF THE LEPTIN GENE IN PATIENTS WITH CHRONIC SCHIZOPHRENIA

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Background: Clozapine is known to cause severe weight gain. A variety of genetic polymorphisms have been reported as putative mechanisms for antipsychotics-induced weight gain. Antipsychotics-induced weight gain has an inverse correlation with body mass index at baseline. A functional polymorphism in the leptin promoter region G-2548A is a candidate polymorphism for antipsychotics-induced weight change, but results are inconsistent.

Methods: We examined the association between clozapine-induced weight change and LEP G-2548A polymorphism in 113 Korean patients with schizophrenia taking clozapine for at least one year at Seoul National Hospital. All patients enrolled in this study fulfilled the following criteria: (1) had schizophrenia or schizoaffective disorder, diagnosed by DSM-IV-TR criteria, (2) had been taking clozapine for at least one year, (3) were more than 18 years and less than 65 years old, and (4) had no physical disease that affected body weight, such as diabetes or tuberculosis. Body weight and BMI were cross-sectionally measured at the study period. Body weight and BMI before starting clozapine were abstracted from medical records.

Results: All 113 subjects were Koreans. The mean clozapine dosage was 419.0 ± 127.6 mg/day, and the mean duration of clozapine use was 50.4 ± 31.0 months. Body weight increased by 3.9 ± 13.7% after treatment with clozapine. Clozapine-induced weight change was inversely correlated with baseline BMI (r = -0.30, p = 0.01), and LEP G-2548A polymorphism was significantly associated with this negative correlation. During clozapine treatment, the A/A group had lower baseline BMI and gained weight, whereas the G/G group had higher baseline BMI and lost weight during clozapine treatment. When the baseline BMI was adjusted in the regression analysis, the association between clozapine-induced weight change and the polymorphism became weaker; thus, baseline BMI may affect the direction of AP-induced weight change due to the polymorphism.

Discussion: The LEP G-2548A polymorphism is significantly associated with the negative correlation between weight change and baseline BMI during clozapine treatment. To the best of our knowledge, this is the first study to show that LEP G-2548A polymorphism is significantly associated with a negative correlation between weight change and baseline BMI during clozapine treatment. The polymorphism may be associated with homeostatic control of body weight during antipsychotic treatment.

doi: 10.1016/j.schres.2010.02.581

Poster 87
EVIDENCE THAT PUTATIVE ADHD LOW RISK ALLELES AT SNAP25 MAY INCREASE THE RISK OF SCHIZOPHRENIA

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Background: Schizophrenia is a complex disorder affecting ~1% of the population. The estimated heritability is 80%, a significant proportion of which is likely due to polygenic factors. Synaptosomal Associated Protein 25 kDa (SNAP25) is an important member of the SNARE complex, a structure that mediates synaptic vesicle exocytosis. Altered SNAP25 levels have been found in schizophrenia and genetic variation at SNAP25 has been reported to be associated with Attention-Deficit/Hyperactivity Disorder (ADHD). Expression of the putative schizophrenia susceptibility gene DTNBP1 has also been shown to influence SNAP25 levels in vitro. We carried out mutation screening of the SNAP25 gene followed by association analysis in a UK schizophrenia case control sample.

Methods: We performed mutation screening of the SNAP25 gene in 14 unrelated schizophrenic individuals (7 male, 7 female) selected at random from our UK association sample. We examined the seven SNPs that emerged from the mutation screen and then a further 31 informative tag SNPs spanning the SNAP25 locus in a case control sample collected from the UK. This consisted of 662 cases (448 males, 214 females) with a consensus diagnosis of schizophrenia according to DSM-IV criteria and 716 controls (482 males, 234 females), all of whom were unrelated and of white European descent. Association analyses were performed using PLINK 1.01 and SNPTEST. Imputation of genotypes was performed using IMPUTE.

Results: We screened 3,965 bases at the SNAP25 locus in 14 unrelated schizophrenics and identified seven SNPs (rs6039769 (intronic), rs362998 (synonymous), rs363006 (intronic), rs3746544 (3UTR), rs1051312 (3UTR), rs8636 (3UTR)). A novel SNP (G/T transversion, rs107056528) was found in the putative promoter region. Genotyping these seven SNPs in our case control sample revealed significant evidence for allelic association at rs3746544 (P = 0.004, OR = 1.26) and rs8636 (P = 0.003, OR = 1.27). These results remained significant after 10,000 permutations to allow for multiple testing (P = 0.02). Intermarker LD analysis revealed rs8636 and rs3746544 were strongly correlated (D' = 1, r^2 = 0.997). 31 additional tag SNPs were combined with the original six independent SNPs to capture 79% of the 131 SNPs genotyped in the HapMap CEU samples at this locus (r^2>0.8, MAF>0.01). This revealed nominally significant association at an additional five SNPs. The strongest of these was at rs3787283 (P = 0.006, OR = 1.25). Taken together with the SNPs identified for primary association no SNP survived correction for multiple testing (best experiment-wise permuted P-value = 0.10 at rs3746544). Imputation of genotypes for the 131 HapMap SNPs spanning the SNAP25 locus failed to identify evidence for allelic association greater than our original observation at rs3746544 (maximum P = 0.003 at rs3746544).

Discussion: Our results should be considered as hypothesis generating and require follow up in additional samples. We compared our results to studies reporting evidence for association with (i) antipsychotic response in schizophrenia and (ii) ADHD. In schizophrenia, carriers of the allele which showed the strongest association in our study (G allele at rs3746544) show significantly poorer clinical response to antipsychotic treatment than non-carriers. Two of the SNPs nominally associated with schizophrenia in our study (rs3787283, rs3746544) have been found to be associated with ADHD but in the reverse allelic direction i.e. risk alleles for schizophrenia are protective in ADHD. Our findings suggest that SNAP25 may influence risk of developing schizophrenia and clinical response to antipsychotic treatment. If this is the case, the same mechanism may reduce the risk of developing ADHD.

doi: 10.1016/j.schres.2010.02.582

Poster 88
COMPLEXIN2 GENE POLYMORPHISMS MODIFY COGNITIVE PERFORMANCE IN SCHIZOPHRENIA

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[Abstract text related to poster 88]
Abstracts

Poster 89
THE EFFECT OF A GENOME-WIDE SUPPORTED VARIANT IN CACNA1C ON NEURAL CORRELATES OF EPISODIC MEMORY ENCODING AND RETRIEVAL

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Background: Schizophrenia is the collective term for a heterogeneous group of psychiatric disorders, classified exclusively by clinical endpoints. Its genetic causes and biological basis are still largely unknown, although multiple lines of evidence indicate that dysfunctions in synaptic transmission between nerve cells play a key role. Molecules like the complexins (CPLXs), key regulators of synaptic transmission, are possibly involved in neuropsychiatric disorders.

Methods: To define biological subgroups of schizophrenia, we established a novel patient database, GRAS (Göttingen Research Association for Schizophrenia), specifically designed to allow the association of genetic information with clinical readouts and phenotypes of the disease. The entire database, which was obtained by an invariant team of investigators, contains standardized phenotypic characterization of 1071 patients, with over 3000 data points per patient. In a first application of the database, we examined the role of the Complexin2 gene (CPLX2) in schizophrenia. The coding region of CPLX2 was analyzed in these patients and in a control population by direct sequencing. Additional, seven single nucleotide polymorphisms (SNPs) were genotyped to cover the entire genomic region of CPLX2. A traditional case-control association study was performed and furthermore a comprehensive genotype-phenotype analysis focusing on cognition. To gain mechanistic insight into Cplx2 null mutant mice were examined and in vitro studies were performed.

Results: In the case-control study, an association of schizophrenia with a low frequency haplotype was found. In the genotype-phenotype analysis, even more interesting results were obtained: six SNPs, distributed over the whole CPLX2 gene, were found to be highly associated with current cognition of schizophrenic subjects, but only marginally with premorbid intelligence. Correspondingly, in Cpxl2 null mutant mice, prominent cognitive loss-of-function was obtained only in combination with minor brain lesion applied during puberty, modeling a clinically relevant environmental risk (“second hit”) for schizophrenia. In the human CPLX2 gene, one of the identified six cognition-relevant SNPs, rs3822674 in the 3’ untranslated region was detected to influence miRNA-498 binding and gene expression.

Discussion: Our data show that cognitive performance in humans and rodents is modified by CPLX2/Cplx2 gene expression. A miRNA-mediated regulation in response to a defined environmental influence may partly explain the modifier role of CPLX2 for cognitive deficits in schizophrenia. The ‘phenomics’-based genetic association study (PGAS) presented here clearly differs from the much popularized genome wide association studies in the field, that simply compare ‘patients’ and healthy controls. PGAS will certainly open new avenues to promote schizophrenia genetics.

doi:10.1016/j.schres.2010.02.583

Poster 90
RELATIONSHIP BETWEEN THE DOPAMINE TRANSPORTER GENE (DAT) CORE PROMOTER POLYMORPHISM -67A/T AND STRIATAL DAT BINDING WITH [123I] FP-CIT SPECT

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Background: Dysfunction of the central dopaminergic neurotransmission seems to play a key role in the etiology of schizophrenia. The dopamine transporter (DAT), mediates the reuptake of dopamine, contributing in the regulation of dopaminergic neurotransmission. The DAT gene core promoter polymorphism -67A/T has previously been related to schizophrenia and its polymorphism has been described to result in a two-fold difference between the two alleles. Objective: Investigate the relationship between the DAT gene core promoter polymorphism -67A/T and striatal DAT availability in the schizophrenic patient’s brain.

Methods: 15 neuroleptic naive patients with schizophréniform disorder or schizophrenia diagnostic were included. The different genotypes of DAT gene core promoter region were identified. Striatal DAT binding was studied with [123I] FP-CIT SPECT. Analysis of covariance (ANCOVA) was employed to study the association between the different genotypes and striatal DAT binding.

Results: One patient was excluded because we could not analyze the images. From the other patients, there were no significant differences in striatal DAT binding among the three major -67A/T genotype groups: AT (n = 10) with a mean binding ratio 2.15 +/- 0.21; AA (n = 3) mean binding ratio 2.18 +/- 0.06; TT (n = 1) mean binding ratio 2.15 +/- 0.18.

doi:10.1016/j.schres.2010.02.584
Discussion: Our results suggest that the DAT gene core promoter-67 A/T polymorphism does not affect DAT gene expression or protein function in schizophrenic brain.

doi:10.1016/j.schres.2010.02.585

Poster 91
PHOSPHODIESTERASE 4B GENETIC VARIANTS ARE NOT ASSOCIATED WITH ANTIPSYCHOTIC-INDUCED TARDIVE DYSKINESIA

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Methods: We found two PDE4B genetic variants to be nominally associated with tardive dyskinesia (rs1338719 and rs7528545) in the overall population and two other variants nominally associated with the presence of tardive dyskinesia and severity in female subjects (rs1890196 and rs783036). None of these results survived correction for multiple testing.

Discussion: Phosphodiesterases are promising therapeutic targets for diseases in the central nervous system. However, we find no association of PDE4B variants with tardive dyskinesia manifestation or tardive dyskinesia severity. Previous genetic association studies have mostly reported significant associations between PDE4B variants and schizophrenia. It is possible that another PDE4 might play a role in predisposition or molecular mechanisms for tardive dyskinesia.

doi:10.1016/j.schres.2010.02.586

Poster 92
HERITABILITY OF CORTICAL GYRIFICATION AND IMPLICATIONS FOR SCHIZOPHRENIA: PRELIMINARY RESULTS FROM THE STAR / EUTWINSS STUDIES

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Background: Several recent studies have found abnormalities of gyrification or the cortical folding in schizophrenia. This parameter is thought to increase during childhood and then remain stable over a longer time period, thus indicating effects determined through genetics and/or early brain development. Unlike other brain morphometric measures, there is little data on whether gyrification is genetically determined and putative candidate genes. Here we analyze data from monozygotic (MZ) and dizygotic (DZ) healthy twins from the STAR consortium using a simplified measure of heritability for gyral and sulcal curvature.

Methods: We used high-resolution 1.5 T MRI scans from 10 MZ healthy twins pairs (age 29.6 yrs, s.d 8.5 yrs; 5 male and 5 female pairs) and 10 DZ healthy twin pairs (age 49.2 yrs, s.d. 13.3 yrs; 2 male and 8 female pairs) from the London node of the STAR consortium. Cortical surfaces of each hemisphere were extracted using FreeSurfer software. Each hemispheric surface consisted of approximately 170000 vertices. Two surfaces were extracted, a pial surface (grey matter-csf border) and a white matter surface (grey matter-white matter border). A central surface was then extracted which lay in between the pial and white matter surface. Absolute mean curvature was calculated at each vertex over 3 mm radius in the native space of the extracted central surface. This method of calculating curvature is relatively stable over changes induced by normalization (Luders et al., 2004). In order to estimate heritability for specific regions, we used parcellations according to the Destrieux atlas and summed up the curvature measurements of all the vertices within gyral and sulcal regions of these regions to obtain an absolute mean curvature of each region. Falconer’s method was used to calculate the heritability of curvature of regional gyri and sulci. This method calculates heritability as $h^2 = (r(MZ-rDZ))$ where ‘r’ is the correlation for the trait within the twin pairs. $h^2$ was considered zero , if negative.

Results: In the right hemisphere, high heritability estimates were found for curvature of precentral gyrus, superior frontal gyrus, superior occipital gyrus and sulcus. In the left hemisphere , high heritability estimates were found for curvature of parahippocampal gyrus, cuneus gyrus, paracentral gyrus and sulcus, subcentral gyrus and sulcus, and post central sulcus. Intracranial volume was highly correlated within both MZ and DZ pairs.

Discussion: Our results demonstrate high heritability of gyrification of several cortical areas, including right prefrontal and left parahippocampal areas. This supports the notion that gyrification might serve as a putative endophenotype of brain morphology for schizophrenia, even though it might additionally be influenced by non genetic markers. While Falconer’s method allows calculation of higher shared phenotypic variance in MZ than DZ twins, it does not provide a more elaborate differentiation between genetic and common environmental factors. Additional studies in extended samples are under way to apply methods like structural equation modeling to more closely differentiate these effects. This study was supported by a grant of the EU (EUTwinsS network; RTN, FP6).

doi:10.1016/j.schres.2010.02.587

Poster 93
WIDESPREAD, HERITABLE, BRAIN ALTERATIONS IN INDIVIDUALS WITH SCHIZOPHRENIA AND INDIVIDUALS 'AT RISK': EVIDENCE FOR A CORTICAL THICKNESS INTERMEDIATE PHENOTYPE

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Background: Studies investigating cortical thickness in schizophrenia using genetically sensitive samples are scarce and it remains unclear to what extent heritable factors are involved in cortical
thickness alterations that have been found in schizophrenia. In the present family study, we examined whether there was evidence for i) an intermediate cortical thickness phenotype in schizophrenia and for ii) heritability of cortical thickness alterations.

**Methods:** T1-weighted MRI scans were acquired on a 3 Tesla scanner from 89 patients with schizophrenia, 98 healthy siblings at higher than average genetic risk for schizophrenia and 87 controls. Freesurfer was used to measure cortical thickness. Differences between study groups were assessed, after the data was transformed into a hierarchical structure consisting of 68 predefined regions of interest (ROI) per subject. The statistical interaction between risk for schizophrenia (group status) and brain region on cortical thickness was assessed with multilevel regression analyses. Heritability was examined by calculating the Risch λ.

**Results:** There was a significant group x ROI interaction, in the model of cortical thickness, for patients compared to controls ($\chi^2 = 14100, P=0.00$) and siblings compared to controls ($\chi^2 = 12828, P=0.00$), indicating that the effect of group status on cortical thickness varied with brain region. Patients and siblings had significant thinning of the cortex in frontal, parietal and temporal regions, compared to controls. Patients and siblings also showed some increases in cortical thickness in cingulate, frontal and temporal regions. In addition, there were patient-specific cortical thickness alterations. The Risch λ heritability values were high in several regions spread over the brain, predominately in frontal and temporal cortices. All regions with similar patterns of cortical thickness alterations in patients and siblings showed high heritability values.

**Discussion:** Beside patient-specific cortical thickness alterations, the results revealed heritable, globally distributed cortical thickness reductions and, to a lesser extent increases, in psychotic patients and their siblings. There was evidence for a cortical thickness intermediate phenotype in frontal, parietal, and temporal regions.

**doi:** 10.1016/j.schres.2010.02.588

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**Poster 94**

**VARIATION IN GREY MATTER VOLUME WITH DEGREE OF INSIGHT IN FIRST EPISODE PSYCHOSIS AND CHRONIC SCHIZOPHRENIA**


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**Background:** The theory that poor insight may be the psychiatric analogue of the anosognosia seen in individuals who are unaware of a neurological deficit has lead to a number of recent studies assessing the relationship between Insight and Structural MRI measurements, with inconsistent results. We examined the relationship between Insight and grey matter density in high-resolution magnetic resonance scans using a brain-wide voxel-based analysis approach obtained from patients with first episode or chronic psychotic illness.

**Methods:** Thirty-two individuals experiencing their first episode of psychosis (FEP, 23 male), and thirty individuals with a chronic psychotic disorder (CP, 22 males) were assessed with the Structured Clinical Interview for DSM-IV (SCID), Positive and Negative Symptom Scale (PANSS) and Beiser Scale (for DUP). Insight was assessed with the Schedule for the Assessment of Insight (SAI-E), whereby higher scores represent poorer insight. MRI scans were obtained using a 1.5 Tesla Siemens Magnetom Symphony. Statistical Non-Parametric Mapping (SnPM5b) was employed for voxel-based analyses and a multi-subject simple regression model was used to assess the relationship between insight and grey matter in FEP and CP groups, separately.

**Results:** In the FEP group, SAI-E insight score correlated negatively with grey matter in the right and left caudate (cluster size = 597, p = 0.034), right thalamus (cluster size = 78, 3 peaks, p = 0.034-0.038) and the right insular cortex (cluster size = 72, 3 peaks, p = 0.034-0.038). There were no positive correlations between insight scores and grey matter in any region of the brain. In the CP group, there were no significant relationships between Insight and grey matter density in any region of the brain. In the FEP group, the severity of positive, negative or general symptoms did not correlate significantly with the grey matter in caudate, thalamus or insula. In addition, the duration of illness did not correlate with grey matter in the caudate, thalamus or insula. The number of days each FEP subject was medicated for correlated negatively with grey matter in the insula ($r = -0.43, p = 0.01$), but not in the thalamus, or caudate. Insight scores did not correlate significantly with the duration of Illness or number of days medicated.

**Discussion:** The major finding in this study is that Insight Impairments in first episode psychosis are associated with increased grey matter in brain regions implicated in cognitive functioning related to awareness. This finding relates to previous studies that established negative correlations between Insight and orbitofrontal cortex, left medial prefrontal, anterior cingulate and Insula volumes. Our findings are consistent with the “motivational Salience” model where over-activity and associated increased volume of brain regions results from efforts to provide a more acceptable rationale for psychotic symptoms than attribution to illness.

**doi:** 10.1016/j.schres.2010.02.589

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**Poster 95**

**SEMANTIC FLUENCY DEFICITS AND GREY MATTER DIFFERENCES BEFORE TRANSITION TO PSYCHOSIS: A VOXELWISE CORRELATIONAL ANALYSIS**

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**Background:** Early identification of subjects with an increased risk of developing psychosis is necessary to develop interventions to delay or prevent disease onset. We recently reported that semantic fluency in ultra high risk (UHR) individuals potentially predicts the development of psychosis (Becker, in press). In schizophrenia, verbal fluency deficits have been associated with cortical changes in frontotemporal areas. The present study investigated whether differential performance on semantic and phonological fluency in UHR individuals was reflected in regional grey matter density.

**Methods:** We assessed grey matter differences using Voxel Based Morphometry in SPM2 and correlated the results with verbal fluency scores in 37 UHR individuals. Additionnally, we assessed two subgroups that did (n=10) and did not (n=27) develop psychosis during a 3 year follow up period.

**Results:** In UHR individuals developing psychosis, lower semantic fluency scores correlated significantly with reduced grey matter in the right medial temporal lobe (p < 0.001, corrected for multiple analyses) and the left anterior cingulate cortex (p < 0.036, corrected). **Discussion:** Our results could suggest that semantic fluency deficits in subjects that subsequently develop psychosis are reflected in grey matter density reductions in task-relevant areas. This structure-function relationship would be a promising tool in more accurately predicting possible development of psychosis in UHR individuals.

**doi:** 10.1016/j.schres.2010.02.590
Poster 96
LONGITUDINAL MRI CHANGES IN HIPPOCAMPAL SHAPE FOLLOWING THE FIRST-EPISTEME OF SCHIZOPHRENIA
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Background: The hippocampus is a brain region involved in the pathophysiology of schizophrenia. While hippocampal volume has been most often investigated in imaging studies, hippocampal shape may be more sensitive to the pathological changes that occur in schizophrenia. However, it remains unclear whether shape alterations are fixed, as suggested by a neurodevelopmental model, or progress over illness course.

Methods: We evaluated 17 First Episode schizophrenia patients (15 males) matched (for age, education, handedness, ethnicity) to 16 healthy controls (9 males). Subjects were scanned at first onset and again after 6 years. An MRI scan (SPGR sequence) was acquired with a 1.5 T scanner. Hippocampal volume and shape morphology were estimated with surface-based anatomical mesh modeling methods. This procedure allows matching of equivalent hippocampal surface points, obtained from manual tracings. Permutation testing was performed to confirm overall significance of statistical mapping results.

Results: There were no significant differences in hippocampal volumes at baseline between cases and controls. At follow-up, patients showed significantly smaller right hippocampus (F = 2.03, P = 0.019), but not left hippocampus, compared to controls. At baseline, there were significant distributed shape differences in left and right hippocampal shape maps between cases and controls (P < 0.05), suggesting a diffused pattern of shape difference. The same spatial pattern of left and right hippocampal shapes was replicated at follow-up, although it became more marked. Within-group comparisons between baseline and follow-up showed significant progressive hippocampal shape changes in patients, particularly in lateral and medial regions of the right hippocampus. Significant shape changes were present in the midbody (CA1 subfield and subiculum) and tail (subiculum) of the right hippocampus (P < 0.001).

Discussion: We examined hippocampal changes in schizophrenia patients longitudinally, following illness onset. Our findings suggest that hippocampal volume differences are small at illness onset, but they become more marked after 6 years, with reductions in schizophrenia patients but not in controls. Furthermore, only schizophrenia patients show a specific pattern of shape change over time, possibly paralleling the volume reduction. The shape changes we found in the subiculum and CA1 regions of the right hippocampus point to a specific functional role of these hippocampal regions in schizophrenia. These findings point to a disturbance in the connections between hippocampus and prefrontal areas. Further longitudinal data can elucidate the exact nature, severity and timing of such anatomical changes.

doi:10.1016/j.schres.2010.02.591

Poster 97
VOXEL-BASED MORPHOMETRY COMPARISON BETWEEN CHRONIC SCHIZOPHRENIA AND BIPOLAR PATIENTS AND HEALTHY CONTROLS
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Background: Direct comparisons of brain structure between major psychoses are scarce, but may help to clarify their nosological boundaries between them.

Methods: We have compared the whole brain gray matter (GM) distribution between chronic schizophrenia and bipolar patients, with similar age and illness duration, using voxel-based morphometry (VBM). A total of 81 subjects were included, of them 38 with schizophrenia (26 males), 19 with bipolar disorder (12 males) and 24 healthy controls (16 males). Differences were considered significant at p < 0.001 with a minimum cluster extension of 20 voxels. Age, sex and intracranial volume were introduced as covariates in the analyses.

Results: In comparison to healthy controls, schizophrenia patients showed a significant GM decrease in both putaminal regions, as well as a significant GM increase in left anterior cerebellum. In comparison to the same controls, bipolar patients showed a significant decrease in right caudate and left superior medial frontal region. The direct comparison between schizophrenia and bipolar patients revealed more GM in the former in the left anterior cerebellum and anterior cingulate (BA 24). In addition, schizophrenia patients had less GM in right pulvinar thalamus, right cerebellar culmen and right cerebellar posterior hemisphere, as well as in left precentral (BA 4), medial frontal (BA 10) and right motor (BA 6) cortices.

Discussion: Grey matter distribution may differ between bipolar disorder and schizophrenia at chronic stages, and at least some of these differences cannot be attributed to the treatment received.

doi:10.1016/j.schres.2010.02.592

Poster 98
LONGITUDINAL CHANGES OF STRUCTURAL BRAIN ASYMMETRY IN PSYCHOSIS AND HEALTHY CONTROLS
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Background: Several cross-sectional MRI studies have shown an absence of, or disruption to, normal patterns of structural brain asymmetry in patients with psychosis. We investigated structural brain asymmetry indices in a longitudinal study of psychosis patients and healthy controls.

Methods: At baseline structural MRI scans were acquired from 39 first-onset psychosis patients (DSM-IV schizophrenia = 17) and 43 healthy controls. At six-eight years follow-up the patients and controls were rescanned. Left/right hemispheric cortical measurements of prefrontal, premotor, sensorimotor and occipital-parietal regions were acquired yielding regional asymmetry indices and a composite measure of cerebral torque. Measures of lateral ventricular volumes were also obtained.

Results: Baseline and follow-up measures showed no significant patient-control differences in asymmetry indices. Both groups displayed normal patterns of cerebral asymmetry, with larger right than left frontal regions and larger left than right occipitoparietal regions. Similarly, both patients and controls displayed greater right over left ventricular volume. There was however a significant main effect of time, with levels of cerebral asymmetry reduced over the follow-up period in both patients and controls. This overall pattern of findings remained when the schizophrenia patients were analysed separately.

Discussion: The finding of relatively normal patterns of asymmetry in the patients at baseline and follow-up ran contrary to our predicted findings and does not appear to be explained by diagnostic heterogeneity. Of great interest was the extent of brain asymmetry reduction over time in both patients and controls. This appears to suggest a
The timing, nature, and progress of such abnormalities are not clear. The folding of the cerebral cortex is mainly determined during gestation and early childhood and thus represents a window for investigating the early development of the brain. The aim of this study was to investigate differences in cortical folding using automated magnetic resonance imaging (MRI) tools between patients with schizophrenia and healthy control subjects.

**Methods:** MRI scans were acquired from 208 patients with schizophrenia and 206 healthy subjects from two separate cohorts, one recruited at the Karolinska Hospital in Stockholm, Sweden (96 patients and 105 healthy subjects, mean age patients and controls 42 years, mean duration of illness among the patients 17 years) and the other recruited at the University of Oslo, Norway (112 patients and 101 healthy subjects, mean age patients 31 years, mean age controls 37 years, mean duration of illness among the patients 4 years). The scans were processed with an automated computer-based method for measuring the local gyrification index (IGI) at numerous points across the cortex. The method is freely available at http://surfer.nmr.harvard.edu/fswiki/IGI. The IGI is computed as the ratio between the area of the folded cortical surface within a defined radius from the vertex and the area of the outer cerebral surface within the same radius. A higher index indicates a higher degree of cortical folding. General linear models controlling for age and gender were used to analyse differences in IGI between patients and controls. A false discovery rate (FDR) of 5% was applied to correct for multiple tests.

**Results:** Lower IGI was found among the patients in areas comprising the lateral posterior temporal cortex in the right hemisphere, and the pericentral cortex in the left hemisphere (p < 0.01, uncorrected). When adjusting for FDR, the group differences in left pericentral cortex remained significant. The results were essentially similar in both cohorts. In the Swedish cohort, including patients in a more chronic phase of the illness, lower IGI was found both in the right posterior temporal cortex and in the left pericentral cortex, while in the Norwegian cohort, including patients in an earlier phase of the illness, lower IGI was found predominantly in the left pericentral cortex (p < 0.01, uncorrected).

**Discussion:** The results indicate that degree of folding is reduced in distinct areas of the cerebral cortex among patients with schizophrenia. The similar pattern of findings across two separate cohorts with patients at different stages of the disease indicates that reduced degree of folding may be an inherent feature of schizophrenia. The results further suggest a neurodevelopmental origin for the disease.

doi:10.1016/j.schres.2010.02.595
schizophrenia [1,2]. Another line of research suggests loss of efficient inter-hemispheric communication as a possible source of schizophrenia pathology [3]. These findings led us to hypothesize differences in inter-hemispheric connections in white matter between left and right superior temporal gyrus (STG) gray matter. Such a study is technically challenging because single-tensor streamline tractography methods do not reliably resolve the fiber tracts of interest. In this study, we used a novel filtered two-tensor tractography method [4] to test the hypothesis in chronic schizophrenia.

**Methods:** Structural magnetic resonance images (MRI) and diffusion weighted images (DWI) were acquired from 18 patients with chronic schizophrenia (SZ) and 16 normal controls (NC). The two groups were matched in age, gender, handedness and parental socio-economic status. For all subjects, the gray matter of the bilateral STG was segmented from the structural MRI, which was registered to the DWI, using Freesurfer (http://surfer.nmr.mgh.harvard.edu, an automatic segmentation tool). They served as regions of interest (ROIs) to extract the inter-hemispheric fiber tracts connecting the STGs from whole-brain filtered two-tensor tractography. A clustering method [5] was then used to remove extraneous fiber tracts. The mean fractional anisotropy (FA), mode, trace, parallel and perpendicular diffusivity of the resulting fiber tracts were computed for each subject.

**Results:** ANOVA test revealed group effects for mean FA (p=0.037) and perpendicular diffusivity (p=0.040), but not for mean mode (p=0.162), trace (p=0.076) or parallel diffusivity (p=0.339). Of note, the filtered two-tensor tractography method, unlike the single-tensor streamline tractography, was able to reliably reproduce the fiber tracts between the bilateral STG gray matter for all subjects. This demonstrates its capability for tracing through crossings and branchings, which is impossible with single-tensor model.

**Discussion:** Findings suggest decreased FA and perpendicular diffusivity in inter-hemispheric fiber tracts between bilateral STG gray matter for SZ compared to NC, indicative of poorer white matter health in the former. Further studies will be carried out to associate these findings with positive and negative syndrome scale (PANSS) for schizophrenia, and to provide new insights into the role played by this inter-hemispheric connection between bilateral STG gray matter in thought and information processing.

**References**


**Poster 102**

**EFFECTS OF CATECHOL-O-METHYLTRANSFERASE VAL158MET ON GREY MATTER VOLUME IN ADOLESCENTS BORN PRETERM**

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**Background:** Preterm birth is associated with altered grey matter and white matter distribution in adolescence, but little is known about how genetic vulnerability affects brain structure in individuals who were born very preterm. We investigated the effect of catechol-O-methyl transferase (COMT) valine (val) 158 methionine (met) (val158met) polymorphism on grey matter development in VPT individuals.

**Methods:** COMT val108/158met genotype was determined from DNA obtained by cheek swabs in 71 adolescents who were born before 33 gestational weeks (very preterm; VPT). These individuals were part of a long-term follow-up study in which structural MRI had been performed in adolescence. Optimized voxel-based morphometry (VBM) was used to study whole-brain gray matter volumes.

**Results:** ANOVA (with COMT val108/158met genotype as between-subject factor) showed significant group differences in grey matter volume at 14 years in left middle temporal gyrus and left parietal areas. There was a gradient relationship, with larger volume in met/met homozygotes; smallest volume in val/val homozygotes; and intermediate values in val/met heterozygotes.

**Discussion:** The met158 allele, which has been extensively studied in relation to prefrontal function, was positively associated with grey matter volume in middle temporal and parietal cortices in VPT individuals. This allele produces a lower-activity form of the enzyme. The COMT met158 allele may moderate vulnerability to the effects of perinatal grey matter damage following very preterm birth.

**doi:** 10.1016/j.schres.2010.02.597

**Poster 103**

**INCREASE OF GREY MATTER IN LENTIFORM NUCLEUS IN SCHIZOPHRENIA AND UNAFFECTED RELATIVES MEASURED WITH VOXEL-BASED VOLUMETRY (VBM): MEDICATION EFFECT OR GENETIC LIABILITY?**

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**Background:** We compared morphological pattern of grey and white matter and cerebrospinal fluid, using high-resolution 3D-anatomical MRI imaging data (Siemens Allegra 3 T scanner, Erlangen, Germany), in three different subject groups: 25 schizophrenia (SZ) patients, 29 age-matched first-degree relatives and 37 healthy controls.

**Methods:** The data were analyzed using voxel-based morphometry (VBM; Ashburner and Friston, 2000, Mechelli et al., 2005) with the SPM5 VBM-tool (SPM5, Wellcome Department of Imaging Neuroscience, London, UK). We added different covariates into the analysis, like age, gender, intracranial volume and years of education. Furthermore, we correlated the imaging data to different psychopathological parameters, like the PANSS scores (Positive and Negative Symptom Scale; Kay et al., 1987), the RHS (Revised Hallucination Scale; Morrison et al., 2002) and the ESI (Eppendorf
Methods: Male Wistar rats weighing between 100-150 g were used in this study. Animals were bred in the animal house of the Faculty of Basic Medical Science, University of Ilorin. Animals were presumed to be in good health and fit for the study. All animals use in the procedures was in accordance with the guidelines of the animal ethic committee of the University of Ilorin. The animals were fed with standard diet and water was provided ad libitum and kept on a physiological day/night rhythm. The rats were divided into three groups with each group containing eight rats. Group 1 (control): Rats in this group received normal saline intramuscularly. Group 2: Rats received intramuscular injection of ketamine at a dose (ket. 5.0 mg/kg/day) Drug: Ketamine (ketamine Hydrochloride) was purchased from one of the popular pharmacy in Lagos and sarfam medical centre, Ilorin, Nigeria. Conditioning of Animals Animals were handled and conditioned for a week to reduced handling stress during experiment. Rats were sacrificed after 7 days by decapitation 90 minutes after ketamine administration. Brains obtained from histological studies were fixed in formaldehyde for 48 hours after which, they were processed for paraffin section. Sections of 5 microns thick were cut using Rotary microtome. Staining procedures such as Cresyl fasty violet for Nissl bodies were employed. Histological slides were analysed using a light microscope (Olympus). Results: Results revealed that 5.0 mg/day of ketamine altered the condensation of Nissl bodies in the neurons of the prefrontal cortex of rats in group 2.

Discussion: 5.0 Mg/kg/day of ketamine alters the synthesis of neurosecretory substances which could inturn affect theproduction some neurotransmitters in the brains of schizophrenia modelled rats.

Poster 105
ROLE OF INSULAR CORTEX IN PHASE LOCKING OF FRONTAL THETA OSCILLATIONS IN SCHIZOPHRENIA: PRELIMINARY EVIDENCE FROM CORTICAL SURFACE ANALYSIS

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Background: Insular cortex abnormalities have been suggested in the pathophysiology of schizophrenia. Insula forms an integral part of a network of brain regions that respond to degree of salience across various cognitive and emotional domains. Recently, this 'salience network' has been implicated in a higher order control process that results in switching between default and executive mode of brain activity (Sridharan et al., 2008). Multiple abnormalities in EEG oscillatory activities have been described in schizophrenia. Phase resetting of baseline oscillatory activity contributes to evoked responses across various tasks. Abnormalities in phase resetting ability may contribute to abnormalities observed in stimulus related brain electrical activity seen in schizophrenia. Though structural correlates of the phase resetting mechanism are yet to be elucidated, fMRI studies have shown association between insular BOLD response and frontal theta oscillations (Sammer, 2007). We report associations between insular thickness and frontal theta phase resetting effect observed during an auditory oddball task.

Methods: The EEG data from auditory oddball task and 3 T MRI data were acquired in 19 male subjects with schizophrenia, during stable phase of illness and receiving antipsychotic medications (mean age = 23.2 years, s.d = 4.0). The thickness of the insular cortex was measured across regional parcellations obtained using a validated automated procedure (FreeSurfer, http://surfer.nmr.mgh.harvard.edu/). Alignment of the coefficients of the frontal (Fz/A9) theta frequency wavelets in the complex plane was measured using a method proposed by Martinez-Montes et al. (2008). Correlations across anterior (short) insular gyrus, combined subregions of central insular sulcus, and posterior (long) insular gyrus were examined in both right and left hemispheres.

Results: Significant positive correlations were observed between frontal theta phase reset measures and thickness of insular regions (n = 18; left anterior r = 0.738 p<0.001; left superior circular contrast, frontal theta phase reset measures were not correlated to anterior cingulate thickness.

Discussion: Anterior insular thickness is significantly correlated with stimulus-related alignment of the phase of ongoing theta oscillations. In schizophrenia, diminished grey matter in the anterior insula might account for the diminished phase re-setting of theta oscillations. Phase synchronization of EEG oscillations is believed to play a key role in coordinating cerebral activity during the processing of information (Varela et al., 2001). While the results presented here are restricted to schizophrenia patients, the role of insula in phase reset remains to be examined in healthy individuals.

References

doi:10.1016/j.schres.2010.02.599

doi:10.1016/j.schres.2010.02.600
Poster 106
CONTRIBUTION OF GENETIC VARIABILITY IN INTERLEUKIN-1 CLUSTER (2Q13) TO THE RISK OF FUNCTIONAL PSYCHOSIS AND ITS ASSOCIATED BRAIN ABNORMALITIES

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Background: Current knowledge indicates an important degree of overlap between schizophrenia and bipolar disorder in terms of epidemiology, psychopathology, symptoms, treatment and risk factors (Murray et al., 2004). This overlap strongly suggests the existence of a common genetic risk Background that may account for some of these similarities (Murray et al., 2004, Lichtenstein et al., 2009, Potash & Bienvenu 2009). Among these shared features, altered levels of cytokines have been classically described in both diagnoses (Maes et al., 1995, 1997; Strous & Shoenfeld 2006; Drzyzga et al., 2006; Nawa & Bienvenu 2009). Among these features, altered levels of cytokines and modulating the dendritic development and complexity in cortical precursors (Potter et al., 1999; Rodriguez-Pallares et al., 2005) and IL1B gene is associated with grey and white matter abnormalities. In healthy subjects, but not the schizophrenic group, lower FA was significantly associated with the A allele in the L and R superior longitudinal fasciculus, irrespective of diagnostic group.

Methods: Genetic variability at IL-1B and IL-1RN genes was analyzed in a new sample of schizophrenic patients (n=40) and their interaction were estimated using a factorial ANOVA. Healthy controls (n=20) with available MRI data, aiming to understand whether the genetic effects of IL-1 cluster on brain morphology, including the estimation of the haplotypic effect of this genetic variability on these structural variables. Results: We present further evidence regarding the effect of IL-1 cluster genetic variability on brain morphology, including the estimation of the haplotypic effect of this genetic variability on these structural variables.

Discussion: The relevance and implications of a cytokine unbalance with regard to the increased risk for psychosis are still unknown. However our data suggest that this risk might be mediated by brain morphological changes, likely to originate from an altered neurodevelopment. In this context the cytokine relative levels might play a key role i) in front of exposures to infection, ii) the development of cortical neurons and/or iii) the differentiation of dopaminergic precursors (Weinberger 1987; Rapport et al., 2005).

Acknowledgements: Supported by Fundació “La Caixa” (99-111-00; 99-042-00), Instituto de Salud Carlos III, CIBER-Salud Mental (CIBERSAM) and Spanish Ministry of Science and Innovation (SAF2008-05674-C03-01).

doi:10.1016/j.schres.2010.02.601

Poster 107
EFFECT OF OLIG2 IN WHITE MATTER INTEGRITY IN HEALTHY SUBJECTS AND PATIENTS WITH SCHIZOPHRENIA

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Background: Altered brain connectivity is a feature of schizophrenia, and genetic, functional and neuroimaging studies have suggested white matter deficits may contribute to it. Factors that affect the myelinisation of white matter, such as the function of oligodendroglia, may thus contribute substantially to the aetiology of the disorder. The oligodendrocyte line - transcrip - tion factor 2 (OLIG2) regulates the genesis of oligodendrocytes and has been previously associated with schizophrenia. We examined the effect of a polymorphism in OLIG2, rs1059004, on cerebral white matter integrity in healthy volunteers and in subjects with schizophrenia. We predicted that the allele previously found to be more frequent in the schizophrenic population would be associated with lower white matter integrity in the healthy and in the schizophrenic population.

Methods: We used Diffusion tensor imaging (DTI) to measure voxel-wise fractional anisotropy (FA), a neuroimaging proxy of white matter integrity, in 78 healthy volunteers and 36 patients with schizophrenia, all Caucasian. The effects of genotype and diagnostic group on activation and their interaction were estimated using a factorial ANOVA.

Results: The A allele, previously found to be significantly more common in schizophrenia patients, was significantly associated with lower FA in the L and R posterior limb of the internal capsule, L and R superior and posterior corona radiata, L corpus callosum, and R superior longitudinal fasciculus, irrespective of diagnostic group. This was mainly driven by an allele-load effect in healthy subjects. In healthy subjects, but not the schizophrenic group, lower FA was also significantly associated with the A allele in the L and R superior and posterior corona radiata.

Discussion: The putative schizophrenia susceptibility gene OLIG2 is associated with differences in FA which is indicative of differences in white matter integrity. This lends further support to the idea that deficits in white matter organization, plausibly related to myelination abnormalities, lie at the origin of the anatomical and functional connectivity abnormalities in schizophrenia.

doi:10.1016/j.schres.2010.02.602

Poster 108
SEPTUM PELLUCIDUM CAVITIES AND SCHIZOPHRENIA 25 YEARS ON: A REVIEW AND META-ANALYSIS

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Background: Septum pellucidum cavities are a neurodevelopmental anomaly. Since a claimed association with psychosis in 1985, many case-control studies using MR and post-mortem have been done, with mixed results. Our aim was to find out if there is an association between presence of cavities in the septum pellucidum and psychosis and whether there is an association with large cavities.

doi:10.1016/j.schres.2010.02.601
Methods: Medline, Embase, Psychinfo, Cochrane, Scopus and Web of knowledge were searched to find the relevant articles published before August 2009. Because of the fast advanced MR imaging techniques meta-analysis was performed only on seven studies that used high quality MR imaging and were constructed similarly. Data was pooled using Mantel–Haenszel Odds Ratio (fixed effect model). With the rest of the included studies a narrative synthesis was used.

Results: 610 studies were found in the searches and 37 studies were extracted. 18 studies with 2849 participants were included. Studies were screened by one reviewer. All the selected studies were case controlled studies. There were 16 MRI studies and 2 post mortem studies. Technical quality varied widely among the studies. Because of this meta-analysis was performed on only seven studies. This showed no overall increased rate of cavities in psychotic patients (n = 555/722) versus healthy controls (n = 397/517), but a significantly increased rate of large (6 mm or more) cavities (OR 95% CI p = 0.04). Men seemed to have a CSP more often than women.

Discussion: The review concluded that presence of a CSP does not constitute a pathological phenomena but is more a normal anatomical variant. However, when the size of the CSP is defined quantitatively using appropriate high resolution techniques, a significant association with psychosis is seen when the CSP is 6 mm or more in it’s anterior to posterior length.

doi:10.1016/j.schres.2010.02.603

Poster 109
VOXEL-BASED MORPHOMETRY AND DEFAULT MODE NETWORK IN SCHIZOPHRENIA: RELATION TO COGNITION, SYMPTOMS AND SOCIAL FUNCTIONING

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Background: The purpose of the present study was to characterize the association between cognition, clinical symptoms and social functioning and anatomical cerebral deficits in a sample of schizophrenia outpatients using voxel-based morphometry (VBM).

Methods: Participants were 6 schizophrenia outpatients and 8 matched (sex, age) healthy comparison subjects. Both patients and healthy controls were assessed using VBM. Cognitive status was assessed by standardised neuropsychological test battery. Psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANS). Social functioning was assessed using Life Skills Profile (LSP).

Results: (preliminary results) Decreased gray matter volume was observed in schizophrenia patients in left medial temporal gyrus, left insula and bilateral superior temporal gyrus (uncorrected data).

Discussion: These preliminary findings revealed volume loss in the left medial temporal gyrus, left insula and bilateral superior temporal gyrus in schizophrenia outpatients.

doi:10.1016/j.schres.2010.02.604

Poster 110
EARLY ONSET PSYCHOSIS: LONGITUDINAL BRAIN CHANGES AT TWO YEARS FOLLOW-UP

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Background: Progressive loss of cortical grey matter and increase of ventricular volumes have been reported, not only in patients with childhood-onset schizophrenia but also in early-onset psychoses. This study examines progressive brain changes in first-episode early-onset psychosis.

Methods: A sample of 110 patients and 98 healthy controls was recruited. Of those, 61 (20 females) patients (mean age at baseline 15.5±1.8) and a matched control sample of 70 (23 females) had anatomical brain MRI valid data both at baseline and at 2 years follow-up (mean = 25 months). Total volumes of gray matter and cerebrospinal fluid of the frontal, parietal, temporal and occipital lobes were obtained using automated method based in Talairach atlas.

Results: Frontal lobe rate of GM volume loss within the 2 yr follow-up was larger in patients -2.9% males; -3.3% females) than in controls (-0.3% males; -0.0% females). Male patients showed a significant increase of CSF volume in the left frontal lobe within the follow up (26.6% males; 24.6% females) than in controls (10.4% males; 11.0% females).

Discussion: Patients showed deficits of GM volume and excess of CSF in the frontal lobe and smaller volume of CSF in the temporal lobes. Differences between groups increased along the two year follow-up. Volume deficits in this population are not static suggesting that patients experience progressive changes larger than expected after the appearance of psychotic symptoms.

doi:10.1016/j.schres.2010.02.605

Poster 111
GREY MATTER REDUCTION IN FIRST-EPIPOSE PSYCHOSIS: RELATIONSHIP TO DIAGNOSIS

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Background: Previous VBM studies in the literature reveal grey matter abnormalities in psychotic patients when compared with healthy controls. But those studies are usually carried out in heterogeneous samples were the patients have different diagnostics and the subjects are not further classified. Here we have investigated a large sample (118) of first episode psychosis patients that are then separated in
three diagnosed-based subgroups and healthy volunteers. Our main objective is to study whether there is a tendency towards reduction in grey matter in schizophrenia patients, and to analyze the differences between schizophrenia and schizophreniform disorders.

**Methods:** 118 patients with a first episode psychosis underwent an MRI scan in the first weeks of inclusion in the PAFIP program. At 6 months of inclusion an independent psychiatrist confirmed diagnosis using the SCID-I. Using this diagnosis patients were separated in three groups: schizophrenia (n = 65, 55.08%), schizophreniform disorder (n = 32, 27.12%) and non-schizophrenic non-affective psychosis (n = 21, 17.80%). A healthy volunteer group matched by age, gender, laterality index and years of education was also included (n = 77). There were no sociodemographic characteristics significant differences between the groups of subjects. All MRI were acquired in a 1.5 T GE scanner; SPGR sequence (TE = 5 ms, TR = 24 ms, slice thickness = 1.5 mm). To analyze the data we used spm5 and DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra), an isotropic Gaussian kernel of 5 mm FWHM was used for smoothing. Age, gender and total intracranial volume were covariates of no interest in the ANCOVA contrast.

**Results:** We find that there is a grey matter reduction in patients that increases with the severity of the diagnosis. This tendency was observed bilaterally in the middle and superior frontal gyri, insula and middle occipital gyrus (p < 0.001corrected). There was no opposite tendency. Moreover, we have not found any significant difference between schizophrenia and schizophreniform patients when we compared both groups.

**Discussion:** Patients diagnosed with schizophrenia showed a pronounced reduction of grey matter, mostly localized in the dorsal temporal lobe (superior and middle temporal gyri and insula) and increased with severity of diagnosis. Since no significant differences between schizophrenia and schizophreniform disorder patients were found our results point towards a common brain morphological endophenotypic marker for both conditions.

**Poster 112**

**REDUCED ABILITY TO ENGAGE DEFAULT-MODE BRAIN REGIONS DURING THE RESTING-STATE PERIODS OF A WORKING MEMORY TASK IN RECENT-ONSET SCHIZOPHRENIA**

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**Background:** The default-mode network (DMN) has gained attention in schizophrenia research due to the involvement of these brain regions during the resting-state, which is a period that reflects the cognitive processes that occur during stimulus-independent thought, such as self-reflection.

**Methods:** Forty-four patients with recent-onset schizophrenia and twenty-four controls underwent functional magnetic resonance imaging while performing a verbal working memory task. There were six baseline fixation blocks embedded throughout the task. The baseline periods were collapsed and served as the resting period which was subsequently analyzed using a whole-brain voxelwise analysis. A secondary analysis explored the impact of task load (i.e. lowest and highest level load conditions) on the subsequent resting phase. Finally, a separate analysis of functional activity during the working memory task was also examined.

**Results:** Group level maps revealed that during rest schizophrenia patients and controls increased activity in expected default-mode network regions, which included the medial frontal, lateral parietal and posterior cingulate cortices. However, the between-group analysis revealed overall greater activation in the control group within the posterior cingulate cortex (PCC), precuneus, inferior parietal lobule (IPL), and middle and superior temporal lobes. In the between-groups parametric analysis the controls exhibited increased activity in the PCC, IPL and middle and superior temporal lobes after the least challenging 3-load condition. Conversely, the patients increased activity in the PCC after the more cognitively demanding 9-load condition. Schizophrenia patients also exhibited increased activity compared to controls during the working memory task in DMN regions, including the right middle and superior temporal lobes, precuneus and ventral anterior cingulate.

**Discussion:** Although the DMN has been consistently localized in focal brain regions, previous reports of the DMN activity in schizophrenia patients have yielded contradictory findings. This study reveals that recent-onset schizophrenia patients have altered physiological dynamics of the DMN over the course of a working memory task which extends into the resting phase following the task. Patients exhibited a reduced ability to deactivate DMN regions during a cognitively demanding task and subsequently fail to engage these DMN regions to similar levels as control participants during rest. That the patients increased activity in the PCC during the resting-state following only the most difficult trials may reflect the patients' cognitive disengagement during the task, which was evidenced by the patient group's recruitment of the DMN regions during the working memory task. Therefore, the residual activity of the PCC that elevated after the difficult task, in the absence of external stimuli, may be an indicator of increased DMN cognitive-related processes only when the patient had previously become neurally "exhausted" by the task at hand. These findings suggest that during cognitively demanding tasks schizophrenia patients may be excessively attributing brain regions involved in internal representations to external stimulation and in turn not allowing sufficient neural processing levels to be obtained during periods reserved for introspective thought.

**Poster 113**

"TURN IT UP TO 11": THE RELATIONSHIP BETWEEN BRAIN NOISE AND LEARNING IN SCHIZOPHRENIA

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**Background:** Increasing evidence suggests that variability in brain signal may be beneficial when performing various cognitive operations. "Noise" in this case may aid in switching brain network configurations as the brain learns a new task. Persons with schizophrenia are often impaired in measures of cognitive flexibility and learning. Our study aims to explore the extent to which these impairments may be explainable via differences in brain noise as well as behaviour. This study is the first part in exploring our extended hypothesis that, in contrast to some earlier work suggesting global increases in noise in schizophrenia, the noise story is more nuanced with both large-scale dynamic increases and decreases.

**Methods:** We used a learning paradigm in which subjects learned a novel lexicon (Breitenstein and Knecht, 2002) while undergoing
event-related fMRI scanning on two separate scanning days. Fourteen subjects with a diagnosis of schizophrenia, stabilized on atypical antipsychotics, were matched with twelve healthy control subjects. Multiscale Entropy (MSE) (Costa, 2002) was used as a measure of predictability of the BOLD signal as function of timescale. A noisier signal would be seen as less predictable and, thus, have a higher entropy value. MSE was calculated for each voxel in each of ten learning runs. “Partial least squares” (PLS) (McIntosh, 2004) was used to analyze the spatio-temporal brain changes in MSE across runs and between groups.

**Results:** Both groups were able to learn the lexicon. There were significant learning effects across runs (F(9, 207) = 104.87, p < 0.001) and main effects of group (F(1, 23) = 9.06, p < 0.01). The patients reached a lower level of asymptote than the healthy control participants. There was no significant interaction between group and learning (F(9,207) = 0.85, n.s.). As both control participants and participants with schizophrenia learned the new lexicon, MSE decreased at fine temporal scales and increased at coarser temporal scales. Specifically, decreases were noted in precuneus, inferior parietal and dorsomedial prefrontal cortices. Increases were noted in occipito-temporal, medial temporal cortices and medial parietal cortices. Our inquiry of interest was the interaction between learning-related noise changes by group. The schizophrenia group showed reduced MSE in left anterior prefrontal cortex that the controls did not exhibit. They did not demonstrate the increased entropy in bilateral superior frontal and inferotemporal cortices that was quite prominent in the controls as they learned.

**Discussion:** Within a nonlinear dynamical system such as the brain, noise is a critical enabler of the transition between functional networks and an index of the dynamic repertoire of a given large-scale system. The repertoire may change as a function of learning and, by this reasoning, so too would measures of noise. The systematic changes in MSE in healthy participants may reflect engagement of regions involved in the formation of new functional networks as learning proceeds. The fact that there is some overlap with the spatial pattern in findings in the participants with schizophrenia suggests some similar capacities for learning in schizophrenia. Behaviourally, however, persons with schizophrenia, although they certainly learn, do not achieve the same asymptotic level as control subjects. These data suggest that these differences may be in part due to the lack of brain noise modulation identified in analyses of group differences.

**Poster 114**  
**CHRONIC DEREALISATION PHENOMENON IN A 17-YEAR OLD BOY AFTER TWOFOLD CANNABIS USE: WHEN ACUTE BECOMES CHRONIC**

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**Background:** Depersonalisation/derealisation (DP/DR) phenomena are characterized by the subjective experiences of feeling unreal and detached from oneself as well as from the external world. These symptoms are relatively common in normal (1-2%) and psychiatric populations (up to 42-91% dependent on the underlying disorder). Beside severe stress and panic disorder cannabis (ab-)use is a well-known elicitor of DP/DR phenomena. after experimental cannabis administration, increased resting activity and activation of the frontal and anterior cingulate cortex were described, possibly being responsible for the subjective experience of the DP/DR. Here we investigate the cerebral blood flow (CBF) of a 17-year-old boy with a chronic derealisation phenomenon after having used cannabis twice 2 years ago. His distressing symptomatology was characterized by feeling detached, like being in a dream, with 1-2 incidents per week of being uncertain whether or not he has actually experienced or dreamt a situation.

**Methods:** We used pseudo continuous ASL for the measurement of cerebral blood flow (CBF) (TR 4000 ms, 16 slices, label time 1.6 s, postlabeling delay 1.25 s) in a 3 T MR scanner. CBF was assessed at rest and under provocation of the DR phenomenon. Functional images were acquired using a multi-slice single-shot T2*-weighted echo planar imaging (EPI) sequence (TR 2000 ms, TE 30 ms) applying a block design using an individual paradigm of the DR phenomena. Anatomy was assessed by a 3D T1-weighted and T2*-weighted axial scans. ASL data analysis was performed using Matlab®, statistical parametric mapping (SPM) and in-house software. fMRI analysis was realized using BrainVoyager QX® software.

**Results:** Using ASL, we found increased regional CBF in the anterior cingulate gyrus as well as in the right inferior frontal gyrus relative to other brain regions in a resting condition. Subjectively, the patient reported 4-5/10 on a visual analogue scale for experience/feeling of DR. Under provocation of DR, 7-8/10 on the visual analogue scale, these increases were even more pronounced. The very same regions showed higher activations during the fMRI measurements under provocation (level 9/10) compared with a resting state (4/10). In the fMRI we assessed the % BOLD signal changes in a resting (Δr = 4/10) and provocation (Δr = 9/10) condition following a classical block design. Here, we found activation in the very same regions found in the CBF measurement: Right Broca aequivalent, dorsolateral prefrontal cortex and anterior cingulate gyrus.

**Discussion:** Little is known about neurobiological mechanisms of persistent DP/DR phenomena. Here, we found the pattern of increased local brain perfusion in the same cerebral regions previously described under experimental THC administration. With and without provocation of DR, we found CBF as well as the BOLD signal increases in these specific regions. These effects correlated with the patient’s subjective experience of DR. Identifying localized brain regions with pathologically higher CBF resp. BOLD activations might yield target regions for inhibiting transcranial magnetic stimulation (TMS). TMS might offer a therapeutic alternative to the frequently unsuccessful psychopharmacological treatment of DP/DR.

**Poster 115**  
**ALTERED FUNCTIONAL CONNECTIVITY IN SUBJECTS WITH ULTRA-HIGH RISK FOR PSYCHOSIS USING RESTING STATE fMRI**

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**Background:** Several functional magnetic resonance imaging (fMRI) studies of schizophrenia have revealed the default mode network (DMN) and task-related network (TRN) abnormalities during
resting-state. Midline default network areas, including the medial prefrontal cortex and posterior cingulate cortex, are implicated in self-referential and social cognitive tasks, and individuals at ultra-high risk (UHR) for psychosis were recently reported to have self-disturbances and deficits in social cognition and functioning. Thus, the DMN has its potential to reveal the neural substrates of self-referential and social cognitive information processing in UHR subjects. In this study, we investigated resting-state DMN and TRN functional connectivity in UHR subjects and healthy controls.

**Methods:** Twenty UHR subjects and 20 matched healthy controls underwent fMRI while resting quietly. We selected bilateral posterior cingulate cortex (Brodmann area 23) as a seed region and reconstructed the intrinsic organization in the UHR subjects and healthy controls on the basis of fMRI time series correlation (also known as functional connectivity). Between-group comparison of the DMN and TRN was restricted to regions belonging to the intrinsic networks of control group. Additionally, we also conducted between-group region of interest (ROI)-based connectivity analyses on areas in which UHR subjects showed altered connectivities, within a priori selected anatomical ROIs.

**Results:** Default mode and task-related areas were observed in regions previously associated with the DMN and TRN for both groups. Default mode areas included the posterior/anterior cingulate, medial prefrontal and lateral parietal cortices, and inferior/superior temporal gyri, whereas task-related areas included the dorsolateral prefrontal and middle temporal cortex, supplementary motor area, and frontal eye field. Compared to healthy controls, UHR subjects exhibited hyperconnectivity within the default network regions and reduced anti-correlations between the posterior cingulate cortex and task-related areas. Between-group ROI analysis also confirmed these findings.

**Discussion:** Our findings suggest that abnormal hyperconnectivity of the default areas in UHR subjects might be related with clinical features of UHR subjects like disturbance of self-perception and heightened social anxiety. Neurodevelopmental and anatomical alterations of cortical midline structure might underlie altered intrinsic networks in UHR subjects. We also speculate that reduced anti-correlation between two networks might be related with impaired neurocognitive function in UHR subjects, which might be mediated by weaker task-induced deactivation of the DMN.

**doi:** 10.1016/j.schres.2010.02.610

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**Poster 116**

**FUNCTIONAL MRI OF WORKING MEMORY RELATED ACTIVATION IN MONOZYGOTIC TWINS DISCORDANT FOR SCHIZOPHRENIA: PRELIMINARY RESULTS FROM THE EUTWINNDS STUDY**

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**Background:** Functional MRI has demonstrated differences in activation of working memory related networks in schizophrenia, which appear to be one of the most robust and consistent marker of enduring cognitive deficits in this disorder. Here, we present preliminary findings from the European Twin Study Network on Schizophrenia (EUTwinS), examining monozygotic (MZ) twins discordant for schizophrenia (Sz) as a model for assessing disease effects whilst controlling for genetic Background.

**Methods:** We studied 20 subjects using event-related fMRI (3 Tesla, whole brain) with an adaptation of a previously developed Sternberg task (Schlösser et al., 2008), including 5 MZ twin pairs discordant for schizophrenia (4 female pairs/1 male pair; mean age 33.6, SD 7.3) and 5 MZ healthy control pairs (4 female pairs/1 male pair; mean age 32.2, SD 5.3), matched for age, gender, handedness, and premorbid IQ. The task included a three-letter version of the Sternberg task with two variations: in the first (forward) the subjects only had to remember the three-letter sequence during the delay period, in the second (alphabetize) condition they were asked to rearrange the letters according to their alphabetic order. Data were analyzed using SPM5, including slice-time correction, motion correction, and smoothing with a 8 mm FWHM Gaussian kernel. We analyzed three different main contrasts: a) overall task-induced activation, b) differential activation contrasting alphabetize trials vs. forward trials (isolating the mental manipulation component), and c) contrasting alphabetize vs. forward only during the delay phase (using a more complex model with three different HRFs for the three stages of the task).

**Results:** Comparing Sz-affected MZ twins with either their unaffected twin or healthy MZ twins did not show differences in overall task-related activation. However, activation differences were observed in the other contrasts. Comparing the alphabetize vs. forward trials, Sz-affected MZ twins showed higher activation than healthy control MZ twins in right lateral prefrontal cortex (middle frontal gyrus), right ventrolateral PFC (inferior frontal gyrus), left lateral cingulate and small area of the left hippocampus. In the same contrast, unaffected MZ twins (at risk) compared to healthy MZs showed higher activation in the left dorsolateral PFC, BA 9 and 10, right middle temporal gyrus and left visual cortex (BA 18/19). When using different HRFs to model the different temporal stages of the task and looking only at the delay period, we found Sz-affected MZ twins to show higher right medial PFC and left lateral cerebellar activation, while unaffected MZ twins at risk in fact showed higher activation than healthy controls in left cerebellum.

**Discussion:** Although our findings are preliminary and suffer from the limitations of a small sample size of twins, they are consistent with the assumption that the expression of the disease phenotype is associated with prefrontal (and possibly also contralateral cerebellar) activation deficits. In many instances, unaffected co-twins (sharing the genetic Background) show intermediate activation levels, implying a mixture of genetic effects and those related to actual manifestation of the disorder. This study was supported by grants of the EU (EUTwinS network; RTN, FP6) and the Thuringian State Department of Culture (TKM).

**doi:** 10.1016/j.schres.2010.02.611

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**Poster 117**

**ASSOCIATION OF GENETIC VARIATION OF THE DOPAMINE D2 RECEPTOR GENE WITH ACTIVITY IN CORTICAL AND SUBCORTICAL MOTOR BRAIN REGIONS IN HUMANS**

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**Background:** Functional MRI of working memory related activation in monozygotic twins discordant for schizophrenia: preliminary results from the EUTWINNDS study
Background: Several studies have reported abnormalities of motor processing in schizophrenia. Motor functions are crucially modulated by striatal dopamine D2 receptors that provide inhibitory modulation of motor thalamo-cortical projections. Previous studies have indicated that an intronic single nucleotide polymorphism (SNP rs1076560 G>T) in the dopamine D2 receptor gene (DRD2) affects mRNA splicing to two distinct isoforms, the short form of D2 (D2S) and the long form (D2L). The purpose of the present study with fMRI was to investigate in healthy subjects the association of brain activity and functional connectivity of prefrontal cortex and striatum during a motor task with rs1076560 genotype.

Methods: 36 healthy subjects, genotyped for DRD2 rs1076560 polymorphisms (GG = 17, GT = 19) underwent BOLD-fMRI at 3 T while performing a visually paced motor task with their right hand. SPM5 random-effects models were used for statistical analyses (all p < 0.005).

Results: Genotype groups did not differ for a series of socio-demographic variables. fMRI data analysis indicated a statistically significant effect of rs1076560 genotype: GT subjects have greater BOLD activity than GG in left striatum and left supplementary motor area (SMA). Functional connectivity analysis indicated that GT subjects have greater functional connectivity between right and left striatum when compared with GG subjects.

Discussion: The present results demonstrate association of a functional intronic SNP within DRD2 with activity and functional connectivity of the motor circuitry. Our results are consistent with the known neurobiology of cortical and subcortical motor circuits. D2 receptors are densely expressed in striatum and, to a lesser extent, in SMA. In both anatomical areas D2 receptors strongly contribute to the known neurobiology of cortical and subcortical motor circuits. D2 receptors are densely expressed in striatum and, to a lesser extent, in SMA. In both anatomical areas D2 receptors strongly contribute to the known neurobiology of cortical and subcortical motor circuits.

References


doi:10.1016/j.schres.2010.02.612

Poster 119

TRAIT AND STATE BRAIN-ACTIVATION MARKERS OF SCHIZOPHRENIA

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Background: Functional imaging studies reveal that patients with schizophrenia can exhibit either diminished or excessive regional brain activity during cognitive tasks, and suggest that regional activation is below normal when the task is difficult but excessive when the task is easy (1). Moreover, although evidence suggests that siblings of schizophrenic patients have only about 9% risk of illness (2) they tend to exhibit excessive regional activity compared with healthy controls (3). This suggests that inefficient neural recruitment is a trait characteristic of risk for schizophrenia, resulting in diminished recruitment when the task demands exceed capability, but excessive recruitment when the individual is capable of performing the task. Furthermore, the observation of diverse dimensions of cognitive dysfunction in siblings (4), of whom only a minority are likely to develop overt illness, suggests that some degree of abnormality is present in a large proportion of siblings. This is consistent with the hypothesis that familial risk arises from a large number of genes, each of small effect.

Methods: Twenty six young healthy controls, 18 young healthy siblings of patients with schizophrenia and 18 young people with schizophrenia performed an auditory target-detection task in a 3 T MRI scanner. BOLD responses to non-target stimuli in subjects with schizophrenic trait (siblings and patients) were compared with that of healthy controls, and responses in patients (schizophrenic state) were compared with that of healthy siblings. Participants groups were matched on accuracy on the task, both on commission and omission errors.

Results: Patients had significantly longer reaction times to targets than healthy subjects (siblings and healthy controls). Compared with healthy controls, schizophrenic trait-bearers (siblings and patients) showed significant clusters of voxels (p < 0.05, corrected) of hyper-activation in brain areas associated with task-positive responses in healthy controls (superior temporal gyri and supplementary motor area, bilaterally), as well clusters of reduced deactivation in areas associated with task-negative responses in healthy controls (Default Mode Network and fusiform gyrus, bilaterally). Compared with patients, siblings showed greater activation in two clusters, a medial frontal cluster and a right pre-central cluster.

Discussion: Despite the fact that the groups were matched for task accuracy, both siblings and patients showed greater brain activation in response to irrelevant (non-target) stimuli as compared with healthy controls. However, siblings showed additional frontal activation that may have been compensatory. The only compensatory strategy apparently available to schizophrenic subjects was to delay responses.

References


doi:10.1016/j.schres.2010.02.613

Poster 119

FUNCTIONAL NETWORK DISCONNECTIVITY IN SCHIZOPHRENIA: EVIDENCE FROM THREE FMRI EXPERIMENTS

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Background: Altered anatomical and functional cerebral connectivity has been hypothesized to be the central impairment in schizophrenia. Research in the last decade has identified that the brain is organized into distinct functional networks that allow a multitude of cognitive tasks to be carried out in parallel. fMRI Studies on cognitive processing has identified an central executive network (CEN) correlated with tasks and a default mode network (DMN) in which activity is anticorrelated with tasks. A salience or attentional network comprising of anterior cingulate-insular-frontal regions is thought to mediate the switch between the CEN and the DMN (Dosenbach, 2006; Sridharan, 2008) The complex interplay between the three networks could explain the cerebral disconnection in schizophrenia, which could provide explanations for the diverse range of symptoms seen in this disorder. We performed
three fMRI studies to investigate the interaction between the CEN, default-mode and the salience networks in patients with schizophrenia and healthy volunteers.

**Methods:** 20 patients with DSM-IV schizophrenia and 20 age, gender and parental socio-occupational status matched controls participated in the study after providing informed consent. The subjects performed two functional tasks (n-back memory task and auditory oddball task) and data was also acquired when the subjects were in resting state for 5 minutes, with eyes closed. Functional MR Imaging was performed on a 3 Tesla Philips MR device employing echo-planar (EPI) acquisition (TE / TR 35 / 2100 ms; 64 × 64 matrix, voxel size 3.25 × 3.25 × 3.25; 35 slices). Images were reoriented, realigned, coregistered, spatially normalized and smoothed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm). The smoothed images from all the subjects were subjected to Independent Component Analysis (ICA) using the GIFT software (http://icatb.sourceforge.net) to decompose the data into 20 spatially independent components. The resulting components were subjected to visual inspection and correlation with apriori masks created in MRicron. The correlation between the networks were tested using the Functional Network Connectivity software (Jafri et al., 2008).

**Results:** Both in the two functional tasks and the resting stage, the three components correlating to the CEN, DMN and salience networks were clearly identified in the combined group ICA. Separate group ICA of the patients and controls also led to identification of the three networks in each group. The time courses of the three components showed that the CEN, and Salience components were correlated with active tasks in the functional tasks, and the DMN was anticorrelated with the tasks. The functional connectivity analysis showed the complex interplay differences between patients with schizophrenia and controls.

**Discussion:** The three networks (CEN, DMN and Salience networks) were clearly identifiable using model-free ICA analysis in both functional tasks and the resting stage for both groups, which suggests that three networks are key to information processing in both resting and active states of brain activity. The complex interplay between the three networks that is aberrant in schizophrenia may explain the ‘disconnection’ resulting in the diverse range of symptoms in schizophrenia.

**References**


doi:10.1016/j.schres.2010.02.614
heritability for the pathophysiology of emotions in schizophrenia. Aim of this study is to investigate with fMRI in unaffected siblings of schizophrenia patients if emotional network activity previously associated with schizophrenia could represent a heritable phenotype.

**Methods:** We enrolled 19 patients with schizophrenia, 18 healthy siblings and 31 normal controls. All samples were well matched (p > 0.05) for a series of demographic variables. Schizophrenia patients were on stable treatment with antipsychotic drugs; symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). All subjects underwent fMRI at 3 T during implicit (gender discrimination) and explicit (approach or avoid evaluation) processing of faces with different expression (angry, fearful, happy, neutral). SPM5 was used for imaging analysis (p < 0.05, after small volume correction).

**Results:** Repeated Measures ANOVA revealed a main effect of diagnosis in right dorsolateral prefrontal cortex (DLPFC) (Brodmann area 46; x 56, y 26 ± 26; K = 4; Z = 3.43). In particular, DLPFC response was lower in patients than in controls, while it was intermediate in the siblings group. Furthermore, there was an interaction between task and diagnosis on anterior cingulate activity (Brodmann area 32; x 11, y 26 ± 34; K = 4; Z = 2.90). In this area, activity was greater during explicit relative to implicit processing in both siblings and controls, while the opposite pattern was present in schizophrenic patients.

**Discussion:** These data suggest that DLPFC activity during emotion processing in schizophrenia may be heritable. On the other hand, altered activity in anterior cingulate does not seem to be present in siblings or a heritable trait. We conclude that state and trait variables may differentially impact functional responses in different brain areas during emotion processing in schizophrenia.

doi:10.1016/j.schres.2010.02.616

**Poster 122**
**LEFT TEMPORAL DYSFUNCTION, ATTENTION CONTROL DEFICIT AND AUDITORY HALLUCINATION: AN FMRI STUDY**

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**Background:** Previous studies have related auditory hallucinations to dysfunctions of speech sound processing localized to the left temporal lobe. Furthermore, auditory hallucinations have been suggested to be a failure of inhibiting internally generated speech perceptions. We used an fMRI paradigm with dichotic listening to consonant vowels (CV)-syllables and instructions to focus attention to either the right or left ear syllable in order to model such a dysfunction. We expected that the schizophrenia patients with frequent auditory hallucinations would show dysfunctional temporal lobe activation patterns when listening to dichotic presentations of CV-syllables. In addition, we examined possible effects of attention instructions, which could provide clues to failure of fronto-parietal attention control in hallucinating patients.

**Methods:** Seventeen patients with schizophrenia were grouped into two sub-groups based on their hallucinations score on the PANSS (hallucinatory behaviour item) and a validation of the auditory quality of their hallucinations. This yielded a frequent hallucinatory group with scores of 4 or more (n = 4), and a non-frequent hallucinatory group with scores of 3 or less (n = 13). The schizophrenia patients and 16 healthy controls were scanned while listening to dichotic presentations of CV-syllables. The subjects were scanned with a GE Signa 3.0 T scanner, and the data analyzed with the SPM5 software. The dichotic presentations during the scanning included both trials with and without attention instructions.

**Results:** As compared to the healthy controls, the patient group failed to show activation in the anterior cingulate cortex when instructed to focus attention (p < 0.05, corrected), and particularly in the situation with attention focused on the left ear syllable. In addition, the hallucinating patients failed to activate the speech areas in the upper posterior part of the temporal lobe, and on the left side (p < 0.001, uncorrected) while listening to the CV-syllables.

**Discussion:** The patient group as a whole failed to activate the anterior cingulate cortex, which is a part of a generalized cognitive effort network, when instructed to focus attention. As expected, the frequent hallucinating group also failed to activate the speech areas in the temporal lobe, indicating dysfunctional speech perception. Possibly, a combination of attention control and speech dysfunctions may underlie the hallucination experience. The neuronal mechanism mediating this effect could be an inability to inhibit internally generated ‘voices’ in the form of speech mis-representations. This is further enhanced by dysfunctional focusing of attention on the voices once they are elicited, as part of a dysfunctional fronto-parietal neuronal network.

doi:10.1016/j.schres.2010.02.617

**Poster 123**
**PREFRONTAL ACTIVITY AND COMT GENOTYPE EFFECTS IN SCHIZOPHRENIA**

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**Background:** Dopamine levels in the prefrontal cortex (PFC) seem to play a crucial role in cognitive function in schizophrenia. The COMT enzyme has a functional polymorphism (val158met): val/val individuals have a higher functioning enzyme leading to lower dopamine levels in PFC and therefore to poorer cognitive performance. This genetic polymorphism could mediate the relationship between dopamine levels, cognitive functioning and neural activity of PFC. We used global neuropsychological and specific cognitive assessments and fMRI to study the influence of COMT genotype on cognition and brain function in schizophrenia spectrum disorder patients, relatives and healthy control subjects.

**Methods:** 73 schizophrenia spectrum disorder patients, 54 relatives and 42 healthy controls performed the MATRICS Consensus Cognitive Battery to evaluate several neuropsychological domains. A sample of 19 schizophrenia spectrum disorder patients, 17 relatives and 20 controls performed the Dot version of the expectancy AX continuous performance task (DPX task) to study context processing. We used functional Magnetic Resonance Imaging (fMRI) during the performance of the DPX task.

**Results:** For the MATRICS battery, no group x genotype interaction was observed for any cognitive measure. There was a significant main effect of group for all neuropsychological subtests. Verbal learning (HVLT retention) showed a main effect of genotype (F = 3.28; p = 0.04). For the context processing task (DPX test) a genotype effect was present behaviorally and in the brain activations.
Relative to controls, patients need to activate more PFC regions (DLPFC, BA10) to perform the context processing task, reflecting inefficiency. In patients there are frontal activity differences according to the genotype, with met carriers activating more DLPFC (left BA47, right BA 45) and anterior cingulate (BA32) than val carriers.

**Discussion:** COMT genotype exerts little impact on neuropsychological functions. Differences in cognitive performance across groups are reliably measured by the MATRICS Consensus Cognitive Battery, however this instrument seems to be not sensitive enough to capture COMT genotype effects. Specific cognitive domains (context processing) are more sensitive to COMT genotype effects. Although patients with schizophrenia spectrum disorder exhibit more prominent deficits in context processing, these deficits are also seen in their relatives. The DPX task, which assesses context processing, is sensitive to COMT genotype in patients. Val/val carriers exhibit more context processing impairment than met/met carriers, probably due to less dopamine availability in the PFC. Prefrontal brain activity of context processing deficits in schizophrenia may be mediated by COMT genotype effects.

doi:10.1016/j.schres.2010.02.618

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**Poster 124**

INCREASED LIMBIC SYSTEM ACTIVITY ASSOCIATED WITH APPETITE DYSFUNCTION IN SCHIZOPHRENIC PATIENTS FOLLOWING AN OLANZAPINE TREATMENT

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**Background:** There is increasing evidence that some atypical antipsychotics can produce metabolic side effects. For instance, it has been shown that 40% of schizophrenic patients have gained weight at the end of a 16 weeks Olanzapine treatment. This side effect can originate from an increased appetite and, in long term, it could lead to a significant weight gain and its associated health problems, such as diabetes. The present study was designed to uncover the psychological, physiological and neuronal correlates associated with metabolic changes following Olanzapine medication in schizophrenic patients.

**Methods:** We recruited 24 schizophrenic patients (assessed using DSM-IV criteria) to follow 16 weeks of Olanzapine treatment. Out of these, 15 patients were scanned both before and after the treatment using functional magnetic resonance imaging (fMRI), while they watched images depicting appetizing foods or neutral objects. The same procedure, but no treatment, was employed for a group of 10 healthy individuals (control group). In addition to the imaging data, various physiological measurements were collected from the patients based on blood samples (e.g., insulin, glucose, cholesterol, leptine, ghrelin, etc.) and participants’ weight and body size were properly measured. The data were analyzed using Brain Voyager QX and SPSS software packages.

**Results:** At the end of the 16 weeks of antipsychotic treatment there was a significant change in the abdominal circumference and weight gain in the patient group. The concentration of insulin and leptine in patients’ blood increased after the treatment, whereas that of ghrelin decreased. Prior to the treatment, the patients displayed more activity in the parieto-occipital areas, amygdala and parahippocampal gyrus than healthy controls during presentation of appetitive food versus neutral objects images. These differences increased even more after the treatment (both the spatial extent of activation and the magnitude of the difference) and included in addition the insular cortex. The activity changes in amygdala during presentation of appetitive images correlated in patients with the initial level of leptine. Also, the initial neuronal activity in the insular cortex correlated positively with the difference in prolactine concentration as a result of the treatment.

**Discussion:** We found that schizophrenic patients undergoing an antipsychotic medication with Olanzapine are likely to show gain weight, increased levels of insulin and leptine and decreased concentration of ghrelin in their blood. Appetitive images increased significantly the neuronal activity in the limbic system (amygdala, insula, parahippocampal gyrus) in patients relative to controls and the activity in amygdala and insula also correlated with some physiological measurements related to appetite regulation. In the past, among the areas of the limbic system found to be activated by fasting (intrinsic influence) only the amygdala and orbitofrontal cortex were activated in response to the processing of extrinsic appetitive incentive information. The changes in insulin, leptine and ghrelin concentrations in our study and the increase in neuronal activity of amygdala (the site typically integrating homeostatic and extrinsic influences related to eating behavior) are consistent with the hypothesis of a dopaminergically mediated feeding control. Our results suggest that Olanzapine treatment alters dopamine transmission as leptin, ghrelin and insulin do. With the above interconnections in mind, we strongly suspect an alteration of the appetite control somewhere in corticolimbic area. Further studies are needed to untangle this network and pinpoint the precise involvement of Olanzapine in the appetite control.

doi:10.1016/j.schres.2010.02.619

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**Poster 125**

RECRUITMENT OF BILATERAL FRONTAL REGIONS IN SCHIZOPHRENIA DURING NOVEL METAMORPHIC PROCESSING: AN FMRI STUDY

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**Background:** Previous studies had demonstrated that the normal lateralization of language is reversed during the processing of novel metaphoric language. Thus, whereas conventional metaphors are processed by left lateralized brain regions, novel metaphors show unique right hemisphere involvement. Understanding these two types of linguistic expressions depends on different brain mechanisms: Whereas understanding conventional metaphors (e.g., bright student) involves reliance on an automatic process of meaning retrieval directly from the mental lexicon, understanding novel metaphors (e.g., conscience storm), requires the creation of novel semantic connections between two remotely associated words and inhibition of the non-relevant literal interpretation. Schizophrenia patients exhibit decrease or loss of normal anatomical brain asymmetry that also extends to functional levels, and especially, to language processing. Furthermore, schizophrenic patients demonstrate reduced inhibition corresponding to a failure to inhibit irrelevant semantic information. We applied functional magnetic resonance imaging (fMRI) to investigate the neural bases of metaphoric language processing in schizophrenia patients during novel metaphoric processing.

**Methods:** We report preliminary results from an fMRI study obtained from eight patients with schizophrenia and eight control
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HEALTHY CONTROLS AND PATIENTS WITH SCHIZOPHRENIA AND DIFFERENTIAL EPISTATIC EFFECTS BETWEEN DAAO AND G72 IN Poster 126

doi:10.1016/j.schres.2010.02.620

A. Healthy controls and patients with schizophrenia demonstrate loss of normal functional brain asymmetry, as reflected in diminished lateralization of language-related activation during novel metaphoric processing in frontal region and over recruitment of bilateral prefrontal regions. Furthermore, our results support impairment in inhibition is a semantically irrelevant information in patients with schizophrenia.

Discussion: We conclude that schizophrenia patients appear to demonstrate loss of normal functional brain asymmetry, as reflected in diminished lateralization of language-related activation during novel metaphoric processing in frontal region and over recruitment of bilateral prefrontal regions. Furthermore, our results support impairment in inhibition is a semantically irrelevant information in patients with schizophrenia.

doi:10.1016/j.schres.2010.02.620

Poster 126
DIFFERENTIAL EPISTATIC EFFECTS BETWEEN DAAO AND G72 IN HEALTHY CONTROLS AND PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Recent studies have identified DAAO and G72 as probable susceptibility genes for schizophrenia and bipolar disorder. Both genes modulate glutamate neurotransmission, which is thought to be altered in schizophrenia and bipolar disorder. In addition, the two genes have been shown to interact with each other at molecular level using in vitro transcription. At present, however, little is known about how these genes may affect brain function to increase vulnerability to these disorders. The present investigation examined the impact of DAAO and G72 genotypes on brain function in patients with schizophrenia, patients with bipolar I disorder and healthy volunteers. We tested the hypothesis that the two genes would show an epistatic effect on brain function. In addition, based of recent studies showing evidence of a diagnosis-specific pattern of gene action, we hypothesised that epistatic effects between DAAO and G72 would differ between controls and patients.

Methods: We used functional magnetic resonance imaging to measure brain responses during a verbal fluency task in a total of 120 subjects comprising 40 patients with schizophrenia, 32 patients with bipolar disorder and 48 clinically healthy volunteers. After pre-processing the data, we used statistical parametric mapping (SPM) to estimate, for each diagnostic category, the effects of DAAO rs2111902 and G72 rs746187 genotype and their interaction on brain function. Statistical inferences were made at p < 0.05 after family-wise error (FWE) correction for multiple comparisons.

Results: The SPM analysis revealed a diagnosis × DAAO × G72 interaction in the right middle temporal gyrus (x=60 y=-12 z=-12; z-score: 5.32; p < 0.001 after FWE correction). In this region, the A allele for G72 was associated with greater activation than the G allele for G72 in individuals who were A homozygote for DAAO but not in those who carried one or two copies of the C allele for DAAO; this epistatic effect was evident in patients with bipolar disorder and schizophrenia, but was almost absent in healthy controls. There were no epistatic effects expressed consistently across all three diagnostic groups.

Discussion: These data demonstrate, for the first time, that the DAAO and G72 genes interact non-additively to modulate cortical function during executive processing in a middle temporal region which has been implicated in psychosis in previous studies. In addition, the nature of this interaction appears to be different in patients relative to healthy controls, with significantly stronger epistatic effects in the former than the latter. Diagnosis-specific epistatic effects may reflect the alteration in glutamate function associated with the disorders and suggest that future genetic studies would benefit from assessing the DAAO and G72 genotypes together rather than either in isolation.

doi:10.1016/j.schres.2010.02.620

Poster 127
EXPLORING THE NEURAL BASIS OF GAZE PERCEPTION ERRORS IN SCHIZOPHRENIA

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Background: Previous research has suggested that patients with schizophrenia might show a self-referential bias in judging the direction of eye gaze and are more likely than controls to misinterpret averted gaze as directed at them, despite being as accurate at controls at correctly identifying direct gaze.

Methods: In the current study we wished to explore whether this bias was associated with activations in different brain regions in the controls and patients. Schizophrenia patients with prominent referential delusions and healthy controls with no history of mental illness were shown faces while in the MRI scanner and asked to judge whether the person in the picture was looking directly at them or looking away. The faces all had neutral expressions and the only changes were in the gaze direction. Each face was shown for 500 ms and then masked.

Results: Both groups showed similar levels of accuracy in judging direct and averted gaze. Our contrast of interest was the difference between false positive errors (when the averted gaze was incorrectly judged as being direct gaze) vs the true negatives (when the averted gaze was corrected judged as averted). There were a number of differences in brain activity in this contrast between the two groups. Patients showed greater activity than controls in the left ACC, right angular gyrus, right middle temporal gyrus, and parts of the right medial frontal lobe. Controls showed greater activity in the right temporal pole, right medial temporal lobe, left hippocampus, and bilateral orbito-frontal- cortex.

Discussion: Differences in brain activity associated with these false positive errors might be related the associated self-referential bias seen in patients.

doi:10.1016/j.schres.2010.02.622
Background: Working memory (WM) deficits occur in both Schizophrenia and patients with Bipolar Psychosis, however the neural substrates of these deficits are unclear. While the medial prefrontal cortex (mPFC) plays an important role in cognitive and other psychological functions known to be disturbed in the psychoses, previous studies have not explicitly compared mPFC activity in these two disorders.

Methods: We used functional MRI (fMRI) to study the specificity of mPFC activity during a verbal WM (N-back) task in 10 patients with schizophrenia (SZ), 12 with Bipolar Disorder with Psychotic Features (BPP), and 19 controls (NC). We assessed the effect of time (first vs. second stimulus “run”) on WM performance and mPFC activity, as well as dorsolateral prefrontal cortical (DLPFC) activity.

Results: NC had consistent 2-back performance across both runs. SZ and BPP patients showed significantly reduced performance on the 2-back task relative to controls, with BPP performing significantly worse than controls during the first run and SZ significantly worse than controls during the second run. There was a non-significant trend for better performance in SZ than BPP in the first and worse in the second run. NC demonstrated mPFC suppression and DLPFC activation in both runs, while 2-back performance correlated with activity in both regions during the run 1 only. BPP, on the other hand, exhibited a trend toward mPFC hypoperfusion during the first run, with normalization of mPFC activity and improvement in TM performance during the second run. SZ showed mPFC suppression during the first and activation during the second run, neither correlating with 2-back performance. Further, BPP and SZ activated DLPFC during both runs, but in contrast to NC, there was no correlation with 2-back performance.

Discussion: In NC there is a tight correlation between 2-back performance, mPFC suppression and DLPFC activation, but in the first run only. Once the encoding process becomes automatic, mPFC and DLPFC are not essential for maintaining the performance level in the run 2. BPP patients don’t reach the encoding automaticity during the course of two 2-back runs. However, their performance improvement is correlated with the capacity to correct the mPFC inhibition by bringing it to the NC range. SZ performance is not correlated with mPFC inhibition or DLPFC activation in either run. Even though 2-back performance is better compared to BPPs in the first run, SZ patients do not automatize in the second run and instead demonstrate decline in the performance. Our exploratory data has shown that in SZ run 1 performance is tightly correlated with the anterior cingulate (AC) and likely contributing to better performance when compared to BPP patients. This is the first report, to our knowledge, to demonstrate that mPFC activity differs over the course of an experiment between SZ and BPP patients, and that activity is related to WM performance in NC and BPP groups, but not to the SZ. In contrast to controls who utilize mPFC and DLPFC during the task acquisition, BPP performance is closely linked to mPFC only, while SZ performance relies tightly on the AC activation. The latter is not sufficient to ensure adequate performance level in the second run, nor the automatization of the encoding process.

doi:10.1016/j.schres.2010.02.623

Poster 128
MEDIAL PREFRONTAL CORTICAL ACTIVATION DURING WORKING MEMORY DIFFERENTIATES SCHIZOPHRENIA AND BIPOLAR PSYCHOTIC PATIENTS: A PILOT STUDY

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Discussion: activated DLPFC during both runs, but in contrast to NC, there was neither correlating with 2-back performance. Further, BPp and SZ suppression during the first and activation during the second run, WM performance during the second run. SZ showed mPFC first run, with normalization of mPFC activity and improvement in hand, exhibited a trend toward mPFC hypersuppression during the second run. BPp, on the other hand, demonstrated mPFC suppression and DLPFC activation, but in the second stimulus “run”) on WM performance and mPFC activity, as well as dorsolateral prefrontal cortical (DLPFC) activity.

Results: NC had consistent 2-back performance across both runs. SZ and BPP patients showed significantly reduced performance on the 2-back task relative to controls, with BPP performing significantly worse than controls during the first run and SZ significantly worse than controls during the second run. There was a non-significant trend for better performance in SZ than BPP in the first and worse in the second run. NC demonstrated mPFC suppression and DLPFC activation in both runs, while 2-back performance correlated with activity in both regions during the run 1 only. BPP, on the other hand, exhibited a trend toward mPFC hypoperfusion during the first run, with normalization of mPFC activity and improvement in TM performance during the second run. SZ showed mPFC suppression during the first and activation during the second run, neither correlating with 2-back performance. Further, BPP and SZ activated DLPFC during both runs, but in contrast to NC, there was no correlation with 2-back performance.

Discussion: In NC there is a tight correlation between 2-back performance, mPFC suppression and DLPFC activation, but in the first run only. Once the encoding process becomes automatic, mPFC and DLPFC are not essential for maintaining the performance level in the run 2. BPP patients don’t reach the encoding automaticity during the course of two 2-back runs. However, their performance improvement is correlated with the capacity to correct the mPFC inhibition by bringing it to the NC range. SZ performance is not correlated with mPFC inhibition or DLPFC activation in either run. Even though 2-back performance is better compared to BPPs in the first run, SZ patients do not automatize in the second run and instead demonstrate decline in the performance. Our exploratory data has shown that in SZ run 1 performance is tightly correlated with the anterior cingulate (AC) and likely contributing to better performance when compared to BPP patients. This is the first report, to our knowledge, to demonstrate that mPFC activity differs over the course of an experiment between SZ and BPP patients, and that activity is related to WM performance in NC and BPP groups, but not to the SZ. In contrast to controls who utilize mPFC and DLPFC during the task acquisition, BPP performance is closely linked to mPFC only, while SZ performance relies tightly on the AC activation. The latter is not sufficient to ensure adequate performance level in the second run, nor the automatization of the encoding process.

doi:10.1016/j.schres.2010.02.623

Poster 129
ALTERED DEFAULT-MODE NETWORK ACTIVITY IN SCHIZOPHRENIA: A RESTING STATE fMRI STUDY

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Background: While functional MRI and PET studies have shown altered task-related brain activity/activation in schizophrenia, more recent studies suggest that such differences might also be found in the resting state, i.e. when subjects do not perform a cognitive task. Here, we used independent component analysis (ICA) to analyse resting state fMRI data to compare connectivity of the default mode network (DMN), a set of spatially distributed areas implicated in non-task-driven spontaneous cognition between patients with schizophrenia and healthy controls.

Methods: We obtained resting state fMRI series (3 Tesla, T2* weighted EPI, 3x3x3 mm resolution, 45 slices, TR 2.55s, 210 volumes) in 16 schizophrenia patients (mean age 29.4a±6.5), on stable antipsychotic medication and 18 healthy controls (26.7a±2.8), matched for age, gender, and handedness. Subjects were asked to lie in the scanner keeping their eyes closed with no further specific instructions. Data were pre-processed using SPM5 (motion correction, co-registration/normalization and smoothing). We then applied FSL MELODIC software to perform a probabilistic Independent Component Analysis (pICA) yielding 30 independent components. Our method reliably identified a DMN component in every patient and control, and the groups showed mostly overlapping distribution in PCC, medial prefrontal / ACC and bilateral parietal areas. We found significant differences (p < 0.05 FWE corrected) in the anatomical pattern of areas with healthy controls showing larger extent of the network prefrontal and parietal areas, including left middle frontal gyrus (BA9), bilateral medial frontal gyrus (BA40), and left precuneus (BA7) but larger effects in schizophrenia patients in the right amygdala, left orbito-
Poster 130
NEURAL BASIS OF SELF-REFERENTIAL PROCESSING IN PSYCHOSIS PRONENESS

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Background: Schizophrenia has been conceptualized as a disorder of the self. Self-disturbance is thought to play a key role in patients’ maladaptive social functioning, and in the genesis of positive psychotic symptoms such as hallucinations and delusions. Functional neuroimaging has identified a number of regions located in the midline of the human cerebral cortex (cortical midline structures, CMS), specifically in anterior and posterior portions of the cingulate gyrus (ACC, PCC), and adjacent medial prefrontal cortex (MPFC), which are engaged during self-referential cognitive or emotional tasks. Abnormalities within this network have been reported in schizophrenia patients and in individuals at genetic risk relative to psychotic symptoms such as hallucinations and delusions. Functional connectivity in schizophrenia, which are independent of task-related cognitive activity. It supports models of prefrontal cortical dysfunction in the absence of specific cognitive activity. Our correlations with psychopathology, although preliminary, suggest a direct relation to psychopathological items, which would support a clinical significance of altered DMN activity. This work was partially funded through an EU grant (FP6; MC RTN: EUtwinS network).

doi:10.1016/j.schres.2010.02.624

Poster 131
MATCH AND MISMATCH IN AUDITORY FEEDBACK TO SPOKEN WORDS. AN FMRI STUDY

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Background: Self-monitoring is a basis of higher cognitive functions like planning and supervising own actions and includes the anticipation of perceptual consequences of intended acts. Patients with schizophrenia (and more so auditory hallucinators) may fail to distinguish between internal or external sources when listening to their own or alien voices (Johns 2001, Allen, 2007,). Frith (1992) proposed that the comparison has been assessed in studies on self- and speech-monitoring (e.g.: Shergill 2005, Allen, 2007, Kumar 2008). Here, in a speech-task with unchanged and pitch-shifted immediate auditory feedback we investigated neural correlates of self-monitoring in an fMRI study.

Methods: 27 healthy subjects (14 m, 34.0y (+/-10.7)) and 8 patients with schizophrenia (7 m, 39.1y (+/-8.3)) / 1f, 27 y; five with auditory hallucinations) were assessed in three conditions: Subjects had to “speak aloud” words presented visually on a computer screen (750 ms duration, Presentation, Neurobehavioral Systems Inc.). While speaking, subjects listened to their own voices (Resonance Tech. Headphone) in either a non-shifted (normal voice) or shifted (lowered in pitch by 4 semitones, VoicePro, TC-Helicon) mode. In the second condition, subjects were asked to “silently read” the words (baseline). Words within the shift and non-shift conditions were randomized. Subjects were presented two runs of 22 shift, 22 non-shift and 22 read only trials. Functional MRI-data were acquired using a clustered acquisition sequence on a 3 T Siemens scanner (TR 4s,
acquisition delay 2 s., TE 30 ms, FoV 12 cm, 64x64x32 voxel, slice thickness 3.3 mm, distance factor 10%, flip angle 90°). Data and statistical analyses were conducted with SPM8. Activations were detected by using t-tests for the following contrasts: shift > non-shift, non-shift > shift; shift > reading, non-shift > reading. Additional between subject analyses were conducted by using independent 2-sample t-tests.

**Results:** Between subject analyses (controls vs. patients, p < .001 unc.) in the shift > non-shift contrast revealed increased BOLD activation in the anterior right STG (BA38) in patients. Furthermore, we found increased activation in controls in the left MTG in the non-shift > reading contrast. In patients, within subject comparisons for the shift > non-shift contrast revealed increased activation in the left anterior MTG (BA21) (p < .001 unc.) whereas in the non-shift > shift contrast we found activation in the right MTG (BA21) (p < .001 unc.). Both baseline contrasts (shift > reading, non-shift > reading) in controls revealed robust BOLD effects (p < .05 FWE) with peak activations in the left STG (BA22). In patients we found activation (p < .001 unc.) in the left precentral gyrus (BA6) for shift > reading and in the STG (BA22) for non-shift > reading contrasts.

**Discussion:** In our study, we found robust speech versus reading contrasts which were largely comparable between shift and non-shift conditions in patients and controls. Direct comparisons of shift versus non-shift conditions in patients vs. controls showed increased right anterior STG activation in Patients. In patients, the shift-condition was associated with left anterior MTG activation. Overall, our results are not fully compatible with the theory of auditory information processing on prediction deficits in patients with schizophrenia but may also include aspects of match and mismatch processing. Our results will have to be replicated in a larger sample and with increased within-condition power.

**doi:** 10.1016/j.schres.2010.02.626

**Poster 133**

**AN OPTIMIZED FMRI PULSE SEQUENCE FOR MEASURING BOLD SIGNAL CHANGE IN SUBCORTICAL BRAIN AREAS**

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**Background:** Many mental health problems probably include diseases of subcortical areas such as the basal ganglia and their dopaminergic neuronal projections. Increasingly, functional magnetic resonance imaging revealing Blood Oxygenation Level Dependent (BOLD) signal changes revealing sites of increased neuronal activation is used to investigate the neurobiological origins of such disabling diseases. Nevertheless, only a limited number of studies report alterations of neuronal signaling in subcortical areas in schizophrenia. This is probably not due to the fact that subcortical areas are unaffected, as deep brain structures are difficult to investigate using standard fMRI measurements. Rather, the widely used echo planar imaging (EPI) pulse sequence at relatively low spatial resolutions (~4x4x4 mm³) covering the whole brain at once is known to be biased to cortical signal change detection. It is not optimal to detect BOLD signal changes in the basal ganglia for several reasons. First, due to the large distance from the send and receive coils, signal to noise is poor. Second, as EPI scanning was originally designed mainly for cortical signal change detection long echo times are often used, further reducing signal to noise in subcortical areas. Third, higher acquisition resolutions known to be superior when using scanners with higher field strengths might reveal the detailed functional representations in the small basal ganglia nuclei as they are known from animal research. This could demonstrate essential aspects of basal ganglia dysfunction that remain obscure to standard EPI measurements. Finally, high cardiac and respiratory noise rhythms in the BOLD signal in subcortical areas are known to cause further reduction in signal to noise.

**Methods:** Here we present a functional MRI pulse sequence at 3 T which deals with most of the above problems, and demonstrate that it is possible to detect basal ganglia signal changes. High-resolution (2x2x2 mm³) EPI and parallel imaging (SENSE) was used to keep bandwidth relatively low (and thus SNR high). This was combined with physiological rhythm correction (RETROICOR) during post processing, and optimized registration techniques.

**Results:** Using an eye movement countermanding task, we could pick up signal changes in the striatum, putamen, superior colliculus and other subcortical and cortical brain areas at a detail previously not achievable using standard EPI sequences.

**Discussion:** This technique might enable further investigations into mechanisms underlying the development of schizophrenia and other mental health problems in subcortical areas, and remove the methodological bias towards cortical signal change detection as is often observed in fMRI studies of psychiatric illnesses.

**doi:** 10.1016/j.schres.2010.02.628
Poster 134
DYSFUNCTIONAL NEURAL NETWORKS OF TIMING IN SCHIZOPHRENIA: AN ALE META-ANALYSIS

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Background: Over the last decade functional neuroimaging and electrophysiological data have showed that there may be thalamic-cortico-striatal Networks related with interval timing (Buhusi et al., 2005). Timing task and its neural networks have been strongly related with several other cognitive functions (attention and working memory) that may be critical impaired in schizophrenia. Two own PET-O15-water studies in schizophrenia suggested a dysfunctional pattern of underactivated supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPc), and parietal cortex in schizophrenia during an auditory attention and timing estimation task paradigm study (Ortuño et al., 2002, 2005). Our goals were, first to examine the hypothesis of the thalamo-cortico-striatal physiological timing network and, second to test if there is a dysconnectivity timing pattern in schizophrenia.

Methods: ISI Web of Science databases were searched through December 2009 using the keywords positron emission tomography and functional magnetic resonance Imaging cross-referenced with time estimation, timing OR time perception where * indicates a wild-card. A latter search was conducting for the second meta-analysis adding schizophrenia as keyword. Papers were selected following the criteria of a similar ALE meta-analysis previously conducted (Petacchi et al., 2005). Analyses were performed after recommendations from BrainMap (http://www.brainmap.org). We used MRICron software (http://www.sph.sc.edu/comd/orden/mricron/) to visualize ALE maps overlaid onto a high-resolution brain template generated by the International Consortium for Brain Mapping (Kochunov et al., 2002). We ran two separate ALE analyses of neuroimaging (fMRI and PET studies) activation of timing task studies. One, including neuroimaging studies only in healthy subjects and another that includes comparative studies between healthy subjects and schizophrenia patients.

Results: A final pool of studies for the meta-analysis consisted of 34 articles in healthy states and 3 articles in patients with schizophrenia. 477 resulting foci are were analysed in the first and 10 in the second study, respectively. The first meta-analysis replicated that timing studies of interval timing show significantly activations, most bilaterally on frontal (BA: 6,8,9,10,32), parietal (BA: 40), temporal (BA: 22, 37, 41) regions and the caudate, putamen and thalamus. The second meta-analysis showed a significantly (p<0.05) lower activation of right frontal regions: right supplementary motor area (BA 6), superior (BA 9), middle (BA 8 and10) frontal gyrus, left cingulate gyrus (BA 32), right parietal cortex (BA 39) as well as right Globus Pallidus, Putamen and Thalamus.

Discussion: Our ALE meta-analysis results replicate the findings of functional neuroimaging and electrophysiological studies suggest there is timing network that involves functionally specific cortical areas (cingulate, SMA, parietal) and subcortical areas. A dysfunctional implication of cortical (SMA, prefrontal and parietal) and subcortical areas characterize a dysconnectivity pattern in Schizophrenia.

doi:10.1016/j.schres.2010.02.629

Poster 135
THE HIS452TYR POLYMORPHISM OF THE 5-HT2A RECEPTOR GENE MODULATES ACTIVITY IN PREFRONTAL CORTEX DURING ATTENTIONAL CONTROL IN HEALTHY SUBJECTS

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Background: Attentional control allows flexible allocation of attentional resources to relevant stimuli while suppressing those that are less relevant. Several studies have demonstrated that the prefrontal cortex is crucially involved in attentional control processing. Furthermore, other evidence has suggested that serotonergic signaling modulates physiological response during cognitive processing. In this context, serotonin 5-HT2A receptors are abundantly expressed in prefrontal cortex. Recent studies have indicated that a single nucleotide polymorphism (SNP) of the 5-HT2A gene (His452Tyr, rs6314) is associated with differential protein expression. In particular, the T allele has been associated with abnormal 5HT2A signaling. Aim of the present study was to investigate with fMRI in healthy subjects the potential impact of 5-HT2A rs6314 on prefrontal activity during increasing levels of attentional control.

Methods: 93 healthy subjects (61 females; mean±SD age: 25.3±5; Hollingshead: 39.6±16.7; Handedness: 0.7±0.5; WAIS IQ: 110.6±10.6) performed the Variable Attentional Control (VAC) task during event-related fMRI at 3 Tesla, allowing to investigate brain activity during increasing demands of attentional control (low, intermediate, high). All subjects were genotyped and grouped for 5-HT2A His452Tyr (77 C/C and 16 T carriers). The two genotype groups were matched for gender, age, handedness, parental socio-economical status and IQ (p>0.5). SPM5 was used for imaging analysis.

Results: No effects of 5HT2A rs 6314 were present on behavioral performance. On the other hand, SPM analysis of imaging data indicated a main effect of increasing attentional load in parietal cortex, cingulate cortex, middle and inferior frontal gyrus. Furthermore, there was a main effect of genotype in middle and inferior frontal gyrus (BA 45, BA46 and BA 9) (p<0.001, FWE corrected for prefrontal cortex volume). No interaction between genotype and attentional control load was found. Post-hoc analysis revealed that subjects homozygous for the C allele were associated with lower BOLD signal in middle and inferior frontal gyrus relative to T carriers.

Discussion: These results suggest that individual genetic variability in the 5-HT2A receptor gene affects activity in prefrontal cortex during attentional control in a load independent manner, despite lack of behavioral effects. Therefore, it is possible that this 5-HT2A genetic variant may modulate background activity in prefrontal cortex during attentional control, which may interact with other variables in determining load associated activity during this cognitive process.

doi:10.1016/j.schres.2010.02.630
Background: Abnormalities in the frontal lobe are central to the pathology of schizophrenia and have been linked to negative symptoms and disinorganization. Functional neuroimaging studies report impaired frontal functioning in schizophrenia patients. However, the nature of these abnormalities is unclear, in particular whether they are affected by medication. Here we investigate frontal lobe function in medication naive, first episode schizophrenia patients in comparison to matched healthy controls. We previously showed that in healthy controls practice of a working memory task induces improved performance accompanied by a significant decrease in brain activation, especially in the dorsolateral prefrontal cortex (1). In the current study, we tested whether practice of a working memory task induces a comparable decrease in frontal brain activation in medication-naive schizophrenia patients. In addition we related the change of frontal activation to symptomatology.

Methods: First episode schizophrenia patients (SZ, n=35;32 medication naive) and matched healthy controls (HC, n=40) performed a Sternberg working memory task, while fMRI data were acquired. During the task, subjects had to indicate whether a letter was part of a memory set of five letters presented at the onset of each block. This memory set could either be novel (i.e. varying letters, Novel Task) or practiced (i.e. same letters throughout the task, Practiced Task). This latter set was also practiced for 20 minutes prior to scanning. The effect of practice was defined as the difference between novel and practice, both on behaviour and fMRI signal. Data acquisition was performed on a 1.5 Tesla scanner using a navigated 3D-PRESTO pulse sequence with 384 dynamics. Pre-processing and analysis were performed using SPM5. We used Regions of Interest (ROIs) determined in an independent sample from an earlier study of our group using the same task (2). The ROIs were left fusiform gyrus, left and right superior parietal cortex, anterior cingulate cortex, and the left prefrontal cortex.

Results: Practice significantly reduced reaction times for both SZ and HC (group by practice interaction $F(1,68)=.03$, $p=0.85$) but practice induced a significant larger increase in accuracy in SZ ($F(1,68)=5.88$, $p=0.02$). This was probably due to a ceiling effect in HC, as their accuracy for the Novel Task was already 94%. Practice significantly reduced brain activity in all ROIs in both groups (main effect of practice $F(1, 73)=322.55$, $p<0.001$). Practice induced a smaller drop in brain activity in all ROIs in both groups, but this effect was smaller in SZ, specifically in the left DLPFC. This deficiency was found to be correlated with the severity of negative symptoms. Our results therefore suggest that DLPFC function is deficient in the early phases of schizophrenia and cannot be attributed to the use of antipsychotics.

Discussion: In this study both HC and SZ improved performance of a working memory task with practice. Practice was associated with a reduction in brain activation in both groups, but this effect was smaller in SZ, specifically in the left DLPFC. This deficiency was found to be correlated with the severity of negative symptoms. Our results therefore suggest that DLPFC function is deficient in the early phases of schizophrenia and cannot be attributed to the use of antipsychotics.

doi:10.1016/j.schres.2010.02.631
Background: Abnormalities in the neurotransmitters glutamate and GABA have been implicated in schizophrenia. Alterations in the GABA system have been found in postmortem studies in the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC), where changes in pre- and postsynaptic markers have been found consistent with neurotransmitter deficits in specific classes of fast-spiking GABAergic interneurons. The NMDA receptor hypofunction hypothesis of schizophrenia suggests glutamate level changes in these regions, and in vivo magnetic resonance spectroscopy (MRS) studies have begun to report such findings. The goal of this study was to assess GABA and combined glutamate-glutamine (Glx) levels in these regions in vivo in schizophrenia.

Methods: We enrolled 26 patients (age 32 ± 9 years) with schizophrenia and 19 healthy controls (age 35 ± 13 years). Twelve patients were on stable doses of antipsychotic medication for at least 4 weeks, and 14 were unmedicated for at least 21 days. MRS data were acquired from the DLPFC (9.6 cc voxel, all subjects) and ACC (18.8 cc voxel, n = 18 patients, 12 medicated and 6 unmedicated; n = 14 controls). All spectra were recorded on a 3 T GE 'EXCITE' MR system using an 8-channel phased-array head coil. The edited spin echo difference technique followed by a frequency-domain nonlinear least-squares spectral fitting procedure was used to determine the two main outcome measures GABA and Glx, which were normalized to the internal water signal recorded simultaneously. Test-retest reliability using these methods was previously shown to be high (percent coefficient of variation or %CV was 5.2%, and intraclass correlation coefficient or ICC was 0.84 for GABA/water). Voxel volumes were segmented into gray and white matter and cerebrospinal fluid to assess possible group differences in these measures.

Results: Both main outcome measures showed the same rank order in both regions: unmedicated patients > controls > medicated patients. Levels were significantly or strongly trending higher in unmedicated compared to medicated patients. For example ACC GABA/water was 2.3 ± 0.4 and 1.7 ± 0.6 (unmedicated and medicated patients, respectively, units × 10⁻³, p = .04). P values were .03 for ACC Glx/water and .06 and .02 for these comparisons in DLPFC. Furthermore, unmedicated patients had significantly or strongly trending higher GABA/water and Glx/water in the ACC than controls (p = .04 and .07, respectively). Voxel segmentation into gray matter / white matter / cerebrospinal fluid did show lower gray matter content of the voxels in the patient group, but correction for this difference with ANCOVA did not affect these findings. The medicated and unmedicated patient groups did not differ on segmentation measures.

Discussion: These results suggest that antipsychotic medication may significantly lower frontal GABA and glutamate levels. They also suggest possible GABA and glutamate elevations in patients in the unmedicated state compared with healthy controls. Relationships of these preliminary MRS data with postmortem GABA findings and the NMDA receptor hypofunction hypothesis will be discussed. Additional studies with longitudinal within-subject assessment of medication status effects will be needed to further investigate these preliminary data. Supported by the Dana Foundation and the Lieber Center for Schizophrenia Research.

doi:10.1016/j.schres.2010.02.633

Poster 139
MAGNETIC RESONANCE SPECTROSCOPY (31P CHEMICAL SHIFT IMAGING) IN MONOZYGOTIC Discordant TWINS WITH SCHIZOPHRENA SPECTRUM DISORDERS

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Background: Magnetic resonance spectroscopy (MRS) allows the quantification of brain metabolites in vivo, which can be assessed in different brain regions simultaneously applying 2D-chemical shift imaging (CSI). Previous studies using 31P-phosphorous MRS have shown alterations of phospholipid compounds and high-energy phosphates like ATP in prefrontal and temporal regions of the brain in schizophrenia. It remains unclear, however, whether some of these metabolic alterations might reflect genetic susceptibility or effects related to the onset or progression of the disease. We used a twin design investigating monozygotic (MZ) twins discordant for a (psychotic) schizophrenia spectrum disorder (i.e. schizophrenia, schizoaffective disorder, or schizopreniform psychosis), and a healthy control twin group.

Methods: We investigated 7 discordant MZ twin pairs (3 male, 4 female; mean age 29.9, SD 7.9) with a DSM-IV and ICD-10 diagnosis of schizophrenia (3 pairs), acute schizophreniform psychosis (1 pair), or schizoaffective disorder (3 pairs) and 7 age- and gender-matched healthy control twins (mean age: 29.1, SD 10.2).

Results: Affected MZ twins compared to healthy control twins only showed higher ATP concentration in the right insula and posterior medial cerebellum. Unaffected twins compared to healthy control twins, however, had higher concentrations of both high-energy phosphoates (ATP and phosphocreatinine) as well as phospholipid markers PME and PDE in the left prefrontal cortex (and for ATP also in the left anterior temporal cortex). As the latter pattern was similar to previous findings in (unmedicated) schizophrenia patients, we compared the unmedicated schizophrenia singletons to the healthy control singletons, which revealed a similar pattern of increased ATP in left prefrontal and anterior temporal cortices.

Discussion: Our results are the first demonstration of potentially genetically mediated effects of prefrontal metabolic abnormalities of PME, PDE, and ATP in unaffected co-twins of MZ twins with schizophrenia spectrum psychotic disorders. The focal left prefrontal abnormalities are consistent with patterns seen in (unmedicated) schizophrenia patients. The failure to show this alteration in the affected MZ twins might be related to antipsychotic medication, which appears to lead to a (at least partial) normalisation of these metabolic abnormalities. This would, however, suggest that despite the genetic effects these markers are strongly influenced by medication and/or clinical variables. On the other hand, it would support the use of these parameters as risk markers for schizophrenia.

doi:10.1016/j.schres.2010.02.634

Poster 140
MISMATCH NEGATIVITY IS REDUCED IN SCHIZOPHRENA PATIENTS WITH DEFICIT SYNDROME

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Background: Across the different models of psychopathology related to schizophrenia, negative symptoms, i.e. affective flattening, alogia...
Background: One of the cognitive deficiencies consistently found in schizophrenia patients relates to working memory. Increases in frontal theta oscillations (between 4-8 Hz) in the electroencephalogram (EEG) have frequently been related to working memory. Previous studies have demonstrated attenuated increase in theta oscillations in schizophrenia (Schmiedt et al., 2005). Evoked activity largely reflects activity driven directly by stimuli whereas induced activity largely reflects ‘top down’ attentional or executive processes. Here, we set out to study whether theta oscillations evoked or induced after onset of the working memory related stimuli are deficient in patients compared with controls.

Methods: We tested 22 healthy controls and 18 patients with schizophrenia in a concurrent EEG and fMRI paradigm. The N-back task consisted of 30 second blocks of 0-back, 2-back or rest, totalling 32 target (stimuli to respond to with button-press) and 32 non-target (stimuli to ignore) trials for each condition. EEG artefacts related to scanning and heartbeat were removed using Brain Vision Analyzer and EEGlab software. Then, epochs were extracted around stimulus onset and evoked and induced theta was calculated for electrodes Fz, Fcz, Cz and Pz. Area under the curve (AUC) values in post-stimulus period for evoked and induced theta were extracted for an ANOVA containing 3 ‘within’ factors (4 Conditions [targets and non-targets in 0-back and 2-back conditions], 2 Measures [evoked, induced] and 4 Electrode Sites [Fz, Fcz, Cz and Pz]) and 1 between subjects factor (Group [patients and controls]).

Results: We found significant main effects at p < 0.05 for Condition, Measure and Group, as well as interaction effects between Measure and Group, Condition and Measure. Post hoc testing revealed that AUC values for induced post-stimulus theta were higher for targets compared with non-targets in both 0-back and 2-back conditions in multiple channels (p < 0.01), and higher in controls than in patients in Fcz (p < 0.01). This effect was absent for evoked theta (p > 0.05).

Discussion: We have shown that schizophrenia patients show less induced theta following the onset of a target, both in 0-back and 2-back condition, compared with controls. Previous studies have detected a deficiency in theta power, but here we show that induced rather than evoked theta is related to previously shown deficiencies in working memory in patients with schizophrenia. Furthermore, we have shown that this effect remains identifiable in the lower signal to noise conditions of EEG recording in a 3 T MR scanner. Future directions are to combine these results with the concurrently acquired fMRI BOLD data.
increased for the possibility of interventions to prevent onset, or to minimize severity of psychosis. The aim of this study is to investigate whether P300 could help to identify those who are particularly vulnerable to psychosis.

**Methods:** Eighteen-channel EEG was recorded from 30 antipsychotic-naive subjects at UHR for psychosis meeting the criteria defined by Melbourne group, and age-, gender- and education-matched 20 healthy volunteers. Auditory oddball paradigm was used to obtain P300 potential.

**Results:** Performance measures were comparable between the groups except for slower reaction times in UHR group (p = 0.001). Compared to controls P300 amplitude was significantly reduced in UHR group (p = 0.011). This amplitude reduction was more prominent over the central and parietal regions than those in frontal region (p = 0.01). For P300 latency, a significant electrode by group interaction revealed that in UHR group P300 latency was longer than those in controls over the parietal region, but not over the frontal and central regions (p = 0.008).

**Discussion:** Our results support the notion that P300 abnormality is evident before the first manifestation of psychosis and therefore might be a vulnerability factor for the development of schizophrenia.

doi:10.1016/j.schres.2010.02.637

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**Poster 143**  
**AUDITORY HALLUCINATIONS AND THE P3A: ATTENTION SWITCHING TO SPEECH IN SCHIZOPHRENIA**

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**Background:** It has been suggested that study individual symptoms in schizophrenia, rather than global syndromes, may elucidate more focused information on the nature of this disease. Auditory hallucinations (AH) are a pervasive symptom; we examined the impact of AHs on pre-conscious attention switching.

**Methods:** Participants were schizophrenia patients with (HP; n = 12) and without auditory hallucinations (NP; n = 12) and healthy controls (HC; n = 12). All participants were exposed to a train of frequent (p = 0.9) auditory single-vowel phonemes /a/ randomly interrupted by rare (p = 0.1) deviant phonemes /o/ while EEG was recorded from 32 channels. Patients retrospectively reported the intensity, clarity and frequency of their hallucinations during the test paradigm.

**Results:** There was a main effect of group whereby hallucinating patients showed significantly smaller P3a amplitudes than healthy controls. Further analysis showed that at fronto-central regions, hallucinating patients showed a reduced P3a compared to healthy controls and non-hallucinating patients.

**Discussion:** Schizophrenia patients with AHs show reduced attention switching (as indexed by the P3a) to speech changes compared to patients without AHs and healthy controls. This may suggest global deficits in the processing of relevant incoming auditory information in this sub-group.

doi:10.1016/j.schres.2010.02.638

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**Poster 144**  
**ATTRIBUTION BIAS AND EVENT-RELATED POTENTIAL USING A REAL-TIME BASED ATTRACTION EXPERIMENT (THE ‘COLOUR TEST’)**

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**Background:** The internal attribution for positive events and the external attribution for negative events called as the “externalizing bias” (or the self-serving bias), and among the external attributions, the more attribution for others than for situations for negative events called as “personalizing bias”. Those attribution biases have been suggested as important cognitive processes in developing and maintaining paranoia. This study aimed to investigate the psychophysiological evidences of the externalizing and the personalizing bias using a ‘colour test’.

**Methods:** The colour test developed as a real-time based experiment which could measure three types of attribution (self-other-situation). Twenty healthy controls were informed that they would participate in a color recognition game with other two participants. During the game, they were asked to attribute the cause of the win or the loss to self, others or the situation (level of difficulty of the game). ERP were recorded during the task using a 64-channel Neuroscan system.

**Results:** P3 amplitudes of internal (self)-attribution for negative events were larger than that for positive events in frontal and central channels (reflecting externalizing bias). P3 amplitudes of situation-attribution for negative events were larger than other-attribution in frontal channels (reflecting personalizing bias).

**Discussion:** These findings suggested that unbiased attributions compared with automatic process of biased attributions might require higher-order cognitive controls.

doi:10.1016/j.schres.2010.02.639

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**Poster 145**  
**IMPAIRED GENERATION OF VISUAL MISMATCH NEGATIVITY IS LINKED TO THE DEFICIT SYNDROME IN SCHIZOPHRENIA**

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**Background:** Mismatch negativity (MMN) is an electrophysiological evoked response to a stimulus change or novelty in a series of standard sensory stimuli. MMN reflects events on the border of the pre-attentive sensory and cognitive information processing. The generation of this amplitude deflection with the latency between 100-250 msec in the auditory event related potentials is deficient in schizophrenia(1). It appears to be associated with decreased social functioning of patients (2). The deficient MMN among patients with schizophrenia is also present in evoked responses after motion visual stimuli (vMMN). Because the significance of vMMN is still uncertain, we hypothesized that it may be related to a specific subtype of schizophrenia.

**Methods:** We investigated the ERP to visual motion stimuli in a group of 24 patients with the ICD 10 diagnosis of schizophrenia of schizoaffective disorder and a matched group of healthy controls. The median age of patients was 26 years and the mean duration of schizophrenia in the group was 7.1 years. The method for eliciting and recording event related potentials to motion visual stimulation was described elsewhere (3). The area under curve (AUC) differences between responses to standard and deviant stimuli were computed and their difference was used for the assessment. The global severity ratings of Schedule for the Deficit Syndrome (SDS) assessed by an experienced psychiatrist were used to categorize patients into Deficit (N = 13) and Non-deficit (N = 11) subgroups. The MMN in midline and bilateral occipital leads were compared between patients and their matched controls in Deficit and Non-deficit subgroups.

**Results:** The significant MMN differences to controls in the midline leads with the exception of Oz were present in the subgroup of patients with the severity rating greater than 1 in the severity categorization of SDS. There were present no significant differences from controls in the non-deficit subgroup, that did not score on the SDS severity rating. Significant differences in vMMN between severity-defined deficit and non-deficit groups were confirmed in frontal (t = 3.79; p = 0.001) and central (t = 2.19; p = 0.0396) midline leads.

**Discussion:** Visual mismatch negativity deficit in schizophrenia, in analogy to auditory MMN deficit, is associated with poor social functioning. Our data suggest that it may be linked to deficit syndrome in schizophrenia. The visual MMN deficit in schizophrenia may be interpreted as an index of a core cognitive dysfunction common to different sensory inputs in a schizophrenia subgroup, which may be manifested by cognitive and negative symptoms and requires different treatment approach. References: Umbricht D, Krljes S Mismatch negativity in Schizophrenia: a meta- analysis Schizophrenia Res 2005;76:320-8 Light GA, Braff DL Mismatch negativity deficits are associated with poor functioning in schizophrenia patients, Archives Gen Psychiatry 2005;62:127-36 Urban A, Kremlaček J, Masopust J, Libiger J Visual mismatch negativity among patients with schizophrenia, Schizophrenia Res 2008;102:320-8.

**Poster 146**

**Mismatch Negativity to Duration Deviants in First Episode Psychosis and in the Prodomome**

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**Background:** Reduction in an early pre-attentive measure of auditory change detection, mismatch negativity (MMN), is one of the most consistent findings in schizophrenia. In a recent study, our group showed that a reduced MMN to changes in the duration and intensity of Background sounds is evident early in the course of the illness whereas reduced MMN to changes in the pitch of sounds is evident only in patients with longer illness duration. The aim of this study was to determine whether duration MMN is also reduced in first episode psychosis and those at ultra-high risk of developing a psychotic disorder, some of whom were in the prodromal phase.

**Methods:** Of 63 young adults (mean age 19+/-0.34 years, 20 male) who volunteered for the study, 42 were outpatients of a mental health service focussed on identifying and treating young people at risk of developing psychosis. Of these, 12 met criteria for a first episode psychosis (FEP: mean age 21+/-0.31 years, 6 male), and the remaining 30 met criteria for being at ultra-high risk of developing psychosis (UHR: mean age 17+/-0.34 years, 9 male). Six of the UHR group made a confirmed transition to schizophrenia (UHR-T) in the follow-up period and 20 did not (UHR-NT) with the outcomes for 4 unknown. 21 healthy participants without a personal history of mental illness or a first or second-degree biological relative with a history of a psychotic disorder made up the control group (CON: mean age 20+/-0.24 years, 6 male). ERPs were recorded from Fz, Cz and the mastoids with a nose reference in to standards and deviants delivered in two separate tone sequences (ISI = 600 ms), one where standards (92.5%) were 50 ms and deviants 100 ms and another where the stimulus duration of standards and deviants was reversed. MMN (deviant minus standard ERP) was derived for short and long duration sounds from these 2 sequences.

**Results:** MMN amplitude to long duration sounds was significantly reduced in both the FEP group and the UHR group relative to CON. In addition, the peak latency of MMN was increased in the FEP group relative to controls. Similar results were evident for the short duration sounds but the group differences were not as robust and did not survive correction for group differences in mean amplitude of standard ERPs measured over the same interval as MMN. There was also evidence that the P3a following MMN was reduced in the FEP and UHR groups. Although the numbers were too small in the UHR-T group for statistical comparisons, visual inspection of the distribution of MMN across groups revealed that all of those who later developed schizophrenia (UHR-T group) produced MMNs that were smaller than the median MMN amplitude of CON and were very similar to FEP, whereas UHR-NT exhibited greater overlap with CON.

**Discussion:** The results indicate that MMN to duration deviants is not only reduced and delayed in first episode psychosis but is also reduced in those young people identified as at risk of developing a psychotic disorder and furthermore provide preliminary evidence that reduced duration maybe a marker of the prodromal phase.

**Poster 147**

**ERP Abnormalities During Semantic Processing in Adolescents At-Risk for Psychosis**

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**Background:** Self-reported psychotic-like experiences in adolescents are associated with a 5 to 16 fold increased risk of clinical psychotic disorder in adulthood. A growing body of research suggests similar impairments and risk factor profiles for adolescents with psychotic symptoms and patients with schizophrenia. Adolescence is an important age group for studying the developmental trajectory to psychosis since it is during this period when first psychotic symptoms are most likely to appear. Language processing deficits are among the most common clinical features of schizophrenia. The N400 ERP component is the most reliably identified index of semantic processing with the amplitude and latency of this component being reduced in patients and also in first degree
relatives of patients with schizophrenia and in individuals genetically at-risk for schizophrenia (Guerra et al., 2009).

**Methods:** Participants aged 11-13 years were recruited from schools in the North Kildare region using the 7-item Adolescent Psychotic-like Symptom Screener (APSS) (Kelleher et al., 2009) and interviewed using the Schedule for Affective Disorders and Schizophrenia for School-aged Children. Following the interview, 33 adolescents underwent EEG testing. Of these, 15 were considered to be at-risk for psychosis based on a score of two or more on the screening questionnaire. A comparison group of 18 adolescents who scored one or less on the screening questionnaire comprised the comparison group. While recording 64-channel EEG, the participants completed the semantic language task based on the original Kutas and Hillyard N400 paradigm (Kutas and Hillyard, 1988). Participants were presented with 66 sentences in which the last word was either congruous or incongruous with the preceding context. E.g. “Every year they held their annual dog”. The task was to indicate whether the sentences made sense or not. Thirty-eight sentences were semantically congruous and 28 were semantically incongruous.

**Results:** There were no significant group differences in accuracy and reaction time on the task overall. On comparing accuracy for congruous and incongruous sentences, there was a main effect for sentence type (p = 0.0001). A multivariate ANOVA revealed significant group differences (p < 0.05) in overall amplitude at FP2, and at TP10. Significant group differences (p < 0.005) were also found for amplitude at TP10 on the incongruent incorrect condition, (p = .005), with the at-risk yielding larger amplitude than controls. On comparing congruent and incongruent correct responses, there were significant group differences (p < 0.05) at FP2, and significant group differences in the incongruent incorrect condition, with larger amplitude for controls. The laterality index revealed right lateralization for the at-risk group and left lateralization for the control group.

**Discussion:** The results of the current study revealed significant differences in language processing in adolescents at-risk for psychosis. The main effect of sentence type suggested that accuracy was reduced and reaction time was prolonged for incongruous sentences for both groups. On the task overall, the at-risk and control groups differed significantly in amplitude at fronto-parietal area FP2 and at tempo-parietal area TP10, with controls yielding higher amplitude at FP2 and the at-risk group showing higher amplitude at TP10 during the incongruent incorrect condition. The laterality index and the higher amplitude at TP10 for the at-risk group support the well established literature of reduced left hemispheric lateralization in individuals at-risk for schizophrenia on the P300 component (Bramon et al., 2008, Van der Stelt and Belger, 2005).

**Poster 148**

**CLONIDINE NORMALIZES SENSORMOTOR GATING DEFICITS IN CHRONIC PATIENTS WITH SCHIZOPHRENIA**

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**Background:** Evidence is accumulating that cognitive deficits form core features in schizophrenia. Several studies have shown improvements of prefrontal cognitive function by α2-agonists in schizophrenia. In the present study it was investigated whether clonidine (an α2-adrenoceptor agonist) could normalize sensorimotor gating deficits in schizophrenia.

**Methods:** Twenty male chronic patients with schizophrenia who were stable on their antipsychotic medication and twenty healthy male volunteers were assessed in an auditory prepulse inhibition of the startle reflex (PPI) paradigm on 5 occasions separated by a minimum of one week: once after oral administration of placebo and once after 25, 50, 75 and 150 μg of clonidine.

**Results:** Patients showed deficient PPI compared to the healthy controls in the placebo condition. Dosages of 25, 50 and 75 μg of clonidine significantly increased PPI in the patients compared to placebo, to such a level that it was no longer significantly different from the healthy controls.

**Discussion:** Since even low dosages of clonidine added to the current antipsychotic treatment of the patients were found to normalize their PPI deficits, it suggests that α2-agonists are potent agents to normalize sensorimotor gating deficits in schizophrenia. Since sensorimotor gating deficits are thought to underlie psychotic symptoms, these results have a potentially high clinical relevance.

doi:10.1016/j.schres.2010.02.643

**Poster 149**

**COMPARISON OF CLINICAL ROUTINE EEG AND QUANTITATIVE EEG IN FIRST EPISODE OF PSYCHOSIS AND AT-RISK MENTAL STATE INDIVIDUALS**

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**Background:** Intermittent focal or general pathological slow wave activity detected in routine clinical EEG assessment is more prevalent in patients with a first episode of psychosis (FE) and At-Risk Mental State (ARMS) than in normal controls and helps, in conjunction with psychopathological symptoms, to correctly predict a first psychotic episode in ARMS individuals. We hypothesize that ARMS individuals and FE showing intermittent focal or general slow wave pathology are characterized by an elevated global field power density in the delta and theta range, and that this finding predicts psychosis in ARMS individuals in a similar way as does routine clinical EEG assessment.

**Methods:** EEG of 27 FE and 32 ARMS subjects were recorded under resting state conditions with eyes closed. Two blinded neurologists analyzed the EEGs visually for presence of focal or general slowing and epileptiform discharges. Additionally, Fast Fourier Transform was performed utilizing Brain Vision Analyzer©. The power spectrum was subdivided into 7 bands and was plotted according to the presence and absence of intermittent slow wave activity. An optimal range was defined in order to quantify what in clinical EEG assessment is coined as pathological slow wave activity. Logistic regression analysis was performed to predict incidence of psychosis.

**Results:** Individuals with intermittent slow wave pathology were characterized by a range of increased theta activity (4 - 7 Hz) (t = −2.39, df = 20.1; p = .008). This range has been derived as optimal in terms of a maximal power difference between those with and without intermittent slow wave pathology and a minimal number of bins used. However, there was no power difference in this range with regard to a later onset of psychosis nor was any predictive power related to it.

**Discussion:** Focal or general slow wave pathology in ARMS individuals and FE is reflected by a range of increased power density related to the theta band, but the increase detected in global field analysis is modest due to its restricted manifestation in time and/or

doi:10.1016/j.schres.2010.02.642
Poster 150
RELATIONSHIP BETWEEN ELECTRODERMAL ACTIVITY AND HEART RATE IN PATIENTS WITH ACUTE SCHIZOPHRENIA

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Background: Patients suffering from schizophrenia are known to have an increased risk of cardiac mortality. Past studies showed impaired electrodermal activity and heart rate variability in schizophrenic patients compared with healthy controls. We aimed to examine the interrelation between these two autonomic parameters in patients with acute schizophrenia to better estimate the autonomic dysbalance.

Methods: We investigated 18 unmedicated patients (10 male, 8 female, all dextrals) suffering from paranoid schizophrenia and 18 healthy matched controls by recording their sympathetic skin response to an acoustic stimulus. This experiment was followed by a 30-minute rest condition in which we assessed heart-rate and skin conductance level (SSR). The nonlinear parameter cross-ApEn was calculated and the asymmetry-index was computed. Psychotic symptoms were quantified using the Positive and Negative Syndrome Scale (PANSS).

Results: Heart rate and skin conductance level were increased in patients compared to controls indicating autonomic dysfunction. There was a significant correlation between the subscale of positive symptoms of PANSS and an asymmetry-index of endosomatic electrodermal activity. Similarly cardiac parameters correlated with psychopathology. No overt interaction between SSR and cardiac parameters was observed.

Discussion: We suggest reduced hemispheric asymmetry for regulative electrodermal centers depending on the severity of positive symptoms in patients with schizophrenia. Furthermore, the absence of an association of SSR and cardiac parameters is suggestive for independent cerebral processing. Thus, the vagal domain might be predominately affected in the disease.

doi:10.1016/j.schres.2010.02.645

Poster 151
MEMORY ABNORMALITY (SEMANTIC AND VISUAL PATTERNS) IN SCHIZOPHRENIA

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Background: There is a number of data indicating to several aspects of memory activity abnormality in schizophrenia. It is necessary to investigate these abnormalities and its contribution in pathogenesis of schizophrenia.

Methods: Psychological pictogram method (Luria) as well as neuropsychological Luria’s scheme for visual memory were used. Qualitative and quantitative (retention productivity score (RPS, %); scores of spatial orientation of graphical stimulus (SOGS), delayed recall parameters, order of stimulus recall and volume of visual memory) characteristics were analyzed.

Results: The results demonstrated that the RPS was less in patients compared with controls (p < 0.01). Qualitative peculiarities of pictogram in patients showed disintegration between conception and reflecting its image. This disintegration indicated to disturbances of adequate actualization of information on the basis of past experiences. Among parameters of visual memory SOGS and volume of visual memory in patients was worse than in controls (p < 0.001). These data indicate to spatial characteristics image impairment in schizophrenia which is synchronous with its semantic component impairment.

Discussion: The obtained data demonstrate the impairment of basis process of information decoding in mnestic activity structure in schizophrenia as well by semantic aspect and visual one. This impairment is representative for important links in pathogenesis of schizophrenia connecting with disorder of mental activity organization.

doi:10.1016/j.schres.2010.02.646

Poster 152
NEUROPHYSIOLOGICAL DEFICITS IN PRODROMAL AND RECENT-ONSET SCHIZOPHRENIA

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Background: Deficits in automatic sensory discrimination as indexed by mismatch negativity (MMN) and P3a are well documented in schizophrenia patients. Deficits in those early preattentive processes could underlie deficits in more complex cognitive operations, as well as clinical symptoms and real-life functioning. Although there is ample evidence to suggest that MMN is impaired in chronic schizophrenia, its reduction has not been as robust in the early stages of the disease.

Methods: A repeated measures analysis of variance, with recording electrode (34 levels) as a within-subject factor and group (3 levels) as a between-subject factor, revealed that the amplitude of the MMN to duration deviants was reduced in recent-onset schizophrenia patients relative to healthy comparison subjects at all frontocentral recording sites. The at-risk group had significantly smaller MMN responses relative to the healthy comparison group at FC5, CP5, and T7 only. There were no group differences in the topography of mismatch responses. In contrast to previous reports showing no duration MMN deficits early in the disease process, significant and large effect size MMN reductions at Fz (d = 0.82) were observed in

doi:10.1016/j.schres.2010.02.644
the recent-onset group (M = -2.53, SD = 1.58) relative to the healthy comparison group (M = -3.97; SD = 1.92). Consistent with Brockhaus-Dumke et al.’s findings, the at-risk group’s MMN amplitudes at Fz (M = -3.29; SD = 1.49) were intermediate between those of the healthy comparison group and the recent-onset group, but these differences did not reach statistical significance (d = 0.40).

**Discussion:** We found robust and large effect size duration-deviant MMN deficits in recent-onset patients with schizophrenia. Individuals at risk for developing schizophrenia showed modest effect size MMN reductions relative to age-matched healthy comparison subjects. Future studies are needed to delineate the nature of MMN abnormalities early in the course of schizophrenia and to clarify whether these deficits reflect premorbid neuropathology or ongoing disease processes associated with illness progression.

doi:10.1016/j.schres.2010.02.647

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**Poster 153**

**VISUAL EVENT-RELATED P3A FROM PASSIVE TASK IN PATIENTS WITH SCHIZOPHRENIA**

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**Background:** The paradigm effects were not enough to be elucidated, even though it is well known that the event-related potential P300 was useful for exploring schizophrenia. Most P300 studies require the subject to actively respond to the target stimulus, but P300-like waveforms also can be elicited with 'passive' auditory paradigms in which an intentional discrimination between the two tones is not required.

**Methods:** This study was designed to examine that visual passive paradigm is appropriate for relatively uncooperative and admitted patients with schizophrenia. Visual 3 stimulus oddball paradigm was employed for admitted patients with schizophrenia (N = 50) and controls (N = 35). For the patients, the symptoms severity was assessed by Positive and Negative Syndrome Scale (PANSS). The paradigm was composed of standard (small circle, 80%), distractors (large rectangle, 10%), and targets (large circle, 10%) in a random manner once every 2 s. The passive task was presented first, and the subjects were instructed to look at the monitor in relaxed manner. The active task was presented in second session, and subjects were asked to press a mouse button to the targets. P3a to the distractors is elicited in passive and active tasks. P3b to the targets is elicited in active task.

**Results:** In active paradigm, the P3a and P3b were successfully acquired in all 35 control subjects (100%), but in only 35 patients (75%). In passive paradigm, the P3a was elicited for 45 patients (90%) as well as for 35 control subjects (100%). Passive P3a (F = 3.7, p = 0.08 in amplitude, F = 32, p < 0.0001 in latency), active P3a (F = 12.6, p = 0.001 in amplitude, F = 25, p < 0.0001 in latency), and active P3b (F = 2.6, p = 0.09 in amplitude, F = 14.3, p < 0.001) were smaller and delayed in patients with schizophrenia. With using mixed between (groups) and within (anterior-posterior and laterality) repeated measurement ANOVA, the P300 components showed topographic differences between two groups (F = 4.4, p = 0.03 in passive P3a, F = 5.7, p = 0.001 in active P3a, and F = 5.4, p = 0.01 in active P3b).

**Discussion:** Such a passive paradigm could be very interesting, since it can be used with non-compliant subjects such as young children, individuals with demented illness, and difficult psychiatric patients. However, conventional visual stimuli presented under passive viewing conditions can not elicit reliable P300 components because the attentional demands of a visual target in an oddball sequence are not compelling relative to the alerting qualities of an infrequent auditory target stimulus. Thus, passive and active paradigms can produce P300 waveforms because component outcomes are determined by the eliciting stimuli if only when their physical qualities coerce attentional engagement. The passive 3 stimulus visual P300 paradigm could be used for further exploring the patients with schizophrenia without or minimizing losing the information from some patients who are uncooperative with using only the conventional active P300 paradigms.

doi:10.1016/j.schres.2010.02.647

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**Poster 154**

**N2 EVENT-RELATED POTENTIAL IN SCHIZOPHRENIA – DIFFUSION IN TIME AND SPACE**

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**Background:** Recent theories of schizophrenia have proposed a fundamental instability of information processing on a neurophysiological level. This instability can be measured as an increase in EEG noise or an increase in latency variability of event-related potentials (ERPs). Another common observation is a more diffuse activation of the prefrontal cortex on cognitive tasks, which is thought to reflect compensatory processes required due to inefficient processing. In the present study we examined temporal variability as well as spatial distribution of the N2 component of the visual ERP as an index of prefrontal cortical function.

**Methods:** 28 patients with schizophrenia and 28 control participants matched for gender, age and education participated in the study. Patients were stable patients recruited from a rehabilitation setting with relatively preserved cognitive performance. Subjects performed a visual Go/Nogo task, while event-related potentials were obtained. Trial-to-trial latency variability was calculated with a Wavelet-based method developed by our group (Roth et al., 2007, Int J Psychophysiology). Spatial distribution was assessed using repeated measures ANOVA across frontal electrodes.

**Results:** On a behavioral level patients did not differ from control participants on reaction time. There was trend-level impairment on overall task performance in the Go-condition, but not in the Nogo condition. Patients with schizophrenia showed a reduced N2 amplitude at midline electrodes. Importantly, patients with schizophrenia had increased N2 latency variability at electrodes Fz and Cz in both task conditions (Go and Nogo). This increase in latency variability did not fully account for the amplitude reduction of the average ERPs. Regarding spatial distribution healthy participants showed a focused fronto-central N2 peak in both conditions. In contrast, patients with schizophrenia showed a more diffuse pattern with additional negative peaks over lateral electrodes.

**Discussion:** These results clearly show that schizophrenia is associated with higher temporal variability of ERPs as well as a more diffuse scalp distribution. The present study expands previous observations by demonstrating these effects on the same ERP component measure. This association suggests that the temporal variability might index a fundamental instability of information processing. Since there were few differences in task performance,
the more diffuse spatial distribution might represent processes compensating for this temporal instability.

doi:10.1016/j.schres.2010.02.649

Poster 155
DISTURBANCES IN EXECUTIVE CONTOL IN PATIENTS WITH SCHIZOPHRENIA

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Background: Patients with schizophrenia have difficulties with executive control functions. It has been suggested that these deficits in executive control are related to dysfunctional frontal and fronto-central activation patterns.

Methods: This study investigated the cortical organization of executive control in subjects with schizophrenia and healthy controls using event-related potentials (ERPs). ERPs were collected while subjects performed a visual Go/NoGo task which required them to inhibit successfully during the NoGo trials the potent response tendency that was established by the frequent Go trials. ERPs were acquired from 64 scalp electrodes referenced to the nose and digitized at 512 Hz. Epochs of 900 ms were analyzed including a 100 ms pre-stimulus baseline. The interstimulus interval was 1,000 ms. We compared the event-related brain potential (ERP) over the fronto-central scalp region (FCz) of 38 subjects with a diagnosis of schizophrenia and 23 matched healthy control subjects (18 - 55 years of age).

Results: There was a significant difference between the control subjects and the subjects with schizophrenia in correct rejection accuracy ($t_{\text{adj}} = -2.4, p = .02$). There was a 78% correct rejection rate in the control subjects and a 57% rate in the subjects with schizophrenia. Event-related potentials revealed the neurophysiological substrate of this dysfunction. The N2 enhancement in response to successful NoGo trials relative to Go trials was used as a metric of successful inhibitory control. There was a significant difference between the two groups in N2 peak amplitude ($t_{\text{adj}} = -4.8, p < .0001$), indicating a marked difference in cortical activation during early processing. In the control subjects, there was a pronounced N2 component in the NoGo trials as compared to the Go trials. This component was completely absent in the subjects with schizophrenia. In the later stages of processing (P3 time window), the P3 component was clearly present in the schizophrenic subjects, but it was still significantly less pronounced than in the control subjects ($p < .05$).

Discussion: Schizophrenic patients performed worse than the controls when the button press was to withhold response, indicating a failure of response inhibition. Both behavioral and ERP data demonstrate an impairment in executive control function in these patients. They exhibit deficient processing in a neuronal network in fronto-central regions. This deficit is most prominent in the earlier stages of executive control function, but exists also in the later stages.

doi:10.1016/j.schres.2010.02.650

Poster 156
THE MEDIAL PREFRONTAL AND ORBITOFRONTAL CORTESES INTERACT TO REGULATE NEURONAL ACTIVITY IN NUCLEUS ACCUMBENS SUBREGIONS

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Background: Impairments in behavioral flexibility are consistently observed in schizophrenia patients and likely result from a disruption in prefrontal cortical system function. The major prefrontal regions implicated in schizophrenia are the medial prefrontal cortex (mPFC) and, to a lesser extent, the orbitofrontal cortex (OFC). These regions carry out independent, but complementary forms of cognitive processing in changing environmental conditions. It has been demonstrated that the prefrontal cortex provides a topographic input to medium spiny neurons in the nucleus accumbens (NAc). The data presented here examines how afferents from the mPFC and OFC interact to regulate information processing within individual NAc neurons.

Methods: Male SD rats were anesthetized with chloral hydrate (400 mg/kg i.p.) and placed in a stereotaxic apparatus. Single unit evoked responses were recorded from neurons in the NAc core (AP: +1.5, L: +2.0, DV: -5.5-7.5) and shell (AP: +1.5, L: +1.0, DV: -5.5-7.5). Using concentric bipolar stimulating electrodes, alternating single-current pulses (0.25 msec; 0.2-1.0 mA) were delivered at a rate of 0.5 Hz to the OFC (AP: +3.0, L: +3.5, DV: -5.0) and mPFC (AP: +3.0, L: +0.5, DV: -5.0). Neurons receiving short latency (<25 msec), orthodromic, excitatory input from either the mPFC or OFC were examined.

Results: Here we demonstrate that although the mPFC and OFC innervate anatomically distinct sub-regions of the NAc, activity within these cortical regions is integrated to determine the output of individual NAc neurons. Thus, neurons located in the NAc core preferentially respond to activation of the OFC whereas neurons in the shell subdivision were more likely to be activated by mPFC stimulation. Furthermore, the excitatory response to OFC stimulation in the NAc core was dramatically attenuated by pre-stimulation (10-40 msec prior) of the mPFC. Similarly, the OFC was also able to inhibit mPFC-evoked responses in the shell of the NAc, albeit in a smaller proportion of neurons. Finally, lidocaine inactivation of the OFC resulted in a significant increase in the response to mPFC stimulation in the NAc shell suggesting a tonic suppression of mPFC evoked activity.

Discussion: Taken as a whole, these data demonstrate that the mPFC and OFC interact to negatively regulate evoked activity in the NAc and therefore exist in a delicate state of balance with respect to their influence on information processing within ventral striatal circuits. Such information is of relevance given the impairments in behavioral flexibility consistently observed in schizophrenia patients.

doi:10.1016/j.schres.2010.02.651

Poster 157
CORTICAL THICKNESS DEFICITS AND GAMMA BAND OSCILLATIONS IN SCHIZOPHRENIA

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Background: Synchronisation of oscillatory activity provides a possible mechanism for the communication within and between cortical areas of the brain. There is increasing evidence that the impairment of this mechanism may contribute to the functional connectivity of cortical networks that underlies the profound cognitive deficits and symptoms associated with schizophrenia. The relationship to the underlying anatomical abnormalities, however, are still unclear. The current study aimed to examine the relation-
ship between abnormalities in cortical thickness and reductions in gamma-band oscillations in MEG-data.

Methods: Seventeen participants (mean age: 33.06 ± 9.90), who met the DSM-IV criteria for chronic schizophrenia, and seventeen healthy control subjects (mean age: 31.29 ± 9.89) matched for age and gender underwent high spatial resolution MRI. Cortical thickness analyses were performed on whole-brain level and for regions reported as sources for gamma band activity (60-120 Hz) during face perception in MEG-data.

Results: Patients with schizophrenia showed a widespread impairment of cortical thickness, which was mainly focused in the right frontal and temporal lobes. In addition, there was a close correspondence between the reduction in source-related activity of gamma-band oscillations and reductions in cortical thickness. Thus, cortical thickness reductions of right Fusiform Gyrus, right Inferior Frontal Gyrus, right Superior Temporal Gyrus, and the Superior Parietal Lobule were also associated with decreased gamma-band activity in Schizophrenia. Patients with schizophrenia showed a widespread impairment of cortical thickness, which was mainly focused in the right frontal and temporal lobes. In addition, there was a close correspondence between the reduction in source-related activity of gamma-band oscillations and reductions in cortical thickness. Thus, cortical thickness reductions of right Fusiform Gyrus, right Inferior Frontal Gyrus, right Superior Temporal Gyrus, and the Superior Parietal Lobule were also associated with decreased gamma-band activity in Schizophrenia.

Discussion: These results suggest that reductions in grey matter underlie impairments in gamma-band activity in schizophrenia. Grey matter abnormalities may reflect abnormal synaptic modifications during the development of the disorder that cause imprecise temporal dynamics in cortical networks.

doi:10.1016/j.schres.2010.02.652

Poster 158
INCREASED SERUM BDNF INDUCED BY COGNITIVE TRAINING IN SCHIZOPHRENIA IS NEGATIVELY ASSOCIATED WITH BASELINE SAA

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Background: Brain-derived neurotrophic factor (BDNF) plays a critical role in brain development and neuroplasticity. Recent evidence suggests that schizophrenia may be related to decreased BDNF functioning. Additionally, schizophrenia is treated using medications that raise serum anticholinergic activity (SAA), known to adversely affect cognition. In this study we examined the relationship between BDNF, SAA, cognitive performance, and the response to a neuroplasticity-based targeted cognitive training program (TCT) in outpatients with schizophrenia.

Methods: Fifty-nine adult chronic schizophrenia patients were assessed at baseline on measures of BDNF, SAA, and neurocognitive performance, and randomized into either TCT, or a computer games control group (CG). Patients were reassessed after 8 weeks (40 hours) of training.

Results: Schizophrenia patients (N = 59) demonstrated significantly lower-than-normal BDNF levels at baseline. After 40 hours of training, TCT subjects (N = 34) showed a significant increase in BDNF, while the CG group (N = 25) showed no significant change. In the TCT group, SAA levels showed a significant negative correlation with change in Global Cognition (r = -0.46, p = .03), and with change in BDNF (r = -0.41, p = .05).

Discussion: Our results indicate that neuroplasticity-based cognitive training has a "normalizing" effect on serum BDNF levels in schizophrenia patients. However, the increase in serum BDNF is negatively associated with baseline medication-induced SAA levels. This finding underscores the cognitive and possibly neurotrophic cost of medications that carry a high anticholinergic burden, and has implications for the conceptualization of successful cognitive based treatments in the future.

doi:10.1016/j.schres.2010.02.653

Poster 159
DURATION OF UNTREATED PSYCHOSIS AND ETHNICITY

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Background: The Duration of Untreated Psychosis (DUP) has been associated with a poorer prognosis. Little is known about the relationship between DUP and ethnic background.

Aim: To measure DUP in a consecutively firstly diagnosed cohort of patients with a first episode psychotic disorder in Amsterdam between 01.07.2006 and 01.07.2008 and to evaluate the relation with ethnic background.

Methods: We collected data on DUP and ethnic background of all patients who were referred to and had a diagnostic interview at a specialized clinic for first episode psychosis in Amsterdam or who were admitted to the early intervention psychosis teams in Amsterdam, between 01.07.2006 and 01.07.2008.

Results: Median DUP was 17 weeks. An ethnic background other than Dutch was associated with a longer DUP (p = 0.033). Striking long median DUP was found in patients with a Surinamese, Ghanaese or Moroccan background.

Discussion: DUP in Amsterdam seems to be shorter than in other studies. However, patients with an ethnic background other than Dutch, have a longer DUP. Efforts must be made to find out what causes these differences, so that better strategies can be developed for reaching these groups of patients earlier.

doi:10.1016/j.schres.2010.02.654

Poster 160
IS SERINE RECEMASE AN INDICATOR OF SCHIZOPHRENIA?

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Background: Schizophrenia is a brain disease that has distressed human kind since the beginning of the written history. Firm knowledge about this illness is limited to certain areas including cognitive, risk genes etc. Basic question remains unanswered about the diagnostic heterogeneity and tissue neurochemistry. Several lines of evidence focus on direct involvement of glutamergic system in the pathophysiology of psychosis.

Methods: The pilot study measured the difference between the plasma serine recemase level of normal and schizophrenic patients and estimated the D-isomers excreted in the urine using gas chromatography and Gas chromatography and mass selectivity (GCMS) respectively.
Results: Plasma and urine samples of normal and schizophrenic patients from UAE shows that the level of serine recemase and D-serine respectively is lower in schizophrenic patients than that of the normal subjects.

Discussion: The hypofunction of the glutamate N-methyl-D-Aspartate receptor (NMDAR) has been proposed as a model of schizophrenia in humans using molecular marker and also due to evidence suggesting modulation of glutamate circuits after antipsychotic administration. In this regard there is increasing evidence from pharmacological and genetic studies that suggest that D-serine an endogenous co agonist to the NMDA subtype glutamate receptor, may be implicated in schizophrenia (SCZ). Although an association of genes for D-serine degradation such as D-amino acid oxidase and G72 has been reported, a role of recemase in SCZ is unclear.

doi:10.1016/j.schres.2010.02.655

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**Poster 161**

**BDNF mRNA EXPRESSION OF PERIPHERAL BLOOD MONONUCLEAR CELLS WAS DECREASED IN PATIENTS WITH SCHIZOPHRENIA**

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**Background:** Recent reports have suggested a pathophysiological role for brain-derived neurotrophic factor (BDNF) in major psychiatric disease including schizophrenia and major depression. We evaluate BDNF mRNA in peripheral blood mononuclear cells (PBMCs) of patients with schizophrenia.

**Methods:** BDNF mRNA expression was examined in PBMCs of 40 patients with schizophrenia and 40 healthy controls. It was analyzed in patients with schizophrenia at baseline and after 6-week treatment. All patients were diagnosed with schizophrenia and they were either medication-naïve or medication-free. BDNF mRNA expression was measured using real-time quantitative PCR.

**Results:** The relative level of BDNF mRNA expression in PBMCs of patients with schizophrenia was 0.39 at baseline and 0.45 after 6-week treatment, when the relative level of healthy controls was 1. The relative level of BDNF mRNA expression was significantly decreased in patients with schizophrenia both at baseline, when compared with healthy controls (Z=-6.924, p<0.001). There was no significant difference of the relative level of BDNF mRNA expression between baseline and 6-week treatment (Z=-0.029, p=0.977).

**Discussion:** Our study suggests that the BDNF mRNA expression is reduced in PBMCs of patients with schizophrenia both at baseline and after 6-week treatment.

doi:10.1016/j.schres.2010.02.656

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**Poster 162**

**TH-1/TH-2 CYTOKINE IMBALANCE MORE PRONOUNCED IN NEUROLEPTIC-NAÏVE FIRST EPISODE SCHIZOPHRENIA**

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**Background:** There is major evidence for the involvement of immunological processes in the pathophysiology of schizophrenia. Especially alterations of T-cell function and activation of the inflammatory response system appear to be linked to schizophrenia. A mild chronic inflammation process has been proposed and repeated findings of altered serum cytokine levels led to the hypothesis of a TH-2 shift or cytokine imbalance in schizophrenia. However, data are to some extend ambiguous and therefore discussed critically. Alongside influences of antipsychotic medication on cytokine levels also biological subpopulations and stage of disorder could contribute to different cytokine profiles in schizophrenic patients. We investigated serum levels of TH-1 and TH-2 related cytokines in unmedicated resp. drug-naïve schizophrenic patients at different stages of disorder.

**Methods:** 21 schizophrenic patients and 21 age and gender matched healthy controls were included. Subjects with medical history of chronic inflammatory or autoimmune disease were excluded from the study. To account for different stages of disorder we divided patients into first episode (FEP) and recurrent episode patients (REP) for subgroup analysis. All investigated patients were unmedicated at time of investigation and suffered an acute psychotic episode. First episode patients were naïve in terms of neuroleptic medication. Serum levels of following cytokines were measured by means of commercially available ELISAs: interleukine (IL)-2, sIL-2R, IL-4, IL-6, IL-13 and soluble intercellular adhesion molecule (sICAM)-1.

**Results:** In patients we found increased IL-6 (p=0.03) and IL-13 levels (p=0.03) and decreased sICAM-1 (p=0.02) and sIL-2R levels (p=0.01). The same constellation was found in FEP subgroup when compared to controls. Additionally we found elevated IL-4 (p=0.02) in FEP subgroup. No significant cytokine levels differences could be revealed in REP group at this sample size.

**Discussion:** The finding of decreased sICAM-1, a signalling molecule required for the activation of TH-1 helper cells and therefore a marker of the cellular immune system is in line with previous studies. Also, decreased sIL-2R may refer to a relatively reduced TH-1 response. In contrast, previous studies reported increased sIL-2R. To our knowledge all of these studies were performed on patients receiving antipsychotic medication. In recurrent episode patients we found a broader range of sIL-2R levels than in drug-naïve first episode patients. Thus, different sIL-2R levels could relate to stage of disorder but also to previous neuroleptic medication in REP. Consistent with previous reports, we found an increase of TH-2 system cytokines IL-6, IL-13 and IL-4 (latter only significant in FEP). There were no group differences in IL-8. These findings support the hypothesis of a TH-1/TH-2 imbalance in schizophrenic patients, more pronounced in first episode patients.

doi:10.1016/j.schres.2010.02.657

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**Poster 163**

**DOES STRESS CONTRIBUTE TO INFLAMMATORY AND METABOLIC ABNORMALITIES IN FIRST EPISODE PSYCHOSIS?**

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**Background:** The high incidence of metabolic syndrome and physical illness in patients with psychosis has been mainly attributed to the treatment with antipsychotics. However, it has
been recently suggested that repeated acute and chronic psychological stress may also play a role in physical illnesses, inducing a chronic inflammatory process which may predispose to the development of metabolic abnormalities and cardiovascular problems. The aim of the study is to investigate the association between stress, inflammatory and metabolic markers in subjects with first-episode psychosis and healthy controls.

**Methods:** Weight, BMI, waist circumference, lipid profile, levels of leptin, IL-6, TNF-α, HbA1c, and hs-CRP were measured in 42 first-episode psychosis patients (mean ± SEM age: 27.8 ± 0.8 years; gender: 69% males) and 35 healthy controls (age: 26.4 ± 0.7 years; gender: 62.9% males). In the same subjects we collected information about childhood trauma, recent stressful events and perceived stress, using validated schedules. An independent t-test was used to analyze differences in metabolic and inflammatory parameters between patients and controls. A one-way ANOVA was conducted to analyze differences among controls, patients with less than 2 weeks or more than 2 weeks of antipsychotic treatment. Correlation analyses were conducted to investigate the association between stress variables and inflammatory and metabolic parameters.

**Results:** Patients showed higher triglycerides (p = 0.04), leptin (p = 0.05), hsCRP (p = 0.04), IL-6 (p = 0.03) and TNF-α levels (p = 0.003) than controls, while they did not differ significantly in other metabolic parameters. When splitting the patients for duration of treatment, we found that IL-6 and TNF-α levels were higher in patients with less than 2 weeks of treatment when compared with controls (respectively p = 0.006 and p = 0.004). The number of childhood trauma was positively correlated with hsCRP (r = 0.441, p = 0.04) and TNF-α levels (r = 0.386, p = 0.02) in the patient’s group.

**Discussion:** Our findings suggest that an activation of the inflammatory system is already present in early course of psychosis and possibly precedes clinically relevant changes in metabolic status. Childhood trauma appear to play a role in the increased inflammation found in first-episode psychosis, and might explain the higher incidence of metabolic abnormalities in this population. Childhood trauma was positively correlated with hsCRP (r = 0.441, p = 0.04) and TNF-α levels (p = 0.05), hsCRP (p = 0.04), IL-6 (p = 0.03) and TNF-α levels (p = 0.003) than controls, while they did not differ significantly in other metabolic parameters. When splitting the patients for duration of treatment, we found that IL-6 and TNF-α levels were higher in patients with less than 2 weeks of treatment when compared with controls (respectively p = 0.006 and p = 0.004). The number of childhood trauma was positively correlated with hsCRP (r = 0.441, p = 0.04) and TNF-α levels (r = 0.386, p = 0.02) in the patient’s group.

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**Discussion:** Our findings suggest that an activation of the inflammatory system is already present in early course of psychosis and possibly precedes clinically relevant changes in metabolic status. Childhood trauma appear to play a role in the increased inflammation found in first-episode psychosis, and might explain the higher incidence of metabolic abnormalities in this population. Childhood trauma was positively correlated with hsCRP (r = 0.441, p = 0.04) and TNF-α levels (r = 0.386, p = 0.02) in the patient’s group.

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affected vs. unaffected co-twins). The concentration of this sphingomyelin was significantly associated with the reductions in gray matter density including regions of the temporal and occipital lobes as well as corpus callosum, as confirmed by permutation testing and separately for each hemisphere (Ps < 0.05). The significant association remained if corpus callosum was excluded from the analysis, for the right hemisphere only.

Discussion: Our findings support the view that lipid abnormalities are intrinsic to schizophrenia. Sphingomyelin (SM) is an abundant brain lipid which is also a precursor of lipotoxic ceramide. Elevated ceramide levels have been identified in white matter of schizophrenic subjects in a recent study (Schwartz et al., 2008). SM is also an abundant lipid in circulation, found particularly in LDL and HDL particles (Kotronen et al., 2009). The twin design allowed us to link abnormal lipid SM changes to schizophrenia independent of the genetic Background. Associations of SM to specific brain regions of potential pathogenic relevance suggest SM may play a role in schizophrenia. Our findings emphasize the importance of further studies aimed to establish a mechanistic link between the alterations in circulating SM and related changes in brain ligands and structure.

References

Poster 166
ANTIOXIDANT STATUS IN FIRST EPISODES OF EARLY ONSET PSYCHOSIS COMPARED WITH ASPERGER AND HEALTHY CONTROLadolescents

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Background: Clinical, but not biological, differences have been used to differentiate psychotic and pervasive developmental disorders in children, which were once classified together. Oxidative stress-mediated cell membrane pathology has been considered a contributor to the physiopathology of schizophrenia. Changes in oxidative stress have been associated with the clinical course and the treatment of schizophrenia. Oxidative stress mechanisms have also been involved in the physiopathology of autism spectrum disorders. The present study compares the oxidative status of adolescents diagnosed with first episodes of psychosis, with a group that has been diagnosed with Asperger syndrome. They are also compared with a group of healthy controls.

Methods: We compared plasmatic total antioxidant status (TAOS) and malonyldialdehyde (MDA)—a final product of lipid peroxidation and indicative of oxidative membrane damage—in 27 children and adolescents with Asperger syndrome, 32 with a first episode of psychosis, and 31 healthy controls, both at baseline and 8-week follow-up. Patients in the psychosis group were treated with second-generation antipsychotics during the 8-week period. Age range was 7 to 17 years of age.

Results: TAOS was higher in the psychosis group at both measures (Baseline: Psychosis, 1.30 SD = 0.22; Asperger, 1.12 SD = 0.22; Controls, 1.26 SD = 0.26; 8 weeks: Psychosis, 1.43 SD = 0.32; Asperger, 1.19 SD = 0.22; Controls, 1.27 SD = 0.23). The difference was significant at 8 weeks between the Asperger and Psychosis groups (Asperger vs Psychosis = 0.003); at baseline there was only a tendency for significance (p = 0.072). Covarying by age did not make a difference. MDA differences among the groups were not found at any point in time.

Discussion: We have not been able to replicate previous findings regarding adult schizophrenia, which showed oxidative stress disequilibrium, in the present sample of first-episode early-onset patients with psychosis. However, our results do show that antioxidant capacity of psychotic patients is greater than that of Asperger patients, particularly after the psychotic group received 8 weeks of treatment. The reduced antioxidant capacity shown in the Asperger group could indicate a more chronic type of neurodevelopmental disorder, but this needs confirmation in larger samples and in samples that control for pharmacological treatment.

doi:10.1016/j.schres.2010.02.661

Poster 167
MICROARRAY ANALYSIS OF PARVALBUMIN-CONTAINING INHIBITORY NEURONS IN THE SUPERIOR TEMPORAL GYRUS IN SCHIZOPHRENIA

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Background: Imaging studies have shown that the volume of gray matter in the cerebral cortex, such as the superior temporal gyrus (STG), is significantly reduced in schizophrenia. Furthermore, multiple lines of evidence strongly suggest that GABA (gamma-aminobutyric acid)ergic neurotransmission mediated by the fast-spiking neurons that contain the calcium buffer protein parvalbumin (PV) is perturbed in schizophrenia. These neurons play a crucial role in regulating the synchronized oscillatory firing of pyramidal neurons through perisomatic and axo-axonic inhibition. Interestingly, disturbances of pyramidal neuronal oscillatory synchrony is increasingly believed to be a major mechanism that mediates a wide range of symptoms and cognitive deficits of schizophrenia. In addition, ongoing experiments in our laboratory support the notion that deficient PV neuronal inhibition of pyramidal neurons may trigger a cascade of molecular events that ultimately lead to cytoskeletal changes and deficient dendritic architecture, hence contributing to, at least in part, the imaging finding of reduced gray matter volume. Taken together, understanding the molecular nature of PV neuronal disturbances would provide important insight into the pathophysiology of schizophrenia.

Methods: In a cohort of postmortem brains from 8 schizophrenia and 8 demographically matched normal control subjects that were obtained from the Harvard Brain Tissue Resource Center, we used the Arcturus
Laser Capture Microdissection system in combination with gene expression profiling using the Affymetrix platform to isolate PV-immunoreactive neurons (N=350) from layer 3 in the STG to interrogate the possible alterations in the transcriptome of PV neurons in schizophrenia.

**Results:** We were able to obtain very good quality RNA, as measured by the A260/280 ratio (2.5 - 2.8) and transcript length (>600 nucleotides), with RNA concentrations averaging approximately 1microgram/ml. A preliminary pathway analysis revealed that signaling pathways that affect lipid metabolism, protein transcription, neurite growth and function, and apoptosis appear to be altered in schizophrenia.

**Discussion:** Using gene expression profiling in conjunction with immunolabeling and laser capture microdissection, we were able to identify molecular pathways that may underlie the disturbances of PV-containing neurons in schizophrenia. This line of research may ultimately inspire the conceptualisation of rational therapeutic strategies that aim at recalibrating the functioning of PV neurons.

doi:10.1016/j.schres.2010.02.662

**Poster 168**

**SELECTION OF REFERENCE GENE EXPRESSION IN A SCHIZOPHRENIA BRAIN COHORT**

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**Background:** To conduct postmortem human brain research into the neuropathological basis of schizophrenia, it is critical to establish cohorts that are well-characterised and well-matched. Our objective was to determine if specimen characteristics, including: diagnosis, age, postmortem interval (PMI), brain acidity (pH), and/or the agonal state of the subject at death related to RNA quality, and to determine the most appropriate reference gene mRNAs.

**Methods:** We selected a matched cohort of 74 cases (37 schizophrenia / schizoaffective disorder cases and 37 controls cases). Middle frontal gyrus tissue was pulverised, tissue pH was measured, RNA isolated for cDNA from each case, and RNA integrity number (RIN) measurements were assessed. Using qRT-PCR, we measured nine housekeeper genes and calculated a geometric mean in each diagnostic group.

**Results:** We found that the RINs were very good (mean 7.3) and all nine housekeeper control genes were significantly correlated with RIN. Seven of nine housekeeper genes were also correlated with pH, and two clinical variables, agonal state and duration of illness did have an effect on some control mRNAs. No major impact of PMI or freezer time on housekeeper mRNAs was detected. Our results show that people with schizophrenia had significantly less PPIA, SDHA and mtubulin B2M mRNA suggesting that these control genes may not be good candidates for normalisation.

**Discussion:** In our cohort, less than 10% variability in RIN values was detected and the diagnostic groups were well matched overall. Our cohort was adequately powered (0.80-0.90) to detect mRNA differences (25%) due to disease. Our study suggests that multiple factors should be considered in mRNA expression studies of human brain tissues. When schizophrenia cases are adequately matched to control cases subtle differences in gene expression can be reliably detected.

doi:10.1016/j.schres.2010.02.663

**Poster 169**

**PROTEOMIC ANALYSIS OF THE BASIC SUB-PROTEOME (PH 6-11) IN THE HIPPOCAMPUS IN SCHIZOPHRENIA AND BIPOLAR AFFECTIVE DISORDER**

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**Background:** Structural and functional changes of the hippocampus in psychotic disorders have been demonstrated in numerous studies. However, underlying molecular mechanisms are not well understood. Proteomic studies in this brain region have thus far focused on proteins of the acidic sub-proteome (pI range pH 4-7) or on low resolution proteome screens (pI range pH 3-10). The basic sub-proteome (pI pH 6-11), which contains functionally important DNA-binding proteins, membrane proteins, and mitochondrial proteins, has not been studied in detail to date.

**Methods:** Using post-mortem brain samples, we applied the Difference In-Gel Electrophoresis method (Dige) to analyze the expression of basic proteins (pI range pH 6-11) in schizophrenia and bipolar affective disorder. Homogenates of whole hippocampi were derived from a well matched sub-sample of the Array series of the Stanley Brain Collection which consisted of 10 subjects with schizophrenia, bipolar affective disorder, and control cases, respectively.

**Results:** Analysis revealed differential expression of 23 proteins in schizophrenia and 17 proteins in bipolar affective disorder. Seven of these proteins were altered in both disorders. 26 differentially expressed proteins could be identified using Q-ToF MS/MS mass spectrometry. Results indicate abnormalities in a range of cytoplasmatic and mitochondrial pathways in psychotic disorders. Abnormal levels of proteins involved in the cytoplasmatic pathways of clathrin-mediated endocytosis (CME), microtubule assembly, oligodendrocyte function, and glycolysis/glucosegenesis were found. Additionally, we detected abnormalities of proteins regulating mitochondrial protein- and fatty acid metabolism, oxidative stress defence, and oxidative phosphorylation. Validation of the results using ELISA/Western Blot in an extended sub-sample of the Stanley Brain Collection Array series is currently undertaken for selected proteins.

**Discussion:** This study examined the basic sub-proteome in the hippocampus in psychotic disorders for the first time. Results are in keeping with previous proteomic studies which consistently indicate abnormalities in cytoskeletal function, glycolysis/glucosegenesis, synaptic mechanisms, and mitochondrial function in these diseases. The approach taken may yield novel biomarker proteins and drug targets for diagnosis and treatment of psychotic disorders.

doi:10.1016/j.schres.2010.02.664

**Poster 170**

**NEUROLOGICAL SOFT SIGNS IN SCHIZOPHRENIA AND THE INFLUENCE OF FAMILY HISTORY AND SCHIZOTYPAL PERSONALITY: A FAMILY-BASED STUDY**

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**Background:** Neurological soft signs (NSS) are non-organic neurological deficits, which are associated with the clinical expression of psychiatric diseases. The study has focused on NSS, as assessed by the Neurological Soft Signs Scale (NSSS), in a sample of people with schizophrenia and bipolar disorder. We have previously shown that NSS are associated with a range of other common mental disorders and neurological disorders. The purpose of this study is to investigate the relationship between NSS and schizophrenia, and other psychotic disorders.

**Methods:** Using post-mortem brain samples, we applied the Difference In-Gel Electrophoresis method (Dige) to analyze the expression of basic proteins (pI range pH 6-11) in schizophrenia and bipolar affective disorder. Homogenates of whole hippocampi were derived from a well matched sub-sample of the Array series of the Stanley Brain Collection which consisted of 10 subjects with schizophrenia, bipolar affective disorder, and control cases, respectively.

**Results:** Analysis revealed differential expression of 23 proteins in schizophrenia and 17 proteins in bipolar affective disorder. Seven of these proteins were altered in both disorders. 26 differentially expressed proteins could be identified using Q-ToF MS/MS mass spectrometry. Results indicate abnormalities in a range of cytoplasmatic and mitochondrial pathways in psychotic disorders. Abnormal levels of proteins involved in the cytoplasmatic pathways of clathrin-mediated endocytosis (CME), microtubule assembly, oligodendrocyte function, and glycolysis/glucosegenesis were found. Additionally, we detected abnormalities of proteins regulating mitochondrial protein- and fatty acid metabolism, oxidative stress defence, and oxidative phosphorylation. Validation of the results using ELISA/Western Blot in an extended sub-sample of the Stanley Brain Collection Array series is currently undertaken for selected proteins.

**Discussion:** This study examined the basic sub-proteome in the hippocampus in psychotic disorders for the first time. Results are in keeping with previous proteomic studies which consistently indicate abnormalities in cytoskeletal function, glycolysis/glucosegenesis, synaptic mechanisms, and mitochondrial function in these diseases. The approach taken may yield novel biomarker proteins and drug targets for diagnosis and treatment of psychotic disorders.

doi:10.1016/j.schres.2010.02.664
Background: Neurological Soft Signs (NSS) are subtle signs that indicate non-specific cerebral dysfunction (Dazan & Murray, 2002). It has been suggested that NSS might be markers for schizophrenia as studies have reported that NSS are more frequently present in schizophrenic patients compared to healthy controls (Heinrichs & Buchanan, 1988; Dazan & Murray, 2002). Furthermore, it has been demonstrated that neurological soft signs aggregate in relatives of schizophrenic patients (Chen et al., 2000; Egan et al., 2001; Gourion et al., 2003). The aim of this study was to investigate the influence of psychosis proneness factors, such as family history and Schizotypal personality, on the neurological soft signs observed in patients with recent diagnosis of functional psychosis and their first degree relatives.

Methods: The sample consisted of 137 individuals from 38 nuclear families (proband with schizophrenic spectrum disorders and non-psychotic parents and siblings). Patients had a mean age of 24.26 years (SD = 3.99), a mean age of onset of 22.14 years (SD = 3.92) and a mean duration of illness of 2.42 years (SD = 2.11). Neurological Soft Signs were assessed, in all participants by the same rater, by means of the Spanish version of the Neurological Evaluation Scale (Buchanan & Heinrichs, 1989). This scale consists of 3 main subscales: sensory integration (SI), motor coordination (MC) and sequencing of complex motor acts (SCMA). To test the genetic loading effect, subjects were classified into relatives of psychotic parents and siblings. Schizotypal personality was measured, in all family members, with the Schizotypal Personality Questionnaire-B (SPQ-B) (Raine & Benishay, 1995). This self-reported questionnaire consists of three factors: interpersonal, disorganized and cognitive-perceptual. ANOVA analyses were carried out to investigate differences in NSS between the status groups (patients, parents and siblings). Furthermore, linear regressions were carried out to investigate the influence of SPQ and family history on neurological soft signs. All analyses were corrected for age and gender and performed with SPSS 17.0.

Results: The results from the ANOVA’s validated results from previous studies that found differences in NSS between patients, parents and siblings. In all three subscales parents differed significantly from patients (p-values ranging from 0.008 to 0.027). Patients differed from siblings in motor coordination and sequencing of complex motor acts. However, patients and siblings showed similar sensory integration. The regression analysis did not reveal any significant effect for family history, but did show an effect of Schizotypal personality (disorganized factor) on integrative sensory dysfunction in siblings (B = 0.370, SE = 0.140, p = 0.014). In parents and patients no relation was found between the SPQ and NSS.

Discussion: These results suggest that overall patients have more NSS compared to their unaffected parents and siblings. However, the unaffected siblings do have equally elevated scores on the sensory integration subscale. This might indicate that this discussion is more related to genetic Background than specifically to schizophrenia. Furthermore, the elevated NSS in siblings may possibly be explained by the positive relation between the disorganized factor of the SPQ and integrative sensory dysfunction. This may suggest that using composite phenotypes is useful in elucidating genetic liability of schizophrenia spectrum disorders (Mechri et al., 2009).

doi:10.1016/j.schres.2010.02.665
antibody. Co-immunoprecipitated proteins were separated by SDS-PAGE, systematically digested by trypsin and generated peptides analyzed by Nano-LC-MS/MS with a Fourier transform tandem mass spectrometer (LTQ Orbitrap XL). Protein identification and validation were performed using Mascot and myProMS softwares, respectively. Activation of the mammalian target of rapamycin (mTOR) pathway was assessed by immunofluorescence staining of brain sections of mice using polyclonal antibodies against activated mTOR (phosphorylated at Ser2448) and the phosphorylated forms of eukaryotic translation initiation factor 4E-binding protein (eIF4E-BP, Ser65) and ribosomal protein S6 (Ser235/236 and Ser240/244), respectively. In the social recognition procedure, the same juvenile was presented to an adult rat for two consecutive 5-min sessions. Using a procedure of spontaneous loss of recognition, employing an inter-session interval of 120 min, WAY181,187, SB258,585 or scopolamine were administered just after the first session, and the specific mTOR inhibitor, rapamycin injected 30 min earlier.

**Results:** A set of proteins interacting directly and/or indirectly with 5-HT6 receptors was identified. These included three members of the mTOR complex: phosphatidylinositol 3-kinase catalytic subunit type 3, neurofibromin and mTOR itself. This pathway modulates synaptic plasticity and cognition. In mice, the 5-HT6 receptor agonist, WAY181,187 (10.0 mg/kg, i.p., 30 min), increased phosphorylation of the mTOR complex; phosphorylated at Ser2448 in a sub-set of neurons of both the striatum and frontal cortex. Correspondingly, WAY181,187 increased phosphorylation of two downstream targets of mTOR, eIF4E-BP, Ser65 and S6 (Ser235/236 and Ser240/244). Phosphorylation of S6 by WAY181,187 was abolished by the 5-HT6 receptor antagonist, SB258,585 (10.0 mg/kg, i.p.), which itself did not affect phosphorylation. Further supporting engagement of the mTOR pathway was the preferential effect of mesolimbic versus nigrostriatal dopamine pathways, although this decrease was modest. Finally, Compound 1 completely reversed an MK-801 induced deficit in sensory gating as measured in the rat at a dose of 100 mg/kg i.p., suggestive of efficacy versus positive symptoms. In the conditioned avoidance response assay, a model predictive of antipsychotic efficacy, 100 mg/kg was calculated to be an IC50 for decreasing avoidance response assay, which demonstrated the compound’s interaction with the target. Compound 1 completely reversed an MK-801 induced deficit in sensory gating as measured in the rat at a dose of 100 mg/kg i.p., suggestive of efficacy versus positive symptoms. In the conditioned avoidance response assay, a model predictive of antipsychotic efficacy, 100 mg/kg was calculated to be an IC50 for decreasing avoidance response in both rats and mice. Profiled in the mouse apomorphine-induced climbing and stereotypy model, Compound 1 (100 mg/kg i.p.) significantly attenuated climbing behavior without an effect on stereotypy, suggesting an atypical like profile, with a preferential effect of mesolimbic versus nigrostriatal dopamine pathways, although this decrease was modest. Finally, Compound 1 was tested in the mouse social odor recognition model, and was able to reverse an MK-801 induced deficit at 10 mg/kg i.p.

**Discussion:** Thus, activation of 5 HT6 receptors recruits mTOR signalling in brain including the frontal cortex, the site of modulation of social recognition by 5-HT6 receptors. These studies support the relevance of mTOR and 5-HT6 receptors to the etiology and control of the cognitive deficits of CNS disorders.

**doi:**10.1016/j.schres.2010.02.667

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**Poster 173**

**COMPOUND 1, A POTENT AND SELECTIVE DAO INHIBITOR, DEMONSTRATES EFFICACY IN SEVERAL PRECLINICAL ANIMAL MODELS OF SCHIZOPHRENIA**

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**Background:** Multiple lines of evidence suggest that impaired N-methyl-D-aspartic acid (NMDA) receptor function contributes to the pathophysiology of schizophrenia, and as such, multiple novel approaches are being pursued to counter this hypo-function. Increasing levels of d-serine, an obligatory co-agonist at the allosteric ‘Glycine Modulatory Site’ (GMS) on the NR1 subunit of the NMDA receptor may have the benefit of avoiding neurotoxicity associated with direct agonists. Decreases in d-serine in the CSF, serum and prefrontal cortex have been observed in schizophrenics, and multiple double blind, placebo control studies have demonstrated that d-serine, administered as an adjunct to atypical antipsychotics, improves positive, negative and cognitive symptoms of the disease. Inhibition of d-amino acid oxidase (DAO), a flavoenzyme that oxidatively deaminates small neutral amino acids including d-serine, is an example of an approach to elevate d-serine levels. A recent publication (Sparey et al., Bioorganic + Med Chem Lett (2009) 19(11)3386-91) describes Compound 1 (4H-furo[3,2-b]pyrrole-5-carboxylic acid), as a potent and selective DAO inhibitor.

**Methods:** Compound 1’s ability to inhibit human DAO was assessed both in a cellular assay using HEK293 cells stably expressing DAO, and in a purified enzyme assay, while its selectivity was determined in a cellular assay against the nearest neighbor of DAO, d-aspartate oxidase (DDO), which has 38% homology to DAO. A Biacore assay was utilized to demonstrate binding to the target. Following this determination, Compound 1 was evaluated behaviorally in several preclinical animal models with relevance to schizophrenia. Specifically, Compound 1’s ability to attenuate an NMDA antagonist induced deficit in prepulse inhibition was determined, followed by characterization in both the rat and mouse conditioned avoidance response assays, evaluation of its ability to antagonize apomorphine induced climbing and stereotypy, and an assessment of its ability to reverse an NMDA antagonist induced deficit in social odor recognition.

**Results:** Compound 1 has an IC\(_{50}\) of 33 nM against the purified hDAO enzyme, and an IC\(_{50}\) of 19 nM in a cellular assay, while exhibiting greater than 300 fold selectivity over hDDO, in the cellular assay. A similar potency (Kd = 9 nM) was observed in a Biacore binding assay, which demonstrated the compound’s interaction with the target. Compound 1 completely reversed an MK-801 induced deficit in sensory gating as measured in the rat at a dose of 100 mg/kg i.p., suggestive of efficacy versus positive symptoms. In the conditioned avoidance response assay, a model predictive of antipsychotic efficacy, 100 mg/kg was calculated to be an IC50 for decreasing avoidance response in both rats and mice. Profiled in the mouse apomorphine-induced climbing and stereotypy model, Compound 1 (100 mg/kg i.p.) significantly attenuated climbing behavior without an effect on stereotypy, suggesting an atypical like profile, with a preferential effect of mesolimbic versus nigrorstral dopamine pathways, although this decrease was modest. Finally, Compound 1 was tested in the mouse social odor recognition model, and was able to reverse an MK-801 induced deficit at 10 mg/kg i.p.

**Discussion:** The profile that emerges of Compound 1 in these assays supports the idea of broad spectrum therapeutic utility of a DAO inhibitor for the treatment of schizophrenia.

**doi:**10.1016/j.schres.2010.02.668

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**Poster 174**

**A THREE ARM DOSE FINDING STUDY OF LURASIDONE: EFFICACY AND TOLERABILITY DATA**

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**Background:** Lurasidone is a new atypical antipsychotic agent that has shown superiority to placebo in several registration trials. This compound has also shown a side effect profile notable for minimal metabolic effects and weight gain. Previous short-term, fixed dose studies have not examined daily doses below 40 mg and have been limited to inpatient samples. We report here an 8-week dose-
response study of lurasidone that compared 20, 40, and 80 mg/d in a sample of inpatients and outpatients in Japan.

**Methods:** A total of 200 patients with schizophrenia were randomized in double-blind fashion to fixed, single-daily doses of lurasidone for 8 weeks, followed by a 44-week extension period. Assessments included the PANSS, BPRS and CGI. Subjects were switched directly from previous antipsychotics without a washout period. If the daily dose of the previous antipsychotic medication exceeded 12 mg/day of haloperidol or its equivalent, the medication was tapered to the 12 mg/day equivalence level prior to switching. Safety assessments included a comprehensive movement disorder measure (DIEPSS), laboratory measures, weight, ECG and vital signs.

**Results:** ANCOVA LOCF analyses demonstrated that single-daily doses of 40 and 80 mg of lurasidone were associated with significant improvements from baseline on the PANSS and the BPRS. The 40 mg/d dose was significantly superior to 20 mg/d on the BPRS. Drop out rates were equivalent across the dose arms, with more dropouts due to lack of efficacy for 20 mg and more for adverse events for the 80 mg dose. Serious adverse events were rare and 5/7 occurred at the 20 mg dose. All three dose arms were associated with decreases in weight that were less than 1.35 kg. In all three arms of the study, 2% or fewer of the patients gained 7% or more in their body weight. In an exploratory analysis for the total sample, patients treated 28 or more days had equivalent improvements across the three medication dosages. In addition, there was a linear apparent dose-response relationship for inpatients, with 80 mg superior, but for outpatients 40 mg appeared to be the optimal dose for clinical response.

**Discussion:** This dose response study indicated that a 40 mg dose of lurasidone had optimal efficacy, but that all three doses had minimal side effects, particularly weight gain.

doi:10.1016/j.schres.2010.02.669

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**Poster 175**

**A DOUBLE BLIND, PLACEBO CONTROLLED STUDY OF THE SAFETY AND TOLERABILITY OF QUETIAPINE 1200 MG/D VERSUS 800 MG/D IN PATIENTS WITH PERSISTENT SYMPTOMS OF SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER**

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**Background:** Quetiapine is often prescribed at higher than approved doses, with limited evidence from controlled trials supporting the safety, tolerability of efficacy of this approach. We investigated the safety and tolerability of quetiapine 1200 mg/day compared with quetiapine 800 mg/day in patients with an incomplete early treatment response. A secondary objective was to evaluate the efficacy of the 1200 mg/day dose compared with 800 mg/day.

**Methods:** A multi-centre, randomized controlled trial was carried out. Patients with poor initial response to quetiapine 800 mg/day participated in an eight week, randomized, double-blind study comparing high dose quetiapine 1200 mg/day versus continuation of quetiapine 800 mg/day. The main outcome measure was emergent or worsening extrapyramidal symptoms. Secondary measures were adverse events and side effects, including metabolic measures and ECG. Change in symptom severity was also evaluated.

**Results:** The frequency of deterioration or emergence of Parkinsonism in the >800 mg/day group was 3.1% greater (95% CI: -7.1% to +14%, p = 0.76) than the 800 mg/day group, within the a priori limit of 16% defined as non-inferiority for the >800 mg/day dose. Both doses of quetiapine were safe and well tolerated. However, BMI and weight increases during randomized treatment were greater in the >800 mg/day group, with statistically significant differences observed for weight (mean difference >800 mg/day minus 800 mg/day = 1.25 kg, 95% CI: 0.03 to 2.47, p = 0.044). The mean severity of symptoms decreased in both groups during randomized treatment, the difference between groups was not statistically significant.

**Discussion:** Although >800 mg/day quetiapine did not result in increased extrapyramidal symptoms, greater weight gain was observed and no advantage in reduction of symptom severity was demonstrated.

doi:10.1016/j.schres.2010.02.670

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**Poster 176**

**SCHIZOTYPAL PERSONALITY IN HEALTHY ADULTS IS RELATED TO BLUNTED HPA AXIS REACTIVITY**

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**Background:** Schizotypy is conceptualized as a non-clinical manifestation of the underlying biological factors that contribute to schizophrenia spectrum disorders and is viewed as a dimensional trait ranging from healthy people to schizophrenic spectrum patients. In accord with this view, schizotypal personality and schizophrenia have been suggested to share common genetic, neuroimaging, neuropsychological and neurocognitive abnormalities. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis, and schizophrenia, a disorder where stress plays an important role in its development and course, has been associated with altered HPA axis function including hypercortisolism and blunted cortisol reactivity; however, HPA axis function in relation to schizotypal personality has not been well documented. One of the frequently used measures to assess HPA axis function is the pharmacological challenge paradigm such as the dexamethasone suppression test (DST) and dexamethasone/corticotropic releasing hormone (Dex/CRH) test. The Dex/CRH test is an integrated challenge test for HPA axis function that combines Dex-pretreatment with CRH administration on the following day; thus, it is essentially a DST followed by CRH challenge. In studies of patients with mood disorder, the sensitivity of this test has been shown to be high.

**Methods:** We examined the relationship between schizotypal traits as assessed with the Schizotypal Personality Questionnaire (SPQ) and cortisol response to the Dex/CRH test in 131 volunteers without DSM-IV axis I disorders. The Dex/CRH test was performed based on a simple test protocol. First, participants took 1.5 mg of Dex orally at 2300 h. On the next day, they attended our laboratory and sat on a comfortable couch in a calm room. A vein was cannulated at 1430 h to collect blood at 1500 and 1600 h and to administer CRH at 1500 h, via an intravenous catheter. Outcome measures of this test were the DST- Cortisol (i.e., the concentration of cortisol just before CRH infusion) and Dex/CRH-Cortisol (i.e., the concentration of cortisol 1 h after the CRH infusion). By referring to several previous studies, a cut-off criterion for cortisol suppression status was considered as follows; ‘incomplete-suppressors’ were defined to be individuals where either or both of DST- and Dex/CRH-Cortisol were equal to or more than 5 μg/dL. ‘Enhanced-suppressors’ were defined as those individuals who...
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THE PHARMACOLOGICAL MANAGEMENT OF AGITATED PATIENTS IN EMERGENCY PSYCHIATRIC HOSPITALS IN RIO DE JANEIRO - BRAZIL: THE RESULTS OF TWO PRAGMATIC RANDOMIZED CLINICAL TRIALS

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Background: In Brazil the combination of haloperidol plus promethazine is frequently used (>80%) for agitated and violent patients. TREC trials (Rapid Tranquilisation Clinical Trial [translated from Portugese]) were designed to determine the relative value of this combination.

Methods: Design, Setting, and Patients Two randomised, pragmatic, open trials in three psychiatric emergency rooms in Rio de Janeiro, Brazil. Patients requiring urgent IM sedation because of agitation and/or dangerous behavior. Interventions TREC-Rio-1 (ISRCTN44153243) haloperidol 5-10 mg IM plus promethazine up to 50 mg IM compared with midazolam (up to 15 mg). TREC-Rio-2 (ISRCTN83261243) haloperidol 5-10 mg IM plus promethazine up to 50 mg IM compared with haloperidol 5-10 mg IM. Doses were at discretion of prescribing clinician. Outcome Measures Primary outcome, chosen by the staff of the emergency rooms: proportion of patients tranquil or asleep by 20 minutes. Secondary outcomes: tranquil or asleep by 40, 60 and 120 minutes, physically restrained or given additional medication within 2 hours, severe adverse events, another episode of agitation/aggression, additional visit from the doctor during the subsequent 24 hours, overall antipsychotic load in the first 24 hours and still in hospital after 2 weeks.

Results: TREC-Rio-1 - 151 patients were randomised to midazolam, and 150 to the haloperidol-promethazine mix. Primary outcome available for 298 (99%), 73% of whom were thought to have a psychotic illness. Patients allocated midazolam were more likely to be tranquil or asleep by 20 minutes compared with those receiving haloperidol-promethazine IM (RR 1.32 95%CI 1.16 to 1.49, NNT 5 95%CI 3-8). By 40 minutes, midazolam still had a statistically and clinically significant 13% relative advantage but after 1 hour, about 90% of both groups were tranquil or asleep. One important adverse event occurred in each group: a patient given midazolam had transient respiratory depression, and one given haloperidol-promethazine had a grade mal seizure. TREC-Rio-2 - 160 patients were randomised to haloperidol-promethazine and 156 to haloperidol alone. The Data Monitoring Committee advised that the study should be stopped after they saw the results of the interim analysis. Primary outcome data available for 311 (98.4%), 77% of whom were thought to have a psychotic illness. Patients allocated haloperidol-promethazine were more likely to be tranquil or asleep by 20 minutes compared with those receiving haloperidol IM alone (RR 1.30 95% CI 1.10-1.55, NNT 6 95% CI 4-16). There were no differences after 20 minutes. There were, however, ten cases of acute dystonia, all in the haloperidol alone group.

Discussion: Haloperidol-promethazine is a better option than haloperidol alone in terms of speed of onset of action and safety. Compared to midazolam, both treatments were effective. Midazolam was more rapidly sedating than haloperidol-promethazine, reducing the time people are exposed to aggression. Adverse effects and resources to deal with them should be considered in the choice of the treatment. There are now enough data to change guidelines and haloperidol alone should no longer be recommended. Trials evaluating new generation of anti-psychotics should use haloperidol plus promethazine as a comparator.

doi:10.1016/j.schres.2010.02.671

Poster 178
INVESTIGATION THE ROLE OF DOPAMINE D1 AND 5-HT1A RECEPTORS IN THE REVERSAL OF SUB-CHRONIC PHENCYCLIDINE INDUCED DEFICITS IN COGNITION AND SOCIAL BEHAVIOR, BY THE ATYPICAL ANTIPSYCHOTIC CLOZAPINE

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Background: We have consistently shown that sub-chronic phencyclidine (PCP), produces robust cognitive and behavioural deficits of particular relevance to schizophrenia. Acute administration of the atypical antipsychotic clozapine can reverse some of these deficits (Grayson et al., 2007 Behav Brain Res. 184(1), 31-38, Abdul-Monim et al., 2006 Behav Brain Res 169(2), 263-273.). The aim of this study was to investigate receptor mechanisms involved in the reversal of these deficits by clozapine.

Methods: Adult female hooded-Lister rats were treated with PCP at 2 mg/kg (i.p.) or vehicle twice daily for 7 days, followed by 7 days washout. Rats were tested for cognitive function using the novel object recognition (NOR) and reversal learning tasks and social behaviour deficits. We then determined the ability of clozapine (2.5 mg/kg) alone, and in the presence of the dopamine D1 or 5HT1A receptor antagonists, SCH-23390 (0.05 mg/kg) or WAY100635 (1 mg/kg) respectively, to reverse these deficits.

Results: In all experiments sub-chronic PCP induced a significant and selective impairment in performance of the cognitive tests and social behaviour (p<0.01-p<0.001). Clozapine attenuated the PCP-induced deficit in both cognitive tests (p<0.01-p<0.001), this effect of clozapine was blocked by SCH23390, (p<0.01-p<0.001) compared with PCP alone, but was not affected by WAY100635, showing D1 but not 5-HT1A receptor involvement. The effect of clozapine to reverse PCP-induced cognitive deficits was antagonised by SCH23390 but not WAY100635. In contrast, the effects of clozapine to reverse PCP-induced social behavior deficits were antagonised by WAY100635 but not by SCH23390. Clozapine restored the normal exploratory sniffing behaviour (p<0.01) which was significantly reduced in PCP-

doi:10.1016/j.schres.2010.02.672
treated animals (p < 0.01). A significant effect was also observed on avoiding behaviours with the clozapine treated animals spending significantly less time avoiding compared to the PCP group (p < 0.001). Co-administration of WAY100635 with clozapine prevented the beneficial effects of clozapine, rats showed significantly less sniffing behaviour (p < 0.05) and more avoiding behaviour (p < 0.05) when compared with the vehicle group.

Discussion: These results show a clear distinction of the mechanism by which clozapine can reverse cognitive and social behaviour deficits in animal models of relevance to schizophrenia. D1 receptor mechanisms are involved in effects of clozapine to improve cognitive deficits while 5-HT1A receptor mechanisms are important for its enhancement of social behaviour deficits. The use of such animal models in combination with pharmacological investigation will improve our understanding of the mechanisms underlying these symptoms and allow evaluation of novel therapies.

doi:10.1016/j.schres.2010.02.673

Poster 179
EFFECTS OF ADD-ON MIRTAZAPINE ON NEUROCognition IN SCHIZOPHRENIA: AN OPEN LABEL EXTENSION PHASE OF A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY, AND BOTH PHASES

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Background: Neurocognition has a crucial effect on functional outcome in schizophrenia. Mirtazapine added to antipsychotics appears to improve negative and likely also positive symptoms of schizophrenia. Preliminary studies have shown also desirable effects of add-on mirtazapine on neurocognition in schizophrenic patients. This study explored the effects of adjunctive mirtazapine on neurocognition in patients with chronic schizophrenia who had an insufficient response to first generation antipsychotics (FGAs). The results of our previously reported 6 week study favored add-on mirtazapine over placebo, but the short duration of treatment was a limitation. The 6 week extension phase study was set up to explore the effects of a prolonged mirtazapine treatment.

Methods: Thirty six patients with chronic schizophrenia, at least moderately ill despite their FGAs in stable doses, received add-on mirtazapine (n=18) or placebo (n=18) in a 6-week double-blind, randomized trial with a 6 week open label extension phase. Visual-spatial functions, verbal and visual memory, executive functions, verbal fluency, and general mental and psychomotor speed were explored with widely used neuropsychological tests. The Modified Intent-to-Treat data (those for patients with at least one on-medication, i.e., week 12 assessment) for open label phase were analyzed with Last Observations Carried Forward (LOCF). Corrections for multiple testing were performed with False Discovery Rate.

Results: At double-blind phase, 8 tests of 21 measured improved with add-on mirtazapine (vs. 1 test with add-on placebo); in between group comparison, mirtazapine outperformed placebo on the Block Design (change of 23.4% vs. 4.5%, respectively, t = 3.0, p = 0.007). During open label mirtazapine extension phase, the 36 patients showed statistically significant improvement on 12/21 tests. During both phases, patients who received mirtazapine throughout the whole 12 week study (middle-term group) demonstrated improvement on 17/21 tests (vs. 10/21 for those who received mirtazapine during 6 weeks of the open label phase only, i.e. short-term group). Between group analysis favored middle-term add-on mirtazapine treatment over short-term treatment as shown with a statistically significant difference on Stroop Dots time (change of -17.7% vs. -0.3% t = -2.56, p = 0.035) and number of mistakes in Trail Making Test, part B (-72.5% vs. -27.1%, t = -2.42, p = 0.043).

Discussion: Add-on mirtazapine seems to improve neurocognition in FGA treated patients with difficult-to-treat schizophrenia. A prolonged treatment may yield additional benefits. Further studies are needed to elucidate the effects of mirtazapine-induced neurocognitive enhancement on the psychosocial functioning in this challenging population.

doi:10.1016/j.schres.2010.02.674

Poster 180
ANTI-DEPRESSIVE EFFECTIVENESS OF OLANZAPINE, QUETIAPINE, RISPERIDONE, AND ZIPRASIDONE: A RANDOMIZED, NATURALISTIC STUDY

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Background: Mood stabilizing properties including anti-depressive effects have been disclosed for some of the second generation antipsychotics (SGAs). We have previously demonstrated differential antipsychotic effectiveness among olanzapine, quetiapine, risperidone, and ziprasidone. The main aim of this rater-blind, randomized, naturalistic study was to determine whether differences exist among these first-line SGAs regarding relief of symptoms related to depression and suicidal ideation.

Methods: Patients (age ≥ 18 years) acutely admitted with psychosis to a single-site hospital were eligible for the study. The hospital is responsible for all the acute admissions in the catchment area of about 400000 inhabitants, thus supplying information from a diverse population representing everyday clinical practice. The patients were randomized to risperidone, olanzapine, quetiapine, and ziprasidone, and tested at intervals for up to 2 years. The main outcome measures were change of the scores of item G6 (Depression) in the Positive and Negative Syndrome Scale (PANSS), general psychopathology subscale; as well as the use of concomitant mood stabilizers, antidepressants, and benzodiazepines.

Results: A total of 226 men (67.3%) and women (32.7%) were included. At baseline mean age with standard deviation (SD) was 34.1 (13.5) years and 44.2% were antipsychotic drug naïve. The distribution of ICD–10 diagnoses were: schizophrenia and related disorders 44.5%; acute and transient psychotic disorder 21.3%; drug-induced psychotic disorder 13.4%; mood disorders with psychotic symptoms 10.6%; non-organic unspecified psychotic disorder 5.1%; miscellaneous psychotic disorders 5.1%. Baseline CDSS total score with SD was 6.5 (5.3) and PANSS G6 score was 3.2 (1.6). Baseline PANSS total score with SD was 74.0 (13.4), the Clinical Global Impression – Severity of Illness scale score was 5.2 (0.6), and the Global Assessment of Functioning scale – Split Version, Functions score scale score was 30.7 (6.0). Mean doses in milligrams with SD for the antipsychotics were for olanzapine 14.5 (5.0); quetiapine 339.3
(193.4); risperidone 3.3 (1.1); and ziprasidone 100.3 (42.2). There were no substantial differences among the SGAs with regards to change of any depression item in the rating scales. There were no substantial differences among the SGAs regarding concomitant use of mood stabilizers, antidepressants, or benzodiazepines.

**Discussion:** Differential effectiveness among the SGAs against symptoms of depression was not disclosed in this heterogeneous sample. The results do not support preference of any particular agent among the SGAs under investigation for targeting symptoms of depression in a patient acutely admitted with psychosis.

**References**


doi:10.1016/j.schres.2010.02.675

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**Poster 181**

**GENE EXPRESSIONS IN FRONTAL CORTEX OF RATS INDUCED BY CHRONIC ADMINISTRATION OF RISPERIDONE**

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**Background:** Novel direction of antipsychotic target identification is using gene array. Although risperidone is a dopamine and serotonin antagonist that rapidly regulates those system's receptors in the brain, the therapeutic effect takes several weeks after administration, which suggests that altered gene expression is involved in the antipsychotic action. We studied the gene expressions in the rat frontal cortex induced by the risperidone chronic release form (Consta).

**Methods:** After 2-time injection of Consta (2 mg/kg) with a 15 day-interval, total RNA was extracted from the frontal cortex of rats (Wistar male rat, 350 gr) and cDNA was synthesized by reverse transcriptase. Differential expressed genes were screened by the ACP-based PCR method (Kim et al., 2004) using the GeneFishing™, DEG kits (SeeGene, Seoul, South Korea). The differentially expressed bands were re-amplified and extracted from the gel by using the GENCLEAN® II Kit (Q-BIO gene, Calsbad, CA, USA), and directly sequenced with ABI PRISM® 3100-Avant Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). The differential expression of DEG was confirmed by RT-PCR using gene specific primer pair.

**Results:** This study shows that the expressions of Kcnq2 gene for the regulation of neuronal excitability, Resp18 for the regulation of corticotropes, RapPh gene for prion protein, Snpa2 gene for the membrane organization, Ptpns1 gene for membrane signaling, Protein kinase, cAMP dependent regulatory, type I, beta, mRNA, and Phospholipid-transporting ATPase II B, mRNA in the frontal cortex of rats are upregulated 1 month after risperidone injection (Consta; 2 mg/kg) compared with those of control. But the expression of Neurofilament polypeptide NF-H C-terminus mRNA in the frontal cortex of rats is downregulated 1 month after risperidone injection (Consta; 2 mg/kg) compared with those of control. Also Erthyrocyte protein band 4.1-like 4b (predicted) (Epba114b_predicted) mRNA, Nitrogen fixation cluster-like (predicted) (LOC288740), mRNA, Brain specific membrane-anchored protein precursor (predicted) (RGD105557_predicted), mRNA in the frontal cortex of rats that their function are not shown are upregulated 1 month after risperidone injection (Consta; 2 mg/kg) compared with those of control.

**Discussion:** Organized neuronal firing is important for cortical processing and is disrupted in schizophrenia. In this study, Kcnq2 gene related to the regulation of neuronal excitability is upregulated. The effect of risperidone might be related to the neuronal firing by the regulation of potassium channel. Chronic treatment of risperidone increases Resp-18 expression that is regulated by dopamine in the CNS and is involved in regulation of limbic and autonomic function. This might mean the effects of risperidone is related to the upregulation of Resp-18 gene. Upregulated RapPh gene for prion protein also might be associated with schizophrenia followed by slowly processing cognitive impairment and focal cortical atrophy. Ptpns1 upregulated in this study increases the function of BDNF that has been implicated with the pathogenesis of schizophrenia. Other genes, including Snpa2 and Protein kinase mRNA, that may be involved in the therapeutic effect, the therapeutic leg time and the adverse effects of risperidone are upregulated and downregulated, and further studies for the correlation between the changes of gene expression by chronic treatment of risperidone and the clinical effect, the therapeutic leg time, and the adverse effect of risperidone are needed.

doi:10.1016/j.schres.2010.02.676

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**Poster 182**

**A DOUBLE-BLIND, RANDOMIZED, RISPERIDONE-COMPARATIVE STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BLONANSERIN IN PATIENTS WITH SCHIZOPHRENIA**

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**Background:** The objective of this study was to evaluate the efficacy and tolerability of Blonanserin, a combined 5-HT2A and D2 receptor antagonist, for the treatment of adult patients with schizophrenia.

**Methods:** This was a multi-center, randomized, double-blind, risperidone-comparative trial from January 2006 to December 2008. Patients aged 18 through 65 years with schizophrenia (DSM-IV criteria) and a baseline PANSS score of ≥60 were randomly assigned to blonanserin or risperidone for 8 weeks. The efficacy was assessed by mean change from baseline to week 8 on the PANSS total score as the primary variable. Mean change from baseline to week 8 was also assessed for the BPRS and CGI-I scores. Safely assessments included vital sign, physical routine clinical laboratory tests, and adverse events including extrapyramidal adverse drug reactions assessed according to the Drug-induced extrapyramidal symptom scale. The full analysis set was used in the primary efficacy analysis and the per-protocol set was used in an additional analysis to verify the accuracy of results of the primary analysis.

**Results:** Of 212 randomly screened patients, 103 receiving blonanserin and 103 receiving risperidone were included in the analysis. The change in PANSS total score at the final evaluation time point was -10.80 ± 9.57 for the blonanserin group and -11.87 ± 9.52 for the risperidone group. The BPRS total score was decreased from baseline in
both treatment groups (-14.58 ± 11.60 vs. -15.84 ± 11.79). Adverse drug reactions (ADR) occurred in 72 of 96 subjects (75.0%) in the blonanserin group and 73 of 93 subjects (78.5%) in the risperidone group. ADRs of which incidences were lower in the blonanserin than in the risperidone group (p<0.05) included dizziness (p=0.0139), dysarthria (0.0288), blurred vision (0.0288) and increased ALT and AST (p=0.0183, 0.0067, respectively). Blonanserin may have advantage in weight gain and hyperprolactinemia (p<0.0504) although there was no statistical significance (p=0.0504). On the other hand, ADRs of which incidences were higher in the blonanserin than in the risperidone group (p<0.05) included tremor (p=0.0010).

**Discussion:** This study indicated that the therapeutic effect of blonanserin was comparable to that of risperidone while having a better safety profile, suggesting that blonanserin is useful for the treatment of schizophrenia.

doi:10.1016/j.schres.2010.02.677

**Poster 183**  
EFFECTIVENESS OF SWITCHING FROM ARIPIPRAZOLE TO ZIPRASIDONE IN PATIENTS WITH SCHIZOPHRENIA

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**Background:** Aripiprazole and ziprasidone are the second generation antipsychotics with the lowest risk for metabolic disturbances. This study aimed to evaluate the effectiveness of switching to ziprasidone in patients who had insufficient response or intolerance to aripiprazole for treatment of schizophrenia.

**Methods:** Nineteen patients receiving aripiprazole treatment for schizophrenia participated in this open-label, 12-week study. Outcome measures included the Positive and Negative Syndrome Scale, Social and Occupational Functioning Assessment Scale, Calgary Depression Scale for Schizophrenia, Beck Depression Inventory, and Subjective Wellbeing under Neuroleptics Scale. Safety measures included metabolic parameters and scales to evaluate extrapyramidal side effects.

**Results:** After switching to ziprasidone from aripiprazole, significant improvement of scores on the negative symptom subscale of the Positive and Negative Syndrome Scale, the Social and Occupational Functioning Assessment Scale, the Calgary Depression Scale for Schizophrenia, and the Beck Depression Inventory were observed at the study end-point evaluation. Metabolic parameters including body weight, waist and hip circumference, fasting blood glucose, and ALT showed statistically significantly decreases. However, serum prolactin levels were significantly increased, and sedation was the most common adverse event.

**Discussion:** Switching to ziprasidone in patients with schizophrenia who showed insufficient response or intolerance to aripiprazole improved depression, negative symptoms, and metabolic disturbances. However, sedation and hyperprolactinemia were commonly associated with the switch to ziprasidone.

doi:10.1016/j.schres.2010.02.678
Background: Dopamine D2 receptors are the primary target of antipsychotic treatment; antagonism at this receptor is thought to be critical to antipsychotic function. The D2 dopamine receptor has emerged as a possible pharmacological target, in part because of its high density in the ventral striatum, a core area involved in schizophrenia pathology. In animal models, D2-selective antagonism appears to modulate motor disturbances and improve cognition. The addition of significant D3 antagonism to D2 antagonism is hypothesized to offer reduced risk for extrapyramidal symptoms, cognitive enhancement, and improvement in the negative symptoms of schizophrenia. Cariprazine is a novel D3/D2 antagonist-partial agonist in clinical development for the treatment of schizophrenia and acute mania. The pharmacological profile of cariprazine as determined by in vitro, ex vivo, and in vivo evaluation is reported.

Methods: In vitro studies: receptor binding profile and D3/D2 functional activity were evaluated. Behavioral assays: cariprazine was tested in a battery of standard antipsychotic assays supplemented with a cognitive test. Receptor occupancy studies: [3H]cariprazine binding in rat brain sections was determined by autoradiography. In vivo occupancy of striatal and limbic dopamine D3/D2 receptors was measured by displacement of [3H]raclopride (D2/D3 receptor antagonist) in mice. In cynomolgus monkeys, PET scanning measured D3/D2 occupancy using [11C]MNPA (D2/D3 agonist) and [11C]raclopride: occupancy at 5-HT1A receptors was measured by [11C]WAY-100635 (selective 5-HT1A antagonist).

Results: Cariprazine displayed high affinity for human D3 receptors, 5- to 8-fold selectivity over D3, 5-HT2B, and 5-HT1A receptors, and >200-fold selectivity over other targets studied. In functional assays, cariprazine showed both antagonist and partial agonist activity at D3 and D2 receptors. Cariprazine potent inhibits apomorphine-induced climbing, psychostimulant-induced hypermotility, and conditioned avoidance response (CAR). Cariprazine reduced catalepsy and improved learning performance of scopolamine-impaired rats in the water-labyrinth. [3H]Cariprazine binds to striatum, nucleus accumbens, islands of Calleja, and to lesser degree, hippocampus, indicating its primary sites of action. Cariprazine dose-dependently and almost completely displaced [3H]raclopride binding from striatal and olfactory tubercle D3/D2 receptors in mice. PET primate studies showed significant D3/D2 occupancy with much higher affinity for these receptors compared with 5-HT1A.

Discussion: Cariprazine has high affinity for D3/D2 receptors with D3 preference and demonstrates antagonist-partial agonist characteristics in vitro and in vivo. In a battery of behavioral tests, cariprazine shows potent antipsychotic-like activity with cognitive enhancing-like effects and low risk of catalepsy. Autoradiography and PET studies indicated that cariprazine strongly binds to dopaminergic regions; receptor occupancy is within the effective range predicted by currently used atypical antipsychotics. Cariprazine has a unique pharmacological profile that may provide benefits in the treatment of schizophrenia, bipolar mania, and depression. Further clinical development is planned based on positive results in recent Phase II trials in schizophrenia and bipolar mania.

doi:10.1016/j.schres.2010.02.680

Poster 187
THE ADDITION OF TIAGABINE TO ANTIPSYCHOTIC MEDICATION IN THE TREATMENT OF RECENT-ONSET SCHIZOPHRENIA BY MODIFICATION OF DEVELOPMENTAL PRUNING OF PREFRONTAL CIRCUITRY

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Background: The overt symptoms and deficits of schizophrenia (SZ) typically begin to emerge during late adolescence and early adulthood, followed by a period of post-onset functional deterioration. This peri-onset period temporally coincides with the final maturation of the prefrontal cortex (PFC), which is characterized by a process of extensive pruning of synaptic connectivities. Increasing evidence suggests that upregulation of GABA (gamma aminobutyric acid) neurotransmission may play an important role in regulating the onset and duration of peri-adolescent synaptic pruning. It is postulated that deficient GABA neurotransmission, especially one that is mediated by the inhibitory neurons that contain the calcium buffer protein parvalbumin (PV), may disturb the synaptic pruning process and hence contribute to the onset of schizophrenia. Enhancement of GABA neurotransmission may therefore restore the integrity of PFC neural circuits, which may then lead to lasting improvement in cognitive deficits and clinical symptoms.

doi:10.1016/j.schres.2010.02.681

Poster 186
LARGE EFFECT OF BASELINE TREATMENT WITH LONG ACTING ANTIPSYCHOTIC DRUGS ON RANDOMIZED TREATMENT OUTCOMES

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Background: In the CUtLASS 1 Trial (Jones et al., 2006) patients with an inadequate clinical response or intolerance were randomised to either a first generation antipsychotic (FGA) drug or a (non-clozapine) second generation antipsychotic (SGA) with assessments at baseline, 12, 26 and 52 weeks following randomisation. The primary outcome was quality of life (QOL) measured using the QLS, with secondary outcome measures including symptoms (PANSS), depression (CDSS), overall functioning (GAF), drug attitude (DAI) and adherence (Kemp). Non-neurological side effects (ANNERS) and neurological side effects (Simpson-Angus, AIMS, Barnes) were also assessed. Would outcome during the course of the trial be affected by the delivery route of the antipsychotic drug prescribed at trial entry?

Methods: Forty per cent (N=90) of the 227 patients entering the CUtLASS 1 Trial were being treated with a depot FGA antipsychotic prior to randomisation.

Results: Fitting multi-level mixed-effects models using Stata 11 and including demographic variables and baseline attitudes to medication as predictors showed that: QLS was significantly reduced (~5.7 points; CI -10.1, -1.4) at final visit in those receiving depot before randomisation. There was no significant difference in this effect between those who were randomised to first or second generation antipsychotics during the trial. The same pattern of results held for PANSS total score and GAF. Modelling centre as a separate level had little effect on coefficients of baseline covariates. Baseline DAI score indicating adherent attitudes predicted better outcome on all three measures (p<0.001).

Discussion: Participants randomised from depot medication at baseline had a significantly worse one-year outcome regardless of subsequent allocation to FGA or SGA than those taking oral medication at baseline. This may be due to reduced adherence. Once participants were randomised into the study, adherent attitudes were predictive of outcome. The effect was present whether the patient was randomised to a first or second generation antipsychotic during the course of the trial.

doi:10.1016/j.schres.2010.02.680
**Methods:** Thirty-six male or female SZ subjects with onset of psychosis within 3 years and between 18-25 years of age will be randomized to receive tiagabine (Gabitril), a selective uptake inhibitor of the GABA transporter GAT-1, which may preferentially enhance GABA neurotransmission furnished by the PV-containing cells during the peri-onset period, or placebo, added onto their antipsychotic regimen. We use a 2-back task and the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) battery to assess possible improve-ment in working memory and other aspects of cognition including attention, processing speed, reasoning and social cognition. In addition, we will explore the possible effects of tiagabine on clinical symptoms.

**Results:** Preliminary open-label phase of the study based on two young adult, recent-onset schizophrenia patients suggests that treatment with tiagabine during the early course of illness can modulate PFC activation, as demonstrated by functional magnetic resonance imaging during working memory, and improve negative symptoms.

**Discussion:** There has been compelling evidence in the literature suggesting that GABA neuronal circuits, especially those that are mediated by PV-containing neurons, are deficient in SZ. We postulate that deficits of these neurons during the peri-adolescent period may contribute to the onset of SZ by perturbing development-mental synaptic pruning. Hence, enhancement of GABA neuro-transmission during the early course of SZ may restore, at least in part, these synaptic deficits. We have provided very preliminary yet promising evidence suggesting that tiagabine treatment during the early course of SZ might in fact be effective in normalizing PFC functions and improving clinical symptoms. Data to be obtained from the ongoing double-blind placebo-controlled clinical trial are expected to provide adequate statistical power to directly address our hypothesis.

doi: 10.1016/j.schres.2010.02.682

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### Poster 188

**ANALYSIS OF THE EFFECTS OF KETAMINE AND PHENCYCLIDINE ON ATTENTION AND WORKING MEMORY IN RATS**

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**Background:** Attentional deficits are a core feature of schizophrenia that may also precede the onset of psychotic symptoms resulting in cognitive impairments. The 5-choice-serial-reaction-time-task (5CSRTT) is used to measure aspects of attentional performance such as selective attention, vigilance, impulsivity and motivation (Carli et al., 1983). Working memory (WM) is often conceptualised as utilization of information over short intervals. Delayed matching to position (DMTP) is considered to tax working memory and has been shown to depend upon prefrontal cortex function (Sloan et al., 2006). NMDA receptor hypofunction has been suggested to underlie aspects of the symptomatology of schizophrenia and is associated with disruptions in learning and memory mechanisms in animals (Koek 1999). The NMDA receptor antagonists phencyclidine (PCP) and ketamine showed no significant disruptive effects. However at 10 mg/kg, there was a trend level increases in latencies (p>0.05).

**Discussion:** These data show effects on motoric but not motiva-otional measures that were not confounded by motor impairments and may reflect specific cognitive deficits; this is unlike the effects seen with this dose at shorter pre-treatments in our tasks for working memory, attention and impulsivity.

**References**


doi: 10.1016/j.schres.2010.02.683

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### Poster 189

**ASSESSMENT OF THE MAXIMUM TOLERATED DOSE (MTD) OF LURASIDONE IN PATIENTS WITH SCHIZOPHRENIA**

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**Background:** Lurasidone is a novel psychotropıc agent with a high affinity for dopamine D2 receptors (Ki 168), serotonin 5-HT2A (Ki 2.03), 5-HT1A (Ki 0.49), and 5-HT1A (Ki 6.75) receptors, and noradrenaline α2C receptors (Ki 10.80). Determining the MTD is a key component in the successful transition from Phase I to II. The MTD for antipsychotic agents is frequently considerably higher in patients than would be predicted from animal and healthy normal volunteer studies. We report here two linked studies in which we determine the MTD for patients treated with lurasidone.

**Methods:** Male Lister Hooded rats were trained on 5CSRTT or DMTP tasks. In 5CSRTT, animals nose-poked into recessed apertures on illumination of a light (0.5 s in training; 0.25 s in test) during the 5 s limited hold to earn a food pellet and to initiate a 5 s inter-trial interval (ITI). If animals made an incorrect response or no response (omission), the house-light extinguished, and a 5 s time-out period was imposed. Premature responses (during the ITI) were punished. Preseverative (additional responses in any hole) were counted but not punished. For the DMTP task, animals were required to respond when presented with a lever and the light stimulus above it. A delay period of between 1 and 32 s began. At the end of the delay, a head entry into the magazine initiated the choice phase. Rats were required to press the same lever, to earn a food pellet and a 5 s ITI began. If animals failed to make the appropriate response, the trial was recorded as an omission, the house-light extinguished, and the ITI proceeded in darkness. For both studies, PCP (1-3 mg/kg) was dosed 180 minutes prior, and ketamine (2.5-10 mg/kg) 120 minutes prior to start of test session, both sub-cutaneously.

**Results:** In 5CSRTT, following PCP administration, significant disruptive effects were seen at 3 mg/kg (using between-subjects analysis followed by planned comparisons where significant main effects were found) in measures indicating increases in impulsive and compulsive behaviours (p<0.01) and increases in latencies (p<0.001). Significant disruptive effects were seen at 5 and 10 mg/kg ketamine (using between-subjects analysis followed by planned comparisons where significant main effects were found) in measures indicating decrease in compulsive behaviours (p<0.01) and increases in latencies (p<0.001). Significant disruptive effects were seen at 2.5 and 5 mg/kg (using between-subjects analysis followed by planned comparisons where significant main effects were found) in measures indicating increases in bias and accuracy (p<0.001) and increases in latencies (p<0.001). Ketamine showed no significant disruptive effects. However at 10 mg/kg, there was a trend level increases in latencies (p>0.05).

**Discussion:** These data show effects on motoric but not motiva-otional measures that were not confounded by motor impairments and may reflect specific cognitive deficits; this is unlike the effects seen with this dose at shorter pre-treatments in our tasks for working memory, attention and impulsivity.

**References**

Poster 190

PRO-COGNITIVE EFFECTS OF METABOTROPIC GLUTAMATE RECEPTOR (mGLUR)/2/3 AND 5 AGONISTS IN RATS: A COMPARISON TO GLYCINE/NMDA RECEPTOR MODULATORS

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Background: Altered glutamatergic transmission is implicated in the mood and cognitive deficits of schizophrenia, and stimulation of the co-agonist GlycineB site on N-Methyl-D-Aspartate (NMDA) receptor has been proposed for its treatment. mGlur receptors have now also emerged as potential new targets, in particular agents that activate mGlur2/3 or mGlur5 receptors. However, behavioural studies of their influence on cognitive function remain limited. Thus, we examined the actions of a mGlur2/3 receptor agonist, LY354,740 (++)-15,25,5R,6S-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid) and a mGlur5 receptor agonist, CDPPB (3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide), in cognitive procedures in rats. Their actions were compared to those of the GlycineB/NMDA receptor agonists, glycine and D-serine.

Methods: In the novelty discrimination paradigm, the ability of an animal (male, adult, Wistar rat) to differentiate a relevant from an irrelevant stimulus is evaluated. A first juvenile was presented to for a 5-min period (P1). 30 minutes later, this juvenile was reintroduced for a second 5-min period (P2), together with a novel juvenile. Times of investigation of the juvenile by the adult during P1, and of each juvenile (novel and familiar) during P2, were recorded. Drug or vehicle was administered intraperitoneally (IP) or subcutaneously (SC), 30 min before P1. In the social recognition procedure, the same juvenile was presented to an adult rat for two consecutive 5-min sessions (T1 and T2). In a procedure of spontaneous loss of recognition, employing an inter-session interval of 120 min, drugs were administered just after the first session. In a second procedure without an inter-session interval, “amnesia” was induced by the muscarinic antagonist, scopolamine (1.25 mg/kg, s.c.), injected 30 minutes before the test, and drugs were given 45 minutes before scopolamine. Drug doses are expressed in terms of the base.

Results: LY354,740 (0.63-2.5 mg/kg, IP) and CDPPB (0.16-10 mg/kg, IP) both dose-dependently and significantly improved novelty discrimination. Further, they did not modify times of investigation during P1, or total exploration time (familiar + novel) during P2, suggesting a specific effect upon cognition. Similarly, glycine (0.63-800 mg/kg, IP) and D-serine (40-160 mg/kg, IP) improved cognitive performance. In the social recognition test, CDPPB (2.5 mg/kg, IP) and LY354,740 (2.5 mg/kg, IP), as well as Glycine (10-200 mg/kg, SC) and D-serine (40-200 mg/kg), attenuated scopolamine-induced amnesia. Further, though LY354,740 (0.63 mg/kg, IP) was ineffective, CDPPB (0.63-10 mg/kg, IP), mimicked glycine (10-800 mg/kg, IP) and D-serine (2.5-160 mg/kg, IP), in dose-dependently reversing the delay-induced loss of recognition. When a different juvenile was presented to the adult rat during the second test session, the drugs did not decrease investigation time, revealing their specificity of action.

Discussion: Like GlycineB/NMDA receptor agonists, both mGlur2/3 and mGlur5 receptors agonists improve novelty discrimination in rat and reverse scopolamine-induced disruption of social recognition. These data suggest that stimulation of mGlur2/3 and mGlur5 receptors may be beneficial for alleviating certain cognitive deficits associated with schizophrenia.

doi:10.1016/j.schres.2010.02.685
Background: The primary aim of this study is to investigate status of the neuro-and enteroendocrine axes with focus on beta - cell function in relation to insulin resistance, lipid profile abnormalities, proinflammatory adipsokins and weight gain in patients during treatment with antipsychotics (AP). The second aim is to evaluate the association between weight gain and patients' perception of their quality of life and health.

Methods: Cross-sectional study. We will compare effect parameters in patients who were treated with AP and who have gained weight or not gained weight compared with healthy controls, matched by age, gender and waist circumference. Only one-time blood sampling for each person will take place. Psychiatric data and effect parameters will be analyzed by validated scales. Effect parameters: Enteroendocrine / insulin axe: GLP-1 and GIP Neuroendocrine / insulin axe: GH, IGF-1 and IGFBP-3 Well-known beta - cell markers: HbA1c, proinsulin, C-peptide, glucagon. Markers which influence on beta - cell function: leptin, adiponectin, IL-6,TNF-alfa, PAI-1, ghrelin Metabolic syndrom (MS) markers: plasmaglycerides, HDL-cholesterol, plasmainsulin, plasmaglucose, IGFBP-2 Other markers: prolactin, ASAT/ALAT and CRP. Psychiatric data and effect -targetets: Psychiatric symptoms and functional abilities (GAF and GGI scales), patients' satisfaction with medication/compliance (DAI-30 scale), patients' experience of side - effects (UKU-SERS-Pat-scale), patients quality of life (WHOGQL scale).

Statistic: \(\chi^2\)-test and regressions analyses. Subjects: 50 patients and 100 healthy control persons. Patients should be treated with minimum one antipsychotic and hospitalized or treated as out-patients in the Capital Region of Copenhagen. Healthy controls will be chosen from the database at the Institute of Health and Prevention, Glostrup.

Inclusion criteria: Gender: male Age: 18-45 Treatment with minimum one AP Ethnicity: Caucasian Informed consent given to take part in the project Exclusion criteria: One criteria is sufficient to exclude patients from the study: Compliance problems Unable to read, write and talk Danish Major lungs-, heart-, liver- and kidneys disorders Treatment with cholesterol-reducing and antihypertensive medication Abuse of alcohol or drugs Durass Mental illness for more than 15 years Diagnosis/treatment for NIDDM / IDDM.

Results: There are no results yet, because the project is in the data-collection stage. There have been collected data (plasma and scales) from 48 patients and 64 healthy controls at the moment (december 2009).

Discussion: There are no discussion of the results yet, because the project is in the stage of data-collection.

doi:10.1016/j.schres.2010.02.686

Poster 192
CONTEMPORANEOUS IMPROVEMENT OF COGNITIVE DYSFUNCTIONS AND PSYCHOTIC SYMPTOMS IN DRUG NAÏVE ACUTE PSYCHOSIS WITH ARIPIPRAZOLE

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Background: Several investigators have reported cognitive dysfunction in acute psychoses such as schizophrenia. The cognitive dysfunction in these patients was associated with insight and social skills. Therefore, cognitive dysfunction seriously hinders an immediate return to normal life. Other reports have described improvements of cognitive dysfunction with antipsychotic agents such as olanzapine. The antipsychotic aripiprazole is known to be a dopamine system stabilizer, the pharmacological mechanism of which is a unique partial agonistic action on dopamine 2 receptors. This study investigated improvement in cognitive function in drug naïve acute psychosis with aripiprazole.

Methods: Thirty-two drug naïve acute schizophrenia and schizophréniform disorder patients with adverse symptoms or side effects were assigned to a 24-week, open-label, and flexible-dose (6–30 mg/day) regimen of aripiprazole. Patients were assessed at baseline, 2, 4, 8, 12 and 24 weeks, and included the Positive and Negative Syndrome Scale (PANSS) and the Brief Assessment of Cognition in Schizophrenia, Japanese-language version (BACS-J)(except at 2 week). Written informed consent was obtained from each subject. This study was approved by the ethics committees at Fujita Health University School of Medicine and Okehazama Hospital.

Results: 20 patients accomplished this trial. The mean total scores of PANSS for the severity of symptoms decreased from baseline to 2, 4, 8, 12 and 24 weeks. Moreover, the mean composite scores of BACS-J for the recovery of symptoms increased from baseline to 4, 8, 12 and 24 weeks.

Discussion: Aripiprazole improved not only the psychotic symptoms but also cognitive dysfunction in acute drug naïve acute psychotic patients. However, because our subject group was small, it will be necessary to conduct a replication study using a larger number of patients.

doi:10.1016/j.schres.2010.02.687

Poster 193
PARTIAL AGONISTS IN SCHIZOPHRENIA – WHY SOME SUCCEED AND OTHERS DON’T. INSIGHTS FROM PRECLINICAL COMPARISONS

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Background: Until recently, the only mechanism that had been clinically successful in treating schizophrenia were D2-receptor blocking antagonists. While partial agonists have been considered for nearly four decades only one, aripiprazole, has succeeded while a host of previous partial agonists (preclamol, terguride, roxindole, talipexole, (+)-UH232, OPC-4392 and bifeprunox) have failed. This raises critically important mechanistic questions: What is unique about aripiprazole? Why did aripiprazole succeed while other partial agonists have failed? Can one distinguish between these drugs in acute preclinical animal models?

Methods: We compared and contrasted aripiprazole (0.3–30 mg/kg) with other clinically failed partial agonists: preclamol (0.3–30 mg/kg), terguride (0.03–3 mg/kg), OPC-4392 (0.3–30 mg/kg) and bifeprunox (0.3–10 mg/kg) in several convergent preclinical animal models. They consisted of brain D2 receptor occupancy (D2RO), catalepsy (motor side-effect), hyper-dopaminergia (amphetamine induced locomotion AIL), tests predictive of antipsychotic effects (inhibition of conditioned avoidance response CAR), ability to elicit motor activity in a model of hypodopaminergia (inhibition of contralateral movement in unilateral medial forebrain bundle 6-OH dopamine lesioned rats), Fos-immunohistochemistry, and prolactemia.

Results: These agents have affinity to a wide variety of receptors but affinity and partial agonism to the D2 receptor was the common denominator. The standard antipsychotic haloperidol was also used for comparison. All the partial agonists occupied D2 receptors and lacked motor side effects or prolactemia inspite of occupancies exceeding 90%. In this regard they are all similar, and contrast to haloperidol. They were all more effective in reducing AIL versus CAR, again a finding highlighting differences between partial agonists versus antagonists. The ability to inhibit (ED50) AIL (< 50% D2RO) and CAR (> 90% D2RO) were in a similar occupancy range indicating that though the partial agonists have affinity to a number receptors,
occupancy to dopamine D₂ receptors was the key. The tests amongst which they stood out were their ability to cause contralateral rotation in 6-OH dopamine lesioned rats and Fos expression in the nucleus accumbens. Aripiprazole caused the least rotation in 6-OH dopamine lesion model indicating very little intrinsic activity. The order of intrinsic activity in in-vitro assays corresponded to their ability to cause contralateral rotation (Pregabalin > Terguride > OPC4392 > Biplenox > Aripiprazole). Interestingly Fos expression in the nucleus accumbens above a certain threshold also predicted the success of aripiprazole. Aripiprazole induced Fos in the nucleus accumbens in a significant manner while other partial agonists minimally expressed them.

Discussion: In summary, though partial agonists are active in a number of antipsychotic animal models, low intrinsic activity and ability to induce Fos in the nucleus accumbens have been found to be a discriminator amongst them.

doi:10.1016/j.schres.2010.02.688

Poster 194
Poster not available

doi:10.1016/j.schres.2010.02.689

Poster 195
A FLEXIBLE-DOSE STUDY OF PALIPERIDONE ER IN NON-ACUTE PATIENTS WITH SCHIZOPHRENIA PREVIOUSLY UNSUCCESSFULLY TREATED WITH ORAL RISPERIDONE

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Background: To explore tolerability, safety and treatment response of flexible doses of paliperidone ER in adult non-acute patients with schizophrenia previously unsuccessfully treated with oral risperidone.

Methods: International prospective 6-month open-label study. Endpoints were the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity Scale (CGI-S), adverse events (AEs), extrapyramidal symptoms (Extrapyramidal Symptom Rating Scale; ERS) and weight change.

Results: 694 patients were included (59.2% male, mean age 40.0±12.8 years, 74.8% paranoid schizophrenia); most were enrolled because of lack of efficacy (n=366) or lack of tolerability (n=178) with prior oral risperidone treatment. 74.1% of patients (n=514) completed the 6-month study. Most frequent reasons for early discontinuation were patient choice (7.3%) and lack of efficacy (5.2%). The median mode dose of paliperidone ER was 6 mg/day, independent of the reason for switching. For all patients, mean total PANSS decreased significantly from 78.6±20.5 at baseline to 65.6±22.5 at endpoint (mean change -13.0±19.4; 95% confidence interval -14.5,-11.5, p<0.0001). The percentage of patients rated mildly ill or less in CGI-S increased from 28.3% to 52.5% at endpoint, and the rate of patients with mild functional impairment increased from 16.5% to 36.6%. AEs reported in >5% of patients were insomnia (8.8%) and anxiety (7.3%). Extrapyramidal symptoms in ERS decreased significantly from 3.8±6.1 to 2.3±5.1 (p<0.0001). Mean weight gain from baseline to endpoint was 0.4±4.3 kg.

Discussion: These data support results from recent randomized controlled studies that paliperidone ER is safe, well tolerated and effective in patients previously unsuccessfully treated with oral risperidone.

doi:10.1016/j.schres.2010.02.690

Poster 196
A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL OF PALIPERIDONE ER VERSUS ORAL OLANZAPINE IN PATIENTS WITH SCHIZOPHRENIA

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Background: To compare the longer-term metabolic effects and efficacy of paliperidone ER and olanzapine in patients with schizophrenia.

Methods: Prospective 6-month randomized open-label study evaluating flexible doses of paliperidone ER and oral olanzapine (OLA). Primary endpoint was the change in triglyceride to high-density lipoprotein (TG:HDIL ratio, a sensitive measure of insulin resistance. Additional endpoints were the Positive and Negative Syndrome Scale (PANSS), body weight, lipids, homoeostasis model of insulin resistance (HOMA-IR) and adverse events (AEs).

Results: 239 patients were randomized to paliperidone ER, 220 to olanzapine. Demographics and baseline characteristics were comparable. Mean daily doses were 6.9±1.3 mg for paliperidone ER and 11.6±2.3 mg for olanzapine. The TG:HDIL ratio for olanzapine significantly worsened from baseline to endpoint (0.42±1.19; p<0.0001); it remained unchanged for paliperidone ER (-0.08±1.10;p=0.4718; between-group difference p<0.0001). PANSS total scores at endpoint significantly improved (olanzapine -16.6±15.0; paliperidone ER -13.5±15.9; both p<0.0001 vs. baseline); the between-group difference met prespecified non-inferiority criteria. Weight change at endpoint was 3.8±5.9 kg for olanzapine and 1.2±4.6 kg for paliperidone ER (p<0.0001). Insulin resistance in HOMA-IR did not change with paliperidone ER (p=0.1507) but significantly worsened with olanzapine (p=0.003 vs. baseline). The most frequently reported treatment-emergent AEs (>5%) were weight increase (OLA 18.2%;Pali ER 9.6%), insomnia (OLA 1.4%;Pali ER 9.6%), somnolence (OLA 9.5%;Pali ER 3.3%) and schizophrenia (OLA 1.8%; Pali ER 5.0%).

Discussion: In this randomized controlled study paliperidone ER was superior to olanzapine with regards to insulin resistance, weight gain, lipid changes and other relevant metabolic endpoints. Efficacy was non-inferior between paliperidone ER and olanzapine.

doi:10.1016/j.schres.2010.02.691
Background: Suicide is substantially more frequent in individuals with schizophrenia than in the general population (Miles, 1977; Caldwell and Gottesman, 1990; Palmer et al., 2005). This report analyses the incidence of completed and attempted suicides in a population of patients with schizophrenia who took part in the sertindole cohort prospective (SCoP) study. With 9,809 patients enrolled, the SCoP study is one of the largest prospective randomized studies ever conducted in patients with schizophrenia. The size of the study allowed a relevant evaluation of the risk of suicide attempts in patients treated with sertindole compared with risperidone.

Methods: The incidence of suicide attempts (fatal and non-fatal) was analyzed in a prospective cohort of patients with schizophrenia who were randomly assigned to treatment with sertindole (4,905 pts.) or risperidone (4,904 pts.) in a parallel-group open-label study with blinded classification of outcomes (SCoP study). Firstly, completed suicide and suicide attempts were reported by the treating psychiatrists (investigators) according to the Medical Dictionary for Regulatory Activities (MedDRA). Secondly, suicide attempts were blindly reviewed by an independent expert group at Columbia University (New York), in accordance with the Columbia Classification Algorithm of Suicide Assessment (C-CASA) (Posner et al., 2007). Thirdly, an Independent Safety Committee, reviewed blinded case reports, and recorded completed suicide and suicidal behavior.

Results: The total exposure was 6,978 and 7,975 patient-years in the sertindole and risperidone groups, respectively. Suicide mortality in the study was low (0.21 and 0.28 per 100 patients per year with sertindole and risperidone, respectively). The majority (84%) of suicide attempts occurred within the first year of treatment. Cox’s proportional hazards model analysis of the time to the first suicide attempt, as reported by treating psychiatrists and blindly reviewed by an independent expert group according to C-CASA (both defined suicide attempts by the association of suicidal act and intent to die), showed a significantly lower risk of suicide attempt for sertindole-treated patients than for risperidone-treated patients. The effect was stronger during the first year of treatment. When suicide attempts were classified by an independent safety committee using a broader definition including all incidences of intentional self-harm, also those for which there was no clear suicidal intent, the results favored sertindole though not significantly. High-risk patients were those with a history of at least one suicide attempt during the five years prior to study entry. This high-risk group represented 7% of the total population but accounted for nearly 50% of the suicide attempts during the study. 35% of the high-risk patients had attempted suicide during the year prior to study entry. In this high-risk group, Cox’s proportional hazards model analysis of the time to suicide, as reported by the treating psychiatrists, showed a significantly lower risk of suicide attempt in the sertindole than in the risperidone group. As with the overall population, the effect became visible within the first year.

Discussion: Sertindole with its particular pharmacological profile might confer additional protection from suicide attempts in patients with schizophrenia, compared with risperidone.

References

doi:10.1016/j.schres.2010.02.692
**Discussion:** This work has confirmed previous findings using computerised tests of a broader range of impairments to attention in schizophrenia than is generally recognized. These and other core cognitive deficits in schizophrenia should be the initial therapeutic targets, and the recent successful treatment of the attentional deficits in DLB and PDD could partly inform future therapeutic strategies for treating the debilitating cognitive dysfunction in the condition.

doi:10.1016/j.schres.2010.02.693

**Poster 199**

**SERUM BDNF LEVELS ARE DETERMINED BY FUNCTIONAL POLYMORPHISM VAL66MET AND ASSOCIATED WITH COGNITIVE IMPAIRMENT IN CHRONIC SCHIZOPHRENIA**

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**Background:** The common functional polymorphism of brain-derived neurotrophic factor gene (BDNF Val66Met) is associated with episodic memory decrements in healthy controls and patients with schizophrenia. Studies suggest that the Val66Met may mediate hippocampal cognitive functions by modulating BDNF intracellular trafficking and activity-dependent BDNF release. Few studies however have reported its role in determining cognitive deficits in schizophrenia and whether peripheral BDNF levels may be useful to assess cognitive measures in schizophrenia. Objectives: To investigate the association between the functional BDNF Val66Met polymorphism, serum BDNF levels and cognitive performance and specificity of the BDNF Met variant on cognitive dysfunction in schizophrenia.

**Methods:** Design, Setting, and Participants: We compared the performance of 776 schizophrenic inpatients and 560 healthy controls on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Patient psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS). The BDNF Val66Met polymorphism was genotyped and serum BDNF levels measured and compared in both groups. Main Outcome Measures: Genotype effects on cognitive measures, BDNF serum levels, and clinical phenotype were examined using general linear models.

**Results:** Visuospatial/constructional abilities, significantly differed by genotype but not genotype × diagnosis. The Met allele was associated with poorer visuospatial/constructional performance than the Val allele in patients with schizophrenia and healthy controls. On attention performance, there were significant genotype and genotype × diagnosis effects. Met allele-associated attention impairment was specific to patients with schizophrenia but not healthy controls. Decreased serum BDNF levels and the degree of cognitive impairment in schizophrenia patients was dependent on the presence of the BDNFVal66Met polymorphism. Variation in BDNF was not associated with increased risk for schizophrenia; however, patients with the Met variant allele had an earlier age of onset.

**Discussion:** Our findings demonstrate the association between the BDNFMet variant and poor visuospatial/constructional performance. Furthermore, the BDNFMet variant may be specific to attentional decrements. This variant is also associated with earlier age of onset in schizophrenia. In addition, the presence of the BDNF Val66Met polymorphism is associated with decreased BDNF serum levels and cognitive deficits in schizophrenia.

doi:10.1016/j.schres.2010.02.694

**Poster 200**

**THE INITIAL PHASE OF THERAPY WITH CLOZAPINE: BEYOND WHITE BLOOD CELL SCREENING**

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**Background:** Clozapine is an effective antipsychotic drug in the treatment of therapy-resistant schizophrenia. Traditionally, to detect treatment-emergent agranulocytosis in an early stage, white blood cell count is mandatory in clozapine therapy. In recent years, two other serious side-effects, diabetic ketoacidosis and gastro-intestinal hypomotility, have come to the fore. The question is whether screening of these two side-effects should be included in regular screening in the initial phase of clozapine therapy.

**Methods:** We selected articles that informed us on the incidence rates of diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic syndrome and gastro intestinal hypomotility (GIH) respectively. With clozapine as the starting point we performed three searches of Pubmed and Medline using the terms diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome or gastro intestinal hypomotility. The compared the incidence rates found with that of the well-established incidence of treatment-emergent agranulocytosis.

**Results:** The incidence of agranulocytosis varied between 3.8‰ and 7.3‰. The mortality of the affected cases varied between 2.2% and 3.1%. We found two studies on the incidence rate of DK, which varied between 1.6‰ and 3.1‰. Only one of the two studies reported on the mortality rates; we found a third study that reported the mortality rate of DKA. The mortality rates of affected cases varied between 20% and 31%. We found only one case register study on GIH, that reported an incidence rates of 3% and a mortality rate of affected cases of 20.3%.

**Discussion:** The incidence rate of agranulocytosis is 2-5 times higher than that of the two side effects, DKA and GIH, under discussion. The mortality rates of affected cases is 10 times lower in agranulocytosis than in DKA or GIH. The mandatory status of white blood cell screening in clozapine therapy probably contributes significantly to the lower mortality rate of agranulocytosis. We therefore suggest to add standard screening of treatment emergent diabetes mellitus and gastro intestinal hypomotility in the initial phase of clozapine therapy to reduce their mortality.

doi:10.1016/j.schres.2010.02.695

**Poster 201**

**PREVALENCE AND SEVERITY OF ANTIPSYCHOTIC RELATED CONSTIPATION**

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**Background:** Constipation is a common, potentially lethal, but poorly researched side-effect of antipsychotic medication.

**Methods:** Retrospective record linking study (somatic medical files, pharmacy data and radiological data) on all consecutively admitted schizophrenia patients treated with antipsychotic in a University Psychiatric Hospital between June 2007 and March 2009.

doi:10.1016/j.schres.2010.02.694
Results: In the period studied there were 371 admissions of 273 patients with schizophrenia. 65.6% were male and the average age was 40 (+/0.13.5) years. 41.9% (N=99) of patients underwent at least one pharmacological intervention for constipation. Osmotic laxatives were most frequently used. The intervention with osmotic laxatives lasted more than one week in 90% of the cases. 10.2% of treatments for constipation involved enemas. In the study period there were 144 referrals (54 patients) to the medical centre for treatment and follow-up. 99 radiological (Rx, in 50 patients) examinations were performed to evaluate constipation after failure of first treatment. Only 5.8% of Rx did not confirm constipation. In 26.5% of case constipation was considered severe and 68.4% of Rx showed faecal impaction.

Discussion: Constipation is a frequently observed side-effect and it often requires medical intervention. Monitoring, early detection and treatment can prevent severe complications such as obstruction and ileus.

doi:10.1016/j.schres.2010.02.696

Poster 202
PROLACTIN SERUM LEVELS IN INSTITUTIONALIZED SCHIZOPHRENIC PATIENTS

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Background: High prolactin blood level is an adverse effect of neuroleptic treatment. Typical antipsychotics seem to produce it more frequently than atypical ones. Few studies look forward to study long-term inpatients. Institutionalized schizophrenic patients suffer of medical conditions but few studies have established if they differ in frequency to previous published data in schizophrenic population. Hyperprolactinemia is a risk factor for amenorrhea, osteoporosis and bone fracture.

Methods: We aim to find out the frequency of hyperprolactinemia in a group of schizophrenic institutionalized patients related to the type of antipsychotic drug used. This is an observational transversal study. Inpatients of our Hospital were asked to participate. Ethical approval and informed consent was given. We asked for participation to institutionalized schizophrenic patients, 171 inpatients accepted to participate, 31 male patients and 140 female ones, with a mean age of 61.67 years old and a mean hospital stay of 18.20 years. They were diagnosed of schizophrenia following ICD-10 criteria Prolactin serum levels were determined (normal values: 1.5-25 ng/ml for fertile age women, 0.7-20 ng/ml for post-menopause women and 0-20 ng/ml for men were set by our reference Pathology Service). Frequency of hyperprolactinemia for every group, single antipsychotic drugs, class of antipsychotic, age, gender and diagnosis were obtained.

Results: Frequency of hyperprolactinemia was 66.1% for the global sample. Results for the different groups were the following: - Typical antipsychotics group: 73.0% - Atypical antipsychotics group: 60.9% - Typical and atypical antipsychotics group: 71.4% - Statistical analysis according to specific antipsychotic drug showed the following frequencies of hyperprolactinemia: - Risperidone: 90.0% - Haloperidol: 69.2% - Olanzapine: 44.4% - Quetiapine: 33% - Aripiprazol: 14.3% - Clozapine: 11.1% - Hyperprolactinemia fluctuated in moderate values (between 25 and 99 ng/ml), but 20% of the patients showed higher values than 100 ng/ml.

Discussion: Our study finds lower hyperprolactinemia blood levels in the group of patients on atypical antipsychotic treatment than on typical antipsychotics. Haloperidol and risperidone got the highest frequency while clozapine and aripiprazol showed the lowest ones.

doi:10.1016/j.schres.2010.02.697

Poster 203
TARDIVE DYSKINESIA AND OTHER MOVEMENT DISORDERS IN FIRST EPISODE SCHIZOPHRENIC PATIENTS TREATED WITH SECOND GENERATION ANTIPSYCHOTICS

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Background: Higher risk of Tardive Dyskinesia (TD) has been classically associated with older ages and time under neuroleptic treatment. Use of second generation antipsychotics is considered to have resulted in a very low risk of extrapyramidal disorders including TD, but there is a lack of longitudinal systematic studies in recent onset first episode schizophrenic patients. We aim to describe the pattern of appearance of dyskinesia and other movement disorders in a sample of 112 first episode schizophrenia patients and study its possible relationship with personal and outcome variables.

Methods: Longitudinal and prospective study design. Patients were one hundred and twelve (mean age 23.35, median 22, SD 4.98). They were recruited at their first-episode schizophrenia (75%), schizophreniform (17%) or schizoaffective disorder (8%). Patients were randomly treated with either risperidone or olanzapine. Personal data inventory was collected and measures of movement disorder were included using the Hillside modified versions of Simpson Dyskinesia Scale, Sympson and Angus Scale - for parkinsonism and extrapyramidal disorders- and Barnes Akathisia Scale. Also CGI for positive symptoms and CGI for global symptomatology were used as a measure of improvement. Patients were assessed at baseline and periodically during follow-up.

Results: At first year of follow-up 75% of the patients remained in the study. 63% at the second and 47% at the third year. Fifty seven patients showed at least questionable signs of tardive dyskinesia during the three years follow-up. Thirteen patients showed at least mild dyskinetic features and in two cases dyskinetic movements were moderate. Three out of thirteen patients developed dyskinesia in the first year of follow-up. Kaplan-Meier survival analysis are shown. Younger patients were associated with higher risk of developing tardive dyskinesia (Mann-Whitney U p = 0.048). Also a tendency of younger age at first psychotic symptoms and treatment features was observed. Drug abuse or addiction and family history of schizophrenia failed to show any statistical significance. Ratings of Parkinsonism at the initial two weeks and two months of treatment were associated with CGI global measure of improvement at the first year of treatment (N:70, Spearman's rho p = 0.027, N:56, Spearman's rho p = 0.023) and, but not with CGI positive symptom improvement. Rating of at least mild dyskinesia throughout the study was not associated with CGI improvement at one year follow-up.

Discussion: Tardive dyskinesia is not a rare phenomenon during treatment with second generation antipsychotics. Lower age at first episode in schizophrenic patients is associated with development of tardive dyskinesia in the following years of atypical antipsychotics use. Movement disorders at onset and initial years of schizophrenia seems to be linked to measures of outcome and warrants further study as a marker of refractoriness.

doi:10.1016/j.schres.2010.02.698
Poster 204
ADOLESCENT RATS SHOW A REDUCED NEUROCHEMICAL REACTION COMPARED TO ADULTS IN RESPONSE TO CANNABINOID ADMINISTRATION

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Background: In humans, adolescent cannabis exposure is linked to the development of psychoses such as schizophrenia. Few studies in animal models though have examined the underlying neurochemical changes that occur in the brain after adolescent cannabinoid exposure. In this study, we compared the effects of treatment with HU210, a synthetic cannabinoid, in adolescent and adult rats. We focused on the cannabinoid CB1 receptor system and one of its downstream effectors, dopamine.

Methods: Adolescent (PN 35) and adult (PN 70) rats were treated daily with 25, 50 or 100 μg/kg HU210 for 4 or 14 days, or received a single dose of 100 μg/kg HU210 and sacrificed 24 hours later. Receptor density was investigated using in vitro autoradiography with the CB1 receptor ligand [3H] CP55,940 and dopamine D1 and D2 receptor ligands, [3H] SCH 23390 and [3H] raclopride, in cortical, limbic and subcortical brain regions. Body weight was recorded daily.

Results: In adolescent and adult rats, a similar pattern of dose and time dependent, region specific downregulation in CB1 receptor binding was seen after HU210 treatment. The highest dose of HU210 and longest treatment period resulted in the greatest reductions in binding. Regions where the largest reductions (78-88%; p<0.003) in binding took place included the hippocampus and hypothalamus. Smaller reductions (51-76%; p<0.0001) were seen in the thalamus and medial caudate putamen. The magnitude of CB1 downregulation however was smaller in adolescents than in adults by 10-16% and 6-28% in rats treated for 4 and 14 days respectively. The rate at which CB1 receptor downregulation took place was also slower in adolescents. After an acute dose of HU210 for example, a reduction of 30-55% was observed in adult rats, but in adolescents the acute dose only resulted in a decrease 8-31% in CB1 receptor density. An increase of 2-16% (p<0.003) in D1 receptor density was seen in adolescents after an acute dose of HU210 but no significant variation in D1 binding was noted in adolescents treated for 4 and 14 days. In contrast, in adults, an increase of 21-27% (p<0.0001) in D1 receptor density was found in rats treated for 14 days. No significant variation was found in D2 receptor density in any group of adolescent rats. In adults, significant variation in D2 receptor density was found in all groups with an increase of 1-19% (p<0.0001) in animals treated for 14 days.

Discussion: The smaller, slower decrease in cannabinoid receptor density in adolescents compared to adults following HU210 administration does not appear to be reflected in the ability of adolescent rats to develop tolerance to cannabinoids. In fact, in the present study, adolescents developed tolerance to the weight loss inducing effects of HU210 more rapidly than adult rats. The reduced neurochemical reaction in adolescents versus adults could contribute however to the long-term, adverse psychological consequences of cannabinoid exposure during adolescence. The smaller, slower reduction in CB1 receptor density in the adolescent brain after HU210 treatment may lead to over-stimulation of the CB1 receptor for a longer period than in adults. The lack of dopamine receptor upregulation in adolescents treated for 4 and 14 days also suggests a reduced ability to adapt to the drug stimulus. It appears that adolescent rats do not display the same compensatory mechanisms that are activated in the adult brain in order to maintain biological equilibria, following HU210 treatment. This may have adverse effects on the plastic changes occurring in the adolescent brain given the role of the endocannabinoid system in development and its interaction with other neurotransmitter systems.


Poster 205
REDOX DYSREGULATION AFFECTS PARVALBUMINE INTERNEURON’S INTEGRITY AND NEURAL SYNCHRONISATION IN VENTRAL BUT NOT DORSAL HIPPOCAMPUS

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Background: Increasing evidence points to involvement of oxidative stress in schizophrenia. GSH, a major redox regulator and antioxidant, is necessary for protection against cellular oxidative damage. Patients have decreased GSH levels in cerebrospinal-fluid and prefrontal cortex. Genetic and functional data indicate that impaired GSH synthesis represents a susceptibility factor for the disorder (Do et al., 2009).

Methods: Morphological, electrophysiological and behavioral studies were performed in knockout mice for the GCL modifier subunit (GCLM-/-) which showed 70% decrease in brain GSH levels.

Results: In GCLM-/- mice, GSH deficit induced induces a selective decrease of parvalbumin-immunoreactive (PV-IR) interneurons in CA3 and dentate gyrus of the ventral but not dorsal hippocampus. The regions showing deficit in PV also displayed signs of elevated oxidative stress, as revealed by DNA oxidation marker. Concomitantly, kainate-induced b/g oscillations (20-80 Hz) are significantly smaller in the ventral but not dorsal hippocampal slices of GCLM-/- compared to wild-type mice. Impairment of PV-IR interneurons emerges at the end of adolescence / early adulthood as oxidative stress increases or cumulates selectively in CA3 and DG of the ventral hippocampus. Such redox dysregulation altered stress and emotion-related behaviours but leaves spatial abilities intact, indicating functional disruption of the ventral but not dorsal hippocampus. Thus, a GSH deficit affects PV-IR interneuron’s integrity and neuronal synchrony in a region- and time-specific manner leading to behavioral phenotypes related to psychiatric disorders.

Discussion: Clinical and experimental evidence, combined with favorable outcomes of a clinical trial with the GSH precursor N-Acetyl-Cysteine on both negative symptoms (Berk et al., 2008) and auditory evoked potentials. The NMDA-dependent mismatch negativity (Lavoie et al., 2008) suggest that a genetic GSH synthesis impairment represents one major risk factor in schizophrenia. Redox dysregulation may constitute a “hub” where genetic and environmental vulnerability factors converge and their timing during neurodevelopment may play a critical role on schizophrenia phenotypes.

doi:10.1016/j.schres.2010.02.700
ADULT-ONSET GLUTAMATE RECEPTOR EXPRESSION DEFICITS IN THE HIPPOCAMPUS OF GLUTAMINASE-DEFICIENT MICE

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Background: Glutamate signaling in the hippocampus is fundamental to learning and memory; its disruption has been linked to schizophrenia and other disorders. Glutaminase-deficient mice (GLS1 hets), with reduced glutamate recycling, have a focal reduction in hippocampal activity and a selective deficit in hippocampal-dependent contextual learning. We asked whether expression of other enzymes in the glutamate-glutamine recycling pathway or glutamate receptors was affected in the hippocampus of GLS1 hets, and whether expression patterns change during development.

Methods: We collected hippocampal and cortical samples from GLS1 het and littermate controls at 3 ages and assessed gene expression using Affymetrix gene chips and rTPCR. We compared GLS1 hets to NR1 hypomorphs, which have reduced expression of the NMDA receptor subunit NR1 and model aspects of schizophrenia. Additionally, we examined context-dependent fear conditioning.

Results: In adult mice, GLS1 was downregulated, as expected, by ∼50%, while enzymes in related metabolic pathways were unaffected. Gene expression was altered in long-term plasticity pathway genes. GluR2 was downregulated by ∼40%. rTPCR confirmed the latter finding and further revealed an increase in GluR2 in cortex. In adolescent mice, GluR2 and NR1 expression were unaffected. Gene expression in GLS1 hets differed significantly from NR1 hypomorphs. In parallel to the genetid findings, contextual fear conditioning was unaffected in adolescence, but disrupted in adulthood, as we had shown previously.

Discussion: GLS1 deficiency does not affect other metabolic pathways, but does lead to adult-onset alterations in glutamate receptor expression, possibly accounting for adult-onset alterations in context-dependent learning. In the context of current knowledge of glutamate abnormalities in schizophrenia, and since GLS1 het gene expression patterns differ striking from NR1 hypomorphs, these findings support the idea that GLS1 hets do not model schizophrenia, but rather resilience to pro-schizophrenic challenges, and that inhibition of glutaminase may prove therapeutic in this disorder.

doi:10.1016/j.schres.2010.02.701

THE PUZZLE BOX AS A SIMPLE AND EFFICIENT BEHAVIORAL TEST FOR IMPAIRMENTS OF GENERAL COGNITION AND EXECUTIVE FUNCTIONS IN MOUSE MODELS OF SCHIZOPHRENIA

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Background: In light of the current breakthroughs that are unraveling molecular and genetic underpinnings of schizophrenia, it becomes indispensable to establish and/or refine new or currently available analytical tools in animal models. Cognitive symptoms of schizophrenia that primarily depend on the prefrontal cortex, and to some extent also on the hippocampus, i.e. attention deficits, working memory and executive function impairments, are important features of chronic manifestation of schizophrenia. Various behavioral rodent models have therefore been used when attempting to find animal correlates of cognitive symptoms, most of which require extensive labor and time, to name only few of their limitations. We tried here to establish a simple but informative test on executive functions in mice in different schizophrenia models.

Methods: The puzzle box is a behavioral test developed in rodents, in which subjects are presented with different problems of increasing difficulties, and are expected to solve the problems during a limited lapse of time. The arena consists of a white Plexiglas box divided by a removable barrier into two separate compartments: a big and brightly-lit start zone (58 cm long, 28 cm wide), and a smaller protected goal zone (15 cm long, 28 cm wide) containing sawdust and cardboards. Mice are trained to escape the start zone through an underpass (∼4 cm wide) located under a wall separating both zones. They have to undergo a total of nine trials (T1-T9) over 3 consecutive days (3 trials per day) with increasing difficulty of passing the underpass. The underpass is first marked and open (T1), then only open (T2-T4), then filled with sawdust (T5-T7), then closed by a plug (T8-T9). Thus, at days 2 and 3, the difficulty of the task corresponds to that of the last trial of the day before.

Results: We used five different mouse models of schizophrenia, namely mice with prefrontal cortex and hippocampus lesions, respectively, mice treated sub-chronically with the NMDA-antagonist MK-801, mice constitutively lacking the GluR-1 subunit of AMPA-receptors (GluR-1 knock-out mice), and mice over-expressing the D2 dopamine receptor in the striatum. Compared to their corresponding experimental controls, all mice models used here demonstrated altered executive functions though to an extent that (not surprisingly) varied between the different models. Strongest deficits were observed in hippocampal lesioned mice and GluR-1 knock-out mice, while subtle but specific deficits (particularly in advanced trial 8) were found in prefrontally lesioned mice and in animals over-expressing D2 receptors.

Discussion: With this report we demonstrate face validity of the puzzle box as a behavioral screening tool for executive functions in general and for schizophrenia mouse models in particular. Interestingly, among the various models studied here, specific behavioral deficits were also found in two models with previously demonstrated deficits of prefrontal cortical functions, i.e. one lesion models and one transgenic model (D2 receptor overexpressing mice). Additional experiments will be performed in an effort to rescue the observed deficiencies in different models by classical and atypical antipsychotic drugs.
with behavioural changes in humans and rodents. Infected rodents are shown to be more prone to be attacked by cats, in which the sexual life cycle is completed, through reduced levels of anxiety and the attraction to the odour of the cat’s urine. As T. gondii forms cysts that are located mainly in the brain during a chronic infection, it is well placed anatomically to mediate these effects. Recently, changes in the immune response have also been associated with mood and behavioural alterations and compounds designed to alter mood, such as fluoxetine, have been demonstrated to alter aspects of immune function.

**Methods:** The ability of T. gondii to alter murine behaviour was assessed through a series of behavioural tests (open field task and PPI). Possible molecular mechanisms for T. gondii to alter behaviour through the action of the immune response were investigated. In particular the ability of T. gondii to alter levels of tryptophan metabolising enzymes including indolamine 2,3, dioxygenase (IDO), tryptophan hydroxylase (TPH2) and tryptophan oxygenase (TDO) which could in turn affect levels of serotonin.

**Results:** Infected mice spent more time in the centre of the open field in comparison to uninfected controls significantly at one and two months after infection. PPI levels in infected mice were reduced significantly at one month after infection. Transcripts for IFN-γ were increased in the brains of T. gondii infected mice. However, no differences were found in the transcript levels of TPH2, IDO, TDO between infected and non-infected mice.

**Discussion:** Lower anxiety levels were measured in T. gondii-infected mice in the open field task. This may lead to a reduced chance of survival in the wild and an increased likelihood of attack by felines, thus increasing the perpetuation of the parasite’s life-cycle. The reduction of PPI in infected mice demonstrates a novel effect of T. gondii on the sensorimotor gating circuit, which is also deficit in schizophrenic patients. Although no significant differences were detected in transcript levels of TPH2, IDO and TDO potential differences in protein levels of these enzymes need to be assessed by Western blotting.

doi:10.1016/j.schres.2010.02.703

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**Poster 209**

**THE MGLUR2/3 AGONIST LY379268 REVERSES POST-WEANING SOCIAL ISOLATION-INDUCED RECOGNITION MEMORY DEFICITS IN THE RAT**

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**Background:** An mGluR2/3 receptor agonist, LY404039 has previously shown clinical efficacy against some positive and negative symptoms of schizophrenia. However, the preclinical understanding of how mGluR2/3 agonists modulate schizophrenia-like symptoms is limited. Given both the lack of studies of the potent, selective, mGluR2/3 agonist, LY379268, in neurodevelopmental models of psychosis and the unknown contribution that changes in glutamatergic neuronal function make to the isolation rearing syndrome, this study explored the ability of acute, systemic administration of a single dose of LY379268 (1 mg/kg) to reverse isolation rearing-induced behavioural changes.

**Methods:** Male Lister Hooded rats obtained immediately after weaning on post-natal day (PND) 23-25 were either group-housed (GH; 4 per cage) or isolation-reared (IR) for 6 weeks. At subsequent weekly intervals, animals received either saline (1 ml/kg; i.p) or LY379268 (1 mg/kg; i.p. n = 9-12 per group) 30 min prior to recording, locomotor activity in a novel arena, novel object discrimination (NOD), pre-pulse inhibition (PPI) of the acoustic startle response and contextual fear conditioning. Statistical analyses were all carried out using either a one-way or two-way RM ANOVA with post-hoc Bonferroni tests.

**Results:** Isolation rearing induced locomotor hyperactivity that was significantly reversed by LY379268 (mean total activity counts/60 min±SEM; GH vehicle: 1201±92; IR vehicle: 1635±95; IR LY379268: 1183±91, GH LY379268: 920±75; p≤0.0001). GH vehicle-treated rats successfully discriminated the novel from the familiar object in a two-trial object discrimination task (inter-trial interval 2 h), whilst no significant object discrimination was seen in vehicle-treated IR rats (Object p≤0.0001; Treatment p=0.62; Object x Treatment p=0.16). This NOD deficit was fully reversed in LY379268-treated isolates such that they spent a greater amount of time on the novel object (mean exploratory activity sec±SEM; GH vehicle 16±2 and 7±1 sec; IR vehicle 14±2 and 12±2; IR LY379268 16±2 and 9±2 sec; GH LY379268 13±2 and 8±1 sec at novel and familiar object respectively). % PPI increased with increasing pre-pulse intensity in all treatment groups (Pre-pulse intensity p≤0.0001; Treatment p<0.01; Interaction p=0.50). There was no effect of IR alone on % PPI, but post-hoc analysis showed that LY379268 significantly impaired % PPI in IR and not GH rats. The initial startle response of vehicle-treated IR rats was significantly lower than all other treatment groups, however this was reversed by LY379268 (p<0.0001). Isolation-rearing induced a significant contextual fear conditioning deficit that was unaltered by LY379268. 24 h and 48 h post-training, freezing behaviour was significantly reduced in IR-vehicle and IR-LY379268 compared to both vehicle- and LY379268-treated GH rats (mean freezing sec±SEM 24 h and 48 h post-training; GH vehicle 205±19 and 149±27 sec; IR vehicle 146±27 and 71±17; IR LY379268 113±17 and 72±18; GH LY379268 216±16 and 148±32 sec). In all groups a significant attenuation in freezing behaviour was seen between 24 h and 48 h post-training (Trial p<0.0001; Treatment p<0.01; Trial x Treatment p=0.62).

**Discussion:** These data show that modulation of glutamatergic receptor function by LY379268 can reverse some post-weaning, social isolation-induced changes which have translational relevance to core symptom deficits in schizophrenia and support a potential therapeutic role of mGluR2/3 agonists in its treatment of positive and some cognitive symptoms.

doi:10.1016/j.schres.2010.02.704

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**Poster 210**

**CANNABINOIDS: ENVIRONMENTAL RISK FACTORS FOR A NEUREGULIN 1 MOUSE MODEL FOR SCHIZOPHRENIA?**

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**Background:** Heavy cannabis consumption is associated with increased risk of developing schizophrenia in susceptible individuals. Adolescence appears to be a particular time of vulnerability to the detrimental effects of cannabis. Importantly, cannabis is a mixture of cannabinoids, including the psychotomimetic Δ9-tetra-
hydrocannabinol (THC) and the potentially anti-psychotic-like cannabidiol (CBD). Thus, we investigated the behavioural effects of chronic adolescent THC exposure and chronic adult cannabidiol treatment in heterozygous transmembrane domain neuregulin 1 mutant mice (Nrg1 HET). NRG1 is a susceptibility gene for schizophrenia.

Methods: Adolescent male Nrg1 HET mice and their wild type-like (WT) littermates received vehicle or THC (10 mg/kg i.p.) for 21 days whereas an adult cohort was treated with vehicle or CBD (1, 50, 100 mg/kg). On the first day of treatment and throughout chronic treatment, behavioural tests were performed to assess locomotion, anxiety, prepulse inhibition, cognition and memory as well as social interaction.

Results: Nrg1 HET and WT mice were equally sensitive to the locomotor suppressant effects of adolescent THC. THC decreased the startle response, but there were no main effects of treatment or genotype on prepulse inhibition. THC had cognition-impairing and social interaction-suppressing effects only in WT mice. Chronic exposure to high dose CBD attenuated the hyperlocomotor activity and prepulse inhibition deficit observed in vehicle-treated Nrg1 HET mice.

Discussion: Male Nrg1 HET mice exposed to THC during early adolescence appear to be less sensitive to some of its behavioural effects than WT mice. Importantly, chronic treatment with CBD could partially rescue some of the behavioural abnormalities observed in this mouse model for Nrg1.

doi:10.1016/j.schres.2010.02.705

Poster 211
EFFECTS OF SYSTEMIC PHENCYCLIDINE ON NEURONAL ACTIVITY OF VENTRAL TEGMENTAL AREA IN A CLASSICAL CONDITIONING PARADIGM

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Background: Patients with schizophrenia exhibit deficits in motivation and learning, which suggests impairment in the reward system. Many studies have reported that phencyclidine (PCP) also induces schizophrenia-like negative symptoms, such as reduced motivation, blunted affect and social withdrawal in both human and animals. PCP-administered animals are therefore considered to be a reliable pharmacological model of schizophrenia. The pathophysiology of PCP-induced disturbances in motivation and learning, however, remains still unknown. Previous studies indicated that the dopaminergic neurons in the ventral tegmental area (VTA) play a pivotal role in the development of reward-associated learning and motivation. However, there is no study so far that examines the effects of PCP on firing activity of VTA neurons in a classical conditioning paradigm. In the present study we recorded for the first time the unit activity of VTA neurons in freely-moving rats before and after systemic administration of PCP in a classical conditioning paradigm.

Methods: Male adult Sprague–Dawley rats were used as subjects. A commercial micromanipulator with a tungsten microelectrode was used to record single-unit activity in the VTA. The recording electrode was lowered unilaterally into the right VTA, and the micromanipulator was then fixed onto the cranium using dental cement. Conditioning sessions were started at least 2 weeks after surgery. Two tones (1000 Hz, 2000 Hz) were sequentially presented, in which one of the two tones (CS+) was followed by the unconditioned stimulus. Intracranial stimulation to the medial forebrain bundle was given as an unconditioned stimulus immediately after cessation of the target tone. The CS+ tone was presented with probability 30% of all trials. The total number of tone presentation (trials) was 400 in one conditioning session. Recording sessions were performed on the next day after conditioning sessions. After the first recording session, animals received an intraperitoneal injection of a subanesthetic dose of 10 mg/kg PCP or 1 ml/kg physiological saline. The second and third session was started 15 and 180 min after injection of PCP or saline. The total number of tone presentation (trials) was 200 in one recording session. To analyze the firing activity of recorded neurons for conditioned auditory stimuli, we generated cumulative peristimulus time histograms (PSTHs, 10 msec bin width) for each neuron sampled from 2 sec before to 3 sec after each tone presentation. The baseline period was defined as the 2 sec period preceding the tone presentation.

Results: Most of VTA neurons exhibited clear phasic excitation to CS+. Systemic PCP considerably reduced such phasic responses to both conditioned stimuli (CS+, CS−), regardless of whether the spontaneous activity of neurons was affected by PCP or not. The responsiveness of neurons to CS+ recovered 180 min after PCP injection.

Discussion: Our present results indicate that PCP may affect firing activity of VTA neurons, which are involved in motivation and learning. Therefore, repeated-alteration of VTA activity by repeated administration of PCP may induce long-lasting changes in neural circuits to induce disturbed motivation.

doi:10.1016/j.schres.2010.02.706

Poster 212
THE EFFECTS OF THE CANNABINOID CB2 RECEPTOR ANTAGONIST, AM630, ON ISOLATION REARING-INDUCED BEHAVIOURAL DEFICITS IN RATS

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Background: Exposure to early-life adversity is thought to be a risk factor for the development of schizophrenia. In the last decade much attention has also focused on the potential role of endocannabinoids (ECs) in the pathogenesis of schizophrenia. The present study examined whether the CB2 receptor selective antagonist AM630 (6-Iodo-2-methyl-1-[2-(4-morpholinyl)ethyl][1H-indol-3-yl][4-methoxyphenyl)methanone; CB2 antagonist) can reverse the behavioural defects elicited by rearing rats in social isolation (a developmental model of schizophrenia).

Methods: Male Lister-hooded rats were weaned on postnatal day (PND) 22-24 and half of each litter either group housed (3-4/cage; n=9) or socially isolated (SI; n=9) for 5 weeks, during which they received minimal handling but had visual, auditory and olfactory interaction with each other. Rats were injected with either AM630 (1 mg/kg; i.p; n=10) or saline once daily for 7 consecutive days in the first week of isolation. On PND 61 novel cage-induced locomotor activity (LMA) was recorded in automated infrared activity boxes. On PND 66 all rats were habituated to individual test arenas for 1 hr and on day 67 two trial novel object recognition (NOR) was assessed in same arena using a 2 h intra trial interval (ITI). On PND 81 the conditioned emotional response (CER) was monitored by placing individual
rats into the light compartment of a two chamber CER apparatus, following transfer into the dark side they were conditioned by receiving light and tone paired with a mild unavoidable foot shock on three occasions. On return to the dark side of the chamber 24 and 48 h later the total time spent freezing was recorded to monitor learning and memory.

**Results:** Isolated animals exhibited hyperactivity during the first 30 minutes of LMA compared with GH controls (477.7 ± 130.6 vs 609.6 ± 165.6 counts, respectively) but this just failed to reach statistical significance (p > 0.05 by one-way ANOVA). AM630 had no significant effect on LMA. Saline injected GH rats successfully discriminated the novel object (p < 0.001 by Student’s t-test between novel and familiar object) exploring this for significantly longer than the familiar in the second trial. NOR was however impaired in saline treated SI rats which could not discriminate the familiar and novel objects in choice trial. This NOR deficit was not reversed by AM630 in SI rats (p > 0.05). GH controls froze significantly longer than SI rats irrespective of whether they had received AM630 or not both at 24 h and 48 h after the foot shock in the CER (p < 0.01 by 2 way ANOVA repeated measures).

**Discussion:** SI produced the expected hyperactivity in a novel arena and cognitive deficits in both novel object recognition and contextual fear conditioning, consistent with this being a valuable model of schizophrenia but none of these alterations were reversed by acute treatment with a CB2 receptor antagonist. CB2 receptors are possibly not involved in the long lasting behavioural defects produced by this neurodevelopmental modulation in rats.

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**Poster 213**

**THE TIMING OF PRENATAL IMMUNE CHALLENGE DETERMINES THE EXTENT OF WHITE MATTER MICROSTRUCTURAL ANOMALIES RELEVANT TO SCHIZOPHRENIA**

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**Background:** Imaging and neuropathological studies point to the onset of pathology in neurodevelopmental disorders such as schizophrenia early in fetal life. White matter connections appear to be disrupted, leading to altered functional connectivity during higher-order cognitive processing. We have previously reported diffusion tensor imaging (DTI) evidence of microstructural pathology in our clinical studies of schizophrenia at first-episode and prior to drug treatment, but direct evidence for a fetal trigger of these brain structural differences is sparse. Epidemiological studies implicate maternal inflammation during prenatal life as an environmental risk factor for schizophrenia in the offspring. In this study we tested the hypothesis that maternal immune activation causes post-natal white matter microstructural anomalies in offspring relevant to schizophrenia or autism. We examined the effects of maternal inflammation in early and late gestation on white matter microstructure in the offspring using advanced in-vivo MR-DTI.

**Methods:** We used an mouse model of maternal immune activation (MIA) by the viral mimic Poly(I:C) administered in early (day 9) or late (day 17) gestation. A novel application of automated voxel-based morphometry (VBM) of in-vivo MRI data mapped fractional anisotropy (FA, directional diffusion of water) across white matter pathways of adult offspring. Region-of-interest manual tracing was used to confirm FA changes in selected white matter tracts. In addition we conducted a preliminary immunohistochemical exploration of the oligodendrocyte marker CNPase to determine whether myelination processes might contribute to any changes in FA observed.

**Results:** FA was lower in MIA exposed offspring throughout fronto-striatal-limbic circuits and in the corpus callosum. Regions with lower FA were more extensive in the early exposed group. In both groups there were regions with increased FA but again, these were more extensive in the early exposed group. Preliminary immunohistochemical evidence revealed reduction in the oligodendrocyte marker CNPase in mice exposed to MIA, consistent with a white matter structural insult affecting myelination.

**Discussion:** The present results provide direct experimental evidence that prenatal inflammation causes white matter microstructural abnormalities analogous to those found in schizophrenia. Maternal inflammation earlier in gestation precipitates more extensive changes in offspring, suggesting that the fetus is more vulnerable to environmental insults associated with schizophrenia early in development.

doi:10.1016/j.schres.2010.02.708

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**Poster 214**

**CHRONIC CLOZAPINE TREATMENT IMPROVES PRENATAL INFECTION-INDUCED WORKING MEMORY DEFICITS WITHOUT INFLUENCING ADULT HIPPOCAMPAL NEUROGENESIS**

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**Background:** Converging evidence indicates that prenatal exposure to immune challenge can induce long-term cognitive deficits relevant to schizophrenia. Such cognitive impairments may be related to deficient hippocampal neurogenesis at adult age. In the present study, we sought evidence for the possibility that chronic treatment with the reference atypical antipsychotic drug clozapine may improve prenatal infection-induced cognitive dysfunctions by stimulating adult hippocampal neurogenesis.

**Methods:** To induce a viral-like acute phase response in late gestation, pregnant C57BL/6 mice on gestation day (GD) 17 were treated with the synthetic analogue of double-stranded RNA, polyribosinosinic-polyribocytidilic acid (Poly(I:C); 5 mg/kg, i.v.). Control mothers received vehicle (saline) solution only. The resulting offspring were then subjected to chronic clozapine (CLZ; 5 mg/kg/day, i.p.) or vehicle (VEH) treatment when they reached the adult stage of development, i.e., for 3 weeks starting from postnatal day (PND) 85 to 106. One day following cessation of the chronic drug regime, all offspring were injected with bromodeoxyuridine (BrDU; 50 mg/kg, i.p.) twice daily on three subsequent days (PND 107–109). The offspring were then subjected to cognitive testing in a spatial working memory task on the next eight days (PND 100–118). Two days after completion of cognitive testing (PND 120), all animals were sacrificed for the purpose of immunohistochemical evaluation of BrDU and doublecortin (DCX) expression in the dentate gyrus.

**Results:** We found that maternal Poly(I:C) –induced immune challenge led to significant spatial working memory impairment and reduced hippocampal neurogenesis in the resulting offspring at
adult age. The latter effect was apparent in post-mortem immunohistochemical analyses of the cell proliferation marker BrdU and the microtubule-associated protein DCX, a marker of newborn neuronal cells. Chronic CLZ treatment significantly improved the prenatal PolyLC-induced working memory deficits, whilst at the same time, it negatively affected working memory performance in adult offspring born to control mothers. These bidirectional cognitive effects of clozapine were not paralleled by concomitant effects on adult hippocampal neurogenesis.

**Discussion:** Our findings do not support the hypothesis that the atypical antipsychotic drug clozapine may influence cognitive functions by acting on adult neurogenesis in the hippocampus, regardless of whether the drug is administered to subjects with or without a neurodevelopmental predisposition to adult neuropathology.

doi:10.1016/j.schres.2010.02.709

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**Poster 215**

**THE EFFECT OF NON-COMPETITIVE NMDA RECEPTOR ANTAGONIST MK801 ON HIPPOCAMPUS-PREFRONTAL CORTEX SYNAPTIC RESPONSES AND EXECUTIVE COGNITIVE FUNCTION IN RATS**

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**Background:** Evidence suggests that the pathogenesis of schizophrenia cognitive symptom may involve abnormalities in glutamatergic transmission. Particularly, non-competitive antagonists of N-methyl-D-aspartate (NMDA) receptors such as phencyclidine and MK801 are known to cause cognitive states resembling schizophrenia in healthy humans and exacerbate preexisting symptoms in the patients. In rats, the administration of MK801 alters neuronal activity in the prefrontal cortex (PFC) as well as impairs executive cognitive function. In this study, we tested the effect of MK801 on synaptic responses of the cognitively important, hippocampus-PFC pathway and on executive cognitive function in rats.

**Methods:** Male Sprague-Dawley rats (350–400 g) were anesthetized by urethane (1.5 g/kg, i.p.) and placed in a stereotaxic frame (body temperature maintained at 37 ± 0.1 °C). A recording electrode was placed in the mid layer of the prelimbic area (rat PFC), and a stimulating electrode in ventral hippocampus. The electrode positions were adjusted to obtain the maximum amplitude of postsynaptic potential, whose peak appears with an 18.0-20.0 ms delay after stimulus artifact. The intensity of stimulation was set to evoke 60% of the maximum response (300–500 μA). The protocol for behavioral analysis followed Birrell and Brown (J Neurosci, 20, p4320, 2001).

**Results:** Single injection of MK801 (0.1 mg/kg, i.p.) induced a gradual potentiation of the evoked responses which reached a significant level 2 hours after injection (63 ± 10 at 2 hours, n = 12) compared with saline control (11 ± 6.6%, n = 10, p < 0.0005). This MK801-induced potentiation does not require tetanic stimulation unlike the standard forms of long-term potentiation (LTP). Furthermore, significant MK801-induced LTP was induced even when single test stimuli (at 0.033 Hz) were stopped for 1 hour from the time of MK801 injection (32 ± 2.8% at 2 hours, n = 5, p < 0.001 compared with saline control, 0.7 ± 2.2%, n = 7), suggesting that the MK801-induced LTP occurs in the manner independent of synchronized synaptic stimuli. However, MK801-induced LTP appears to share the common mechanisms with the standard LTP, since a prior induction of LTP by tetani (50 pulses at 250 Hz, repeated 10 times at 0.1 Hz; such a train was applied twice with 6 min interval) severely occluded a subsequent MK801-induced LTP (19 ± 7.5, n = 7, p < 0.005). MK801-induced LTP was blocked also by prior injection of MAP kinase inhibitor SL-327 (10 mg/kg, i.p., 19.2 ± 9.1%, n = 5, p < 0.01) and of mGluR2/3 agonist LY379268 (3 mg/kg, i.p.; 0.2 ± 2.0%, n = 5, p < 0.005). Behavioral data showed that the injection of MK801 impaired PFC-dependent extra-dimensional set shifting (p < 0.05). In another series of experiments, we tested the effect of repeated injections of MK801 (7 or 14 daily injections) on a subsequent induction of LTP by tetani. We had verified that tetani delivered 24 h after single MK801 can induce clear LTP (85 ± 17%, n = 5). But tetani delivered 24 hours after a 7th daily injection of MK801 induced LTP only in 3 out of 6 animals, and tetani 24 hours after a 14th injection resulted in no LTP (-11 ± 4.1%, n = 7, p < 0.001). LTP was still absent 72 hours after the 14th daily injection (-3.1 ± 6.4%, n = 4, p < 0.001). Rats injected with the 14-daily MK801 showed severe impairments in the attentional set shifting task.

**Discussion:** These results suggest that MK801 induces an aberrant form of LTP in the hippocampus-PFC pathway. When injection is repeated, MK801 blocks a subsequent LTP induced by tetanic stimuli. We are currently testing the role of PFC dopamine receptors for the MK801-induced LTP.

doi:10.1016/j.schres.2010.02.710

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**Poster 216**

**TARGETING PLANNING AND PROBLEM SOLVING VERSUS BASIC COGNITION IN COGNITIVE REMEDIATION FOR PATIENTS WITH SCHIZOPHRENIA**

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**Background:** The importance of cognitive impairment for functional outcome in patients with schizophrenia has led to the development of cognitive remediation programs designed to improve cognition. These interventions have targeted a wide range of cognitive functions. However, there are no direct comparisons between treatment programs addressing cognitive functions on different levels of complexity in a rehabilitation setting. The purpose of this study was to assess whether a planning and problem solving training is more effective in improving functional capacity in patients with schizophrenia than a traditional training program addressing basic cognitive functions.

**Methods:** Eighty-nine patients with schizophrenia or schizoaffective disorder were randomly assigned either to a training of planning and problem solving or a training of basic cognition. The dependent variables included functional capacity as a proxy measure for functional outcome, problem solving and planning ability. Assessment of the primary outcome was blind to group allocation. Participants received computer-assisted cognitive training three times a week over a three week period.

**Results:** A main effect of time indicated that both groups improved in functional capacity during the study. Calculation of the reliable change index suggests that this improvement is clinically significant. Contrary to our main hypothesis, no significant time x group interaction was
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FEASIBILITY STUDY OF MULTI-SITE COGNITIVE REMEDIATION IN THE SCHIZOPHRENIA TRIALS NETWORK (CRSTN)

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Background: The NIMH MATRICS Project and related efforts have stimulated the initiation of several studies of treatments for cognitive impairment in schizophrenia. Cognitive remediation may provide an excellent platform for the provision of new learning opportunities and the acquisition of new skills for patients who are engaged in pharmacologic trials to improve cognition. However, it is not clear whether cognitive remediation intervention would be feasible for large trials involving sites without specific cognitive remediation expertise. We sought to address the feasibility of a multi-site trial of cognitive remediation in schizophrenia, called the Cognitive Remediation in the Schizophrenia Trials Network (CRSTN) study.

Methods: Nine sites from the Schizophrenia Trials Network, formerly the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial, were involved in the study. Each site was expected to enroll six patients with chronic DSM-IV schizophrenia over the course of approximately 3 months, estimating a reasonable rate of recruitment for a large-scale efficacy trial. Raters were certified on the MATRICS Approach to Remediation (NEAR), that help patients to learn how ‘bridging groups’ adapted from the Neuropsychological Educational Approach to Remediation (NEAR), that help patients to learn how cognitive improvement can be applied to functional benefit in everyday life; or 2. a control condition that involved computer games and weekly healthy lifestyles groups. Patients were expected to complete the one-hour auditory training intervention or computer game activities 3-5 times per week until study end, which was 40 sessions or 12 weeks, whichever came first. Efficacy with the MCCB and UPSA-2 was assessed after 20 sessions and study end. The key indicator to evaluate the feasibility of this study was rate of enrollment, retention, and completion rate of primary outcome measures.

Results: Within the 3-month enrollment period, 67 patients signed consent, 60 patients were screened, and 53 were enrolled, one short of the maximum allowed. As of the date of abstract submission, 3 patients (1 receiving cognitive remediation) had terminated the study, and 32 patients had completed the trial. Of these, 26 completed the maximum 40 sessions and the other 6 patients completed an average of 30 sessions in 12 weeks. Weekly attendance in the bridging groups was excellent. Efficacy data will be available at the time of this presentation.

Discussion: In terms of training, enrollment and study completion, multi-site trials of cognitive remediation using the PositScience auditory training program with the NEAR method of weekly bridging groups appear to be feasible, supporting large-scale efficacy trials of cognitive remediation and the use of cognitive remediation as a potential platform for large-scale drug trials.

doi:10.1016/j.schres.2010.02.711

Poster 218
CONCEPTUAL BACKGROUND OF IMAGING STUDIES IN PSYCHOTHERAPY RESEARCH: THE EXAMPLE OF CBT INTERVENTIONS IN PATIENTS WITH SCHIZOPHRENIA

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Background: Cognitive behavioural therapy (CBT) is an important treatment in conjunction with psychopharmacotherapy in schizophrenia. However, there is only very little research on the effects of such interventions on brain function. Recent studies have suggested that jumping to conclusions and a specific attributional style is a predominant cognitive style in patients which might lead to the development of delusions.

Methods: In this multi-centre fMRI trial, we investigated the effect of CBT on neural correlates of “jumping to conclusions” and the “attributional style” in patients with schizophrenia. Eighty patients and 80 control subjects were recruited in six centres and measured with 3-Tesla functional magnetic imaging (fMRI) before and after 9 months of cognitive behavioural therapy.

Results: It could be shown that CBT ameliorates differences in brain activations between patients and controls after nine months.
Poster 219
ATTRIBUTIONAL REASONING BIASES, PARANOIA AND DEPRESSION IN FIRST-EPISTODE SCHIZOPHRENIA

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Background: Evidence that paranoid people with schizophrenia show a 'self-serving' bias, whereby they externalize the blame for negative events, has prompted the development of 'attributional interventions' to augment cognitive behavioral therapies. However, longitudinal and first-episode research to validate these interventions is lacking. This study aimed to address this gap in the literature by examining attributional biases, paranoia and depression in a sample of first-episode schizophrenia patients.

Methods: Twenty-four young people with schizophrenia-spectrum disorders (23 males and one female with a mean age of 20.9 years, SD = 1.8) were recruited from two early psychosis intervention services in Sydney, Australia. Inclusion criteria included less than two years since the onset of psychosis, a minimum age of 18 years, English-speaking, and no current major co-morbidity. Nineteen healthy controls (19 males and two females with a mean age of 20.8 years, SD = 1.7) also took part. Patient diagnosis was confirmed using the Diagnostic Interview for Psychosis (Castle et al., 2006) and symptom severity was rated using the SAPS, SANS and BPRS. All participants were assessed for levels of paranoia (Paranoia Scale; Fenigstein & Vanable, 1992), suspiciousness (BPRS), depression (Hamilton Depression Scale: HAM-D; Hamilton, 1967) and attributional biases (Internal, Personal and Situational Attributions Questionnaire: IPSAQ; Kinderman & Bentall, 1997).

Results: Across patients and controls, levels of suspiciousness were associated with a standard measure of self-serving bias (SSB: proportion of positive events attributed to self minus proportion of negative events attributed to self); however, levels of SSB were no more extreme in the first-episode patients than the controls. First-episode patients did, however, show a greater ‘self-promoting’ bias to credit themselves with causing positive (but not negative) events. Whereas controls showed evidence of the commonly observed association between depression and a bias to blame one-self for negative events, levels of depression in the first-episode patients were associated, instead, with a bias to credit one-self with causing both positive and negative events.

Discussion: Findings are not indicative of a universal self-serving bias at early stages of schizophrenic illness and suggest, instead, a form of compensatory self-promoting bias which may be secondary to the onset of psychosis. The novel findings with regard to depression suggest that young people, who develop depression after the onset of psychosis, may experience a need to re-establish a sense of personal control over life events, whether positive or negative.

References


doi:10.1016/j.schres.2010.02.714

Poster 220
SCHEMA QUESTIONNAIRES: PSYCHOMETRIC PROPERTIES AND ASSOCIATIONS WITH SYMPTOMS IN A PSYCHOTIC POPULATION RECEIVING CBT

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Background: Cognitive Behavioral Therapy (CBT) for psychosis is an evidenced-based practice which has been found to reduce psychotic, depressive, and anxiety related symptoms in persons with schizophrenia. CBT is thought to work by changing core beliefs about the world and the self. These core beliefs are typically formed well before the onset of psychosis and thought to influence the form of the psychotic content. While schemas have been reliably measured in psychotic populations, the scales have primarily been used in Anglo populations in the UK.

Methods: In a sample of 58 subjects, we examined the psychometric properties of three schema self-report questionnaires, 1) Brief Core Schema Scale (BCSS), 2) Forms of Self-Criticizing and Self-Reassuring Scale (FSCSR) and 3) Functions of Self-Criticizing/Attacking Scale (FSCS) in a multi-ethnic schizophrenia population, one-half of whom were receiving CBT for psychosis. Correlational analyses were conducted to investigate the relationship between the three scales and schema-targeted symptomatology, including delusional thinking, grandiosity, suspiciousness, depression and anxiety; and divergent validity was tested comparing the scales to conceptual organization. A smaller subgroup (N = 38) completed the schemas questionnaires after 3 and 6 months of treatment to investigate the mechanisms behind the change in related symptoms.

Results: The three scales were significantly correlated to each other, as were individual factors within the scales measuring similar schemas (i.e. negative and/or critical view of self). At baseline, higher scores on all three schema scales (indicating poorer view of self) are correlated to questions regarding depression and suicidality (p < .0001). Additionally, a trend is present for the relationship between lower scores on the FSCS and BCSS and reported grandiosity (p < .07, p < .11). No relationship was found between the scales and subjects’ reported anxiety, suspiciousness, delusional thinking or conceptual organization. While it was hypothesized that Hispanic and non-Hispanic persons would significantly differ on views of self and others, this was not found within any scale or individual factor. A mixed model repeated measures analysis revealed that only the FSCS significantly changed over the 6 months of treatment, indicating this scale is sensitive to change in core schemas during treatment with cognitive behavioral therapy.

Discussion: In summary, the data suggest that these three measures of core schemas can effectively be utilized in a multi-ethnic schizophrenia population. However, the measures may not be equally sensitive to change over brief periods of time and longer treatment duration should be investigated.

doi:10.1016/j.schres.2010.02.715
Poster 221
ADMIXTURE ANALYSIS OF AGE AT ONSET IN SCHIZOPHRENIA AND SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: In this contribution we analyzed the age at onset (AAO) in order to assess the presence of different sub-groups in a schizophrenia population consecutively recruited through an Early Psychosis Service in London (Canada).

Methods: Admixture analysis was applied in order to identify a model of separate normal distribution of AAO characterized by different means, variances and population proportions to allow for evaluation of different sub-groups in a sample of 187 unrelated patients with DSMIV diagnosis of schizophrenia. The Kolmogorov-Smirnov test was used to determine whether the theoretical AAO function identified in our sample is consistent with the theoretical AAO function found by Schurhoff et al. (2004).

Results: The sample had the best-fitting three component model with means (S.D.) of 16.80 (1.87), 22.27(2.05) and 32.67 (5.88) years comprising 41%, 29% and 30% of the schizophrenia sample respectively. Our analysis is aimed to support the hypothesis that early onset acts as a severity marker that can identify a sub-group with less heterogeneity and higher genetic load. Therefore in our investigation the definition of early onset schizophrenia is the main outcome and as most important predictors we considered the variables mainly related to the heritability and neurobiology of schizophrenia (gender, marital status, number of offspring, number of affected relatives, history of alcohol or drug abuse, birth complications and EEG disorganization). Single status (inferring the incapacity to transfer susceptibility genes to the offspring) was strongly associated with early onset (p=0.00007). The male gender was significantly associated with early onset (p=0.026) as well as history of drug abuse (p=0.041). Interestingly the presence of birth complications showed a trend toward early onset schizophrenia (p=0.051) on the other hand the presence and number of affected relatives with schizophrenia spectrum disorders or other psychoses were not associated with early onset excluding any anticipation phenomenon. When we considered the continuous predictors (SANS, SAPS, GAF, WCST, Stroop, length of prodromal symptoms and BMI) we found that shorter prodromic phase (p=0.00008) and lower BMI (p=0.028) were associated with early onset.

Discussion: Thus overall, our study showed that a typical early onset schizophrenia patient is more likely to be a single male, with obstetric complications at birth presenting with a short prodromal phase and drug abuse.

doi:10.1016/j.schres.2010.02.716

Poster 222
WORKSHOPS THE DJ’S CHOICES: AN INTERACTIVE PROGRAM TO SUPPORT ADHERENCE IN PATIENTS WITH FIRST PSYCHOTIC EPISODE

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Background: Non adherence to medication is a widespread challenge in all chronic diseases. In schizophrenia, consequences of non adherence are particularly dramatic since it may lead to relapse and treatment resistance. While it is recognized as a major issue in schizophrenia, there are very few clinical tools available to professionals to support patients in maintaining their medication (1,2).

Methods: We have developed an original program that integrates psycho educational notions, cognitive behavioural techniques and motivational approach to facilitate discussions around medication perceptions, beliefs and challenges over long term adherence after a first psychotic episode. This program, entitled The DJ’s choices, includes four workshops: Workshop 1: Make up your mix shares psychoeducational notions on relapse prevention and treatment efficacy; Workshop 2: Get your beat allows exchange on side effects and impression on medication; Workshop 3: Explore leads facilitates discussion on families’ perception and influence of environment on adherence and Workshop 4: Keep the tempo states an individual action plan on daily integration of adherence.

Results: The program was tested on three different occasions in a first episode clinic in Quebec city. A total of 22 patients participated to the workshops. Mean retention rate was 85%. Patients found the program satisfying with regards to number or workshops, duration of each meeting and information contents. The preferred themes were discussed at workshops 3 and 4, underlying the importance to give patients the chance to discuss together their perception of treatment, the impact in their social environment and courage required to integrate it in daily life. Pre and post-program self-reported adherence was increased, particularly in those who initially reported they miss more doses when they feel well (3). Perception of efficacy, tolerance and knowledge remained unchanged. Proportion of patients with a positive impression according to DAI-10 increased slightly, from 75% to 85% (4).

Discussion: From a qualitative point of view, use of videotapes of patients or family members to witness their own experience with treatment, side-effects, their struggle with non adherence and relapse were particularly appreciated. Moreover, in terms of developing new skills for professionals, this initiative gathered together a psychologist and a pharmacist to share approaches based more on patient perception and support around medication adherence than on knowledge, leading to a real satisfying exchange with patients. This program will lead to a comprehensive publication, in a formal manual to help professionals to discuss adherence with their psychotic patients in an original perspective.

References


doi:10.1016/j.schres.2010.02.717
Poster 223
A PROSPECTIVE STUDY OF THE CLINICAL OUTCOME FOLLOWING TREATMENT DISCONTINUATION AFTER 2 YEARS IN FIRST-EPISODE SCHIZOPHRENIA

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Background: An important unanswered question in the management of schizophrenia is how long antipsychotic treatment should be continued after a first psychotic episode. This study assessed the clinical consequences of antipsychotic discontinuation after 2 years of uninterrupted treatment in patients treated for a first episode of schizophrenia or related illness. This is a pre-specified interim analysis after 1 year of treatment discontinuation.

Methods: This study is an extension of a previously published 24-month, open-label study in which 50 patients with first-episode schizophrenia, schizophreniform disorder, or schizoaffective disorder were treated with flexible doses of risperidone long-acting injection (RLAI). At the completion of that study, patients were offered enrolment in this follow-up study evaluating the effects of treatment discontinuation. Patients opting to participate in the discontinuation trial had RLAI tapered over a period of up to 6 weeks, with follow-up while off antipsychotic therapy or until relapse, defined operationally. Following RLAI discontinuation, patients were assessed every 2 months. RLAI was immediately re-instituted when relapse was identified. This is a pre-specified interim analysis of all subjects who completed 1 year of follow-up. Relapse rates, time to relapse, and antecedents to relapse were evaluated with Positive and Negative Syndrome Scale (PANSS) and Patient-assessed Global Impression of Change (PGI-C) scores.

Results: Of the 50 patients who completed the 2-year treatment study, 19 men and 14 women (mean age 27.5 ± 7.9 years and baseline PANSS score of 45.0 ± 7.4) entered the discontinuation study and were followed for 1 year or until relapse. At baseline, 28 patients (84.8%) were in remission. 26 patients (79%) relapsed within 1 year. Kaplan-Meier estimate of median time to relapse was 163 days (95% CI 96–199). 8 patients were hospitalized as a result of relapse. There were no differences between those who relapsed and those who did not in terms of baseline PANSS scores or remission status. PANSS total scores remained similar to those at baseline up until (and including) the visit prior to relapse.

Discussion: Similar to previously reported studies with oral and depot antipsychotics, 2.3 relapse rates were high within 1 year of treatment discontinuation in patients who had been treated with RLAI for first-episode of schizophrenia for 2 years. First relapses occurred suddenly, without clear-cut warning signs. These findings have important clinical implications, suggesting that antipsychotic discontinuation after 2 years of treatment may not be in the best interest of the majority of patients.

doi: 10.1016/j.schres.2010.02.718

Poster 224
A META-ANALYTIC STUDY ON COGNITION AND FUNCTIONAL OUTCOME IN NON-AFFECTIVE PSYCHOSIS: MUCH VARIANCE LEFT UNEXPLAINED

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Background: Cognitive impairment is associated with poor functional outcome in schizophrenia, a finding which has increasingly rendered cognition a target for treatment intervention. Yet, whether different cognitive domains, i.e. neurocognition or social cognition, show differential patterns of associations with functional outcome, has not been reviewed systematically. The current meta-analytic review investigates the magnitude of the associations between 9 neurocognitive and 3 social cognitive domains and different types of functional outcome.

Methods: Relevant English-language articles from 1977 to present, investigating cross-sectional associations between cognition and functional outcome in individuals with non-affective psychosis were searched in MEDLINE and PsycINFO electronic databases and reference lists from identified articles. Of 283 studies identified as potentially suitable, 52 met all criteria for inclusion into the meta-analysis. Pearson correlations between cognition and outcome, demographic data, sample sizes and potential moderator variables, such as inpatient status, illness duration, age, and gender were extracted from the included articles.

Results: 48 independent meta-analyses, investigating the associations between 12 a priori identified cognitive domains and 4 domains of functional outcome, were conducted on data from 52 studies comprising more than 2692 patients with non-affective psychosis. Combination of mean effect sizes (r) across studies by means of a random effects model yielded a number of 25 significant medium strength correlations that ranged from μ = .16 to .48. Overall, social cognition was more strongly associated with community functioning than neurocognition (μ = .25 vs .38). Pairwise comparisons indicated that this finding is mostly due to stronger associations with theory of mind.

Discussion: Cognitive impairment as indexed by neuropsychological test scores is consistently associated with functional outcome. Social cognition, specifically theory of mind, appears to be stronger associated with current community functioning than neurocognition. Yet, approximately 76% of variance in functional outcome is left unexplained. This finding stresses the need to quest for other explanatory factors.

doi: 10.1016/j.schres.2010.02.719

Poster 225
COGNITIVE DYSFUNCTION AFTER RECOVERY FROM SCHIZOPHRENIA

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Background: Deterioration of cognitive functioning is now viewed as a core feature of schizophrenia. The existing research on cognitive functioning in first-episode schizophrenia suggests that cognitive deficits may be present quite early on in the illness. Less is known about what happens to cognitive abilities in the years following a diagnosis of first-episode schizophrenia, particularly after individuals have, in a
clinical sense, recovered. Once an individual is considered to have recovered from schizophrenia, ideally, it would be anticipated that his or her cognitive functioning would similarly be restored, although some evidence exists to suggest that some dysfunction remains.

**Methods:** This research examined the cognitive function of individuals first diagnosed with schizophrenia and then again ten years later to assess changes in cognitive functioning across this time period. Individuals diagnosed with first-episode schizophrenia, who ten years later were classified as “recovered,” had their cognitive functioning assessed both at the time of diagnosis and at the ten year follow-up. Cognitive functioning was assessed using the Bender-Gestalt II and the Wechsler Memory Scale.

**Results:** Our results indicate deterioration in some abilities at baseline and further decline of cognitive abilities in this group of clinically recovered patients. Visuo-spatial memory, working memory and executive functioning were shown to decrease in the ten years following diagnosis and many individuals classified as “recovered” still demonstrate abnormal cognitive functioning. At the ten year follow up, although being classified as clinically recovered, 68.9% of participants obtained abnormal scores on the Bender-Gestalt II and 54.1% of scores on the Wechsler Memory Scale were in the abnormal range.

**Discussion:** Thus, despite the fact that individuals in the present sample evidenced good clinical recovery at the ten-year follow-up assessment, they did not demonstrate good cognitive recovery which will likely inhibit the extent to which they can fully recover, prevent relapse, and integrate into the community. Treatments which include a focus on cognitive functioning are essential in order to enhance recovery in all domains of life.

doi:10.1016/j.schres.2010.02.720

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**Poster 226**

**USING THE IPAP ALGORITHM TO PREDICT TIME TO TREATMENT RESPONSE IN RECENT-ONSET SCHIZOPHRENIA**

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**Background:** The Schizophrenia Algorithm of the IPAP (www.ipap.org) proposes that patients with schizophrenia should be treated with monotherapy with 2 trials of 4-6 weeks duration, using atypical or, if not available, typical antipsychotics. In case of non-response to the 2 trials he/she is considered to be refractory and is eligible to clozapine. Although the IPAP algorithm is based on evidence of double-blind trials, to our knowledge, it has never been systematically tried in routine clinical practice. We conducted an open randomized controlled trial of first generation antipsychotic (FGA) versus second generation antipsychotic (SGA) to identify time and predictors to treatment response in patients with recent onset schizophrenia.

**Methods:** After screening, subjects aged 18-45 years meeting DSM-IV criteria for schizophrenia or schizoaffective disorder and PANSS > 60 were randomized to receive FGA (haloperidol or chlorpromazine) or SGA (risperidone, olanzapine, quetiapine, ziprasidone or aripiprazole). Exclusion criteria: previous use of clozapine, PANSS < 60, and > 10 years of disease. Treatment followed the IPAP recommendations. Subjects were assessed by independent raters with the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression (CGI), and Simpson-Angus Scale for Extrapyramidal Symptoms at baseline and weeks 2, 4, 6, 8 and 12. Magnetic resonance image (MRI) of the brain was obtained in the first 4 weeks of treatment. Response was defined as 30% decrease at total PANSS score. The study was approved by the Ethics Committee in February 2009 and is registered at ClinicalTrials.gov (NCT01016145). The study is ongoing and the following results are preliminary.

**Results:** Thirty-two patients were screened and 16 (9 males, 7 females) were included in the trial: 6 in the FGA group and 10 in SGA group. Mean time since diagnosis was 2.0 (±2.0) years. Baseline PANSS was 93.6 ± 25.0. The rate of treatment response was 26.7% in the first 4-6 weeks and the cumulative response rate was 53.3% at 8-12 weeks (p = 0.017); 4 patients dropped out, and 2 (13.3%) did not respond to treatment. Brain MRI (N = 12) showed abnormalities in 42% of subjects, while 58% were normal. Abnormalities were hyperintensities in T2 (N = 3) and ventricular enlargement (N = 2). As the number of non-responder was too small at the timepoint of this analysis, it is not possible yet to compare the predictors of response.

**Discussion:** There was a significant difference in the response rate at the first 4-6 weeks, in comparison with 8-12 weeks. Subjects responding at the first 6 weeks continued to improve, showing an additional decrease of PANSS score at weeks 8-12. Such results raise the question whether 6 weeks are enough to evaluate the antipsychotic efficacy. On the other hand, the cumulative response rate after 8-12 weeks was 53.3%, with 25% of dropout, which is similar to double-blind trials, indicating that the IPAP is feasible as an algorithm in the “real world” clinical practice. Patients did not receive any financial help to attend the visits and, except for the randomization to FGA or SGA, the choice of the antipsychotic was at the physician’s discretion. This study is not being sponsored by any pharmaceutical company and the antipsychotics used are available at Brazilian Public Health System. Conclusions: the rate of treatment response in the first 4-6 weeks is lower than at 8-12 weeks. The IPAP is feasible as a treatment algorithm in a “real-world” setting.

doi:10.1016/j.schres.2010.02.721

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**Poster 227**

**VALIDATING AN INDUSTRY-SPONSORED MODEL COMPARING THE COST-EFFECTIVENESS OF ATYPICAL ANTIPSYCHOTICS IN THE TREATMENT OF SCHIZOPHRENIA**

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**Background:** Decision analytic models can provide support for various clinical decisions by pharmacy and health care practitioners working in the managed-care pharmacy arena. However, skepticism about potentially biased, industry-sponsored economic models prevails. The objective of this study was to develop a new industry-sponsored, cost-effectiveness model, using published head-to-head data, to examine the validity of results reported in a previous industry-sponsored decision economic model published in 2001, which used available indirect data to compare olanzapine with ziprasidone in the treatment of schizophrenia from the perspective of a third-party payer in the United States.

**Methods:** A decision analytic modeling approach was used to estimate the annual health care costs and health outcomes associated with the treatment of schizophrenia with the 2 comparators. The decision-tree structure included key clinical events such as response, relapse, and suicide attempts/completion. Patients without response to first-line treatment switched to the other comparator. Decision tree probabilities were extracted from a head-to-head study and other published clinical literature. Direct health care costs and QALYs were estimated based on resource use (inpatient, outpatient, suicide, and drug costs) and utility weights for initial and relapse episodes, maintenance therapy, and extended episodes of schizophrenia. Disutilities associated with adverse
events (extrapyramidal symptoms [EPS], weight gain, and hypotension) were also considered. One-way and probabilistic sensitivity analyses were performed.

**Results:** Consistent with the results of the previous 2001 cost-effectiveness model, the new cost-effectiveness model found that first-line treatment with olanzapine was associated with fewer hospital days, fewer EPS days, and greater number of QALYs than first-line treatment with ziprasidone. Drug acquisition costs were higher for the olanzapine pathway; however, total costs were lower for the olanzapine than the ziprasidone pathway due to cost savings associated with better health outcomes and less health care resource use. The incremental cost per QALY gained indicated that the olanzapine pathway dominated the ziprasidone pathway. One-way and probabilistic sensitivity analyses confirmed the robustness of the model and its results.

**Discussion:** Decision analytic models should be continuously assessed against new data. This case study shows the incorporation of new data validated results of a previously published, industry-sponsored decision analytic model in which olanzapine - despite its higher acquisition cost - was associated with better expected health outcomes and lower total health care costs than ziprasidone.

doi:10.1016/j.schres.2010.02.722

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**Poster 228**

**THE MALAGA SCHIZOPHRENIA CASE-REGISTER (RESMA): FOLLOW-UP ANALYSIS OF A SCHIZOPHRENIC COHORT AND THEIR PATHWAYS IN SPECIALIST MENTAL HEALTH CARE: HOSPITALIZATION AS A MEASURE OF OUTCOME**

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**Background:** Local cumulative psychiatric case registers is a method for data collection in defined geographical areas because contacts with designated services are stored in a linked and cumulative file so that the care of any individual or group can be followed over time which provides useful information about demographic, clinical and patterns of use of services. Hospitalization during a period of time is one of the most frequent outcome measure used in literature concerning evolution of mental severe disorders in the community. Hospitalization is generally reported in three forms: Number of admissions, time to admission and duration of inpatient care. Reduction in hospitalisation has been the most frequent outcome measure in community studies, but results are still inconsistent. The aim of this study is to analyse the characteristics of a schizophrenic patients sample of RESMA cohort who has been admitted in the hospital during a period of two years and to compare them with the patients of the same cohort that had not been hospitalised.

**Methods:** Follow up study of a cohort of schizophrenic patients treated between 1st January 2006 and 31st December 2007. We included those patients having a clinical diagnosis of schizophrenia and related disorders, comprising the ICD-10 codes from F20 to F29, as was definition of case to be entered in RESMA in contact with services during 2006 and 2007. Data on demographic, clinical and use of services variables were obtained from databases of public mental health services, centralized in the RESMA case-register. The main outcome measure defined as total number of hospitalization, duration of inpatient care and legal status of admission during a period of two year was analyzed with a multilevel multivariable linear regression.

**Results:** All patients with diagnosis of schizophrenia in contact with public mental health facilities during year 2006 and 2007 were recruited (n = 1022). The majority of those were male (65%), single (68%), living with original family (50%), with primary educational level (41%) and retired (52%). Concerning use of services, the majority had only out-patient contacts (89%). A total of 240 (23.48% of the cohort) were admitted during the period of study, male (70.8%), single (69.3%), living with original family (41.6%) with primary educational level (46%) and retired (49%).

**Discussion:** Current research in schizophrenia has paid a lot attention to hospitalization as outcome measure. This is controversial because hospitalisation rates can be related with multiples causes. Some of them are related with clinical conditions and are equivalent to relapses but in other cases can be related with policy and organizational model of services or social unmet needs of patients. However hospitalisation offers a valid measure of outcome because gives information about an essential component of health economic analysis a can make a good picture of an integrated model of services in mental health.

doi:10.1016/j.schres.2010.02.723

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**Poster 229**

**LONGITUDINAL STUDY OF FIRST-EPIODE PSYCHOSIS WITHIN THE UNIVERSITÉ DE MONTRÉAL NETWORK: 3 YEARS OUTCOME**

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**Background:** Within the past several years, there has been an emergence of specialized treatment programs across the world for patients with first-episode psychosis. Several of these specialized programs have been found to be more effective than the ‘as-usual’ treatment within general psychiatric services. In Québec, few programs combine the array of biological and psychosocial therapeutic approaches required for optimal treatment of early psychosis. No published Québec study has described the outcome of a cohort for which these treatment modalities were offered from the onset of the illness. In the Université de Montréal network, two clinics have been developed. The existence of these two specialized clinics provides an opportunity to collect new data on early psychosis outcome, and on the impact of psychosocial treatments in first-episode psychosis.

**Methods:** Our prospective longitudinal study includes populations from two areas of Montreal. Beginning in the fall of 2005 and for a period of 5 years all subjects admitted to the two specialized programs with a primary diagnosis of psychosis aged between 18 and 30 years old are asked to participate in the study. Data collected at admission and then annually consist of demographics, social functioning, symptomatology, cognitive functioning, treatments received, services use and relapses. We describe the functional and symptomatic outcome of psychotic disorders as well as the impact of outcome predictors. We present preliminary data for the first 3 years.

**Results:** 220 patients have been included in the study. Symptoms (positive, negative, depressive) and functioning improve over time. As the follow-up go on, more patients have an occupation (study, work) and fewer patients depend on their family for their living arrangement. With time, substance use decreases, medication compliance increases and the hospital admissions stay quite low.

**Discussion:** This study allows us to describe the present reality of first episode psychosis in Quebec. While the absence of a control group does
not allow for a direct assessment of the impact of the treatment programs, it remains that it is possible to document the evolution of patients with first episode psychosis whom are given early and intensive intervention. The specificity and timing of those interventions seem to have a positive impact on outcome. The project is still ongoing.

doi:10.1016/j.schres.2010.02.724

**Poster 230**

**RELATIONSHIPS AMONG MULTIPLE OUTCOME MEASURES IN THE STUDY OF SCHIZOPHRENIA**

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**Background:** A wide array of clinician and patient-rated outcome measures exists to assess diverse symptoms of and treatment response effects on schizophrenia. Incorporating many such measures into clinical trials can lead to collection of redundant information and often poses an unacceptable data collection burden. In this exploratory study, we aimed to quantitatively characterize the relationships among six clinical, functional, cognitive and quality-of-life measures; and to identify a parsimonious set of underlying conceptual domains.

**Methods:** We used baseline data from a randomized, multicenter study (HCMN) of chronically ill patients with schizophrenia or schizoaffective disorder experiencing an acute symptom exacerbation (n=628) to examine the relationship among several outcome measures. Measures included the Positive and Negative Syndrome Scale (PANSS), Montgomery-Asberg Depression Rating Scale (MADRS), Schizophrenia Objective Functioning Instrument (SOFI), Quality of Life Scale (QLS), Symbol Coding Test of the Brief Assessment of Cognition in Schizophrenia (BACS), and the patient-reported Subjective Well-being under Neuroleptics scale – short version (SWN-K). Two analytic approaches were used: (1) path analysis, using only measure total scores; and (2) second order factor analysis, using total score or sub-domain scores on previously identified domains for some measures. For the path analysis, we assumed the PANSS, MADRS and BACS were exogenous and the SOFI, QLS and SWN were endogenous, and selected a final model which optimized goodness-of-fit between model and data (e.g. minimizing goodness-of-fit chi-square and root mean square error of approximation [RMSEA]). For the second order factor analysis, we identified a factor solution, using orthogonal rotation to examine overlap between domains from the various measures.

**Results:** In the optimal path model depicting relationships among the measures, the SWN-K was identified as the final outcome, while the SOFI mediated the effect of the exogenous variables on the QLS (e.g., two-thirds of the effect of PANSS on QLS was mediated by SOFI). The overall model explained 47% of the variance in QLS and 15% of the variance in SWN-K. Factor analysis suggested four factors underlying the measures collectively: functioning, psychopathological symptoms, depressive symptoms, and daily living. Both the QLS and the SOFI loaded on the functioning factor; the SOFI cross loaded on both the functioning and daily living factors.

**Discussion:** Our findings suggest some redundancy exists among the measures studied, particularly among the clinician-rated functional and quality of life measures. However, only a small proportion of the variance in patient-rated SWN-K was explained by a model including the clinician-rated measures, suggesting that the SWN-K captures unique information. This exploratory analysis may guide future efforts aimed at identifying a more parsimonious set of data elements that optimize the value of information collected while minimizing data collection burden.

doi:10.1016/j.schres.2010.02.725

**Poster 231**

**CONCORDANCE BETWEEN MEASURES OF FUNCTIONING, SYMPTOMATOLOGY AND CHANGE: GAF, CGI-S, CGI-C AND PANSS**

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**Background:** Past research extrapolates between symptom measures, including the CGI-S/C (Clinical Global Impressions of severity and change) and PANSS (Positive and Negative Syndrome Scale), to give clinical meaning to the PANSS. Little is known about concordance between the GAF (Global Assessment of Functioning Scale) and symptom measures. We examined the feasibility of extrapolation among GAF, CGI and PANSS.

**Methods:** Equipercentile linking was conducted between the measures at baseline, and weeks 6, 12, and 26 in an international single arm study of risperidone long-acting injectable in early onset schizophrenia (n=303).

**Results:** Across visits GAF categories linked to PANSS total scores as follows: ‘superior functioning’=66; ‘absent or minimal symptoms’=72; ‘slight impairment’=82; ‘some mild symptoms’=88; ‘moderate symptoms’=94; ‘serious symptoms’=96; ‘major impairment’=99 and ‘serious impairment’=108. CGI-S scores linked to mean GAF scores as follows: 1 (not ill)=84; 2=71; 3=61; 4=47; 5=37 and 6 (severe)=31 and to PANSS scores follows 1 =33; 2 =40; 3 =57; 4 =70; 5 =84 and 6 =104. Across time CGI-C ratings linked to PANSS percentage change scores as follows: 1 (Very much improved)=41.5%; 2=25.5%; 3=11.5% 4 (Unchanged)=-1.5%; 5=16 and 6 (Much worse)=47% (35-59).

**Discussion:** The results support extrapolation between symptom and functioning measures and improve clarification of their meaning. For instance, regarding clinical response, PANSS 20% improvement concorded with a CGI-C improvement of 2 (‘Much Improved’) and a change of between 11 and 20 on the GAF rank improvement.

doi:10.1016/j.schres.2010.02.726

**Poster 232**

**IMPROVEMENT IN POLYPHARMACY AFTER INTRODUCTION OF TREATMENT ALGORITHM**

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**Background:** Treatment algorithms in general help reduce variability and enable better treatment and patient outcome including reduction in polypharmacy. Polypharmacy or use of more than one medicine for treating psychiatric conditions such as schizophrenia
is widespread despite well known problems. In this study, we report the impact of Texas algorithm for treatment of schizophrenia (TATS) in the polypharmacy.

**Methods:** In a specialized early psychosis clinic, two physicians (RR and MK) implemented automated staging tool and treatment choice based on TATS. We evaluated the use of medication at the time of new intake of patients and after at least 6 months of treatment in 103 patients.

**Results:** All outcome measures including the average number of psychiatric medications, average number of antipsychotics and use of anticholinergic medications improved on follow up after the intervention (Table).

<table>
<thead>
<tr>
<th>N=103</th>
<th>Before (intake)</th>
<th>After intervention</th>
<th>Mean diff</th>
<th>DF</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean StDev</td>
<td>Mean StDev</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># total meds</td>
<td>2.95 1.872</td>
<td>1.74 0.812</td>
<td>1.21</td>
<td>99</td>
<td>7.087</td>
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</tr>
<tr>
<td># Psych Meds</td>
<td>2.68 1.693</td>
<td>1.69 0.787</td>
<td>0.99</td>
<td>99</td>
<td>6.481</td>
<td>.0001</td>
</tr>
<tr>
<td># anti psychotic</td>
<td>1.78 1.011</td>
<td>1.07 0.256</td>
<td>0.71</td>
<td>99</td>
<td>6.908</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>AntiChol</td>
<td>0.17 0.378</td>
<td>0.1 0.302</td>
<td>0.07</td>
<td>99</td>
<td>2.15</td>
<td>0.0341</td>
</tr>
</tbody>
</table>

**Discussion:** Our findings suggesting that the introduction of algorithm might have contributed to a reduction of polypharmacy. However, this should be considered preliminary as many factors including symptomatic improvement of the individuals between the two points unrelated to the algorithm, nature of early psychosis, physician awareness and bias may have contributed to this improvement.

do:10.1016/j.schres.2010.02.727

**Poster 233**

**RECENT CHARACTERISTICS OF SUICIDE AND SUICIDAL BEHAVIOR IN PATIENT WITH SCHIZOPHRENIA**

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**Background:** Schizophrenic patients are often transferred to emergency unit for committing suicide and demonstrating suicidal behavior. It was reported that 14% of suicidal patients were diagnosed with schizophrenia, and suicide rate of the patient with schizophrenia is 4.9-13%. The aim of this study was to reveal recent characteristics of suicide and suicidal behavior in Japanese schizophrenic patients.

**Methods:** The clinical records of patients who were transferred to Kitasato University Hospital Emergency Center due to suicide attempt were investigated. The term of investigation was between August 1st, 2007 and October 31st, 2009. The data set of age, sex, psychiatric diagnosis according to the ICD-10 criteria, occupation, methods and outcomes of suicidal attempt, and family history were structured and analyzed statistically.

**Results:** A total of 771 patients attempted suicide, of which 106(74 females and 32 males) were diagnosed with schizophrenia (F2). Sixty-five (61.3%) of the suicide attempters with schizophrenia were between 20 and 30 years of age. The distribution of methods used by attempted suicide was different from other psychiatric disorders, especially, the ratio of cut/pierce method was higher in schizophrenic patients. Nineteen (17%) suicidal attempters with schizophrenia died from the act, and 48 (45.3%) were transferred to psychiatric hospital after physical treatments.

**Discussion:** Clinical characteristics of suicidal attempters with schizophrenia were different compared to other psychiatric disorders. To reveal the characteristics of suicidal behavior of schizophrenic patients might contribute to the prevention of suicide and/or suicide attempt in schizophrenia.
Poster 235
THE TEMPORAL STABILITY AND THE DETERMINANTS OF SUBJECTIVE WELL-BEING UNDER ANTIPSYCHOTIC MEDICATION IN FIRST-EPIEDE PSYCHOSIS

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Background: Subjective well-being has no generally agreed upon definition. The key elements include a patient’s self-reported well-being specific to antipsychotic medication (as opposed to general well-being/quality of life). Related conceptualisations include: Awad (1993) “Changed subjective state after just a few doses of neuroleptics”; Naber (1995) “Neuroleptic induced side effects which can affect not only the motor system but also cognitive and emotional abilities which are difficult to detect”; De Haan (2001) “all experiences a patient reports whether positive or negative, at the physical, emotional and cognitive levels related to the treatment with antipsychotic medication”. As the SWN can be used to inform optimal pharmacotherapy from a patient’s perspective (as patient’s opinion of optimal treatment have been shown to differ from clinicians) and may be strongly related to a patient’s adherence to their medication, we sought to examine its determinants and stability in first-episode psychosis population. Primary aim –To examine ways in which SWN may be related to the factors described in Naber (1995) and Lambert et al. (2003) model in a specific first episode population. These factors include: phase and severity of illness; medication side effects; type of medication; psychosocial management; dysaffective and dyscognitive effects of treatment; attitudes and insight; and psychopathology and symptomatic improvements. Secondary aim –To provide preliminary information on temporal stability of SWN controlling for the correlates of SWN over time.

Methods: Subjects – Anyone experiencing a first episode of psychosis within last two years, using antipsychotic medication (and likely to be so for 6 months) and with a good understanding of English. Instruments – Demographics Interview (Vocation, Medical, Family history); Instruments – Demographics Interview (Vocation, Medical, Family history); Instruments – Neuropsychological Tests (Proverbs subtest WAS-III or WTA); Neuropsychological Tests (Proverbs subtest of DKEFS, RBANS Coding, Digit Span and Semantic Fluency, Trail Making Test and RAVLT); Personality (BFI-10); Depression, Anxiety, Stress (DASS-42); Psychopathology (PANSS).

Results: Results will be presented for the first 20 subjects. In terms of preliminary analysis, from the initial interview, a decreased SWN is correlated with depressive symptoms (p<.05), and stress (p<.05), but not positive or negative symptoms, or anxiety (as measured by the DASS). In terms of personality, neuroticism factor correlated with decreased SWA (p<.01) whereas Outgoing/Agreeableness with increased SWA (p<.05). Medication side effects, most demographics, neuropsychological functioning, or attitudes towards medication do not appear to be correlated with SWA at the initial interview.

Discussion: Where available base-line, 3-month and 6-month panel data will be presented and comments made on stability of the SWN over time, controlling for likely moderating influences.

doi:10.1016/j.schres.2010.02.730

Poster 236
THE EFFECTS OF EXPERIENCING SIMULATED AUDITORY HALLUCINATIONS ON ATTITUDES TO SCHIZOPHRENIA IN FINAL YEAR MEDICAL STUDENTS

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Background: Negative public attitudes towards people suffering from mental illness can hinder recovery from illness and limit social participation (Thorncroft, 2006). Mental health advocates and researchers have sought to better understand and combat stigma in the wider community. Clinicians, including doctors, may also exhibit negative attitudes towards people with mental illness. Reducing stigma amongst clinical staff is especially important in ensuring people with mental illness receive optimal health care. This study aimed to foster greater understanding and empathy towards patients suffering from schizophrenia in final year medical students. Student’s attitudes to people with mental illness were measured before and after they participated in a workshop on schizophrenia that included an experience of simulated auditory hallucinations.

Methods: Eighty seven final year medical students attended a three hour workshop which aimed to enhance their understanding of the experience of living with chronic auditory hallucinations. All participants gave written informed consent. The students viewed a DVD about schizophrenia, from a consumer perspective. They then worked in pairs, completing various cognitive tasks and games, for 45 minutes. During this time one student in each pair listened to simulated auditory hallucinations via an mp3 player. The simulated hallucinations were continuous recording of voices and other sounds, typical of those heard by a person with psychosis, but without suicidal or violent content. The other student was able to experience interacting with a person distracted by hallucinations. Students then swapped roles for a further 45 minutes. Attitudes towards mental illness were measured before and after they participated in the workshop.

Results: There was a significant improvement in the student’s attitudes towards mental illness following the workshop. Their mean AMIQ score improved from -1.70 (SD = 2.7) prior to the workshop to -0.62 (SD = 2.7) after the workshop (t(86) = -4.22, p < .001). They found the workshop useful and described a better understanding of the everyday difficulties of living with chronic psychotic symptoms.
Discussion: The results of this study are consistent with a previous study conducted with nursing students (Dearing & Steadman, 2008). Our findings indicate that workshops providing a simulated experience of mental illness are an effective means to improve medical student’s attitudes to people with mental illness. Such workshops can be used to complement more formal teaching and clinical placements. Reduction in stigma amongst clinicians may improve the standard of health care provided to people with chronic psychotic disorders.

doi:10.1016/j.schres.2010.02.733

Poster 239
VICARIOUS EMBARRASSMENT AND VICARIOUS SHAME EXPERIENCES IN SCHIZOPHRENIA

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Background: Models, experiences and consequences of embarrassment and shame have been thoroughly studied from the first-person perspective, in healthy participants as well as in patients with schizophrenia. The present research examines the vicarious forms of these two self-conscious emotions, vicarious embarrassment (VE) and vicarious shame (VS) in a sample of patients with schizophrenia as well as in a matched healthy control sample. It is proposed that the vicarious experience is not dependent on observing actual embarrassment and shame, but is instead shaped by the observer’s perspective. Therefore we classify situations eliciting VE and VS along the two orthogonal vicarious forms of these emotions: 

Methods: In four successive studies with independent samples (overall samples size of N = 1,393) we applied different methods to first validate the dimensionalities of the VE/VS taxonomy, second demonstrate the distinction of these vicarious SCEs to observed embarrassment and shame, third highlight their relation to personality traits and gender, and finally investigate their experience in a sample of patients with schizophrenia (N = 30).

Results: Preliminary data demonstrates that patients with schizophrenia exhibit an impairment in their capability in recognizing vicarious shame, while vicarious embarrassment experiences are broadly unaffected.

Discussion: With greater cognitive demand and perspective taking requirements, patients with schizophrenia display difficulties in experiences of the social emotion vicarious shame. The more automatic processing of vicarious forms of embarrassment however seems to be unaffected. These findings expand classic research findings on basic emotion perception in schizophrenia to more advanced constructs of social emotions which require additional perspective taking qualities and the consideration of social norms to successfully accomplish these processes.

doi:10.1016/j.schres.2010.02.734

Poster 240
THEORY OF MIND IMPAIRMENT IN SCHIZOPHRENIA REFLECTS A DIFFICULTY IN PERSPECTIVE-TAKING

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Background: The significance of functional disability in schizophrenia is recognised world-wide. Theory of mind (ToM) impairment – a difficulty in inferring other people’s mental states – contributes to this functional disability. New psychological treatments are being trialed to target ToM impairment in schizophrenia and, in turn, improve functional disability. Better understanding of the underlying cause of ToM impairment in schizophrenia may inform the design of treatments so as to maximize outcomes. This paper aims to contribute to this better understanding.

Methods: Research is reviewed concerning the primacy of ToM impairment in schizophrenia and its relation to basic neurocognitive deficits. ToM impairments in schizophrenia and autism are then contrasted, before reviewing a series of studies that have tested a ‘perspective-taking’ account of ToM impairment in schizophrenia.

Results: ToM impairment is not secondary to the onset of schizophrenia and may be a trait marker of vulnerability. Basic neurocognitive impairments contribute to, but do not completely explain, the ToM impairment in schizophrenia, suggesting a more selective difficulty. While people with autism may have a difficulty in representing mental states as separate from reality, people with schizophrenia have a difficulty in assuming themselves in the ‘mental shoes’ of other people so as to make appropriate mental-state inferences.

Discussion: ToM impairment in schizophrenia reflects a difficulty in perspective-taking rather than a difficulty in appreciating the representational nature of mental states. Underpinning this perspective-taking difficulty may be a compromised capacity to inhibit the ‘self-perpective’ (i.e., to reason as if one’s own perceived reality is only one of many viewpoints). Implications are discussed concerning the design of interventions to treat ToM impairment in schizophrenia.

doi:10.1016/j.schres.2010.02.735

Poster 241
PREDICTORS AND CORRELATES OF OPTIMISM IN INDIVIDUALS WITH A SEVERE MENTAL ILLNESS

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Background: Given the role optimism is suggested to play in the recovery of individuals with severe mental illness, studies are warranted in order to better understand factors that are linked with or predict optimism within this population. Can optimism be linked to self-esteem and negatively linked to neuroticism, anxiety, and depression, as suggested in studies with non-psychotic individuals? Mueller and colleagues found that individuals with early psychosis with a strong social network fare better in terms of overcoming stigma, than individuals without such support. Could optimism in individuals with psychosis be linked to relational aspects, such as friendship skills, alliance with the therapist or attachment styles? Little is also known about optimism regarding the
work integration of people with severe mental illness – could optimism in this context be linked to feelings of self-efficacy? The purpose of this study was therefore to increase our understanding of correlates of optimism in people with severe mental illness in two samples: individuals with recent onset of psychosis, and individuals engaged in a vocational rehabilitation service.

Methods: Study 1: This sample consisted of 150 individuals with early psychosis, with a mean age of 25 (SD = 6.4), 61.6% (N = 92) male and 60.5% (N = 88) Caucasian. Study 2: This sample consists of a total of 254 individuals taking part in a study on predictors of work outcomes in Prevocational Programs in Montreal (Quebec, Canada). The average age was 38 (SD = 8.7), with 53.2% (N = 135) of the sample being female.

Results: Study 1: Optimism was correlated with conscientiousness, neuroticism and extraversion. As expected, optimism was also correlated with self-esteem, the positive, negative and total scores on the SERS-SF (Lecomte et al., 2006). In terms of symptoms, optimism was indeed negatively correlated with depression, anxiety and suicidality, measured on the BPRS but not with psychotic symptoms, either positive or negative. Insight was also negatively correlated with optimism. Regarding relational variables, significant links were found between optimism and all but the relationship as secondary peer attachment scales on the ASQ, as well as the development of friendships and of having leisure activities as measured by the CASIG. Finally, the alliance, assessed with the WAI was significantly linked with optimism as well. The Stepwise linear regression shows that 53.2% (adjusted R² = 52.8) of the variance on the optimism score can be explained by a model including: self-esteem (total score, B = 0.46), capacity for leisure activities (B = 0.16), confidence in others (B = 0.19), low depression (B = -0.16), and low insight (B = -0.14). Study 2: The correlation matrix revealed significant links between optimism and all of the measured constructs (self-efficacy, symptoms, self-esteem and social support). The Stepwise linear regression revealed that 43.2% (adjusted R² = 42.7) of the variance is explained by a model including self-esteem total score (B = 0.29), depression (B = -0.33), and reflected self-esteem (B = 0.16) - a social support scale.

Discussion: Our results support those of other studies with ‘normal’ populations suggesting links between optimism and self-esteem and depression. However, optimism after a recent psychotic episode is also linked to abilities to have a network and to perceptions regarding social or familial network. Similarly, individuals trying to integrate the workplace will be more positive about the outcome of their efforts if they also believe they are esteemed by others. Limitations and implications for treatment will be presented.

doi:10.1016/j.schres.2010.02.736

Poster 243
THE DEVELOPMENT OF THE MENTAL-STATE REASONING TRAINING (MSR) PROGRAM: PHASE I AND II

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Background: Social cognition, the cognitive operation that underlies social interactions and the understanding of the intention of others, is profoundly impaired in schizophrenia. Thus, improving social disability in schizophrenia is now a high priority in schizophrenia research. This study describes a group-based program designed to improve general understanding of other people’s thoughts and feelings (mental state reasoning training; MSRT). This is a manual-based program developed around videos, computer games, and group games and is delivered in ten sessions over five to seven weeks, twice-weekly. The MSRT program uses probes to target mental-state reasoning aspects of program activities. Our aim was to examine whether the MSRT program produced improvements in social cognitive abilities and social functioning in individuals with schizophrenia.

Methods: Twenty-four participants in the first open clinical trial phase of the study underwent baseline testing to assess their social cognitive abilities (emotion recognition, ‘Theory of Mind’, and attributional style) before entering into the training program. Participants are then retested following completion of the program to assess potential improvements in social cognitive abilities. In the second phase of the study sixteen participants with schizophrenia or schizoaffective disorder were randomly assigned to either an active MSRT group or to a social activities control (SAS) group.

doi:10.1016/j.schres.2010.02.737
Participants in SAS underwent similar activities to the MSRT group but without any social cognitive training. To assess the impact of training on real-world social functioning, participants completed the Empathy Quotient (EQ) at baseline and immediate post-training to examine whether they self-report any subjective changes in their abilities to relate with other people.

**Results:** Participants in the first phase of the study showed improvements on tests of ToM and the Social Skills subscale of the EQ. Further empirical findings regarding the second phase of the study will also be reported.

**Discussion:** In conclusion, although the research is in the early stages, the MSRT program shows good potential to improve social cognitive functioning when tested in an open clinical trial. Moreover, the program has been designed to be easily used in clinical practice and can be implemented by any clinical staff (it does not require clinical psychologists or neuropsychologists). Importantly, participants reported the program to be enjoyable and beneficial.

doi:10.1016/j.schres.2010.02.738

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**Poster 244**

**STRUCTURAL AND SEMANTIC ASPECTS OF DYADIC DISCOURSE IN SCHIZOPHRENIA AND ASPERGER: SIMILARITIES AND DIVERGENCIES**

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**Background:** The present study compares focal linguistic, semantic, pragmatic and social communication characteristics of schizophrenic and Asperger discourse in a language that is typologically far removed from the mainstream languages of schizophrenia and Asperger analysis, viz., Finnish. In addition to extending the data base (and testing existing hypotheses), our aim is to unravel discourse performance in schizophrenia using the case-study approach, an approach that has been found methodologically sound in the cognitive neuroscience of atypical populations (e.g., Caramazza & Badecker, 1991).

**Methods:** In order to ensure sound methodology of data collection, we randomly selected sequences of 100 turns per speaker (2 with schizophrenia, 2 with Asperger, 2 controls) and analyzed these sequences for circa 100 linguistic and pragmatic/social features ranging from phonology to politeness phenomena (see Otsa et al., 2009).

**Results:** We will exemplify the results from two areas: turn structure and select co-operation features. **Turn Structure.** A well-formed discourse turn has a tri-partite structure of an opening, followed by the nucleus, and terminated by the ending, all with their specific discourse/communicative functions. In contrast to Asperger, who tend to fail in all these features, the schizophrenic speakers are generally able to open and end their turn properly, while both groups typically fail in the referential/event-descriptive/declarative nucleus. **Overlapping Speech.** In line with their relative success of turn openings and endings, the schizophrenic speakers are able to incorporate their turns into the discourse by using overlapping speech appropriately. **Shared Elaboration of Topic.** Both schizophrenic speakers (S1 and S2, as well as Asperger speakers) show difficulties or avoidance phenomena when the topic deals with their condition. S1 was apparently confident with his condition, and discussed willingly about his delusions, but, like S2, he also refused to admit that he committed any abnormal incidences in public.

**Discussion:** To sum up: The Asperger subjects have very poor communication skills, while the schizophrenic speakers have good or even superior conversation skills. However, both of them have problems with the structure of discourse (e.g., with turn nuclei). References Caramazza, Alfonso, & William Badecker (1991). Clinical syndromes are not God’s gift to cognitive neuropsychology: A reply to a rebuttal to an answer to a response to the case against syndrome-based research. Brain and Cognition 16: 211–227. Otsa, Lidia, Aleksandra Evtyukova, Laura Lehtoaro, John Niemi & Jussi Niemi (2008). A Linguistic Look into Pertinent Features of Asperger Discourse: Two Case Studies of Spontaneous Speech in Finnish ASD. In Victoria Marrero & Idaira Pineda (eds.), Linguistics: The Challenge of Clinical Application. Madrid: UNED. Pp. 224 – 231.

doi:10.1016/j.schres.2010.02.739

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**Poster 245**

**PERSONALITY TRAITS AND SCHIZOPHRENIA: EVIDENCE FROM A CASE-CONTROL STUDY AND META-ANALYSIS**

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**Background:** Personality is considered to be an important aspect of schizophrenia primarily because it may influence their symptoms and social functioning. Specific personality traits have moderate heritabilities and are related to schizophrenia. The temperament and character inventory (TCI) is a well-established self-report questionnaire. It measures four temperament [novelty seeking (NS), harm avoidance (HA), reward dependence (RD) and persistence (PS)] and three character [self-directedness (SD), cooperativeness (CO) and self-transcendence (ST)] dimensions.

**Methods:** We investigated associations between schizophrenia and personality traits using TCI in our Japanese case-control samples (99 patients and 179 controls). Then, we undertook a meta-analysis of the published literature samples and our samples on associations between personality traits and schizophrenia. The studies included in the meta-analysis were selected using the PubMed with the search terms “TCI”, “temperament and character inventory” and “Schizophrenia”. The meta-analysis was performed using Comprehensive Meta-analysis software package.

**Results:** Patients with schizophrenia indicated higher scores in HA and ST and lower scores in NS, RD, SD and CO compared with controls in our case-control samples (corrected p < 0.0039). A total of seven studies including our samples met inclusion criteria for the meta-analysis (384 patients and 656 controls). We found no evidence of heterogeneity among studies (p > 0.05), except for NS (p = 0.05), except for RD (p = 0.015) and CO (p = 0.031). The effect sizes (Hedges’ g) of temperament traits were 0.98 in HA and -0.23 in PS, while the effect sizes of character traits were -0.96 in SD and 0.61 in ST, respectively.

**Discussion:** These findings suggest that specific personality traits such as higher scores in HA and ST and lower scores in PS and SD were found in schizophrenia compared with those in controls. These personality traits were assessed in patients after the onset of
Symptoms. Careful interpretation of our results would be needed, because we did not indicate whether these findings would reflect pre-clinical personality traits or pre- or post-therapeutic personality traits. For prevention and treatment for schizophrenia, it might be therefore important to further clarify the associations between schizophrenia and personality traits.

doi:10.1016/j.schres.2010.02.740

Poster 246
THE CHALLENGE OF PATIENT ASCERTAINMENT IN CLINICAL TRIALS – NEW DATA

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Background: Clinical trials fail too frequently (up to 50% failures in trials powered at 80–90%). Signal detection might be enhanced with more reliable scales, greater rater reliability, or the use of independent assessments; here we focus on the last of these. Previous studies showed that 1/3 to 1/2 of the patients enrolled in two MDD trials by site raters would be excluded based on the patient’s self-rating or remote blinded clinicians’ ratings of initial severity. New data on the extent and characteristics of patient ascertainment discrepancies and various methods to mediate it will be presented.

Methods: Inter-rater reliability and internal consistency reliability were assessed in one MDD study. Two doses of an experimental compound were compared to placebo in a GAD study in which remote blinded clinicians and site raters assessed patients on the HAMA. In ongoing studies (of MDD, GAD & SZ) patients were assessed by both site raters and by remote blinded clinicians. In two of these studies, accuracy of diagnosis was examined.

Results: Internal consistency reliability (Cronbach’s alpha) was strong for remote blinded clinicians at screening and endpoint and for site raters at endpoint (.67 – .83) but much lower for site raters at screening (.38). In the completed and ongoing studies of MDD, GAD & SZ, 34% (range: 5–56%) of patients included by site raters would have been excluded based on remote blinded clinicians’ ratings of initial severity. SCID-CT assessments by remote blinded clinicians also revealed potential diagnostic errors in patients previously screened for study entry by site-based raters. In one study of GAD, patient ascertainment by remote blinded clinicians increased the drug effect size from .43 to .74.

Discussion: Patient ascertainment issues are pervasive and substantial; on symptom severity alone over 1/3 of patients enrolled in clinical trials may not meet protocol-specified inclusion/exclusion criteria. Diagnosis is an additional source of potential error. Independent assessment of symptom severity by patients appears to have potential benefit in one MDD study. Remote blinded clinicians may be beneficial for diagnosis and symptom severity assessment across several diagnoses. Accurate patient ascertainment may substantially increase effect size.

doi:10.1016/j.schres.2010.02.741

Poster 247
USING THE GLOBAL FUNCTIONING SOCIAL AND ROLE SCALES IN A FIRST EPISODE SAMPLE

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Background: Dysfunction in social and role functioning is a hallmark of schizophrenia. Several lines of research have further demonstrated that such deficits are present not only at the first episode but also in the prodromal phase of the illness. Research with chronic adult patients has tended to use a variety of measures that may not necessarily apply to the more subtle deficits characteristic of younger patients in the prodromal period of the illness or even at their first episode. Two new measures were developed by Cornblatt et al., 2007 to address functioning in the prodromal phase of the illness, namely, Global Functioning: Social and Global Functioning: Role. Both scales have high interrater reliability and good construct validity. The purpose of this study was to determine if these measures would be useful in a first episode population.

Methods: The sample consisted of 48 stable outpatients who had presented with a first episode of psychosis to a specialized Canadian First Episode Program. The sample was administered the two recently developed scales Global Functioning: Social (GFS) and Global Functioning: Role (GFR). For a subsample of 31 patients, the scales were administered at baseline, at 6 months and one year. Subjects were also administered the Positive and Negative Syndrome Scale (PANSS), Birchwood’s Social Functioning Scale (SFS) which has been routinely used to assess functional outcome in a wide range of patients with schizophrenia, a measure of self esteem specifically designed for early psychosis patients and the Personal Beliefs about Illness Questionnaire.

Results: In this sample average ratings on the Social Scale was 6 (SD = 1.60) and on the Role Scale 5.5 (SD = 2.2). The GFS was significantly correlated with the overall score on the SFS (p = 0.0001) as well as all subscales on the SFS (p values ranged from 0.03 to 0.0001). The GFR was significantly associated with the SFS subscale for measuring independent functioning (p = 0.05) and the SFS subscale for measuring employment or school functioning (p = 0.05). Good social but not role functioning was related to low levels of both positive (p = 0.02) and negative symptoms (p = 0.004) and to high self esteem (p = 0.004). Role but not social functioning was related to personal beliefs about the illness, in particular having a sense of control over the illness (p = 0.009) and feeling less stigmatized (p = 0.001) was significantly associated with good role functioning. Repeated measures analyses demonstrated no change over time for either social or role functioning.

Discussion: In this sample of first episode patients the role and social scales appear to be useful scales to use. This preliminary data offers support for the validity of these scales in a first episode sample. Furthermore, the ratings are similar to what has been reported in prodromal studies supporting the idea that poor functioning may be a stable longstanding deficit.

doi:10.1016/j.schres.2010.02.742

Poster 248
STAFF ATTITUDES TOWARDS SCHIZOPHRENIA, WARD ATMOSPHERE AND THE USE OF SECLUSION AND RESTRAINT

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Background: Psychiatric staff’s attitudes to schizophrenia patients do not differ from those of the general public. Better knowledge about psychiatric diseases does not enhance the willingness to interact with mentally ill persons and contact with mental illness outside one's family is not connected with the disapproval of structural discrimination against the mentally ill. Stigma attached to schizophrenia has been considered to affect the treatment of those with a severe mental illness. The use of seclusion and restraint differs considerably between different hospitals and wards and is connected to the prevailing treatment culture. We have studied the relationship between staff attitudes to schizophrenia, ward atmosphere and the use of seclusion and restraint.

Methods: SAKURA is a research and development project on seclusion and restraint in psychiatric hospitals in Finland and Japan. For this part of the study, on all wards using seclusion and / or restraint in each participating hospital (three in Finland, four in Japan) staff filled in several questionnaires (attitudes to restraint methods, attitudes to schizophrenia and opinions about the ward atmosphere). Answers were analyzed to find out whether the nationality, sex, working experience or the use of seclusion or restraint influenced the answers.

Results: All together 579 questionnaires were returned (363 in Finland, 216 in Japan), the response rate was over 85%. The use of restraint was thought to be effective (over 80%) and acceptable (74%), but a considerable minority considered them not humane (28%), even though admitted to using them in everyday practice. Japanese were more critical of the use of seclusion and restraint. Frequent use of seclusion and restraint and stigmatized attitudes towards schizophrenia were correlated. Comprehensive results will be presented in the congress.

Discussion: Despite the controversy over the use of seclusion and restraint, these measures are commonly used to treat and manage disruptive and violent behavior. There is a need to understand the impact of the staff attitudes and ward atmosphere on the use of coercion in psychiatric practice.

doi:10.1016/j.schres.2010.02.743

Poster 249
DO COGNITIVE STATUS AND MOTIVATION PREDICT TREATMENT UTILIZATION IN COGNITIVE REMEDIATION GROUPS FOR INDIVIDUALS WITH SCHIZOPHRENIA?

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Background: The cognitive deficits associated with schizophrenia include difficulties with verbal learning and memory, working memory, attention, information processing speed, psychomotor speed, and executive functioning. Efforts to improve functional outcomes in schizophrenia have prompted the development of several cognitive remediation (CR) programs, or behavioral-based skills-training interventions. Previous clinical outcome studies have found that individuals who were classified as ‘improvers’ on cognitive tasks after completion of treatment had far better attendance rates than ‘non-improvers.’ Additionally, there is a threshold of treatment intensity below which there is no significant improvement. To maximize recovery of cognitive dysfunction in schizophrenia, it is important to understand the factors that influence treatment utilization. The aim of this exploratory analysis was to investigate the relationship between cognitive status, motivation, and treatment utilization in CR groups.

Methods: Participants included 41 individuals with either schizophrenia or schizoaffective disorder who were enrolled in a CR program. The assessment included a neuropsychological battery and a set of self-report questionnaires. Treatment utilization was measured using the percent of scheduled sessions attended over a 4-month period. Using a median-split, subjects were classified as having “good” attendance (attend ≥70% of scheduled sessions), or as having “bad” attendance (attend <70% of scheduled sessions).

Results: Measures of attention (r = .373, p < .05) and working memory (r = .428, p < .01), and the ‘value’ subscale of the Intrinsic Motivation Inventory (r = .312, p < .05) were positively correlated with treatment utilization. ANOVA reveals that individuals with “good” attendance have significantly higher scores on measures of attention (p < .01), mental flexibility (p < .05), working memory (p < .01), and verbal memory (p < .05) than individuals with “bad” attendance.

Discussion: Cognitive impairment seems to be the most salient factor influencing an individual’s ability to attend CR sessions. Knowing that more cognitively impaired clients have difficulty attending regularly suggests that they may need extra help from clinicians to manage and remember their schedules. Possible treatment interventions might include more intensive follow-up care such as weekly phone calls to remind individuals about the importance of their attendance, or teaching these clients how to use planners or organizers to better manage their schedules. The ‘value’ subscale of the Intrinsic Motivation Inventory was the only self-report measure that was correlated with treatment utilization when measured as a continuous variable. Providing preeducation about the value of CR to group members may help promote a better understanding of the importance of good attendance in promoting functional gain.

doi:10.1016/j.schres.2010.02.744

Poster 250
THE INFLUENCE OF INDIVIDUAL AND CONTEXTUAL FACTORS ON QUALITY STANDARDS OF CONTINUITY OF CARE FOR ADULTS WITH SCHIZOPHRENIA LIVING IN THE USA

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Background: Continuity of care demonstrates whether someone is receiving needed services over time. It is particularly important for adults living with schizophrenia because of its long-term challenges. Unfortunately, consumers often face service fragmentation and poor coordination of services, which in turn impacts consumer outcomes. This can be further exacerbated by ethnic and community disparities for quality of care. Various organizations (PORT, CORE, etc.) have created minimum standards for continuity of care that assumes that conformance to this minimum will increase positive outcomes. This study seeks to determine the rate of conformance to these standards of continuity of care in Ohio, USA. It seeks to test what individual and contextual factors are associated with conformance rates to continuity of care, and whether such results demonstrate disparities across these factors.

Methods: A retrospective cohort design was used to examine adults enrolled in a public insurance program in Ohio, USA. The study population included adults between 18 and 64; had two or more outpatient mental health visits; had a primary diagnosis of schizophrenia (ICD-9); and were enrolled in the public program for 1-year period after their index claim (N = 17,419). Given the
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IMPACT OF INITIAL HOSPITALIZATION ON 3-YEAR OUTCOME IN PATIENTS WITH FIRST EPISODE PSYCHOSIS IN HONG KONG

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Background: Psychotic disorders are among the 10 leading causes of disability-adjusted life years (DALYs). Increasing effort has been devoted in identifying factors and interventional strategies associated with better outcome. The Early Assessment Service for young people with psychosis (EASY) was launched in Hong Kong in 2001 aimed to provide early detection and intensive intervention for people with first episode psychosis. This study compared the 3-year outcome of patients receiving the Early Intervention (EI) service with those who received standard care (SC) prior to the launch of the EI service. For the Early Intervention (EI) group, the impact of initial hospitalization was studied for effect on subsequent outcome.

Methods: Seven hundred patients with first episode psychosis consecutively enrolled in EASY programme were compared with 700 matched historical control.

Results: Fewer patients in the Early Intervention programme had been hospitalized at the first month of treatment. Patients in the Early Intervention programme had few number of compulsory admissions, fewer number of subsequent admissions and had shorter duration of hospital stay compared with patients in historical control. Amongst patients in Early Intervention programme, those who were not hospitalized initially were found to have better functional outcome, fewer days in hospital, less suicide attempts.

Discussion: The current study suggests that Early Intervention Programme in Hong Kong is successful in reducing the number of admission and duration of hospitalization. Early Intervention programme should aim for community treatment and to minimize the initial hospitalization in order to bring better outcome.

doi:10.1016/j.schres.2010.02.745
been negative attitudes to LAIs by prescribers themselves. This in turn has been proposed to be a function, at least in part, of knowledge gaps. However other factors may influence these attitudes. This study reports on a multivariate analysis of a previous study that examined depot attitudes in multidisciplinary psychiatric staff. 

**Methods:** Sample - 170 Mental Health professionals from two regions in Australia were approached to complete a questionnaire designed to assess their attitudes to the comparative use and usefulness of LAI antipsychotic medications. Respondents were case managers (allied health = psychologists, social workers, OTs, 24%), nurses (51%), and medical practitioners (psychiatrists and psychiatric registrars, 26%) actively managing persons with schizophrenia. Questionnaire - A 5-point Likert response scale, with response data reduced to a dichotomous measure of importance that incorporated the two top levels (very important) vs. the lower three levels (less important). Domains sampled include: attitude to rate of use of depots (dependent); indications for use of depots; problems with depot use; the most common side effects with depots; barriers to change from depot to oral antipsychotics; the impact of staffing levels on the use of depot versus atypical medications (resources); and confidence in use of different classes/routes of delivery of antipsychotics. Statistics - the binary regression model was constructed in a 2-step backward elimination method. Key independent variables were drawn from attitude and knowledge variables. Each of the factor scores derived for barriers, indications, and problems with depots was recoded as a binary variable split at the median. A binary variable for experience was also entered (<5 years = 0, >5 years = 1). Nursing staff was used as the reference group for profession as they had the strongest endorsement of depot confidence. The independent variables were chosen based on univariate/bivariate analyses (Lambert et al., 2003).

**Results:** The principle predictors of believing LAIs are used ‘too much’ included: being a psychiatrist (OR 35.7); believing strongly in the effectiveness of SGAs (OR 10.03); endorsing the factor comprised of problems with LAIs (patient’s dislike, limitation of rights, injection site reactions, short-term side effects, OR 6.04); having less than 5 years work experience in psychiatry (OR 0.064); not endorsing service-related indicators (being unlikely to acknowledge poor adherence, and prior benefit from LAIs, OR 0.025); and being in a service with relatively higher use of LAIs (OR 0.21).

**Discussion:** The predictors of LAIs being used too much all have good face validity. As in previous research it appears that this attitude is largely driven by medical staff, and being in an environment where there is already wide spread use of LAIs. The findings point to issues of potential knowledge gaps (indication factor, patient problem factors), consistent with analytic framework that acknowledge Knowledge-Attitude-Behaviour paradigms of understanding medical action.

**Poster 254**

**MODEL BASED META-ANALYSIS OF POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS NEGATIVE SUBSCALE) IN STABLE CHRONIC SCHIZOPHRENIC PATIENTS FOR MONOTHERAPY AND ADJUNCT THERAPIES**

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**Background:** Schizophrenia is an area of considerable unmet medical need and an active research field. The negative symptoms of schizophrenia including anhedonia, alogia, lack of motivation or volition are prominent features of the illness and often refractory to treatment. The objectives of the current meta-analysis were to assess the time course of PANSS negative subscale in adjunctive studies with antidepressants, N-methyl-D-aspartate (NMDA) receptor modulators, or neuroactive steroids as add-on therapy to atypical antipsychotics/conventional therapies in stable chronic schizophrenic patients and compare the results with monotherapy studies with atypical antipsychotics.

**Methods:** A search of MEDLINE, or EMBASE identified more than 20 studies which contributed study-arm level data for longitudinal modeling of PANSS negative of atypical antipsychotics in stable chronic schizophrenics. Additive effects were assumed in respect to change from baseline and change from placebo. Placebo effect was characterized by an exponential model over time and active treatments were described by an Emmax model vs. time. Model parameters were estimated using Nonlinear Mixed Effect Modeling (NONMEM). Stochastic simulations were performed to assess the predictive power of the model. In the next step, a database representing 13 published placebo controlled adjunct clinical studies was created for drugs including D-cycloserine, D-serine, glycine, n-acetylcysteine, and the GlyT1 inhibitor sarcosine as NMDA modulators; mirtazapine, selegiline, paroxetine, ritanserin, and ondansetron included in the antidepressant class; and dehydroepiandrosterone (DHEA), and pregnenolone as neuroactive steroids for add on to atypical antipsychotics. The model developed incorporated an additive baseline, placebo, and drug effects with an additive residual error model. Placebo and drug effects were characterized by a linear model. Model parameters were estimated using NONMEM and simulations were performed to assess the predictive power of the model.

**Results:** The relative order of mean placebo adjusted drug effect for PANSS Negative was risperidone > olanzapine > haloperidol in monotherapy at 12 weeks. Addition of NMDA agonists, antidepressants, or neuroactive steroids reduced the PANSS Negative score approximately 28% to 45%. The add on therapy placebo adjusted change from baseline for PANSS Negative in NMDA agonists, antidepressants, and neuroactive steroids were respectively -1.8 (95%CI, -3.9 to -0.01), -1.7 (95%CI, -4.2 to 0.4), -0.8 (95%CI, -1 to -0.6) at 6 weeks, and -3.6 (95%CI, -7.8 to -0.01), -3.5 (95%CI, -8.4 to 0.8), -1.7 (95%CI, -2 to -1.3) at 12 weeks. The model concluded that the treatment effect had not reached a plateau at 12 weeks. The adjunct therapy significantly improved the PANSS negative subscale.

**Discussion:** Quantitative modeling of PANSS negative in stable chronic schizophrenia patients for monotherapy and adjunct therapy using summary level data provided an integrated approach for comparing treatment effects across adjunctive treatments. The minimum clinically important difference from the meta-analysis (from the same class of drugs) was used to power and develop decision criteria for a clinical negative symptom study. Pooling and analyzing data from published clinical trials can inform drug development programs, increase knowledge management of available information for improving study design and decision criteria for clinical trials.

**Poster 255**

**THE ASSOCIATION BETWEEN SEMANTIC CATEGORIZATION DEFICIT AND SYMPTOMS IN FIRST-EPILOGE SCHIZOPHRENIA**


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Background: Semantic memory was defined as a store of culturally shared general knowledge about the meaning of the world, including words and objects, as well as their categorization. Previous studies had found that the deficits are related to some variables (such as age of onset) and symptomatology (such as delusion and formal thought disorder) in chronic patients. However, the relationship might have undermined by other factors such as medication effect in chronic/mixed samples. Importantly, further exploration is essential as clinical and cognitive correlates of the deficit could help elucidate the underlying mechanisms of the disorder. We therefore aim to explore the clinical and cognitive correlates of semantic memory deficit in first-episode schizophrenia patients.

Methods: Semantic memory was assessed using the categorization task in 37 first-episode schizophrenia patients. They were requested to make a category decision (yes/no) as to whether an exemplar word belonged to a category. Exemplars consisted of five semantic relatedness conditions, namely "typical", "atypical", "borderline", "related" and "unrelated". Categorization performance was further operationalized using the reaction time data as typicality effect, false-relatedness effect, borderline peak, borderline shift and overall speed. Data on proportion of yes response in each semantic relatedness condition was also measured. Other than that, positive and negative symptoms, as well as cognitive deficits (executive function, verbal fluency, and sustained attention, verbal and visual memory) were assessed during first episode, after clinical stabilization, and each year for the following three years.

Results: Correlation analysis demonstrated that different dimensions of categorization performance are related to different symptoms and cognitive dimensions. At presentation, negative symptoms was significantly correlated with typicality effect (r = -0.43, P = 0.008), borderline peak (r = -0.44, P = 0.007), overall speed (r = 0.38, P = 0.02), and over inclusiveness (% of yes response in the unrelated condition) (r = 0.37, P = 0.03). Visual memory was related to borderline shift (r = -0.48, P = 0.002) and verbal fluency with overall speed (r = -0.32, P = 0.05). At stabilization, positive symptoms was significantly associated with over-inclusiveness (r = 0.44, P = 0.006). At year 3, while there was a strong correlation between positive symptoms and borderline shift (r = -0.52, P < 0.001), negative symptoms was related to borderline peak (r = 0.33, P = 0.04).

Discussion: Interestingly, positive symptoms were unrelated to semantic memory deficit in first-episode. However, it was strongly related to borderline shift at year 3. The current study had suggested a potential relationship between symptom formation and impairments in semantic memory. Future studies could look at specific symptomatology by separate clinical measure such as formal thought disorder in patients with schizophrenia.

doi:10.1016/j.schres.2010.02.750

Poster 256
COGNITIVE IMPAIRMENT AND RESPONSE TO LOW-DOSE DEPOT CONVENTIONAL ANTI精神病IC IN A SOUTH AFRICAN COHORT OF SUBJECTS WITH FIRST-EPIsODE PSYCHOSIS

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Background: Cognitive impairment is an integral part of the psychopathology of schizophrenia, and a major barrier to functional recovery (Sharma & Harvey, 2001). Research indicates that cognitive functioning improves within a few weeks of treatment with second-generation antipsychotics (Harvey & Keefe, 2001), thus providing compelling evidence for early onset antipsychotic action (Leucht et al., 2005). Insight into symptoms is impaired in schizophrenia and is associated with poor compliance to treatment (Bayard et al., 2009). This study assessed the pattern of associations between subjective reports of cognitive impairment, objective cognitive measurements and psychopathology in a prospective, one year, longitudinal study of first episode psychosis (FEP) patients.

Methods: This study collected demographic, clinical and neurocognitive data in 60 FEP patients with minimal or no prior exposure to antipsychotics. Treatment with fluphenxol decanoate was administered according to a fixed protocol. Patients were evaluated at baseline, 1 month, 3 months, 6 months and 1 year. Assessments included the Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS) (Stip et al., 2003), the MATRICS Consensus Cognitive Battery (MCCB) (Neubertlein & Green, 2006) and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

Results: The final sample consisted of 19 females and 39 males, with a mean age of 23.26 years (sd = 8.8) and a mean educational level of 9.71 (sd = 2.1) completed years of schooling. The mean modal dose of fluphenxol used was 10 mg 2 weekly IMI 68.3% of the sample completed the study. Two patients were excluded from analyses due to protocol violations. Patients were severely ill at baseline with a mean PANSS Total (T) score of 100.5 and PANSS Cognitive (C) score of 19.59. 78.6% of improvement in psychopathology occurred from baseline to 3 months. There were no statistically significant differences in cognitive scores between genders, languages and ethnic groups at baseline. Improvement in cognition plateaued at 6 months. The mean total SSTICS score at baseline was 35.51, with statistical significant improvement occurring between one and 3. There was no correlation between total SSTICS score, PANSS scores, and MCCB scores at baseline. At one month, the total SSTICS score demonstrated significant correlations with PANSS G score and cognitive domains such as Speed of Processing, Working Memory, Verbal Learning, Visual Learning, Reasoning and Problem Solving. No correlation existed between SSTICS, Social Cognition, PANSS C, or Insight (PANSS G12).

Discussion: Cognitive deficits in this South African sample of FEP patients were similar to those identified in samples elsewhere (Good et al., 2004). The nature and reports of subjective cognitive complaints do not strictly correspond with objective cognitive measurements. Low doses of a long-acting conventional antipsychotic are effective in improving some aspects of cognitive function during and after a FEP. These changes occur early with the bulk of improvement occurring between baseline and 3 months, reaching a plateau at 6 months. There is a need to further explore cognitive benefits of conventional antipsychotics and strategies to address subjective awareness of cognitive impairment, insight into illness, compliance, and functioning in schizophrenia.

doi:10.1016/j.schres.2010.02.751

Poster 257
EXPLORING SCHIZOTYPY

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Background: A growing body of research indicates that schizotypal personality traits in the normal range are associated with a variety of endophenotypic characteristics of clinically identified schizophrenia spectrum disorders.
Methods: In three separate undergraduate samples, diverse correlates of different sets of schizotypy measures were explored.

Results: In all three studies, high schizotypy scores were associated with decreased strong right-handedness, and increased mixed right-handedness. There were significant associations between various schizotypy measures on the one hand, and gender, ethnicity, sexual orientation, a history of ADHD, a history of trouble with the law, hemisphericity, temporal-limbic signs, paranormal beliefs, transliminality, sex-role identification, season of birth, body asymmetry, body size, age at puberty, and atopic disorders on the other hand.

Discussion: The complex network of associations explored in these three studies is discussed in terms of neurodevelopmental theory, developmental instability, prenatal adversity, and prenatal androgenic exposure.

doi:10.1016/j.schres.2010.02.752

Poster 258
VITAMIN D LEVELS AND CARDIOMETABOLIC STATUS IN PATIENTS WITH PSYCHOTIC DISORDERS

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Background: Vitamin D deficiency is common and there is great interest in the role of vitamin D, not only in skeletal health but also in chronic diseases such as cancer, autoimmune infectious disease, cardiovascular disease and neuropsychiatric disorders such as mood disorders and schizophrenia. Deficiency has also been linked to metabolic disease such as diabetes and neuropathic pain. The main source is through exposure to sunlight. Older people and ethnic groups with darker skin colour are less able to synthesise Vitamin D. Vitamin D deficiency usually has to be treated with supplementation as insufficient amounts are found in food. A Victorian study found that 58% of psychiatric inpatients were Vitamin D insufficient, mainly in mood disorders. We aimed to examine the relationship between Vit D status and cardiometabolic risks in a range of diagnostic groups.

Methods: Patients - Vit D levels were available for 190 patients receiving short-term inpatient care from the Concord Centre for Mental Health, in Sydney Australia. Further metabolic and diagnostic information was available from a subset who were screened by the Concord Centre for Cardiometabolic Health in Psychosis (ccCHIP) team. Vitamin D (as 25-OHD) - Standard assays were employed as part of routine medical screening for cardiometabolic risks in the hospital population. Normal VitD levels are above 50 nmol/L, a mild insufficiency is 25-50 nmol/L, moderate is 12.5-25 nmol/L, and severe insufficiency is <12.5 nmol/L.

Results: Three (1.6%) had severe insufficiency, 4 (2.1%) moderate, and 53 (27.9%) mild; 68.4% had normal Vit D levels. Diagnostically, there was no relationship to absolute Vit D level or categorical abnormalities and schizophrenia (30.7%), schizoaffective (35.4%), bipolar (16.7%), or depression (18.8%) (Chi2 2.858, p = .414). The genders had equal mean Vit D levels and equally likely to have insufficient levels (OR 1.3 (95% CI .693 to 2.427)). There were no findings of relationships between having a family history of type II diabetes, cardiovascular disease, obesity or psychosis and any insufficiency of Vit D levels. However, those from a higher-risk for diabetes ethnic group (e.g. Asian, Indian, Middle Eastern etc) were significantly more likely to have low Vit D levels (t = 3.720, df = 75, p = .000) with; 69% of this group have insufficient Vit D versus 31% with no ethnic risk. In terms of cardiometabolic risk associations, those who are overweight or obese (ethnically adjusted cut-offs), are more likely to have moderate to severe Vit D insufficiency (chi2 12.98, df = 6, p = .043). There was no relationship between insufficient Vit D and abnormalities of glycaemia (OR .993, 95% CI .287 to 3.436, controlling for ethnicity risk), hyperlipidaemia (gender adjusted HDL OR .866, 95%CI .452 to 1.658; LDL .875, 95%CI .434 to 1.763; TG .633, 95%CI .339 to 1.182), or elevated blood pressure (systolic OR 2.316, 95%CI .451 to 11.891; diastolic OR .767, (95%CI .19 to 4.937), or smoking status (never, previous, current). There were no differences for these analyses when comparing diagnostic groups (schizophrenia versus mood versus other).

Discussion: We found about a third of psychiatric patients had some degree of insufficient Vit D. This was significantly related to having an at-risk ethnic Background for diabetes, and was associated with ethnically adjusted obesity. There were no relationships to other cardiometabolic risk factors. We were unable to demonstrate a relationship between diagnostic group and insufficient Vit D. Although insufficiency is relatively common, its relationship to cardiometabolic illness in schizophrenia requires further examination.

doi:10.1016/j.schres.2010.02.753

Poster 259
PERCEIVED STIGMA AND RECOVERY FOR KOREAN SCHIZOPHRENICS IN PSYCHIATRIC REHABILITATION CENTERS: A COMPARISON BETWEEN THE CLUB HOUSE MODEL AND THE REHABILITATION SKILLS TRAINING MODEL

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Background: This study is to identify the perceived stigma and recovery of psychiatric patients by comparing a club house model to a rehabilitation skills training model in psychiatric rehabilitation. The subjects of this study are schizophrenics.

Methods: A total of 521 individuals with schizophrenia, who participated in one of two different types of psychiatric rehabilitation services for more than 3 months, completed a self-report survey questionnaire about their perceived stigma (Perceived Stigma Scale; PSS) and perceived recovery (Perceived Recovery Scale; PRS). Among them, 232 individuals participated in the services of a club house model, and 289 participated in the services of a psychiatric rehabilitation skills training model.

Results: 1) The mean scores of the 521 consumers for the PSS and PRS were 2.99 and 3.43 respectively. 2) The participants in the club house model reported significantly lower PSS scores than the service recipients of the psychiatric rehabilitation skills training model (p<.05). 3) The participants in the club house model reported significantly higher PRS scores than the service recipients of the psychiatric rehabilitation skills training model (p<.05). 4) The level of perceived stigma and the level of recovery were highly correlated (p<.001).

Discussion: The current results indicate that the individuals with schizophrenia, who participated in the club house model reported significantly lower scores of perceived stigma and higher perceived recovery than those recipients of the rehabilitation skills training model. There was high correlation with the level of perceived stigma and the level of recovery. These findings suggest that consumers’ active participation, self-determination, and increased roles in their rehabilitation programs will be effective decreasing the perceived stigma and promoting their perceived sense of recovery.

doi:10.1016/j.schres.2010.02.754
Poster 260
SALIENCE, ANHEDONIA, AND THE INTERMEDIATE PHENOTYPES OF SCHIZOPHRENIA

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Background: Elevated presynaptic striatal dopamine is thought to be a final common effect of multiple specific aetiologies, which in turn gives rise to psychosis through the disruption of incentive salience. In contrast to psychosis, negative symptoms are thought to emerge from the disruption of multiple neurophysiological systems (Howes & Kapur, 2009, Schizophr. Bull., 35, 549-62). We tested this model by examining the relationship of an ecologically valid measure of reward learning with anhedonia and intermediate phenotypes of schizophrenia, while controlling for neuropsychological impairment.

Methods: Undergraduates (n = 84) completed the stimulus chase task (SCT), which provided a measure of sensitivity to reward, self-report measures ofhedonic capacity, and self-report (Schizotypal Personality Questionnaire [SPQ]) and performance (psychobabble task) measures of intermediate phenotypes of schizophrenia. Motor reaction time, attention, and frontal functions were assessed with a small battery ofneuropsychological tests.

Results: After controlling for neuropsychological functioning, higher cognitive-perceptual SPQ scores predicted poorer performance on the SCT (r = -0.27, p < 0.01). Higher interpersonal SPQ scores also predicted poorer SCT performance (r = -0.26, p < 0.01). However, anhedonia and disorganization features were not associated with SCT scores.

Discussion: The theoretical link between salience, or the efficacy of reward learning, and psychosis is evident at the level of the intermediate phenotypes of schizophrenia reported by ostensibly healthy individuals. However, an equally strong association of salience with intermediate phenotypes of negative symptoms complicates this picture. The observed associations are not attributable to neuropsychological impairment or anhedonia.


Poster 261
SPECIFIC PROGRAM FOR INTERVENTION IN INCipient PSYCHOSIS INTRODUCED IN CATALONIA(Spain)

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Background: The prodrome of psychotic disorders is a well-described entity that manifests as a decline in social and occupational functioning along with increasingly bizarre behavior. The main objective of this communication describes the theoretical Background origins and development of a new clinical service/ program for identifying and intervention in the prodromal phase and in first episode of schizophrenia and other psychotic disorders.

Methods: The specific program for young people with prodromal psychosis and first episode of schizophrenia emerges by the health Department of Catalonia(Spain). Specifically in health region of Tarragona(Catalonia). To describe the two-year follow up of a program introduced in Catalonia through the development of a multidisciplinary group of professionals. To review and discuss the issues and challenges involved in the transition of first-episode in young patients, including facilitating access and early identification, comprehensive assessment, treatment, psychosocial supports and family education and support.

Results: Describe the key components of the program that are required to develop an appropriate and individualized treatment plan. An assessment involves: medication; psychoeducation provided to consumers and the family, counselling, case management / care coordination, cognitive behavioural therapy (CBT) substance abuse / use treatment, supports crisis intervention and psychosocial supports. Other important areas are research and public education. Several variables had been studied to analyze the methodology of the program such us demographic, social and clinical characteristics.

Discussion: Finally, the principal objectives of our program pretends: reducing the duration of untreated psychosis (DUP) through early and appropriate detection and response, thereby potentially reducing the severity of the illness. Minimizing the disruption in the lives of young people who experience psychosis such that educational, vocational, social and other roles can be maintained. Minimizing the societal impact of psychosis including reducing demand in other areas of the mental health, health and social service systems and reducing disruption in the lives of families.

doi:10.1016/j.schres.2010.02.756

Poster 262
ULTRA HIGH RISK (UHR) FOR PSYCHOSIS GROUPS: ARE THERE DIFFERENT LEVELS OF RISK FOR TRANSITION TO PSYCHOSIS?

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Background: Over the last fifteen years, there has been increased interest in the prodromal phase of schizophrenia and other psychotic disorders. Several strategies have been introduced in order to identify individuals in the putatively prodromal phase of psychotic disorder. The most widely used of these approaches is the “ultra-high risk” (UHR) approach. The UHR approach consists of identifying three help-seeking groups: 1. Individuals with attenuated positive psychotic symptoms (APS), 2. Individuals with brief limited intermittent psychotic symptoms (BLIPS), 3. Individuals with a trait vulnerability due to schizotypal personality disorder or psychotic disorder in a first degree relative combined with a recent deterioration in functioning (Trait). These criteria have been found to reliably predict onset of psychotic disorder over a 1-2 year period. However, it remains unclear whether a particular UHR group, or combination of these groups, has a higher risk of transition to psychosis than other groups. In this study, we investigated whether particular UHR groups, or combinations of groups, has a higher risk of transition than other UHR groups over a six-month follow up period. We a priori hypothesized that the transition rate would be BLIPS > APS > Trait.

Methods: 817 UHR subjects were recruited from the PACE clinic, Orygen Youth Health, Melbourne. Transition to psychosis within 6 months was established through research follow up and consultation of PACE clinic and State medical records.

Results: Of the 817 subjects, 72 subjects (8.8%) transitioned to psychosis within 6 months. Three combinations of intake groups were defined: 1. Subjects in the Trait group alone, 2. Subjects in the APS group, either with or without also meeting the Trait group criteria, 3. Subjects in the BLIPS group, regardless of whether they also met criteria for other intake groups. After adjusting for sex, age, antipsychotic medication, year of presentation and type of intervention, intake group remained a significant factor (p = .024), with, as hypothesized, the BLIPS group having the highest rate of transition.
followed by the APS group and the Trait group. For each level increase in the intake group (1-3), the risk was two-fold of that associated with the immediate level below.

**Discussion:** Although the UHR criteria as a whole have been found to reliably identify people at risk of imminent transition to frank psychosis, the current data indicate that particular combinations of these groups are at higher risk than others. Specifically, subjects with BLIPS are at highest risk, followed by subjects with APS, followed by those who meet the Trait group alone. This stratification of risk may provide a means of further “closing in” on those at highest risk of psychotic disorder and inform indicated prevention efforts in this population.

doi:10.1016/j.schres.2010.02.757

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**Poster 263**

**METACOGNITIVE THINKING AND AUDITORY HALLUCINATIONS IN ULTRA-HIGH RISK INDIVIDUALS: AN EXPERIENCE SAMPLING STUDY**

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**Background:** A wealth of literature now suggests an association between metacognitive beliefs, auditory hallucinations (AH) and related distress (e.g. Lobban et al., 2002). However, little research has investigated the temporal relationship between metacognitive thinking (e.g. examining ones own thoughts) and AH in real-world everyday settings. This relationship might best be studied in the early stages of psychosis, without the potential confounds of institutionalisation or prolonged medication.

**Methods:** 30 individuals who have met ultra-high risk (UHR) criteria in the last year, according to the Comprehensive Assessment of at Risk Mental State, are being recruited from early detection services and the Early Detection and Intervention Evaluation Two trial. Participants complete a self-assessment booklet at 10 random times a day, for six days, when prompted by an electronic wristwatch. Questionnaires and interviews are also being employed.

**Results:** Preliminary multilevel modelling analyses were carried out on data from six hallucinating participants. A significant relationship was found between metacognitive thinking (t0) and AH at the following time point (t1; \(p = .038\)). Graphing the data shows this to occur in a dose-dependent fashion. A similar relationship was found between metacognitive thinking (t0) and distress from AH (t1; \(p = .011\)).

**Discussion:** Initial findings suggest that increased metacognitive thinking occurs prior to the onset of AH in UHR individuals. Intense preoccupation with thoughts may be misattributed as originating externally resulting in subsequent AH. Future analyses of the complete dataset will investigate whether belief systems, perceived social support, perceived control and certain contexts moderate this relationship. We will also examine whether everyday-stress triggers metacognitive thinking.

doi:10.1016/j.schres.2010.02.758

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**Poster 264**

**THE COGNITIVE BIASES QUESTIONNAIRE FOR PSYCHOSIS (CBQP)**

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**Background:** A body of research has demonstrated a number of cognitive biases in psychosis. Reasoning biases such as Jumping To Conclusions (JTC) and intentionalising are well established in the paranoia literature, but other Beckian thinking biases such as dichotomous thinking and emotion-based reasoning are often prevalent in individuals with psychosis presenting to Cognitive Behaviour Therapy (CBT). CBT for psychosis (CBTp) often concentrates on process rather than content, for instance working with ways in which day to day evidence is evaluated rather than challenging the content of delusions. New approaches have advocated specific training procedures for thinking biases as a complement to CBTp (eg. Metacognitive Training; Moritz & Woodward, 07). Current methods of assessing cognitive biases consist of experimental tasks (such as the Beads Task) or time-consuming measures (such as the Attributional Style Questionnaire), each tapping a specific bias, which are not practical to use in clinical settings.

**Methods:** The Cognitive Biases Questionnaire for psychosis (CBQp) was developed to measure five biases (JTC, intentionalising, catastrophising, emotion-based reasoning and dichotomous thinking) that are considered to be important in psychosis, and delusions specifically. It was based on the Cognitive Style Test (Blackburn et al., 86), which measures common thinking biases in depression, and the vignettes were adapted to be relevant to psychosis (relating to ‘anomalous experiences’ and ‘threatening events’). Data was collected on two sites (Hamburg, Germany, and South London, UK) on 190 patients with psychosis, and on depressed and healthy controls.

**Results:** The CBQp has good psychometric properties. The 5 biases were highly correlated with each other, although confirmatory factor analysis showed equal goodness of fit indices for 1-factor and 5-factor scales. The CBQp was related to hallucinations, delusions and depression, and there was preliminary evidence that it is sensitive to change following CBTp. None of the biases were related to existing experimental tasks, suggesting the CBQp measures a different construct.

**Discussion:** The CBQp is a potentially useful tool in both research (on cognitive biases in psychosis) and clinical (CBTp outcome) arenas.

doi:10.1016/j.schres.2010.02.759

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**Poster 265**

**SOCIAL COGNITION IN SCHIZOPHRENIA: A QUANTITATIVE REVIEW OF THE LITERATURE**

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**Background:** Impairments in social cognition are considered an important feature of schizophrenia and related disorders, particularly in light of their established association with cognition and social functioning. Impairments in some aspects of social cognition are thought to lead to misinterpretations and misperceptions of the social environment, ultimately resulting in impairments in social functioning and even social withdrawal. Empirical evidence suggests performance deficits across a range of social cognitive processes (i.e. Theory of Mind, emotion processing, social knowledge and social perception).

**Methods:** In the current study, a total of 98 publications (published between 1995 and 2009) on social cognitive impairments in
schizophrenia spectrum disorders were reviewed in order to determine quantitatively the magnitude of deficits across multiple domains of social cognition. The initial literature search using the specified keywords (social cognition, emotion processing, social perception, schizophrenia, psychosis, theory of mind, emotion processing) yielded 301 publications, out of which 115 directly explored social cognition in schizophrenia and first episode psychosis. Following further inspection, 46 out of 115 studies were excluded from the analysis as they did not satisfy inclusion criteria. Additional studies were identified through screening of published meta-analytic reviews. A large majority of the reviewed studies (n=94) examined social cognitive function in patients with established schizophrenia at different stages of chronicity, with an exception of one study that also included a group of patients in their first episode psychosis. Out of these, 7 studies sub-grouped their experimental sample based on symptom ratings (n=6) or duration of illness (n=2). The remaining 3 out of 98 studies included only patients with first episode psychosis as their experimental group.

Results: The total number of subjects in the schizophrenia group across all 98 studies was N=3373 compared with N=2665 controls. Five separate, comparative meta-analyses were conducted for Theory of Mind, Facial emotion processing, prosodic emotion processing, social perception/knowledge and overall social cognitive performance. Compared to healthy volunteers, patients with schizophrenia demonstrated significant impairments in Theory of Mind (d=-1.07), both facial and prosodic emotion processing (d=-0.72 and d=-1.11 respectively), social perception/knowledge (d=-0.90) and overall social cognitive performance (d=-0.94). The effects sizes for individual ToM tests (d=-0.71 to -1.05) and two facial emotion processing (d=-0.78 and -0.88) tests were large.

Discussion: The overall meta-analysis including the three major domains of social cognition indicated a strong significant deficit in patients with schizophrenia. The overwhelming majority of identified studies however, investigated deficits in the emotion processing and ToM domains, which biased the exploration of the social cognitive construct to these domains. Due to the small number of studies in the domain of social perception/knowledge, the current results offer only provisional findings regarding the magnitude of these deficits in schizophrenia. There was a large between studies variation in the assessment of social cognitive domains. Consequently, further sub-analyses based on assessment tasks were limited to ToM and facial affect perception only, indicating a large magnitude of impairment in schizophrenia.

doi:10.1016/j.schres.2010.02.760

Poster 267
EVIDENCE FOR ABERRANT SALIENCE NETWORK CONNECTIVITY DURING INFORMATION PROCESSING IN SCHIZOPHRENIA

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Background: Evidence that blood oxygenation level dependent (BOLD) activity in the salience network, which comprises insula and anterior cingulate cortex (ACC), predicts consequent bi-fronto-parietal attentional and default mode network (DMN) activity has been interpreted as an indication that the salience network sends control signals vital for switching between contrasting modes of brain function (Sridharan et al., 2008; Corbetta et al., 2008). Furthermore, salience misattribution is central to recent reformulations of dopaminergic dysregulation in schizophrenia (Kapur, 2004; Kapur et al., 2005). Functional network connectivity (FNC) assesses correlation between functional networks. Here we present a constrained-lagged correlation FNC analysis of spatial networks identified during somatosensation, performed to test the hypothesis that salience network connectivity is disturbed during information processing in schizophrenia. Method: Participants: 21 medicated patients with schizophrenia (mean age 29 ± 7 years (mean ± standard deviation)) and 20 matched healthy controls (mean age 28 ± 8 years) were recruited to take part in a functional magnetic resonance imaging (fMRI) study of somatosensation. Procedure: 100 Hz vibractile stimuli were presented to the fleshy tip of the right index finger during 14 cycles of a 1 s ON-period
and 16 s OFF-period task performed in the scanner. Participants were instructed to stay relaxed but alert between stimulations and to attend to the stimuli when they occurred. **fMRI data acquisition:** Scanning was performed on a 3T Philips Achieva MRI scanner (Philips, Netherlands). 167 whole-head BOLD contrast gradient-echo-planar images were acquired using an eight-channel SENSE head coil with SENSE factor 2 in anterior–posterior direction, TR/TE 1436/35 ms, and a voxel size of 3 mm × 3 mm × 4 mm. **fMRI data analysis:** Group independent component analysis was performed on preprocessed BOLD data (GIFT toolbox; http://icatb.sourceforge.net). 6 spatial components were identified. These represented the salience network (insula and ACC); the central executive network (left fronto-parietal and right fronto-parietal cortex); and the DMN (medio-frontal and medio-parietal cortex). FNC was assessed using constrained-lagged correlation between components (FNC toolbox; http://icatb.sourceforge.net). Maximal lagged correlation (-5 to +5 seconds) was examined between all pairwise combinations of components. Maximum Pearson correlation value and corresponding lag were calculated for each participant and averaged for each group. Group comparisons were performed on the maximal correlation coefficients.

**Results:** Widespread FNC was found in both groups. Significantly reduced FNC was observed in schizophrenia compared to controls between: (i) the insula and ACC; (ii) insula and medio-frontal DMN; and (iii) left central executive network and medio-parietal DMN. There was no evidence of increased FNC during information processing in schizophrenia. Calculation of event-related average components in addition to the FNC analysis revealed that, while in healthy individuals insula activity preceded ACC activity, in individuals with schizophrenia this temporal relationship was weaker.

**Discussion:** Reduced salience network connectivity during information processing in individuals with schizophrenia suggests a pathophysiological disturbance to the system which effects changes between contextually-relevant functional brain states. This aberrance may in turn provide a mechanistic explanation of several clinical features of the disorder.

doi:10.1016/j.schres.2010.02.1041
of three SNPs within DISC1. We included two SNPs that might be of functional relevance as they cause an amino acid substitution and have been associated with schizophrenia in some previous studies: Rs6675281 (Hodgkinson et al., 2004) and Rs7074Cys (rs821616) (Qu et al., 2007); and rs2793092, which appears to be associated with sustained attention deficits in schizophrenia (Liu et al., 2006). Magnetic resonance images of the whole brain were obtained at the University Hospital Marques de Valdecilla, Santander, Spain, using a 1.5 T General Electric SIGNA System. In addition, a sample of 21 healthy control subjects (13 males, 8 females) who volunteered to undertake a MRI scan and to provide a blood sample for genotyping was also included in this first part of the study. From these control subjects, 15 were also genotyped for the NRG1 polymorphisms. These results were combined with our previously reported genotypes on three SNPs within NRG1.

Results: ANCOVA analyses showed that the genotypes of rs2793092 SNP in DISC1 gene was significantly associated with LV volume (P = 0.02). Considering patients with T/T genotype versus C allele carriers, the former showed significant enlargement of the total LV (P = 0.004), left LV (P = 0.001) and right LV volume (P = 0.03). However, taking into account the rs66994992 SNP in the NRG1 gene, which was also associated with LV volume in a previous study, the DISC1 SNP only predicted LV enlargement among those patients carrying the T allele in the NRG1 SNP. Those patients with the "at risk" allelic combinations in both genes had LV volumes which were 48% greater than those with none of the allelic combinations.

Discussion: In conclusion, these results suggest that some of the structural brain abnormalities observed in patients with schizophrenia since the time of illness onset may be related to neurodevelopment-related genes such as NRG1 and DISC1. These data support the importance of assessing the interaction between genes implicated in the structural brain abnormalities observed in patients with schizophrenia. The present review focuses on clinical studies characterising these phenomena once postulated to be pathognomonic for schizophrenia on each occasion, in counter-balanced order. The study visits were 3 to 10 days apart, and each test battery was separated by a 10 to 15 minute rest period. Test-retest reliability of the various domain scores of the MCCB and CDR was evaluated, and the relationships between the scores from the two systems were examined using Pearson’s product-moment correlations.

Results: Both systems identified deficits in all domains, some of these having effect sizes as large as two. The MCCB showed very good test-retest reliability on the various domains: speed of processing (r = 0.9), attention/vigilance (r = 0.79), working memory (r = 0.84), verbal learning (r = 0.88), visual learning (r = 0.51), reasoning and problem solving (r = 0.77), and social cognition (r = 0.72). The CDR System showed good test-retest reliability on the five domains which used CDR measures (the CDR System uses the same tests as the MCCB for problem solving and social cognition): speed of processing (r = 0.73), attention/vigilance (r = 0.34), working memory (r = 0.7), verbal learning (r = 0.74) and visual learning (r = 0.75). The Global scores from the two systems also showed good test-retest reliability (MCCB r = 0.94; CDR System r = 0.8). Practice effects on the global scores were low on both systems (MCCB 1.6%; CDR 3.5%). There was good concordance of r = 0.85 on the global scores between the two systems. The domain scores showed smaller but acceptable correlations, ranging from 0.41 for speed of processing to 0.73 for working memory.

Discussion: Both the MCCB and the CDR System showed acceptable test-retest reliability, and the systems yielded correlated scores on comparable domains. We conclude that both systems are thus fit for use in clinical trials to detect treatment effects of putative cognitive enhancing agents in schizophrenia. Both systems are well validated and the choice between them for particular trials will depend on the relative sensitivity of the two systems to enhancement, as well as on practical aspects such as the extent of training required for personnel to administer the tests, and the number of parallel forms and language versions available.

doi:10.1016/j.schres.2010.02.1043

Poster 270
A STUDY COMPARING THE MATRICS BATTERY WITH THE CDR SYSTEM IN SCHIZOPHRENIA

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Background: There is growing interest in developing treatments for the cognitive deficits that exist in schizophrenia. The MATRICS Consensus Cognitive Battery (MCCB; www.matrics.uc.edu) was developed to provide an outcome measure for clinical trials of cognition-enhancing drugs for schizophrenia. The battery has tests focussed on eight specified cognitive domains: speed of processing, attention/vigilance, verbal & nonverbal working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. The Cognitive Drug Research computerized cognitive assessment system (CDR System) has been widely used over the past 25 years to study the effects of cognitive enhancers both in normal volunteers and various patient populations, and evidence of enhancements seen with the System has been reported in over 100 peer reviewed papers. The goal of this study was to assess test-retest reliability and correlations between the two batteries in stable patients with schizophrenia.

Methods: 26 males and females aged 18-65 years with a primary DSM-IV diagnosis of schizophrenia or schizoaffective disorder who were clinically stable, on a stable antipsychotic medication dose for ≥ one month, had no active suicidal ideation and had a global severity on the Clinical Global Impression scale ≤ 4 were enrolled. There was a screening visit and a baseline clinical assessment with a training session. There were then two study visits during which participants performed both the MCCB and the CDR System for schizophrenia on each occasion, in counter-balanced order. The study visits were 3 to 10 days apart, and each test battery was separated by a 10 to 15 minute rest period. Test-retest reliability of the various domain scores of the MCCB and CDR was evaluated, and the relationships between the scores from the two systems were examined using Pearson’s product-moment correlations.

Results: Both systems identified deficits in all domains, some of these having effect sizes as large as two. The MCCB showed very good test-retest reliability on the various domains: speed of processing (r = 0.9), attention/vigilance (r = 0.79), working memory (r = 0.84), verbal learning (r = 0.88), visual learning (r = 0.51), reasoning and problem solving (r = 0.77), and social cognition (r = 0.72). The CDR System showed good test-retest reliability on the five domains which used CDR measures (the CDR System uses the same tests as the MCCB for problem solving and social cognition): speed of processing (r = 0.73), attention/vigilance (r = 0.34), working memory (r = 0.7), verbal learning (r = 0.74) and visual learning (r = 0.75). The Global scores from the two systems also showed good test-retest reliability (MCCB r = 0.94; CDR System r = 0.8). Practice effects on the global scores were low on both systems (MCCB 1.6%; CDR 3.5%). There was good concordance of r = 0.85 on the global scores between the two systems. The domain scores showed smaller but acceptable correlations, ranging from 0.41 for speed of processing to 0.73 for working memory.

Discussion: Both the MCCB and the CDR System showed acceptable test-retest reliability, and the systems yielded correlated scores on comparable domains. We conclude that both systems are thus fit for use in clinical trials to detect treatment effects of putative cognitive enhancing agents in schizophrenia. Both systems are well validated and the choice between them for particular trials will depend on the relative sensitivity of the two systems to enhancement, as well as on practical aspects such as the extent of training required for personnel to administer the tests, and the number of parallel forms and language versions available.

doi:10.1016/j.schres.2010.02.1044

POSTER SESSION 3 AND LUNCH
Tuesday, 13 April, 2010-12:00 pm -1:30 pm

Poster 1
CLINICAL RELEVANCE OF SELF-DISORDERS (ICH-STÖRUNGEN) IN SCHIZOPHRENIA: A REVIEW OF STUDIES ON DIAGNOSIS, FACTOR STRUCTURE AND OUTCOME

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Background: The notion of "Ich-Störungen" (self-disorders) depicts a major aspect of Kurt Schneider's concept of first rank symptoms of schizophrenia. Terms such as "passivity phenomena", "delusions of alien control" and "ego pathology" have been used to characterize these phenomena once postulated to be pathognomonic for schizophrenia. The present review focuses on clinical studies examining the symptoms' diagnostic and nosological implications.

Methods: We conducted a semi-structured literature review. 374 references were obtained using the key words "ego disorder/"psycho) pathology", "thought insertion", "alien control", "passivity symptoms/
Background: Although the association between hearing impairment (HI) and psychosis, with the strongest effect for loneliness (χ² = 6.12, p = .001). Further, social isolation was only associated with psychosis in participants without HI (p < .001), but not in those with HI (p = .72), which was potentially explained by the finding that social isolation was much stronger associated with feelings of loneliness in those without HI than in those with HI (χ² = 16.61, p < .001). Finally, the association between HI and psychosis was conditional on level of urbanicity in a dose-response manner, only reaching significance in the most urbanised neighbourhoods (p = .0016).

Discussion: The findings stress the importance of the social environment in the developmental pathway from HI to psychosis. Whereas social isolation may be less deleterious in individuals with HI because of lower perceived loneliness, the complexity of the social environment may render people with HI vulnerable for development of psychotic symptoms.

doi:10.1016/j.schres.2010.02.763
studies have yielded very broad variations in prevalence rates across studies. The current meta-analysis sought to 1) investigate the prevalence of co-occurring AD in SZ by reporting pooled prevalence rates, and 2) identify potential sources of variations in reported rates that could guide our efforts to identify and treat these co-occurring disorders in patients with SZ.

Methods: We performed a systematic search of studies reporting prevalence of AD in SZ and related psychotic disorders. Mean prevalence rates and 95% confidence intervals were first computed for each disorder. We then examined the impact of potential moderators related to patient sampling or to AD assessment methods on these rates.

Results: Fifty-two eligible studies were identified. Pooled prevalence rates and confidence intervals were 12.1% (7.0-17.1%) for obsessive-compulsive disorders, 14.9% (8.1-21.8%) for social phobia, 10.9% (2.9-18.8%) for generalized anxiety disorders, 9.8% (4.3-15.4%) for panic disorders, and 12.4% (4.0-20.8%) for post-traumatic stress disorders. For all disorders, we found significant heterogeneity in rates across studies. This heterogeneity could at least partially be explained by the effect of moderator variables related to patient characteristics or assessment methods.

Discussion: AD are highly prevalent in SZ, but important variations in rates are observed between studies. This meta-analysis highlights several factors that affect risk for, or detection of AD in SZ, and could thus have an important impact on treatment and outcome of SZ patients.

doi:10.1016/j.schres.2010.02.765

Poster 5
PSYCHOTYPAL DISORDER: CRITERIA FOR A NEW PSYCHOSIS SPECTRUM CATEGORY COVERING RISK-SATE RELATED CLINICAL SYNDROMES

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Background: In research and specialized clinical settings, conversion rates associated with current risk criteria for developing psychosis are many times higher than the incidence of psychosis in the general population. Yet, there is an ongoing debate about the justification of prediction and prevention. Almost exclusively focusing on the predictive validity of at-risk criteria, this debate widely disregards a major general finding, i.e., that persons meeting at-risk criteria are already suffering from various current mental and functional disturbances and seeking help for these complaints. Moreover, they exhibit cognitive deficits as well as morphological and functional cerebral changes. Thus, beyond any debate on predictive validity, the majority of help-seeking risk persons fulfills DSM-IV general criteria for mental disorders, i.e., a clinically significant behavioral or psychological syndrome associated with disability and/or severe distress, and, undoubtedly, have to be considered as patients. Therefore, access to standard medical care has to be granted, appropriate treatment (in addition to prevention) strategies have to be investigated and evidence-based guidelines on intervention have to be developed. Due to the structure of current health care systems the most important requirement for achieving these goals is a formal diagnosis. Yet, the current diagnostic systems, i.e. DSM or ICD, do not provide an appropriate classification. Therefore, it has been proposed to introduce a risk state for psychosis into the DSM-V. However, for methodological and systematic reasons, it might be more appropriate and short-term effective to perceive the clinical picture defined by at-risk criteria not as a risk syndrome but, like ICD-10’s schizotypal disorder, as a self-contained psychosis spectrum disorder.

Methods: Based on a comprehensive review of the current literature and current research results, the validity of the available at-risk criteria was reviewed. Based on these findings and new results from a European (EPOS) and a local study of the FETZ, criteria for a new spectrum disorder for DSM-V were developed.

Results: The proposed new category, called ‘Psychototypal disorder’, whereby modifying the ICD-10 term ‘schizotypal disorder’ to avoid its sole association to schizophrenia, but express its psychosis spectrum character, comprises 4 criteria, a description of associated features and classifiers for clinical subtypes, duration and longitudinal course. Criterion A, ‘characteristic symptoms’, includes (A1) 9 cognitive basic symptoms and (A2) 6 attenuated positive symptoms; both are further defined in terms of frequency and cliniic severity. Criterion B demands a functional impairment; C and D have more general contents.

Discussion: The inclusion of a psychosis-spectrum disorder rather than a risk syndrome into DSM-V could help to avoid imponderabilities associated with the prognostic character of a risk syndrome while ensuring access to the health care system for those suffering from current at-risk symptoms. This conceptualization of a self-contained disorder would not preclude consideration of risk-adjusted preventive factors in future treatment guidelines that would have to be developed under the auspices of professional associations. Based on such a disorder, the ability of neuropsychological and biological parameters to further improve its validity as well as the estimation of the associated risk will have to be investigated. These future results would have to be considered when – possibly – transferring the disorder from research to diagnostic criteria in DSM-VI.

doi:10.1016/j.schres.2010.02.766

Poster 6
DSM-V: IMPLICATIONS FOR SCHIZOPHRENIA RESEARCH

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Background: The development of the Diagnostic and Statistical Manual for Mental Disorders (DSM) has evolved to encompass increasing disorders over its many incarnations. 2012 will see the publication of the latest version, DSM-V, and many major changes have been mooted, including major changes to the classification of psychiatric disorders. There has been much secrecy and controversy about the development of DSM-V, and a large volume of publications suggesting or speculating on new disorders and structure of the new edition when it is finally published. The aim of this study is to explore the likely directions of the psychotic disorders in DSM-V and consider the implications for determining caseness, clinical utility, as well as current and future research.

Methods: A literature search was conducted in Medline using the search terms ‘DSM-V’ to identify relevant articles. Documents detailing the progress of the DSM-V taskforce and workgroups were obtained from the American Psychiatry Association website. Reference lists from articles identified above were also searched for relevant articles. Internet searches were also done to identify other relevant articles.

Results: It seems likely that DSM-V will incorporate dimensional assessments of some aspects of psychopathology. Examples given by the DSM-V Psychotic Disorders Workgroup include reality distortion, disorganisation, avolition, restricted affect, cognitive impairment, as well as mood scales such as depression and mania. This may lead to the removal of schizoaffective disorder as a diagnostic entity if the affective components are found through field
trials to be adequately represented by the dimensional assessments of mood. Salience syndrome has also been proposed as a means of reconceptualising schizophrenia; absence of any specific references to this in the DSM-V Workgroups summaries make this seem less likely as an inclusion. There have also been suggestions that catatonia will become its own diagnostic entity, and that other subtypes of schizophrenia may be removed. A category of early or ‘at-risk’ psychosis may also be included.

Discussion: While confusion and secrecy still surrounds the upcoming publication of DSM-V, there remains a great deal of easily accessible information available, including on the APA’s website. The most likely casualty of DSM-V will be the diagnostic category of schizoaffective disorder, which has increasingly come under scrutiny in recent years for a lack of validity. Incorporation of dimensional assessments in DSM-V, particularly of affective symptom dimensions, within psychotic disorders may allow for the elimination of schizoaffective disorder as a diagnostic category, while at the same time enhancing the validity and clinical utility of schizophrenia and other psychotic disorders. Caution needs to be exercised in the creation of sub-threshold diagnostic categories such as at-risk psychosis; while this may allow for increased identification of new cases and allowing individuals to access treatment earlier, the increase in the number of cases could result in overwhelming available treatment services and unnecessary treatments being given. Consideration also needs to be given to the effects on current and future research that use the new diagnostic entities, and the applicability of such results to clinical populations, approval of new medications, and access to insurance. Any new diagnostic categories will create a new knowledge base which will have a direct impact on clinicians, who will need training to learn the new categories, as well as researchers, who may have to redesign studies.

doi:10.1016/j.schres.2010.02.767

Poster 7
THREE LEVELS OF RATER PERFORMANCE IN STANDARDIZED PANS TRAINING
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Background: The importance of rater training for reliability and validity in clinical trials is well documented (Ventura, Green, Shaner & Lieberman, 1993; Ivanchevich, 1979; Muller & Szegedi, 2003; Muller & Wetzel, 1998). There is less agreement about what constitutes adequate training and what defines a successful outcome. Equally, the assumption that “training” and “raters” are a unitary construction is problematic. In this study the authors examined data from several large training events that used standardized training procedures and raters with similar levels of education and experience to determine if there were any differences between rater performance at baseline (before training) and endpoint (after training) that emerge independent of these factors.

Methods: Results from multiple training events held internationally were analyzed to determine if differences between baseline and endpoint scores were significant. 308 raters scored videotaped interviews of the Positive and Negative Syndrome Scale (PANSS) in training events. These results were then grouped into three categories based on concordance with gold-standard scores and change from baseline scores.

Results: Three subgroups of raters emerge based on concordance with gold-standard ratings: raters that score high at baseline and endpoint; raters that score fair at baseline and good at endpoint; raters that do not appear to improve. For the stronger initial raters that continued to perform well after training there was a less substantial change (t(96)=2.953, p<.005) than those raters that did less well at baseline but improved after training (t(160)=4.037, p<.001). The smaller group (n=52) that did not appear to show improvement after training had lower ICCs for negative (range .50-72) and general subscale (range .57-85) items.

Discussion: Within training groups there appear to be three groups of raters that emerge independently of rater qualification and training received: those that performed well initially and well at endpoint; another group that performed marginally at the beginning of training and showed improvement by the end; and a third group that did not improve as a result of training. Analysis of ICCs suggests targeted training for individuals that perform less well at baseline could be beneficial.

doi:10.1016/j.schres.2010.02.768

Poster 8
PARANOIA, SCHIZOTYPY, AND SOCIAL ANXIETY: FACTOR STRUCTURE AND EXPERIENCE IN DAILY LIFE
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Background: Paranoia, a continuum of clinical and subclinical experiences in which others are assumed or suspected to have harmful intentions, is a key symptom of schizotypy (including schizophrenia spectrum disorders). Subclinical paranoia is less well-understood than its clinical expression, but occurs in 10% of the population and is a source of social impairment. Paranoia also shares features with social anxiety, such as discomfort and fear of humiliation in social situations; however, paranoia is differentiated from social anxiety by the belief that other’s motives are malevolent. The current research examined the nature, boundaries, and expression of paranoia across a broad continuum of severity.

Methods: In the first study, 862 young adults completed measures of paranoia, social anxiety, and schizotypy to test hypothesized models of the relation of these constructs using confirmatory factor analyses. Measures included the Chapman Scales, Schizotypal Personality Questionnaire, Paranoia Checklist, MMP-2 Persecutory Ideation Scale, and Social Phobia Scale. The second study employed experience sampling methodology to examine the expression of paranoia and social anxiety in daily life in a subset of 240 participants.

Results: As hypothesized, the data were best described by a four-factor model including positive and negative schizotypy, social anxiety, and paranoia. Paranoia was most strongly associated with positive schizotypy. In the ESAM study, paranoia and social anxiety were both associated with daily reports of negative affect, self-consciousness, and negative social perceptions. Paranoia—but not social anxiety—was characterized by more anger, persecutory beliefs, and self-reference in daily life. People higher in social anxiety experienced improvements in mood when in close social encounters; relationships between mood and the situation did not change across levels of paranoia.

Discussion: Identification of subclinical paranoia can clarify factors that contribute to decompensation and can lead to better targets for prophylactic interventions.

doi:10.1016/j.schres.2010.02.769
Poster 9  
COPIING WITH STIGMA WHILE CARING FOR A FAMILY MEMBER WITH FIRST-EPIsODE PSYCHOSIS: THE EXPERIENCE OF FIRST-TIME PRIMARY CAREGIVERS

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Background: First-time primary caregivers play an important role in the recovery of family members from first-episode psychosis (FEP), often experiencing stigma in their caring role. This study aimed to explore the experience of first-time primary caregivers of young adults with FEP, with an emphasis on examining how they maintained their caring role while coping with stigma.

Methods: Twenty first-time primary caregivers participated, and were recruited through case managers at Orygen Youth Health, a FEP centre in Melbourne, Australia. Semi-structured, in-depth, audio-recorded interviews were carried out, using the interview framework suggested by Eatough and Smith (2008). Interpretative phenomenological analysis of the data was undertaken.

Discussion: Two competing themes in the data reflect the contrasting ways carers sustain their caring role while responding to stigma. The first, being open, highlights that some carers respond to the young person’s illness by disclosing openly their situation to others. This occurs automatically. Instead, family support may be transitional as carers and family adjust to the young person’s illness. The second theme, being secretive, illustrates how some carers cope with their predicament. Secretiveness occurs because of perceptions and/or experiences of stigma, and has adverse implications for the carer and the young person. There are four interrelated sub-themes to being secretive: (i) feeling and experiencing stigma, (ii) stigma as denying and blaming, (iii) stigma as losing status, and (iv) stigma as isolating. A third theme, reducing stigma related burden, illustrates carer’s views about how to minimise stigma which exacerbates their burden of caring. They articulate five overlapping strategies for reducing stigma related burden of care: (i) talking openly and listening; (ii) providing emotional encouragement; (iii) instrumental (problem-solving) and practical support; (iii) increasing understanding and acceptance; (iv) being non-judgemental; and (v) engaging the young person.

Discussion: The findings reinforce the important role family members and others play in supporting first-time carers. A range of competing factors influence the way carers cope, including prior knowledge and understanding of FEP, level of assertiveness, and social and cultural influences. While carers risk stigma by being open about their situation, overall, they are more likely to harness social, emotional and pragmatic support, which, in turn, helps improve their coping and reduce their burden of care. There are benefits and drawbacks to being secretive. On one hand, secrecy protects the young person and the carer from community and mental health clinician support is needed for carers, particularly those with limited understanding of mental illness, and those from culturally and linguistically diverse backgrounds, and this is explored further.

doi:10.1016/j.schres.2010.02.770

Poster 10  
FACTOR STRUCTURE OF CLINICAL SYMPTOMS IN 197 CONSECUTIVE CASES OF FIRST EPISODE PSYCHOSES

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Background: Psychoses, particularly schizophrenia, presents with a complex spectrum of symptoms. This multidimensional aspect of the disease poses diagnostic challenges with therapeutic implications especially in early intervention in psychosis (EIP) programmes. The use of scales to measure severity and track changes and outcomes is now routine in EIP programmes. The Positive and Negative Syndrome Scale (PANSS) is the most commonly used. The aim of this study is to examine the PANSS symptoms domains in EIP patients beyond the traditional positive and negative syndrome dichotomy.

Methods: Consecutive patients admitted to an academic based EIP programme were assessed on the PANSS among other measures. After informing them of the programme’s procedure they signed an informed consent form approved by the university and the hospital’s REB. On admission to the programme, the PANSS was administered by a senior psychiatrist following a structured clinical interview (SCI-PANSS) with the patient and a family member.

Results: A total of 197 patients were included in this report. The total PANSS had excellent internal consistency (Cronbach’s alpha = 0.92), however, low squared multiple correlation was observed for somatic concern. Principal components factor analysis (PCFA) with varimax rotation estimated five components. Bartlett’s test of sphericity ($\chi^2(435) = 3504, p < .001$) and the Kaiser-Meyer-Olin measure of sampling adequacy (0.89) indicated excellent factorability. The variables were all well defined by the factor solution (all communalities > .35) and five components had eigenvalues greater than 1.0. The item loadings resulted in factors that did not fall specifically on the positive, negative, or general scales and based on their content were named, in order of eigenvalues: Social and Emotional Withdrawal, Psychosis, Behavioural Disruption, Affective Dysregulation, and Attentional Disturbance. The group had the most severe symptoms on Affective (Mean Item Score = 2.7, SD = .7) and Psychosis (M = 2.6, SD = 1.2) components, with significantly lower severity on Social and Emotional Withdrawal (M = 2.3, SD = .9), Behavioural (M = 1.9, SD = .8), and Attentional (M = 1.6, SD = .7) components.

Discussion: The patients in the study had their first episode of psychosis. The factor structure PANSS items revealed a structure that differs from the traditional positive-negative symptom dichotomy. The severity of affective symptoms at first episode supports recent findings that underscore the importance of addressing these symptoms early in the course of treatment in EIP programmes.

doi:10.1016/j.schres.2010.02.771

Poster 11  
THE THEORETICAL BASIS OF SELF-DISORDERS (ICH-STÖRUNGEN) IN SCHIZOPHRENIA: A REVIEW OF NEUROBIOLOGICAL AND NEUROPSYCHOLOGICAL STUDIES

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Background: The notion of “Ich-Störungen” (self-disorders) depicts a major aspect of Kurt Schneider’s concept of first rank symptoms of schizophrenia. However, they lack a global definition and clinical
Despite the profusion of candidate phenotypes, the liability to the disorder. In this respect, exploring the distribution of candidate disorders) might overlook those traits that are more likely to be extreme clinical conditions (such as schizophrenia or psychotic traits is still a vexing issue. Indeed, model based on the analysis of delineation of informative Schizophrenia Spectrum vulnerability assessment included subclinical positive symptoms (PS), formal thought disorder (FTD), negative symptoms (NS) as well as personality features (paranoid-obsessive (PO) and impulsive-dramatic (ID) dimensions) and neurocognitive vulnerability (via Continuous Performance Test, CPT). We evaluate the trait distribution and the classificatory power with respect to the experimental subgroups.

Methods: We conducted a semi-structured literature review. 374 references were obtained using the key words “ego disorder/ (psycho)/pathology”, “thought insertion”, “alien control”, “passivity symptoms/phenomena/experiences”, “first rank symptoms”, “schneiderian” and “self disorders”. We distinguished two major fields of research: (1) fundamental research including neurobiological and neuropsychological studies based on phenomenological or neurocognitive paradigms; (2) studies on diagnosis and nosology, outcome and prognostic value (reviewed in a different paper).

Results: Neurocognitive models postulating defects in self-monitoring, metarepresentation and sense of agency have been partly validated by neuropsychological experiments. Neuroimaging studies based on said models have identified the inferior parietal lobule (IPL) and the dorsolateral prefrontal cortex (DLPFC) as potential areas of interest for the emergence of self-disorders. Phenomenological paradigms, examining the structure of the patients’ subjective experience, describe basic defects such as hyperreflexivity, disturbed ipseity or the loss of natural self-evidence. They have produced valid assessment instruments and a foundation for further clinical research.

Discussion: Although they do not contradict each other, phenomenological and neurocognitive paradigms have not been integrated in clinical research on the nature of self-disorders. Since self-disorders remain ill-defined and inconsistently included into diagnostic criteria, clinical studies are limited through issues of patient selection and symptom assessment, perhaps therefore producing inconsistent results. The present review stresses the importance of a sound psychopathological foundation of neuromaging and neurocognitive studies.

doi:10.1016/j.schres.2010.02.772

Poster 12
PERSONALITY IN THE SPECTRUM: THE ELUSIVE FACE OF VULNERABILITY

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Background: Despite the profusion of candidate phenotypes, the delineation of informative Schizophrenia Spectrum vulnerability traits is still a vexing issue. Indeed, model based on the analysis of extreme clinical conditions (such as schizophrenia or psychotic disorders) might overlook those traits that are more likely to be associated with the familial transmission of the liability to the disorder. In this respect, exploring the distribution of candidate traits among unaffected subjects sourced from genetically high risk populations could be a rational and parsimonious screening strategy.

Methods: We extracted a sample 247 genetically high risk subjects (i.e. members of six extended multiplex families, previously assessed during the Copenhagen Schizophrenia Linkage Study). Participants were categorised in three groups: Schizophrenia Spectrum Personality Disorders (SSPD), Other Personality Disorders (OPD) and No detectable Personality Disorder (NPD). Psychopathological assessment included subclinical positive symptoms (PS), formal thought disorder (FTD), negative symptoms (NS) as well as personality features (paranoid-obsessive (PO) and impulsive-dramatic (ID) dimensions) and neurocognitive vulnerability (via Continuous Performance Test, CPT). We evaluate the trait distribution and the classificatory power with respect to the experimental subgroups.

Results: The expected quantitative pattern, SSPD > OPD > NPD, was confirmed for negative symptoms and paranoid-obsessive features. Subclinical positive symptoms and formal thought disorder followed the pattern SSPD > OPD, NPD, whereas impulsive-dramatic features resulted SSPD > OPD > NPD. CPT was not significantly different across the subgroups. The multivariate model revealed an overall good classificatory power (77.2%).

Discussion: A combined, multidimensional phenotype, including subclinical psychopathology (positive, negative and formal thought disorder) and personality features (paranoid-obsessive and impulsive-dramatic) is a promising platform to characterise the unexpressed genetic vulnerability to schizophrenia.

doi:10.1016/j.schres.2010.02.773

Poster 13
FIRST RANK SYMPTOMS IN FIRST EPISODE PSYCHOSIS AND THEIR RELATIONSHIP TO THE DURATION OF UNTREATED ILLNESS

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Background: First Rank Symptoms (FRS) are integral to the diagnosis of schizophrenia in both DSM-IV and ICD-10, yet, most studies of FRS are based on cross-sectional inpatient samples at various stages of illness. We sought to examine the prevalence of FRS in a representative sample of all first episode psychotic (FEP) patients from a defined geographical region and determine if those with a prolonged duration of untreated illness were more likely to exhibit FRS at first presentation.

Methods: Over 3 years we examined all people from a defined geographical region with a suspected psychosis using the SCID-IV and the Schedule for Assessment of Positive Symptoms (SAPS) to determine FRS. We derived the DUP and DUL from the Beiser Scale.

Results: The overall prevalence of FRS among the entire group was 52.5%, with the highest rate among those with schizophrenia (69%) and the lowest among those with a Major Depressive Disorder (29.4). “Thought Broadcasting” was the only FRS that occurred more commonly (p = 0.03) among those with schizophrenia compared to other non-affective psychoses. “Voices Commenting” was the only FRS symptom associated (p = 0.04) with non-affective psychotic disorders. There was no significant relationship between the duration of untreated illness or duration of untreated psychosis and FRS.

Discussion: First rank symptoms are common across all psychotic disorders in both the inpatient and outpatient settings. Thought broadcasting and voices commenting appear to have the most clinical relevance in terms of diagnosis. FRS do not seem to be the end stage of a progressive deterioration of psychotic illness.

doi:10.1016/j.schres.2010.02.774
Poster 14
PROVERBS AND NONLITERAL LANGUAGE IN SCHIZOPHRENIA: A SYSTEMATIC METHODOLOGICAL REVIEW OF ALL STUDIES PUBLISHED 1931-2010

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Background: Deficits in the comprehension of non-literal language (i.e., proverbs, metaphors, irony, sarcasm, and metonymies) are a well-known symptom of schizophrenia. The aim of this systematic literature review is to evaluate current knowledge of this deficit and identify remaining research questions.

Methods: Databases including PubMed and PsychINFO were systematically searched for articles reporting data on the comprehension of non-literal language in schizophrenic patients. Studies were screened for > 20 study quality and outcome criteria.

Results: 128 studies with experimental data were identified. The first experimental study was published by Wegrocki et al. 1940. Since then, N = 105 (82%) studies investigated proverbs, n = 10 metaphor, n = 3 idioms, n = 6 irony/sarcasm, n = 1 metonymy. 29 studies were published since 2000.

Discussion: The Gorham proverb test (Gorham, 1956) is by far the most established test. Only 20 (predominantly older) studies generated longitudinal data (n = 19 with proverbs), so that future research should adopt a longitudinal perspective and investigate non-literal language comprehension over the course of the subjects' premorbid, acute and post-acute phases. Medication effects, especially for atypical antipsychotics, are largely unknown. 23 studies used DSM-IV or ICD-10 diagnostic criteria, whereas 51% (5% > 1990) did not report diagnostic criteria for patients. Most studies have focused on proverb comprehension in English or German speaking subjects, whereas the data on transcultural comparisons is very limited. From a linguistic perspective, expressions with non-literal meaning are a heterogeneous entity. Newer linguistic research and neuroanatomical studies suggest that different types of non-literal language and different tasks involve different cognitive processes and possibly have distinct neural correlates. However, only 6 studies compared different types of NL language in schizophrenia and only 1 fMRI study is available. Stimulus salience is likewise an important factor, however so far studies predominantly investigated salient stimuli. The average number of patients included is 42.6 (between 4 and 211). Only very limited data is available for high risk and premorbid subjects.

 doi:10.1016/j.schres.2010.02.776

Poster 15
BASIC SYMPTOM AND ULTRA-HIGH RISK CRITERIA IN THE PREDICTION OF FIRST-EPISTDE PSYCHOSIS

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Background: In early detection of psychosis, two approaches that have been developed independently of each other are currently mainly followed: the basic symptom (BS) and ultra-high risk (UHR) approach. And although it had been argued that they were complementary, only recently have they been together. Thus it was examined if combining the two criteria would increase predictive accuracy.

Methods: The prognostic value of single criteria (attenuated psychotic symptoms, APS; brief limited intermittent psychotic symptoms, BLIPS; risk factor plus functional decline; RISK; cognitive-perceptive basic symptoms, COPER; cognitive disturbances, COGDIS) and their combination was explored in two large samples.

Sample I: 245 help-seeking participants of the multi-center, naturalistic field European Prediction of Psychosis Study (EPOS) included by UHR or COGDIS, followed up for 18 months. At baseline, 59.6% reported a combination of UHR and COGDIS, 30.2% UHR alone and 10.2% COGDIS alone; hazard rate was 19% after 18 month.

Sample II: 247 participants of a follow-up study of patients having sought help in the FETZ between 1998 and 2003. At first examination, 13.4% had not met UHR or BS criteria, 20.2% only BS (incl. COPER, 4%) and 4.5% only UHR criteria, 61.9% met a combination of UHR and BS criteria. 87 (35.2%) had converted during the follow-up period that was on average 3.4 (SD = 2.2, MD = 3.6) years: 1.3 (SD = 1.2, MD = 0.8) in the conversion group with time of conversion serving as end point and 4.5 (SD = 1.7, MD = 4.5) in the non-conversion group with time of follow-up interview serving as end point.

Results: Considering the two approaches separately, especially APS and COGDIS, respectively, yielded good predictive accuracy. Yet in both samples, the combination of APS and COGDIS outperformed single criteria or UHR and BS criteria alone. This result was robust against the exclusion of cases with BLIPS who have been argued to be no ‘prodromal’ but psychotic cases already.

Discussion: The combination of APS and COGDIS is recommended as inclusion criteria for future early detection study and might serve as a reliable starting point for further risk assessments including also non-specific variables such as functional decline.

 doi:10.1016/j.schres.2010.02.776

Poster 16
THE ROLE OF PERSONALITY DISORDER AND ACCENTUATION IN THE CONVERSION TO PSYCHOSIS

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Background: Schizophrenia spectrum disorders, i.e., cluster A personality disorders (PDs) according to DSM-IV and particularly schizotypal PD, were found to cumulate in patients with a symptomatically defined increased risk of developing first-episode psychosis, and increased prevalence rates of psychosis were reported in persons with schizotypal PD. As regards the ‘ultra-high risk’ (UHR) criteria, attenuated psychotic symptoms (APS), which phenomenologically resemble schizotypal symptoms but differ in course, are the most frequently reported symptomatic criterion in risk samples, and schizotypal PD in combination with a significant decline in psychosocial functioning is one of two ‘vulnerability’ conditions of the UHR criteria. Thus the role of PDs and personality accentuations (PAs) in the conversion to psychosis in a symptomatically defined at-risk sample was examined.

Methods: PDs and PAs were compared between 50 at-risk patients with and 50 without conversion to psychosis; they were assessed by a self-rating questionnaire that had shown good consistency with clinical interview assessments. Groups were matched for intake criteria (16% symptomatic early initial prodromal state, EIPS, 84% late initial prodromal state, LIPS), gender (76% male) and age (24.2 ± 6.0; 16-38 years).

Results: The number of patients with at least any one DSM-IV PD did not differ between those with and without conversion (50% vs.
46%; chi² = .644, df = 1, p = .422); altogether 31% of patients fell above the threshold for any cluster B, 23% for any cluster C and 14% for any cluster A PD. Only for ‘any one cluster A PD’, a statistical trend showed towards a higher frequency in converters (20% vs. 8%; chi² = 2.990, df = 1, p = .084), no group differences were found for any single PD. Comparisons of the severity of PAs (Mann-Whitney tests) showed a higher expression of schizoid features (U = 872.5, p = .006) and, though less clearly, of schizotypal features (U = 959.5, p = .043) in the conversion group. In stepwise regression analyses, schizoid PA was chosen as sole predictor of conversion (OR = 1.685; 95%CI: 1.134-2.504), classifying 62% of non-converters and 68% of converters correctly. A LIPS was positively albeit weakly correlated with schizotypal and paranoid, but not schizoid PAs.

**Discussion:** Surprisingly, cluster A PDs were the least frequent PDs in both at-risk samples, yet significantly cumulating in the ‘true prodromal’ group of converters. The main role in this was not played– as expected – by schizotypal PA but by schizoid PA, which was unrelated to the prodromal state at intake. The deficient social skills and integration that shows in the more severe schizoid PA is in line with genetic high-risk studies, which have repeatedly shown premorbid social deficits in children of schizophrenia parents. It also supports the important protective role that good social functioning and skills might play in psychosis prevention.

**Poster 17**

**ASSESSMENT OF SMELL FUNCTION IN SCHIZOPHRENIA DURING ACUTE PSYCHOTIC EPISODE AND CORRELATION WITH CLINICAL SYMPTOMATOLOGY**

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**Background:** Olfactory processing is becoming of increasing interest as a marker of disturbed cognitive function in schizophrenia. This has been paralleled by several consistent anatomical findings in the illness. Furthermore, olfactory processing is mediated by many of the same medial temporal lobe areas of the brain that have been implicated in schizophrenia. In this study we investigate a range of smell functions in a group of patients with schizophrenia during their first week of hospitalization for acute psychosis. In addition, we tested for correlations between smell scores and clinical symptomatology.

**Methods:** Olfactory function was assessed in 20 schizophrenia patients in their 1st week of hospital admission for acute psychosis and compared with matched controls. Olfaction was evaluated via three stages: threshold, discrimination and identification of different odors utilizing the Sniffin’ Sticks Test Battery. Patients were rated for clinical symptomatology at the time of testing of smell by means of several clinical rating scales.

**Results:** Schizophrenia patients scored significantly lower on total smell score, discrimination, and identification abilities. A significant association was observed between hospitalization duration and total smell score and smell discrimination. No significant associations between smell and clinical symptomatology were observed.

**Discussion:** Study observations confirm demonstrated decreased sense of smell in schizophrenia patients and suggest cautiously that smell impairment may be a potential marker of more serious illness as expressed in longer hospital stay. Several neurophysiological mechanisms may account for these findings which require further investigation in order to substantiate potential hypotheses.

doi:10.1016/j.schres.2010.02.777
variables and categorical variables, respectively. In the case of comparison between two-two subgroups, we used the Mann-Whitney U test and chi-square test for continuous and categorical variables. To avoid an increase in Type I error when comparing several variables, raw p-values were corrected by the step-down Bonferroni method.

**Results:** Throughout our systematic analysis we did not find any parameters which would appropriately set apart deficit syndrome patients from nondeficit ones within cluster S. We found relevant differences between patients with nondeficit syndrome from S and Z clusters in cognitive demographic, certain cognitive (alooia, inattention), and negative clinical symptomatic dimensions. We also found differences in cognitive psychological parameters especially in the executive shifting dimension and in cognitive inhibitory abilities.

**Discussion:** The nondeficit group in our study, proved to be inhomogeneous in several parameters, it was split in two along the border of the clusters S and Z fundamentally by cognitive features.

doi:10.1016/j.schres.2010.02.779

**Poster 19**

**IMPACT OF SUBSTANCE USE DISORDER ON FUNCTIONAL OUTCOME IN FIRST-EPIISODE PSYCHOSIS: A 2 YEARS PROSPECTIVE STUDY WITHIN THE UNIVERSITé DE MONTRéAL NETWORK**

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**Background:** Numerous studies have investigated substance use disorders (SUD) in first-episode psychosis (FEP). However, few of them have looked at the link between the course of substance misuse and functional outcome. The aim of our study is to examine the impact of the course of SUD on functional outcome in a FEP sample.

**Methods:** Prospective longitudinal study of subjects admitted to two specialized early psychosis intervention programs of the Université de Montréal network, with a primary diagnosis of FEP and aged between 18 and 30 years old. DSM-IV criteria were used to diagnose psychotic disorder and SUD (abuse or dependence) at admission and follow-up. Course of SUD was assessed with the DAST in order to differentiate three groups of patients: never SUD, SUD at baseline and follow-up, persistent SUD. Measures of functional outcome are: autonomy in living arrangement, treatment adherence and symptomatology, we will present preliminary data for the first 2 years.

**Results:** More than 225 patients have been included in the study. The prevalence and the evolution of SUD are described. After controlling for the effects of age, gender, diagnosis, social functioning at admission, treatment adherence and symptomatology, we will examine the impact of substance use disorder on functional outcome at 1 and 2 years.

**Discussion:** This study allows to determine the impact of SUD on the evolution of patients with FEP whom are given early and intensive intervention. It also sheds light on the functional outcome of the significant minority of patients who have a severe and persistent SUD over a 2 years follow-up despite intensive intervention in a first episode program. These data raise the hypothesis that integrating specialised first-episode psychosis and specialised SUD treatments within the same team for those young psychotic patients presenting severe SUD comorbidity might be necessary.

doi:10.1016/j.schres.2010.02.780

**Poster 20**

**FIRST-EPIPOSE PSYCHOSIS: GENDER DIFFERENCES IN SUBSTANCE USE**

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**Background:** Patients with a first episode of psychosis (FEP) present high rates of substance use, ranging from 20 to 61% (Mauri et al., 2006). Alcohol and cannabis are the most used substances in FEP patients (Van Mastig et al., 2004; Compton et al., 2009). Gender differences have been widely observed in the clinical presentation, psychosocial functioning and course of illness in FEP patients (Cotton et al., 2009). Therefore, the aim of this study was to assess gender differences in the prevalence and pattern of substance use in FEP patients.

**Methods:** This study corresponds to a database from a longitudinal intervention program of first-episode psychosis carried out in Spain (study protocol 02-0463, code F1D-XB-0171).

**Results:** 114 patients were included in the study, 85 men and 29 women. Men were significantly younger than women (24 ± 5.9 years for men vs 30 ± 11.2 years for women; F = 13.6, p = 0.000, ANOVA). Weeks with psychotic symptoms prior to hospitalization (47 ± 11.5 for men and 63 ± 26.6 for women; F = 5.13, p = 0.02, ANOVA); premorbid adjustment (PAS) (4.02 ± 2.4 vs 3.33 ± 0.19; F = 2.7, p = 0.10), PANS positive (26 ± 6 vs 25 ± 6; F = 1.2, p = 0.25), PANS negative (20 ± 8 vs 17 ± 9; F = 2.0, p = 0.15), PANS total (92 ± 21 vs 88 ± 18; F = 0.88, p = 0.34) and Calgary (3.7 ± 4.5 vs 5.1 ± 4.8; F = 1.7, p = 0.18) scores were not statistically different in men and women. SUBSTANCE USE: Before onset of antipsychotic treatment (baseline), 84.7% of men versus 51.7% women used alcohol (X² = 13; p = 0.001), 64.7% men versus 31% women used cannabis (X² = 9.9; p = 0.002) and 28.2% of men versus 0% women used cocaine (X² = 10.3; p = 0.000). With respect to the NUMBER OF SUBSTANCES consumed, 10.6% of men versus 44.8% of women were not on active substance use, 22.4% of men versus 24% of women were on one substance, 30.6% of men versus 27.6% of women were on two substances and 17.6% of men versus 3.4% of women were on three substances (X² = 21.7; p = 0.000). In women, the number of substances consumed did not influence the AGE OF ONSET OF PSYCHOSIS (no substance: 34 ± 13.3 years; one substance: 25.1 ± 10.6 years; two substances: 27.5 ± 4.8 years and three substances: 33 years; F = 1.2, p = 0.30). Therefore, a lack of statistically significant association between the number of substances and age of onset was noted in women (r = -0.23; p = 0.21).

In contrast, a significant correlation was noted in men between age and number of substances used (r = -0.40; p = 0.000), with earlier
onset of psychosis noted in patients consuming multiple substances (no substance: 27.5 ± 7.5 years; one substance: 28 ± 7.9 years; two substances: 23.4 ± 4.4 years and three substances: 20.4 ± 2.5 years; F = 5.8; p = 0.00). AGE AT FIRST CONSUMPTION of alcohol (16 ± 2 years in men vs 15.7 ± 0.8 years in women; F = 0.3, p = 0.58) and cocaine (18 ± 0.9 years in men vs 20 ± 0 years in women; F = 3.7, p = 0.06) was not different in men and women. However, men showed a statistically significant earlier age of first consumption of cannabis in comparison to women (16 ± 2.1 years in men vs 18 ± 3.8 years in women; F = 5, p = 0.02).

Discussion: 1) FEP patients show high rates of substance use, with men significantly consuming more alcohol, cannabis and cocaine than women. 2) An earlier onset of psychosis (7 years earlier) was noted in patients consuming multiple substances. This association was only present in men. 3) Age at first consumption of cannabis was significantly lower for men.

doi:10.1016/j.schres.2010.02.781

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### Poster 21

**COGNITION AND IMPULSIVITY RELATED BRAIN VOLUME CHANGES IN SCHIZOPHRENIA-ADDICTION CO-MORBIDITY**

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**Background:** Despite the high prevalence of co-morbid substance abuse in schizophrenia, there is still little knowledge about its impact on the brain. Therefore we sought to determine whether addicted and non-addicted schizophrenic patients are impaired differentially on local brain volumes, relevant domains of executive functions and impulsivity, and whether specific gray matter volumes are associated with these cognitive and affective variables.

**Methods:** We neuropsychologically assessed 51 participants (age range: 23–55) on executive functions, trait impulsivity, and voxel-based morphometry on high-resolution magnetic resonance imaging data. The schizophrenia group comprised 24 chronic patients (12 patients with paranoid schizophrenia and 12 with additional co-morbid substance use disorders). The comparison group comprised 27 age and education matched non-schizophrenic individuals (14 healthy controls and 13 patients with substance use disorders).

**Results:** Total gray matter volume deficits were present in all patient groups as compared to healthy controls, but were greatest (8–9%) in both addicted groups. Lateral orbitofrontal and temporal volume reductions were more schizophrenia related, whereas medial orbitofrontal, anterior cingulate and frontopolar volume decreases were more related to addiction. Co-morbid subjects compared to non-addicted schizophrenics showed significant volume decreases in anterior cingulate, frontopolar, and superior parietal regions. Additionally, they showed elevated non-planning impulsivity, which structurally was negatively associated with gray matter volumes in the same regions, except parietal ones.

**Discussion:** The present study indicates severe volume and functional executive deficits in schizophrenia, which were only partially exacerbated by co-morbid addiction. However, the structural association between schizophrenia-addiction co-morbidity, non-planning impulsivity and anterior cingulate and frontopolar gray matter volumes, indicate a specific structure-function relationship which seem to be disturbed in schizophrenia-addiction co-morbidity.

doi:10.1016/j.schres.2010.02.782

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### Poster 22

**COGNITIVE, EXECUTIVE AND SOCIAL FUNCTIONING IN SCHIZOPHRENIA WITH AND WITHOUT COMORBID CANNABIS USE**

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**Background:** Evidence for an association between cannabis and schizophrenia has been strengthening from epidemiological and neurobiological studies. Similarity between cognitive impairment associated with long term heavy cannabis use and cognitive deficits in schizophrenia is becoming increasingly apparent. Cannabis use is highly prevalent among people with schizophrenia, exacerbates positive symptoms, and worsens the course of illness. Cannabis use has therefore been hypothesised to exacerbate existing cognitive deficits in schizophrenia.

**Methods:** This study recruited medicated schizophrenia patients (n=49) from the general community who were either currently using cannabis (22 years of use, near daily) (n=17, 10 male), former regular users of cannabis (at least one year prior) (n=11, 8 male), or non-users (n=21, 11 male). The groups were matched on age (mean 37.2 years) and estimated premorbid IQ (mean 109.5). They were screened for other substance use and comorbidities using structured interviews, diagnostic tools and urinalyses. Patients completed the Scales for Assessment of Positive and Negative Symptoms (SAPS/SANS), Apathy Evaluation Scale (AES), Social Functioning Scale, Frontal Systems Behaviour Scale (FrSBe) and seven tests of working memory and executive function from the Cambridge Neuropsychological Test Automated Battery (CANTAB). Performance measures were also compared with healthy cannabis users and non-users (without schizophrenia) (n=50 each), and subsamples also completed the Rey Auditory Verbal Learning Test (RAVLT).

**Results:** Cannabis-using patients with schizophrenia showed significantly higher positive and negative symptoms (p<0.05) and greater apathy on the AES (p<0.001) and the FrSBe (p<0.005) compared to non-users with schizophrenia. Disinhibition and executive function measures from the FrSBe did not differ between groups. Cannabis users’ performance on the Delayed Matching to Sample and Spatial Working Memory tests was significantly better than non-users (p<0.05), with non-significant trends in the same direction across all tests. Despite this, several CANTAB outcome measures, and clinical measures, worsened as a function of exposure to cannabis. Ex-users’ performance fell between that of cannabis users’ and non-users. Patient groups did not differ on RAVLT performance, which was similar to that of healthy cannabis users and significantly poorer than healthy non-users (p<0.05). Social functioning measures did not differ between groups (p>0.3), indicating that preserved cognitive performance in the cannabis users could not be explained by greater functionality in this domain.

**Discussion:** These results support other recent work suggesting that concurrent cannabis use by people with schizophrenia does not generate significant additional adverse effects on cognitive function. This study builds on existing literature by including an ex-user group and by investigating the moderating effects of apathy and social functioning. Further interpretations will be discussed involving neurobiology, genes, various cannabinoid compounds, premorbid functioning and relative deficits in light of poorer performance as a result of greater exposure to cannabis.

doi:10.1016/j.schres.2010.02.783
Poster 23
ALTERATIONS OF HIPPOCAMPAL SHAPE IN CANNABIS USERS WITH AND WITHOUT SCHIZOPHRENIA

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Background: There is a paucity of research examining the long-term impact of cannabis use on the human brain. We have previously reported significant reduction in hippocampal volume in long-term heavy cannabis users1. Hippocampal alterations are implicated in psychosis and significant numbers of patients also use cannabis. In this study we performed hippocampal shape analysis in the same cohort of healthy cannabis users and a sample of patients with schizophrenia with and without comorbid cannabis use.

Methods: Participants were recruited from the general community to form the following groups for comparison: long-term heavy cannabis users (THC: n = 16, 1 female, mean age 39 yrs, 21 yrs regular use, near daily); non-user controls (CON: n = 18, 2 female, 35 yrs); cannabis users with schizophrenia (SZ+THC: n = 10, 2 female, 35 yrs, 19 yrs regular use, near daily); and non-users with schizophrenia (SZ–THC: n = 12, 3 female, 42 yrs). Groups did not differ in age, education or IQ (p > 0.05) and THC and SZ+THC were matched on cannabis use parameters and alcohol and tobacco use. Hippocampal volumes were traced from 3T magnetic resonance images and shape analysis was undertaken using the University of North Carolina toolkit. Segmented 3D binaries underwent morphological closing and minimal smoothing, and were subjected to spherical harmonic shape description (SPHARM-PDM). All surfaces were uniformly sampled into sets of 1002 surface points each and aligned to a study-averaged template with normalization for head size. To compare structural shape between groups, we computed the local Hotelling T2 two-sample mean difference, and corrected for multiple comparisons using false discovery rate. We generated mean difference magnitude displacement maps and significance maps of the local p-values in displacement maps and significance maps of the local p-values in raw format, and corrected for multiple comparisons.

Results: Significant differences between groups were found bilaterally in the hippocampus as follows. Compared to CON: THC showed a significant shape change in right hippocampus (p < 0.05) but only a trend in left hippocampus (p < 0.08); SZ–THC showed a marginally significant shape change for left hippocampus (p < 0.056) but not right hippocampus (p > 0.2); SZ + TH showed a highly significant change in left hippocampus (p < 0.003) and a marginal change in right hippocampus (p < 0.058). When THC were compared to SCZ + TH, there was a significant difference on the left (p < 0.05) and a trend on the right (p = 0.077). There was no significant shape difference between THC and SCZ–THC for either left or right hippocampus (p > 0.3). Significant regional changes were not confined to a particular subregion of the hippocampus, tending to be dispersed. Relationships with various cannabis use parameters and symptom measures were also observed.

Discussion: Our findings continue to challenge the widespread perception of cannabis as having limited or no neuroanatomical sequelae. We found highly significant shape changes in the left hippocampus of patients with schizophrenia and comorbid cannabis use compared to controls, and some evidence of hippocampal shape alterations in healthy cannabis users and non-users with schizophrenia. These showed differentially laterised effects in each group, suggesting specific effects associated with cannabis use and with schizophrenia per se, and an interaction effect evident in the cannabis-using group with schizophrenia. Shape analysis provides further information beyond simple volumetric analysis and this study is the first to report an additional adverse effect of cannabis use on brain structure in chronic schizophrenia, in this instance specific to hippocampus. I. Yücel, M., Solowij, N., Respondek, C., et al. (2008) Arch Gen Psychiatry, 65, 694-701.

doi:10.1016/j.schres.2010.02.784

Poster 24
BRIEF SCHIZOPHRENIA ADDICTION SCALE (BSAS): A PILOT STUDY

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Background: Addiction is a frequent comorbid diagnosis in schizophrenia, that can be either one aetiological factor or a consequence of the disease. But the systematic evaluation of the use of drugs of abuse is still not an habitual clinical practice in schizophrenia, except in the cases where one drug-induced psychosis is suspected. The lack of useful and brief scales specifically designed for the evaluation of addiction in schizophrenia could contribute to this problem. The objective is to present a new tool to briefly measure addiction in schizophrenia and to study its main psychometric characteristics.

Methods: We conduct one cross-sectional study on 60 schizophrenia out-patients (43 male; average age: 38.9 years, SD 9.4). The diagnose were: paranoid schizophrenia 26.7%, schizoaffective disorder 25.0%, residual schizophrenia 21.7%, other subtypes of schizophrenia 26.6%. The BSAS reflects life use of drugs and addiction: tobacco, coffee, alcohol, cannabis, cocaine, amphetamines, hallucinogens, opiates and gambling. For every substance and gambling, one five-point scale (lower 0, higher 4) was applied regarding to five characteristics: first use, frequency, length of use, last time use and harmful consequences. PANNS, FCQ-3, CGI and GAF were applied as clinical variables. The composite score was obtained for every substance and gambling. One factor analysis using principal components (Varimax rotation) was performed to study the dimensionality of BSAS. It was also studied the correlation between the factors and the clinical variables.

Results: Two factors were defined, that explains for 66.1% of the variance: 1) Illegal addiction: cocaine, opiates, cannabis, hallucinogens, cannabis, amphetamines (mean score: 16.4, SD:20.4); 2) Legal addiction: addiction: cocaine, coffee, tobacco, gambling (mean score: 41.7, SD: 19.2). The distribution of both factors do not adjust to the normal curve but they suggest three subgroups of patients: those without addiction, one second group with moderate addictive trend and a third group highly addictive. The correlation (Spearman’s Rho) between both factors was r = 0.58 (p < 0.001). The legal addiction factor did not correlate with any clinical variable. The illegal addiction factor was associated only with the negative syndrome (r = -0.30, p = 0.18).

Discussion: Addiction in schizophrenia has two factors (illegal and legal addiction), which are independent from symptoms and severity of the disease. The quantification of the addictive syndrome as one independent dimension from the psychotic one could contribute to a better differentiation between the different disorders that constitute the schizophrenia syndrome. We propose that
Poster 25
CIGARETTE SMOKING IN PATIENTS WITH SCHIZOPHRENIA IN CHINA: A PROSPECTIVE, MULTI-CENTER STUDY

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Background: Understanding the patterns of smoking and its socio-demographic and clinical correlates in schizophrenia patients is vitally important for policymakers and health care providers in the implementation of appropriate strategies and execution of effective measures to reduce its harmful consequences. However, to date there has been no study investigating rate of smoking involving both in- and out-patients with schizophrenia based on multi-center design in China. This study aimed to explore the rate of cigarette smoking and its socio-demographic and clinical characteristics in Chinese schizophrenia patients.

Methods: In a multi-center, randomized, controlled, longitudinal study involving 19 mental health centers nationwide that represented a range of clinical settings in which schizophrenia patients receive treatment in China, 374 clinically stable patients with schizophrenia were interviewed at entry using standardized assessment instruments, and followed up for 1 - 2 years.

Results: The study involved 19 mental health centers nationwide that represented a range of clinical settings in which schizophrenia patients receive treatment in China. The rate of cigarette smoking was 13.9% in the whole sample, and 26.2% in men and 3.5% in women. In univariate analyses, male sex, unemployment, alcohol consumption, older age, older age at onset, longer duration of illness, more frequent admissions, more sever hostility-excitement over the study period were significantly associated with cigarette smoking. In the multivariate analysis, more male sex, unemployment, alcohol consumption, more frequent admissions, less severe positive and negative symptoms at entry, smaller decline in negative symptoms and more deterioration in disorganized thoughts over the study period were independently associated with cigarette smoking.

Discussion: The rate of cigarette smoking in Chinese schizophrenia patients is considerably lower than most figures reported in the Western literature.

doi:10.1016/j.schres.2010.02.786

Poster 26
PROFILE OF POLYSUBSTANCE ABUSERS WITH THE ACUTE PSYCHOTIC EPISODE

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Background: Nowadays it is very unusual, among young people who misuse drugs, to find individuals who abuse only one psychoactive substance. So, the trend of using many substances was observed. In Serbia it is noticed that appearance of psychotic episodes is growing in this group of young patients. The aims of this study is to try to discover personality dimensions, social characteristics and possible risk factors for the polysubstance abusers who developed acute psychotic symptoms not related to intoxication with substances.

Methods: The sample consisted of one hundred patients, 51 male and 49 female. It was divided into four groups, experimental and three controls. Experimental group consisted of 30 polysubstance abusers with psychotic episode (18-27 years of age, 22.93 ± 2.48 years). The first control group consisted of 30 polysubstance abusers without psychotic symptoms (23.97 ± 4.07 years), the second of 20 patients with acute psychotic disorder with polymorphic symptoms (25.40 ± 6.64) and the third consists of 20 patients with the first manic episode with psychotic symptoms (25.90 ± 6.22 years). Before filling in the battery of tests, patients with psychotic symptoms were examined with BPRS (the Brief Psychiatry Rating Scale) at the beginning and at the end of treatment in order to check the clinical condition and their ability to fulfill other scales. The instruments of self-examination that we used were: MCMI (The Millon Clinical Multiaxial Inventory), TPQ (Three-dimensional Personality Questionnaire) and the Social Psychiatric Scale. For the analysis of data we used various methods of uni-variant statistical analysis.

Results: Our results showed that polysubstance abusers with psychotic episode have normal profile of personality with higher passive-aggressive dimension. Emotional instability was confirmed (novelty seeking (NS) component is high), but less than with the other polysubstance abusers without psychotic episode. The patterns of substance abuse in experimental group are milder than in the group of polysubstance abusers without psychosis. The beginning of abuse of substances is probably the same, but the amount of abused substances in experimental group is much smaller. Our results showed that 75% of patients in the experimental group takes cannabis, alcohol and tobacco, but polysubstance abusers without psychoses takes more often opiates or psychostimulants.

Discussion: Paradoxically, more expressed pathology of personality and more severe patterns of substance abuse less often lead to appearance of psychotic symptoms. Experimental group does not have histrionic dimensions and clinical syndromes of alcohol and substance addiction as polysubstance abusers without psychosis, but they have more prominent passive-aggressive, schizoid, avoidant and schizotypal dimensions which are more often features of schizophrenic patients. We did not noticed specific social risk factors for appearance of psychosis, but we noticed visible social detachment among polysubstance abusers with psychotic episode (lower educational level, lower employment and willingness to work, lower social level and weaker social implementation). It would be interesting to follow up the patients in the experimental group and after several years to see how many of them would fulfill diagnostic criteria for chronic psychosis, probably some of schizophrenia-spectrum disorders.

doi:10.1016/j.schres.2010.02.787

Poster 27
THE AUSTRALIAN SCHIZOPHRENIA RESEARCH BANK (ASRB): AN EXAMPLE OF ERESEARCH

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Background: Discovering the causes of schizophrenia is vitally important for policymakers and health care providers in the implementation of appropriate strategies and execution of effective measures to reduce its harmful consequences. However, to date there has been no study investigating rate of smoking involving both in- and out-patients with schizophrenia based on multi-center design in China. This study aimed to explore the rate of cigarette smoking and its socio-demographic and clinical characteristics in Chinese schizophrenia patients.

Methods: In a multi-center, randomized, controlled, longitudinal study involving 19 mental health centers nationwide that represented a range of clinical settings in which schizophrenia patients receive treatment in China, 374 clinically stable patients with schizophrenia were interviewed at entry using standardized assessment instruments, and followed up for 1 - 2 years.

Results: The study involved 19 mental health centers nationwide that represented a range of clinical settings in which schizophrenia patients receive treatment in China. The rate of cigarette smoking was 13.9% in the whole sample, and 26.2% in men and 3.5% in women. In univariate analyses, male sex, unemployment, alcohol consumption, older age, older age at onset, longer duration of illness, more frequent admissions, more sever hostility-excitement over the study period were significantly associated with cigarette smoking. In the multivariate analysis, more male sex, unemployment, alcohol consumption, more frequent admissions, less severe positive and negative symptoms at entry, smaller decline in negative symptoms and more deterioration in disorganized thoughts over the study period were independently associated with cigarette smoking.

Discussion: The rate of cigarette smoking in Chinese schizophrenia patients is considerably lower than most figures reported in the Western literature.

doi:10.1016/j.schres.2010.02.786
Background: The Australian Schizophrenia Research Bank (ASRB) operates to collect, store and distribute linked clinical, cognitive, neuroimaging and genetic data from a large sample of people with schizophrenia and matched healthy controls.

Methods: Currently there are over 1000 individuals in the database. The ASRB system is implemented on a Sun Server with 14 terabytes of storage, and was originally developed using Globus style grid computing. Recently an Intersect (www.intersect.org.au) professional development team has completely remanufactured the software system. This new system manages all phases of data collection, from recruitment of subjects and controls, through comprehensive clinical assessment, collection and storage of genetic samples, and storage and manipulation of brain images, and subsequent control over access to the dataset. The Sun server still hosts the ASRB storage and web site, supplemented by laptop computers used for clinical assessments. Following assessment, the assessment data is expeditiously uploaded to the server using a secure pipe, after which it is removed from the laptop. Open source technologies are used, including the Java language (java.sun.com), PostgreSQL database management system (www.postgresql.org), and Apache Tomcat servlet engine (tomcat.apache.org), which underpin the system; server access is achieved using a Liferay enterprise portal (www.liferay.com); the Clinical Assessment Officer (CAS) laptop software executes in an Apache Pluto portal; Spring (www.springframework.com) provides the application, authentication and security frameworks. A feature of the new system is its powerful yet easy to use search facility, which is available to all authenticated users through the ASRB web site. This search engine is highly secure, allowing researchers to view data for which they have access approval, and also to confirm the existence of relevant datasets as a precursor to application for approval.

Results: The development of the ASRB central web presence, web site, underlying database management system and tablet-based Clinical Assessment Software system is operational. The ability to use automated processes, where available, to assist in data and image processing would be highly desirable, and provision for these capabilities is being built into the new infrastructure.

Discussion: Data from this initiative will be available to Australian researcher July 2010 and to international research groups in July 2011.

doi:10.1016/j.schres.2010.02.788

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Poster 28

INFLUENCE OF GENDER AND AGE ON SCHIZOTYPAL PERSONALITY FEATURES IN A NON-CLINICAL SAMPLE OF UNIVERSITY STUDENTS

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Background: Schizotypy is a multidimensional personality construct that appears to indicate psychosis proneness. There is some evidence that demographic factors especially gender and age influence expression of schizotypal personality traits in the normal population. The aim of the present study was to investigate the effect of gender and age on schizotypal personality features in a non clinical sample of university students.

Methods: A total of 490 university students (70.4% female) aged between 18 and 32 years were assessed using the Arabic version of the schizotypal personality questionnaire (SPQ). The differences in the SPQ total and subscale scores and dimensions according to gender and age were analyzed.

Results: The results show significant differences in gender and age groups. Mean SPQ total score was significantly higher in female than male subjects (30.5 ± 12.0 vs. 24.4 ± 12.6; P < 0.0001). Gender differences were significant in cognitive perceptual and paranoid dimensions of schizotypy. Female subjects scored significantly higher in social anxiety (3.6 ± 2.2 vs. 2.6 ± 2.2; P < 0.0001), odd beliefs (2.4 ± 1.7 vs. 1.6 ± 1.5; P < 0.0001), unusual perceptual experiences (2.9 ± 2.1 vs. 1.9 ± 1.9; P < 0.0001), ideas of reference (4.1 ± 2.3 vs. 2.9 ± 2.2; P < 0.0001) and paranoid ideation subscales (4.4 ± 1.9 vs. 3.5 ± 2.1; P < 0.0001). However, no significant differences were found according to gender in constricted affect, no close friends, odd speech and behaviour subscales. The ten percent high and low cutoff scores on the distribution of SPQ scores were respectively 45/74 and 12/74 for the total sample. However, gender differences were observed: 45/74 and 14/74 for females; 44/74 and 10/74 for males. A positive correlation was found between age and SPQ total score (r = 0.17, P < 0.0001), and some disorganized and negative dimensions of SPQ: odd beliefs (r = 0.15, P = 0.002), odd behaviour (r = 0.18, P < 0.0001), odd Speech (r = 0.16, P = 0.001), no close friends (r = 0.14, P = 0.003) and constricted affect (r = 0.11, P = 0.02).

Discussion: The present findings about the impact of gender on schizotypy were in accordance with the published findings. Increased social anxiety, reference ideas and odd beliefs subscale scores have been reported in female subjects, but our results did not support that higher scores for negative and disorganized dimensions in male subjects. The limitation that must be considered when interpreting those results is the overrepresentation of female subjects in our sample. Age is also one of the important confounders of schizotypal traits, but discrepancy findings about the impact of age were reported. These findings suggest that gender and age may be important variables to consider in future studies of schizotypy.

doi:10.1016/j.schres.2010.02.789

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Poster 29

PREVALENCE AND BURDEN OF AT-RISK CRITERIA OF PSYCHOSIS AND HELP-SEEKING BEHAVIOUR – A POPULATION SURVEY – PREVALENCE

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Background: One of the most promising strategies to reduce disability and costs associated with psychoses is an early detection and treatment. For this purpose two complementary approaches are mainly followed: (i) the ‘ultra high risk’ (UHR) criteria of an imminent risk including attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS) and a combination of a genetic risk factor and a recent persistent significant decline in functioning and (ii) the basic symptom criteria ‘cognitive-perceptive basic symptoms’ (COPER) and ‘cognitive disturbances’ (COGDIS) that partially overlap but delineate risk of different imminence. However, based on epidemiological studies that have reported much higher prevalence and annual incidence rates of psychotic-like symptoms (PLEs) and psychotic symptoms in the general population than the clinical phenotype of psychotic disorders, the clinical validity of at-risk criteria had been questioned. Yet, PLEs do not equal at-risk criteria and seem to be more common. The aim of this pilot study was to assess the prevalence of at-risk criteria in the general population clinical interviews conducted by mental health professionals.
Methods: The enrolment sample comprised 85 persons. Inclusion criteria were (i) residency in the Canton Bern, (ii) age between 16 and 35 years and (iii) telephone number available. To preserve a high representativeness of the sample, exclusion criteria were restricted to (i) life-time diagnosis of psychosis and (ii) insufficient language skills in German, French or English. 60 persons (70.5%) participated in the telephone interview, two of them met exclusion criteria. The 22 psychopathological at-risk symptoms were assessed for their occurrence and severity within the three months prior to the telephone interview using the (i) Schizophrenia Prediction Instrument, Adult version (SPIA) for the evaluation of the 14 basic symptoms included in COPER and COGDIS and (ii) the Structured Interview for Prodromal Syndromes (SIPS) for the evaluation of the 5 APS and 3 BLIPS of the UHR criteria.

Results: Only one person fulfilled APS-criteria according to SIPS, none BLIPS-criteria. Furthermore eight persons reported APS relevant symptoms but did not meet the occurrence and severity criteria for APS, and nine persons reported symptoms captured by the SIPS-P dimensions but "below" APS-rating. Nobody fulfilled at-risk criteria according to the basic symptom concept, although eight persons reported basic symptoms according to COPER and/or COGDIS but at an insufficient frequency or as lacking change (i.e. as a trait symptom). Four persons reported both APS relevant symptoms plus COPER/COGDIS basic symptoms. Thus, altogether twelve persons (14.1%) had sub-threshold at-risk criteria for psychoses, and only one additional person (1.2%) actually met at-risk criteria.

Discussion: The results indicate that the 3-months prevalence of at-risk criteria is similar to the incidence of psychotic disorders. This yields the conclusion that at-risk criteria are not as common as PLEs reported in epidemiological studies, and thus might be able to delineate a clinically relevant psychopathological state. These results, however, have to be confirmed in a larger sample.

doi:10.1016/j.schres.2010.02.790

Poster 30
INFLUENCE OF PATERNAL AGE IN SCHIZOPHRENIA

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Background: Schizophrenia is an aetiologically heterogeneous syndrome, with a strong genetic component. Despite a reduced fertility in this disorder, its prevalence is maintained and could be explained by de novo genetic mutations. Advanced paternal age (APA) is a major source of new mutations in human beings and could thus be associated with an increased risk of developing schizophrenia in offspring. New mutations related to APA have been implicated as a cause of sporadic cases in several autosomal dominant diseases and also in neurodevelopmental diseases, autism, intellectual disabilities, and social functioning. The aim of the present study was to summarize the results of studies investigating the role of APA, and to discuss some interpretations.

Methods: All relevant studies were identified through the National Library of Medicine (PubMed® database). Key-words used for research were "age" and "schizophrenia" linked to "paternal or father". We have identified and analysed 7 cohort studies, 4 case-control studies, 2 meta-analyses, and 1 review concerning different father’s mutations potentially transmitted, 2 studies comparing paternal age at conception between sporadic versus familial cases of schizophrenia. All studies selected have been published between 2000 and 2009.

Results: After controlling for several confounding factors including maternal age, the relative risk of schizophrenia increased from 1.84 to 4.62 in offspring of fathers with an older age of fatherhood. Mother's age showed no significant effects after adjusting for paternal age. There was a significant association between paternal age and risk of developing schizophrenia, there was a weaker association with psychosis.

Discussion: The results of these different studies are confirmed by two recent meta-analyses which found an increased risk of schizophrenia in offspring of father older than 35 years. Two main hypotheses could explain these results. The first one is based on the presence of new mutations in the spermatogonia, possibly because of accumulating replication errors in spermatogonial cell lines. The second hypothesis is based on the fact that father with schizophrenia spectrum personality disorder, known to be genetically related to schizophrenia, could have an advanced age at conception. However, regarding this hypothesis, advanced maternal age at conception should be a risk factor for schizophrenia, and this is not the case. Thus, the first hypothesis seems more plausible than the second one. However, APA has been identified as a risk factor for other psychiatric disorders such as autism, bipolar disorder, phobia, and its association with impaired neurocognitive outcomes during infancy and childhood in normal populations raises the question of the phenotype linked to APA.

Conclusion: APA at conception appears to be a risk factor for schizophrenia. To date, there is no validated cut-off at which the risk is significantly increased in offspring. In the future, studies could benefit from analyzing the phenotype related to APA.

doi:10.1016/j.schres.2010.02.791

Poster 31
THE INFLUENCE OF MATERNAL SENSITIVITY, PARENTAL RELATIONSHIP AND CHILDHOOD SEXUAL ABUSE ON ADULT DELUSIONAL-LIKE EXPERIENCES: A BIRTH COHORT STUDY

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Background: There is a growing body of research suggesting that exposure to childhood sexual abuse (CSA) is associated with delusional-like experiences (DLE) in adulthood. There is less information on the influence of factors such as maternal sensitivity and parental relationship during childhood on DLE in adulthood. The aim of this study was to examine the association between these childhood exposures and DLE in a birth cohort.

Methods: The study was based on a birth cohort of 3617 young adults born between 1981 and 1984. Childhood sexual abuse was retrospectively reported and categorised into absent, non-penetrative or penetrative abuse. Adult DLE were measured using the Peters Delusional Inventory at the 21 year follow up. Scales were developed using items pertaining to maternal sensitivity towards the offspring during infancy and at 5 years, use of physical discipline by the mother at 5 years and quality of parental relationship at 5 and 14 years. The association between maternal sensitivity, physical discipline, quality of
parental relationship and CSA versus adult DLE was examined using logistic regression.

**Results:** Retrospectively reported exposure to non-penetrative and penetrative sexual abuse during childhood was associated with an increased likelihood of subjects being in the highest quartile of PDI scores (OR and 95% CI: 3.11; 2.37 – 4.10: 3.80; 2.69 – 5.33 respectively). There was no association between early maternal sensitivity, parental conflict between infancy and 5 years and adult DLE and these factors did not moderate the relationship between CSA and adult DLE. However the presence of maternal reported violence between parents at the 14 year follow-up non significantly increased the strength of the association between CSA and highest quartile PDI score (OR and 95% CI: 5.70; 1.10-29.45).

**Discussion:** There is a significant and strong association between childhood sexual abuse and adult delusional-like experiences. The variables examined in this study pertaining to the relationship between mother and her young child had no influence on this association. Parental violence may increase the association between CSA and adult DLE. This study suggests that sexual abuse during childhood is a potentially preventable risk factor for onset of delusional-like experiences in adulthood.

doi:10.1016/j.schres.2010.02.792

**Poster 32**
**SCHIZOPHRENIA AND 1957 PANDEMIC OF INFLUENZA: META-ANALYSIS**

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**Background:** Maternal influenza during pregnancy is a controversial risk factor for schizophrenia in the child. The evidence to support this hypothesis relates mainly to studies of the 1957 pandemic of A2 influenza. The aim of this study was to examine whether birth during the 9-month period after the pandemic was a risk factor for schizophrenia.

**Methods:** A Medline search was performed. A number of studies compared the risk of schizophrenia among subjects born after the pandemic to that among subjects born in corresponding time periods in surrounding years. These studies were divided into those conducted in the USA, Europe or Australia (Type A studies) and those from Japan, where the epidemic came in two waves (Type B studies). Other studies examined the risk among subjects born to mothers who were pregnant during the pandemic and reported having had influenza (Type C studies). Relative Risks (RRs) were extracted or calculated for each month and/or trimester of possible exposure by two independent authors. Discrepancies were resolved by discussion. All analyses were performed using a fixed-effects model.

**Results:** Eight Type A studies, 3 Type B studies, and 2 Type C studies were retrieved. The first Type A study, from Uusimaa County, Finland, had employed an unusual analysis (Mednick et al., 1988). Using monthly population data from Uusimaa County, we reanalyzed the data and found a decreased risk for subjects exposed during the second trimester. The weighted results of the Type A studies did not indicate a significantly increased risk of schizophrenia among children exposed during any trimester or month of prenatal life. Not a single study found a significant first- or second-trimester effect. The mean weighted RR for subjects who were in their first, second, or third trimester of prenatal life during the pandemic (eight effect sizes) was 0.91 (95% CI: 0.85-0.98), 1.00 (0.93-1.07), and 1.05 (0.98-1.12), respectively. The pooled results of the Type B and Type C studies were also negative.

**Discussion:** Given high infection rates during the pandemic (about 50%), there is insufficient evidence to support the hypothesis that maternal influenza contributes to the etiology of schizophrenia.

doi:10.1016/j.schres.2010.02.793

**Poster 33**
**REAL-LIFE USE OF SERTINDOLE: A DANISH REGISTRY-BASED COHORT ANALYSIS**

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**Background:** Sertindole, an atypical antipsychotic agent, was first launched in 1996 but withdrawn from the market due to the risk of QTc prolongation. It was reintroduced in the European markets in 2006, for the treatment of schizophrenia in patients intolerant to at least one other antipsychotic agent. The objective of this study was to evaluate the use of sertindole after its relaunch with changes occurred in the Summary of Product Characteristics (SPC).

**Methods:** A retrospective cohort study was conducted through prescription databases from 4 regions in Denmark (population approximately 1.8 million). The cohort included all patients with at least one prescription of sertindole from January 1st 2006 to May 31st 2008. The key outcomes of interest were: patient’s characteristics, previous antipsychotic treatment, sertindole treatment duration, concomitant medications, hospitalisations and deaths. The protocol was replicated for the cohort of patients who had received at least one prescription of sertindole before 2006 (i.e. following first launch). The prescription data was linked to the Civil Registration System, Danish Psychiatric Central Register and Danish National Patient Registry using the personal identification number. In these registers, information on ECG was not recorded.

**Results:** A total of 153 patients received at least one prescription for sertindole between January 2006 and May 2008. Most of patients had been previously hospitalized with schizophrenia (74%) and had received an antipsychotic prior to sertindole (98%). No patient had been previously hospitalized with heart disease. Patients receiving sertindole after the relaunch had more previous antipsychotic switches (98% vs 92%), a longer duration of psychiatric illness (median 7 years vs 4 years) and more comorbidities (15% vs 9% had 1 or more comorbidities on the Charlson index) than those after the first launch of sertindole. According to a Kaplan-Meier analysis in the cohort of patients treated after the relaunch of sertindole, the median duration of sertindole treatment was around 300 days and more than 40% of patients were still using sertindole one year after treatment initiation. Few patients (<1%) had short somatic hospitalisations, but none had a heart-related hospitalization. Patients could have co-prescriptions for cardiovascular disease (18%). Very few patients (<1%) had been prescribed contra-indicated drugs. Finally the overall death rate was low (n = 1) (0.98 death per 1000 months of treatment [95%CI: 0.025-5.47]) and reduced compared to the first launch period (n = 3) (3.1 per 1000 months of treatment [95% CI: 0.38-11.29]). Only three patients belonged to both treatment periods.

**Discussion:** These data indicate overall that patients received sertindole in good accordance with the new SPC. Sertindole was prescribed for a long period and seemed to be well tolerated which suggests that pre-
scribes and patients see a benefit in the use of sertindole. These findings will be confirmed in a study based on the overall Danish population.

doi:10.1016/j.jchres.2010.02.794

Postera

ABSOLUTE RISK VERSUS RISK RATIO IN FRAMINGHAM SCORING ALGORITHM FOR PREVENTION OF CARDIOVASCULAR RISK

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Data source: (DP), Inc. Ringoes, NJ, USA; Applied Mathematics and Information Technologies Institute, National Research Council, Milan, Italy

Background: The Framingham Risk Score (FRS) function is an important and well-established primary prevention tool for guiding the assessment and management of risk for coronary heart disease (CHD). Previous studies applying FRS have been all focused on "absolute risk" (Goff et al., 2005; Daumit et al., 2008), i.e. the probability of developing CHD over a given period of time. This might not be most appropriate for the individuals in schizophrenia population, since the original Framingham Cox Survival model (Wilson et al., 1998) was developed based on a white middle-class population, since the original Framingham Cox Survival model might not be most appropriate for the individuals in schizophrenia population, since the original Framingham Cox Survival model (Wilson et al., 1998) was developed based on a white middle-class population.

Methods: The objective of this paper was to examine the FRS function before baseline risk can be established. We compared the mean (or proportion) for each of the categories of the FRS risk factors in CATIE and FHS studies: mean age 40 in CATIE versus 49 in FHS, total cholesterol \( \geq 240 \text{mg/dL} \) is 20% in CATIE versus 26% in FHS, HDL < 35 mg/dL is 25% in CATIE versus 11% in FHS, Stage I-IV hypertension 28% in CATIE versus 32% in FHS, Diabetes mellitus (women 16% and men 11%) in CATIE versus (women 4% and men 5%) in FHS, and smoking (women 56% versus men 73%) in CATIE versus (women 38% and men 40%) in FHS. Specifically, for age 55-59, the low 10-year FHS risk is 7% for both men and women. Replacing the FHS RISK0 and GMEAN with new study values (RISK0=0.95 and GMEAN=11), the low 10-year CHD risk for women aged 55-59 is 13%. We developed a simple proof to show that risk ratio (relative to the low risk state) does not depend on baseline risk (RISK0) and mean risk factors GMEAN when the cumulative hazard is small, and hence is more useful to be compared across populations.

Results: Table 1 presents the results from invariance testing. Some values of \( \Delta \chi^2 \) were significant but understandable due to the large sample sizes. The changes in CFI were moderately acceptable although erring to non-invariance when constraining the structural co-variances in comparison of age groups. Table 1: Results from the multigroup CFA testing invariance across sample, age group, sex and ethnicity.

Discussion: The 4 factor paranoid model of SPQ was shown to be invariant across sex and ethnicity, and questionably across age group. Few studies have examined ethnic differences in schizotypal levels, but invariance testing paves the way for future work safe in the knowledge that this particular model is non-invariant across three main ethnic groups in the UK: white Europeans and people with Asian and black African heritage. The questionable findings across age group could suggest some differences in the model related to age. Follow-up work will attempt to identify sources of non-invariance most likely related to the addition of an adolescent sample and the inherent difficulty in differentiating schizotypal features in this group. Raine, A. (1991). The SPQ - A Scale for the Assessment of Schizotypal Personality Based on DSM-III-R Criteria. Schizophrenia Bulletin, 17(4), 555-564. Reynolds, C. A., Raine, A., Mellingen, K., Venables, P. H., & Mednick, S. A. (2000). Three-factor model of schizotypal personality: Invariance across culture, gender, religious affiliation, family adversity, and psychopathology. Schizophrenia Bulletin, 26(3), 603-618.

doi:10.1016/j.jchres.2010.02.795

Poster 36

A POPULATION-BASED ELABORATION ON PREMORBID FUNCTIONING IN SCHIZOPHRENIA DURING THE EARLY TEENAGE YEARS: COMPARISON, INCIDENCE AND ONSET

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Background: Background- Population-based studies primarily examine cognitive and behavioral premorbid functioning during late adolescence, and rarely during early adolescence. Aims- To examine premorbid cognitive and behavioral functioning during early adolescence (a) in controls as compared to youth to be hospitalized with schizophrenia; and (b) as predictors of subsequent hospitalization for schizophrenia using a large population-based cohort.

Methods: Method- Using a historical prospective design school reports on cognitive, behavioral and nonacademic ratings of school children (n=21,448) aged 13-14 (1964-1974) in Jerusalem were merged with the National Psychiatric Hospitalization Case Registry of the State of Israel on people later hospitalized with a diagnosis of schizophrenia (n = 194, 0.9%).

Results: Results- Compared with population-based controls people subsequently hospitalized with schizophrenia had lower nonacademic and general premorbid deficits, and yet higher behavioral ratings. Males who developed schizophrenia had lower nonacademic premorbid functioning scores, while females did not differ. Compared with matched-cases on birth year, sex and school, people prior to hospitalization for schizophrenia had lower nonacademic performance, and higher behavioral ratings. Both Cox and logistic regression showed that poorer premorbid nonacademic performance was significantly associated with an earlier onset and increased risk. This association was significant among males and not females, among whom poorer behavioral functioning predicted incidence and earlier hospitalization.

Discussion: Conclusions- Based on population-based data, premorbid deficits are evident in the early adolescence among persons later diagnosed with schizophrenia, and have prognostic utility.

doi:10.1016/j.schres.2010.02.797

Poster 37
CHILDHOOD TRAUMA, FKBP5 AND RISK OF PSYCHOSIS

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Background: Childhood traumatic experiences are more common in patients with psychosis, but possible causality is contentious. It is conceivable that any given causal role of trauma would be mediated by HPA-axis dysregulation, since suggests a link between HPA-axis dysregulation and psychosis. FK506 binding protein 51 (FKBP5), a co-chaperone that binds to hsp90, induces lower affinity of the glucocorticoid receptor (GR) to cortisol when bound to the GR-complex. Individuals with FKBP5 high-induction alleles were previously shown to have a greater risk to develop PTSD following childhood abuse. Furthermore, whereas high-induction alleles were associated with relative GR resistance in individuals without PTSD, there was a reversal of this association in persons exposed to childhood trauma, high-induction genotypes with a diagnosis of PTSD displaying GR supersensitivity rather than GR resistance.

Methods: Given the role of FKBP5 in moderating risk for PTSD, we hypothesized that a causal contribution of childhood trauma to psychosis would be moderated by FKBP5, persons with high-induction alleles carrying the highest risk when exposed. Furthermore, it was hypothesized that, similarly to previous findings in PTSD, exposure to childhood trauma would increase GR supersensitivity in individuals with high-induction alleles as evidenced by lower mean cortisol levels. This was investigated in a large sample of twins and triplets recruited from the general population (n = 401), whose subclinical psychosis expression was assessed with the Community Assessment of Psychotic Experiences (CAPE).

Results: There was a trend-level main effect of FKBP5 rs1360780 genotype on CAPE score (p = 0.069). More importantly, there was a significant interaction between childhood trauma and FKBP5 genotype on CAPE score (p = 0.002), with a dose-response pattern according to T-allele loading. The genotype effect was apparent and strong in participants exposed to severe trauma, defined as scoring in the upper tertile of the Childhood Trauma Questionnaire (p = 0.002), whereas it was absent in participants with lower tertile; p = 0.105) and moderate trauma exposure (intermediate tertile; p = 0.627). In addition, there was a significant FKBP5 X trauma interaction on mean cortisol level (p = 0.030). Again, the genotype effect was apparent and strong in participants exposed to severe trauma (p < 0.001), whereas it was absent in participants with low (p = 0.545) or moderate trauma exposure (p = 0.707). As hypothesized, T/T genotypes displayed the lowest mean cortisol scores after severe trauma exposure, suggesting GR supersensitivity, whereas they had the highest levels when exposed to low or moderate childhood trauma. Furthermore, there was a suggestive three-way interaction between having a FKBP5 T allele, level of childhood trauma exposure and mean cortisol level (p = 0.067). In those with both a FKBP5 T allele and exposure to severe trauma, there was a significant inverse association between mean cortisol level and CAPE score (b = -0.003, SE 0.001, p = 0.011), whereas no association was found in the other groups.

Discussion: These data provide a possible mechanism relating childhood trauma to psychosis expression and may partly explain high PTSD comorbidity rates in psychotic disorder.

doi:10.1016/j.schres.2010.02.798
Poster 38
DETECTION OF SUBJECTS WITH PRODROMAL SYNDROME FOR PSYCHOSIS IN A GENERAL POPULATION SAMPLE

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Background: It would be important to be able to detect subjects with prodromal syndrome for psychosis in the general population. We constructed a setting within the Northern Finland Birth 1986 Cohort (NFBC1986) to detect subjects vulnerable for psychosis.

Methods: The NFBC1986 consists of 9,332 subjects. We used various data collected in earlier phases of the study together with register data. With this data we defined a group of subjects At Risk for Psychosis (ARP): subjects having familial risk for psychosis and subjects having prodromal symptoms of psychosis. Two patient comparison groups were formed: subjects with psychosis and subjects with Attention Deficit Hyperactivity Disorder, ADHD. A random sample of the rest of the NFBC1986 were also invited. Structured Interview for Prodromal Syndromes (SIPS) was used to detect index cases. The field study was conducted between 2007-2009. Of the invited 743 subjects 280 (38%) participated the field study.

Results: The participation rate of the subjects having familial risk for psychosis 28% (77/272) and 49% (57/117) in the group with prodromal symptoms. Respective figures for psychosis, ADHD and controls were 22 %, 51 % and 42 %. Of the participants 27 (9 %) had prodromal symptoms. Respective figures for psychosis, ADHD and controls were 22 %, 51 % and 42 %.

Discussion: Even though the setting was established to detect index cases. The field study was conducted between 2007-2009. Of the invited 743 subjects 280 (38%) participated the field study.

doi:10.1016/j.schres.2010.02.799

Poster 39
ACTIVITIES OF DAILY LIVING, SOCIAL FUNCTIONING AND THEIR DETERMINANTS IN PERSONS WITH PSYCHOTIC DISORDER

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Background: Psychotic disorders are associated with deficits in everyday functioning. Our aim was to investigate limitations in activities of daily living (ADL), instrumental activities of daily living (IADL) and social functioning and their determinants among subjects with psychotic disorder in a general population-based sample.

Methods: Everyday functioning was assessed in a nationally representative sample of 7,112 persons aged 30 and older. The field work consisted of an interview at home or in an institution and a health examination at the local health centre. Those with a possible psychotic disorder were interviewed with the Research Version of the Structured Clinical Interview for DSM-IV-TR (SCID-I). We collected all case notes from hospital and outpatient treatments. Lifetime-ever diagnoses of psychotic disorder were classified into schizophrenia (n = 61), other non-affective psychotic disorders (ONAP) (n = 79) and affective psychoses (n = 45). Everyday functioning items were included in the health interview and we divided them into three groups according to how demanding the items were and what characteristics were required to perform the tasks. ADL items were: getting in and out of bed, dressing, eating, bathing and toileting. IADL items were: shopping, cooking, laundering, heavy cleaning and cutting toenails. Items of social functioning were: using the phone, taking care of matters together with other people, handling matters in public offices and travelling on public transportation. Cognitive functioning was examined using selected tasks from the CERAD neuropsychological test battery: verbal memory and verbal fluency. The participants reported if they had received regular assistance because of their reduced functional capacity in their everyday activities and if that assistance was sufficient enough. The home interviewers estimated how much help the participants needed in their daily tasks, how well the participants understood speech and how much difficulty they had with speaking understandably.

Results: Limitations in everyday functioning were highly prevalent in persons with schizophrenia and ONAP, but less in the affective psychosis group. After adjusting for age and sex, persons with schizophrenia and ONAP had significantly increased odds of having limitations in ADL (OR 2.20, 95%CI 1.05-4.60) and OR 2.06, 95%CI 1.05-4.04), but even more in IADL (OR 9.85, 95%CI 4.85-20.02 and OR 3.74, 95%CI 2.15-6.50) and social functioning (OR 12.24, 95%CI 5.55-27.03 and OR 4.88, 95%CI 2.67-8.93). They also had deficits in verbal fluency and memory, and difficulties in speaking understandably and understandable speech. Negative symptoms, depression, age, gender, verbal memory deficits and reduced visual acuity were predictors of limitations in everyday functioning even after controlling for sociodemographic factors and chronic medical conditions, and difficulties in social functioning were also related to expressed speech problems. Persons with schizophrenia (39.0%, \( \chi^2 = 15.33, df = 1, P = 0.0001 \)) and ONAP (24.6%, \( \chi^2 = 7.20, df = 1, P = 0.0074 \)) received more assistance than the general population (9.5%), but the help they got was still not sufficient enough.

Discussion: Persons with non-affective psychotic disorder have significantly more problems in everyday functioning than the general population and they do not receive enough help in their daily tasks. Rehabilitation to gain skills needed in everyday life in addition to domestic help from outside would improve the everyday functioning of these patients. More attention should be paid to problems in visual acuity, because they could often be easily corrected with proper glasses.

doi:10.1016/j.schres.2010.02.800

Poster 40
GENDER DIFFERENCES AMONG SCHIZOPHRENIC PATIENTS ADMITTED TO THE PSYCHIATRIC EMERGENCY ROOM AND THE INSUFFICIENCY OF OUTPATIENT CARE IN BRAZIL

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Background: Schizophrenia and related psychoses represent the main cause of psychiatric hospitalizations in the state of Minas
Poster 41
RISK FOR SUICIDE AMONG INDIVIDUALS WITH SCHIZOPHRENIA

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Background: Suicide is the largest cause of premature death among individuals with schizophrenia. The reported risk for suicide among schizophrenia patients is 8.5 times higher than that expected (Harris et al., 1997). Despite this increase in risk for suicide among individuals diagnosed with schizophrenia, risk factors for completed suicide remain largely unexamined in this population. Fenton (2000) found that patients at high risk for suicide had a history of good adolescent functioning and higher IQ. The current study used a historical prospective design to assess risk for suicide among individuals diagnosed with schizophrenia.

Methods: Data from the Israeli Draft Board Register for 1.5 million Israeli male adolescents aged 16-17 was linked to data from a death registry, enabling up to 46 year follow-up for completed suicide. Hospitalization for schizophrenia was ascertained using a National Psychiatric Hospitalization Case Registry (n = 10,079). Cox regression analysis was used examine risk for suicide among those with schizophrenia compared to individuals with no psychiatric diagnosis. Next, we used non-parametric tests to examine differences in IQ and the prevalence of non-psychotic diagnoses between individuals with schizophrenia who later committed suicide and those who did not.

Results: Individuals hospitalized for schizophrenia were at increased risk for later suicide compared to those with no psychiatric diagnoses (HR = 19.6, 95% CI: 15.0-25.6). The premorbid IQ of individuals who were not ill at the time of the draft board assessment but were later hospitalized for schizophrenia and committed suicide was significantly lower than that of their counterparts who were later hospitalized for schizophrenia and did not commit suicide (mean IQ 86.15 ± 18.75 vs. 93.0 ± 15.0 respectively, p < .05). There were no differences between the groups in the prevalence of premorbid non-psychotic diagnoses (depression, anxiety, personality disorders).

Discussion: Risk for completed suicide is significantly increased among individuals with schizophrenia, particularly those with lower premorbid IQ. Individuals with these characteristics should be monitored for suicide risk.

doi:10.1016/j.schres.2010.02.802

Poster 42
EXAMINING INTERACTIONS BETWEEN RISK FACTORS FOR SCHIZOPHRENIA

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Background: There is an ever-increasing body of literature examining gene-environment interactions in psychiatry. There are 3 main arguments put forward as to why studies of interactions may be helpful: 1) they may make it easier to identify novel genetic or environmental risk factors for disease, 2) they may increase our understanding about underlying pathological mechanisms of disease, and 3) they may aid identification of high-risk groups that might benefit from targeted interventions. To study how exposure to two risk factors in combination affects disease risk we compare data to predictions from statistical models. These can be modeled on either additive or multiplicative scales. The pattern of risk from joint exposure to two risk factors is rarely explicitly described. However, we can hypothesize, on theoretical grounds, that this would usually be greater than additive. It remains unclear if greater than additive relationships are the norm, and to what extent observing interactions under either additive or multiplicative models are likely to lead to any of the benefits described above. We examine whether patterns of risk for joint exposure to different combinations of risk factors for psychosis are more consistent with additive or multiplicative (greater than additive) relationships, and discuss to what extent these findings, or indeed those of other interactions described in psychiatry to date, are likely to lead to any of the potential benefits described above. Although we mainly focus on environment-environment interactions, the arguments we present hold equally well for studies of gene-gene or gene-environment interactions.

Methods: We use data from a cohort study of 50,053 Swedish conscripts. Data on IQ, cannabis use, psychiatric diagnoses, disturbed behaviour, and social relations assessed at age 18 were linked to admissions with schizophrenia or other non-affective
psychoses over a 27-year follow-up period. Statistical interactions between risk factors were examined under both additive and multiplicative models.

**Results:** There was some evidence of statistical interaction under an additive model for 8 of the 10 possible combinations of risk factors, with some support for interaction for the other 2 combinations in the sensitivity analyses. The pattern of risk for joint exposure was greater than additive for all of these, consistent with our a priori expectation. We observed evidence of interaction under a multiplicative model for only 1 combination.

**Discussion:** Multiplicative models appear to describe the joint effect of risk factors for psychosis better than additive ones do. We discuss why, that for diseases of complex multifactorial aetiology, where risk factors are neither necessary nor sufficient to cause disease, the implications of finding interactions such as those observed here or indeed most of those reported within psychiatry to date, remain very limited.

doi:10.1016/j.schres.2010.02.803

**Poster 43**

**HIGH PREVALENCE OF PSYCHOSIS CONTINUUM IN A HIGHLY URBANIZED AREA OF TURKEY: TÜRKSCH STUDY**

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**Background:** There are well replicated links between schizophrenia and urban birth, urban upbringing and urban residence at time of presentation. The association is not reported for the affective psychoses. However subclinical psychotic-like experiences are more prevalent in urban places with high population density. Although urbanicity is a proxy for as yet unidentified environmental or even partly genetic factors, almost all research on urbanicity was conducted in west European settings. TürkSch study aims to investigate the association between urban birth, urban residence and psychosis continuum which covers psychosis-like experiences (PLE), psychotic symptoms (PS) and disorders (PD) in a different social and urban context.

**Methods:** TürkSch study was conducted in İzmir metropolitan area which is the third most crowded urban population (2.7 million) of Turkey. A random sample of 4012 individuals, representative of 15 to 64 years population of İzmir metropolitan area, were screened for the lifetime prevalence of any psychotic-like experiences by trained lay interviewers with the Composite International Diagnostic Interview 2.1 version. Approximately three in four of those with a possible clinically relevant symptom were additionally interviewed by clinicians. Register-based diagnosis were used for the individuals refused to participate the clinical evaluation. Associations between urbanicity measures including urbanicity (based on population census and has 5 levels) of birth place, of places between 6 to 15 years and (1) any rating of PLE, (2) any rating of delusional and/or hallucinational PS, (3) any DSM-IV diagnosis of PD were analysed. Logistic regression yielding odds ratios [ORs] and 95% CIs was used to examine associations adjusted for sociodemographic proper-

ties, familial history of mental health, and alcohol-substance abuse within different additive models.

**Results:** Sample lifetime prevalence of any PLE was 25.3% (95% confidence interval [CI] 23.9-26.6). Sample prevalence of PS and PD were 7.5% (CI: 6.7-8.3) and 2.5% (CI: 1.9-2.9). The prevalence estimates for particular DSM-IV disorders with a psychotic feature were as follows: Schizophrenia and other psychotic disorders 1.43% (CI: 1.05-1.79), affective psychoses 0.77% (CI: 0.50-1.04), substance-related psychosis 0.20% (CI: 0.06-0.33). Any lifetime PLE was significantly higher in individuals who were born in highly urbanized areas (adjusted OR: 1.41; 95% CI: 1.31-2.31) and in individuals who lived in highly urbanized areas between 6-15 years (adjusted OR: 1.42; 95% CI: 1.18-1.70). Any lifetime PS was significantly higher in individuals who were born in highly urbanized areas (adjusted OR: 1.41; 95% CI: 1.31-2.31) and in individuals who lived in highly urbanized areas between 6-15 years (adjusted OR: 1.70; 95%CI: 1.25-2.32). Any lifetime diagnosis of DSM-IV PD was higher in individuals who were born in highly urbanized areas (adjusted OR: 1.86; 95% CI: 1.17-2.96) and in individuals who lived in highly urbanized areas between 6-15 years (adjusted OR: 2.61; 95%CI: 1.08-6.34).

**Discussion:** The lifetime prevalence of psychosis continuum is relatively higher in a highly urbanized area of Turkey. The urban impact on schizophrenia is also present for different levels of psychosis continuum, from subclinical level to clinical level. Urban impact on psychosis continuum is persistent between 0-15 years.

doi:10.1016/j.schres.2010.02.804

**Poster 44**

**NEUROANATOMIC CORRELATES OF DERMATOGLYPHIC COMPLEXITY INDEX IN ANTIPSYCHOTIC-NAÏVE SCHIZOPHRENIA**

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**Background:** Genetic factors and adverse intrauterine events result in impaired neurodevelopment in schizophrenia. Interestingly, epidermal ridges, which share ectodermal origins with the central nervous system, differentiate during 3rd and 4th fetal months - a critical phase of brain development. Previous studies have shown schizophrenia patients to have less complex dermatoglyphic pattern than controls. Thus, dermatoglyphic alterations, markers of disrupted early development support the neurodevelopmental model of schizophrenia. However, relationship between dermatoglyphic complexity and Gray Matter (GM) volume, especially in antipsychotic-naïve patients is yet to be examined.

**Methods:** Sample consisted of 23 antipsychotic-naïve adult patients (Age: 29.7 ± 6.7 years; Age-at-onset (AAO): 29.7 ± 6.9 years; 10 men) meeting DSM-IV criteria for schizophrenia. The diagnosis was made by Mini International Neuropsychiatric Interview. Psychopathology was assessed using Scales for Positive (SAPS: 36.3 ± 13.4) & Negative (SANS: 51.9 ± 29.6) Symptoms. High resolution digitalfinger images were obtained using a 1200-dpi scanner. Using coded images, Dermatoglyphic Complexity Index (DCI) was obtained with good inter-rater reliability (intra-class correlation coefficient>0.8). DCI was calculated by subtracting number of arches (developmentally simple) from number of whorls (developmentally complex) - lesser DCI indicates aberrant neurodevelopment. Magnetic Resonance Images (1-mm without inter-slice gap) were acquired using 3T scanner (Achieva, Philips). Smoothened GM images, obtained using optimized voxel based morphometry (VBM) through Statistical Parametric Mapping (SPM5), were examined for correlation between DCI and GM volume.

doi:10.1016/j.schres.2010.02.804
Results: There was significant positive correlation between DCI and left inferior frontal (Brodmann Area [BA]-47), right superior frontal [BA-10], right medial frontal [BA-6], bilateral middle temporal [BA-21], left cingulate [BA-31] & right post-central [BA-3] gyri and significant negative correlation between DCI and left parahippocampal [BA-19], right supramarginal [BA-39], right fusiform [BA-37], left pre-central [BA-6], left middle temporal [BA-39] gyri and right cerebellum (uncorrected-p ≤ 0.001; SVC-p < 0.05). In males, there was a trend towards significant positive correlation between DCI and AAQ, after controlling for the potential age effects (correlation co-efficient = 0.6; p = 0.079).

Discussion: To the best of our knowledge, this is the first time VBM study to examine GM volume correlates of DCI in antipsychotic-naive schizophrenia patients. Lesser DCI was associated predominantly with decreased frontal & temporal GM volumes. The findings offer support to the neurodevelopmental pathogenesis in schizophrenia. On the contrary, increased parahippocampal and inferior parietal lobule GM volumes (regions implicated in the genesis of first rank symptoms) were associated with lesser DCI which might offer partial explanation to first rank symptoms being less common in younger AAO patients. This possibility is further strengthened by the trend-level relationship suggesting younger AAO male patients having lesser DCI. Together, these findings support a possible clinical role for DCI in early identification of neurodevelopmentally more-impaired patients with poorer outcome. Moreover, the contrasting GM volume correlations need further research to elucidate the probable differential impact of neurodevelopmental insult on brain morphology in schizophrenia.

doi:10.1016/j.schres.2010.02.805

Poster 45
CORTISOL RESPONSIVITY AND PRODROMAL SYMPTOMS AMONG INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: The stress-vulnerability model has been widely accepted as contributing to the onset and progression of psychotic disorders. Specifically, the Hypothalamic Pituitary Adrenal Axis (HPAA) is thought to act as a mediator between the experience of psychosocial stress and psychotic symptoms. Studies to date assessing the HPAA in subjects defined as being at clinical high risk of psychosis have yielded inconsistent results. The purpose of the present study was to examine the relationship between cortisol responsivity to a neuropsychological stressor and psychotic-like symptoms, among a sample of patients identified as prodromal for psychosis.

Methods: Twenty five patients defined as prodromal for psychosis (baseline r = -.15; p = .49; responsivity r = .23; p = .28) symptoms. In exploratory analysis of individual items of the Scale of Prodromal Symptoms, D3 ("Motor disturbances") was found to be positively associated with cortisol responsivity (r = .42; p = .04). Visual inspection through scatterplots suggested that this association was not driven by medication status. Univariate analysis of history of early trauma, medication status and socio-demographic factors revealed no significant associations with the primary variables.

Discussion: Contrary to our hypothesis, no significant correlations were found between cortisol responsivity, a correlate for impaired stress tolerance, and positive or affective symptoms. This is in line with the mixed results in the current literature, though the small sample size and the lack of formal control for confounders make it necessary to interpret this negative finding with caution. The significant association found between cortisol responsivity and motor disturbances in our exploratory analysis has been reported by other authors, and we provide further evidence for the association between these two putative biorisk markers for psychosis. Further, larger studies are warranted in order to help understand the role of the HPAA in the expression of psychosis.

doi:10.1016/j.schres.2010.02.806

Poster 46
THE EFFECT OF EXTREME PREMATURITY AND VERY LOW BIRTH WEIGHT IN EARLY DEVELOPMENTAL MARKERS: A DERMATOGLYPHIC STUDY

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Background: Individuals who are born very preterm (VPT; before 33 weeks’ gestation) are prey to adverse environmental insults, which may act in the prenatal and neonatal periods. In the neonatal periods, these insults are well-recognised, and include hypoxia, ischaemia, sepsis and under nutrition (Hoon et al. 1995). Prenatally, “stress reactive” cortisol (c2), from 0.7 to 4.3 (M = 1.97; SD = .91). No significant correlation was found between either baseline (c1) or cortisol responsivity (c2-c1) and total positive (baseline r = -.042; p = .85; responsivity rs = .42; p = .04). Visual inspection through scatterplots suggested that this association was not driven by medication status. Univariate analysis of history of early trauma, medication status and socio-demographic factors revealed no significant associations with the primary variables.

Discussion: Contrary to our hypothesis, no significant correlations were found between cortisol responsivity, a correlate for impaired stress tolerance, and positive or affective symptoms. This is in line with the mixed results in the current literature, though the small sample size and the lack of formal control for confounders make it necessary to interpret this negative finding with caution. The significant association found between cortisol responsivity and motor disturbances in our exploratory analysis has been reported by other authors, and we provide further evidence for the association between these two putative biorisk markers for psychosis. Further, larger studies are warranted in order to help understand the role of the HPAA in the expression of psychosis.

Results: The 23 high risk participants included in the final analysis ranged from 13 to 24 years old (mean(M) = 18.2 years; standard deviation(SD) = 3.1 years). 21(91.3%) were male, 13 (56.5%) Caucasian, 6 (26.1%) Hispanic, 2 (8%) Afro-American, and 2 (8.7%) multi-racial. 9 (39.1%) were taking antidepressant medication, of which 5 were also receiving antipsychotics. Baseline cortisol (c1) ranged from 1.0 to 4.6 (M = 2.0, SD = .87), and “stress reactive” cortisol (c2), from 0.7 to 4.3 (M = 1.97; SD = .91).
common ectodermal origin, and are influenced by intrauterine environmental factors acting during their formation between weeks 5 and 25 of gestation, which coincides with a critical period of brain development, when neuronal cell migration to the cerebral cortex takes place (Rakic et al. 1998). Total a-b ridge count (TABRC) is a dermatoglyphic measure which has been found to be decreased in neurodevelopmental disorders such as schizophrenia (Fañanás et al. 1996; Fearon et al. 2001; Rosa et al. 2000, 2002), especially in those patients suffering from obstetric complications or very low birth weight (Bramon et al. 2005, Fatjó-Vilas et al. 2008). The aim of our study was to analyze TABRC as a marker of prenatal stress in a sample of very preterm born individuals, taking into account the birth weight as a proxy for adverse influences on the developing fetus, and to compare them with a control group (i.e.: delivered at term).

Methods: Dermatoglyphics were collected from 142 VPT individuals and 63 term-born individuals (between 38 and 42 weeks' gestation) as part of a longitudinal study of brain development at the Institute of Psychiatry, London. TABRC was determined by the sum of the total number of dermal ridges occurring in the second interdigital area of both hands.

Results: The VPT group had a significantly lower mean TABRC compared to the term group (81.15 SD 10.9 vs 85.5 SD 9.4; P = 0.007). VPT individuals were further classified into two groups according to birth weight: very low birth weight (VLBW, less than 1500g) (n = 97) and low birth weight (LBW, between 1500g and 2000g) (n = 41), and compared to the term group. ANOVA showed a significant group effect on the association with decreased TABRC (VLBW = 79.7 ± 10.3; LBW = 83.9 ± 10.9; C = 85.5 ± 9.4; P = 0.001), with TABRC being lowest in the VLBW subgroup.

Discussion: We have shown that dermatoglyphic abnormalities are present in VPT individuals. This suggests that the neurodevelopmental disruption seen in VPT young adults may have early prenatal aetiology, particularly in those individuals who present very low birth weight.

Acknowledgments: The study was supported by the Wellcome Trust and the Psychiatry Research Trust. N.Vilahur was supported by FPI MICINN (BES-2009-023933).

doi:10.1016/j.schres.2010.02.807

Poster 47
A PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF FLEXIBLY DOSED ORAL ZIPRASIDONE IN ADOLESCENT SUBJECTS WITH SCHIZOPHRENIA

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Background: Compared with adult-onset schizophrenia, adolescent-onset schizophrenia is associated with a poorer prognosis. Therefore, safe and effective treatment is needed for adolescents with schizophrenia. This study examined the efficacy, safety, and tolerability of ziprasidone in adolescent subjects with schizophrenia.

Methods: Subjects, aged 13 to 17 years, were enrolled in a 6 week, randomized, double-blind, placebo-controlled study of flexibly dosed ziprasidone. Subjects who met DSM-IV criteria for schizophrenia, confirmed by KID-SCID, were randomized to ziprasidone (oral capsule) or placebo in a 2:1 ratio. Ziprasidone was titrated over the first 1 to 2 weeks to a target dose of 120 to 160 mg/d and then flexibly dosed at 80 to 160 mg/d. For subjects weighing <45 kg, the doses were halved. Primary end point was change from baseline to week 6 in BPRS-A total score; key secondary end points were change from baseline in PANSS total and CGI-S scores. Safety assessments included AE reporting, laboratory testing, physical examination, body weight, height, and BMI z score. Analyses of primary and key secondary end points on the intent-to-treat (ITT) population were conducted using MMRM analysis of covariance with treatment, region, visit, and visit-by-treatment interaction as fixed effects and baseline score as a covariate. A Hochberg procedure was applied to the 2 key secondary end points. Per protocol (PP) population analysis excluded subjects with major protocol deviations determined prior to breaking the blind. The results of a planned interim analysis (IA) concluded in a recommendation to terminate the study for futility. Most of the study was completed by the time of decision to terminate. The alpha significance level was adjusted for the IA; final analysis employed a 2-sided p value <0.0462.

Results: 284 subjects were randomized and 283 were treated (193 ziprasidone and 90 placebo). 135 ziprasidone and 52 placebo subjects completed the study; 58 ziprasidone and 38 placebo subjects discontinued. Change from baseline to week 6 in BPRS-A total score on ITT analysis was not significant (p = 0.1530). The corresponding PP analysis was significant (p = 0.0254). LS means (95% CI) for placebo-adjusted scores for ziprasidone in change from baseline to week 6 in BPRS-A total score were −1.8 (−4.28 to 0.67) for the ITT population and −3.31 (−6.21 to −0.41) for the PP population. Change from baseline to week 6 in PANSS total score and CGI-S on ITT analysis was not significant (p = 0.1987 and p = 0.1289, respectively); PP analysis was also not significant per Hochberg procedure to correct for multiple comparisons (p = 0.0609 and p = 0.0452, respectively). Ziprasidone was generally well tolerated. Treatment-emergent AEs occurring more frequently with ziprasidone than placebo (≥ 5%) in either treatment group were: somnolence, extrapyramidal disorder, insomnia, fatigue, nausea, dizziness, vomiting, headache, tremor, and akathisia. More subjects in the placebo group discontinued due to insufficient clinical response (21.1% vs 9.3% ziprasidone group). In the ziprasidone group, 3 subjects (1.6%) had an AE of weight increased and 5 (2.6%) had an AE of weight decreased. In the placebo group 1 (1.1%) had an AE of weight decreased.

Discussion: Ziprasidone failed to separate from placebo in treatment of schizophrenia in adolescent subjects based on ITT analysis. The PP analysis was statistically significant. Possible factors contributing to this result (eg. placebo response, regional differences) will be explored in additional analyses. Ziprasidone was generally well tolerated in adolescent subjects, with an overall neutral weight and metabolic profile.

Acknowledgments: The study was supported by the National Institute of Mental Health (NIMH) and Pfizer Inc. N.Vilahur was supported by FPI MICINN (BES-2009-023933).

doi:10.1016/j.schres.2010.02.808

Poster 48
CORRELATIONS BETWEEN HIPPOCAMPAL VOLUMES AND MEMORY PERFORMANCE IN EARLY ONSET SCHIZOPHRENIA

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Background: The hippocampus is essential for declarative memory consolidation and retrieval and has been shown to be affected in schizophrenia. Early-onset schizophrenia (EOS) is associated with underlying hippocampal abnormalities.

Methods: 15 EOS patients (age 18–42 years) and 15 matched healthy controls (HC) were enrolled. Subjects underwent T1-weighted MRI scanning and were assessed using the Hopkins Verbal Learning Test (HVLT) and the California Verbal Learning Test (CVLT). Headache and depressive symptomology were assessed using the Headache Impact Test (HIT) and the Hospital Anxiety and Depression Scale (HADS). CVLT performance was analysed using a multiple regression model employing patient age, head size, and hippocampal atrophy as predictors.

Results: EOS patients showed a significantly decreased mean CVLT total recall score compared to HC (p = 0.003). A significant negative correlation was found between total CVLT recall and age in the EOS group (r = -0.55, p = 0.03). The EOS group also showed a trend towards decreased hippocampal volumes compared to HC (p = 0.06). A multiple regression model revealed that age, head size, and hippocampal atrophy were significant predictors of total CVLT recall in the EOS group (p < 0.05). The model explained 43% of the variance in CVLT total recall in the EOS group.

Discussion: The decreased CVLT total recall score in EOS patients is consistent with previous findings and suggests impaired declarative memory consolidation and retrieval. The significant negative correlation between age and CVLT total recall in the EOS group further supports this finding. The significant role of hippocampal atrophy in predicting CVLT total recall in the EOS group suggests a direct relationship between hippocampal structure and memory performance in this patient population.

Acknowledgments: The study was supported by the Norwegian Research Council (210609).
**Background:** Long-term memory impairments are extensively documented in schizophrenia. Despite general acceptance of the idea that memory is not localized to one neural structure, there is overwhelming evidence that the hippocampus plays a central role in memory formation. Brain imaging studies of adult schizophrenia patients have found smaller hippocampal volumes, while in early onset schizophrenia patients (EOS, onset between 12-18 years of age), differences have not reached statistical significance, but bilateral reductions of about 8-9% has been reported. In healthy individuals volume–memory correlations change from generally negative to extremely variable as the age of the sample increases. No other study has looked into correlations between hippocampal volumes and memory functions in EOS.

**Methods:** 25 adolescents with a schizophrenia spectrum diagnosis were included in the study. Mean age was 15.9 (SD = 1.9) years. The average age of onset of psychosis was 14.4 (SD = 2.1) years. 33 healthy controls screened for mental problems were included in the study. Mean age for the controls was 15.8 (SD = 1.8) years. Intelligence quotient (IQ) was above 70 for all subjects in the study. Verbal learning and memory was assessed using the Hopkins Verbal Learning Test (HVLT). The test is composed of 12 items, organized into three semantic categories, and presented over three consecutive learning trials. After 20 minutes, a delayed recall of the list is recorded. All participants were scanned using a 1.5 T Siemens Trio system (Siemens Medical Systems, Erlangen, Germany). Segmentation of the hippocampal formation was performed using Freesurfer v. 4.0.4 software.

**Results:** The groups did not differ in age or handedness. The patients had a significantly lower IQ score (97.2 (SD = 16.1)) IQ points vs 107.3 (SD = 14.8), df = 56, t = -2.478, p = 0.016). The groups did not differ in hippocampal volumes. The patient group performed significantly poorer on all the HVLT subscales: Total learning and delayed recall, both p < 0.01, and percent retained and recognition p < 0.05. There were no significant correlations between any of the HVLT subscales with the hippocampal volumes in the control group. There were significant correlations between left hippocampal volume and delayed recall (correlation = -0.451, p = 0.031) and left hippocampal volume and percent retained (correlation = -0.412, p = 0.051) in the patient group. There was no significant correlation with the other two subscales and the left hippocampus volume, and, finally, no significant correlations between any memory measure and the right hippocampal volume in the patient group.

**Discussion:** There is a significant and moderate negative correlation between left hippocampal volume and performance on both delayed recall and percent retained on HVLT in the EOS group. Why there was no significant relationships in the control group is not clear. Part of the explanation may be that they performed relatively well on the HVLT, and thus had a tighter range of results and standard deviations compared to the patients. This study indicates that there is noteworthy relations between left hippocampal volume and verbal memory performance in an EOS group. This is of importance as schizophrenia in many aspects is considered a neurodegenerative disorder, where one of the most affected structures in adolescent patient populations is the hippocampus. Treatment efforts to preserve the hippocampal structure, can possibly preserve memory functions in this patient group.

**Poster 49**

**NEURAL CORRELATES OF VERBAL WORKING MEMORY DYSFUNCTION IN EARLY-ONSET SCHIZOPHRENIA: A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY**

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**Background:** Working memory (WM) deficits are among the core cognitive abnormalities in schizophrenia. WM is subserved by widely distributed fronto-parietal networks and is undergoing robust development during adolescence. Studying the neural correlates of WM dysfunction in early-onset schizophrenia (EOS) will advance our understanding of aberrant neurodevelopmental processes in the disorder.

**Methods:** Nineteen patients with EOS aged 13-19 and 20 matched healthy participants underwent functional Magnetic Resonance Imaging (fMRI) as they performed a N-back verbal WM task with 3 levels of difficulty (1-back, 2-back, 3-back). Following matching for task performance, 14 patients were compared to 20 controls, using non-parametric whole brain and region of interest (ROI) approaches followed by psycho-physiological interaction analysis (PPI) with seed voxel from the left parietal cluster.

**Results:** Regions within the left prefrontal cortex, the left insula and bilateral anterior cingulate cortex showed reduced activation in EOS patients compared to healthy participants at the 2-back condition. In addition, ROI analysis at the same condition revealed hypoactivation in the EOS group with large effect sizes for left prefrontal and parietal regions. The PPI results revealed negative functional connectivity in the healthy participants’ group but not in EOS between left parietal and right parietal and bilateral frontal regions.

**Discussion:** Our results support compromised function within the left prefrontal-cingulate network and left insula during the N-Back verbal WM task in patients with EOS compared to healthy participants. They also indicate the possibility of more widespread fronto-parietal network dysfunction, most noted in the left hemisphere in the disorder.

**doi:**10.1016/j.schres.2010.02.810

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**Poster 50**

**EVIDENCE MAPPING FOR EARLY PSYCHOTIC DISORDERS IN YOUNG PEOPLE**

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**Background:** The onset of psychotic disorders peaks in young people aged 12-30 years. Given the traditionally poor prognosis associated with chronic schizophrenia, a clinical research agenda has emerged in the last 2 decades focusing on interventions during the early phases of psychosis, where opportunities for clinical and functional recovery are greater. As a large volume of such research now exists, there is a need to summarise the extent and distribution of this research to ascertain what is known, and not yet known, about the evidence for preventing and treating early psychotic disorders.

**Methods:** Using an evidence mapping methodology, we conducted a comprehensive search of high-level evidence (RCTs, CCTs and systematic reviews) since 1980 using the Cochrane Central Register of Controlled Trials, PSYCHINFO, MEDLINE and EMBASE. Detailed inclusion and exclusion criteria were defined. Studies were screened according to these criteria and mapped according to predefined study characteristics, including the type of intervention (e.g. psychological, biological, integrated) and
stage of illness (e.g., ultra high risk (UHR) for psychosis, first episode of psychosis (FEP), established disorder and relapse prevention).

**Results:** Our search strategies identified 5980 references, of which 58 studies and 8 systematic reviews met the inclusion criteria. The distribution of the included studies was as follows: 17 psychosocial intervention studies were found across UHR (3 CBT), FEP (7 CBT, 4 miscellaneous psychotherapies), and relapse prevention stages (3 family therapy); 31 biological intervention studies covered UHR (3 atypical antipsychotics), FEP (9 typical antipsychotics, 17 atypical antipsychotics, 2 atypical antipsychotics plus other medications, 1 electroconvulsive therapy), established disorder (2 atypical antipsychotics, 1 electroconvulsive therapy), and relapse prevention stages (4 typical antipsychotics, 1 atypical antipsychotics). 9 integrated intervention studies were included (3 for UHR, 6 for FEP) and 2 trials investigating strategies for withdrawing antipsychotic medications.

**Discussion:** Mapping evidence within a distinct field or clinical disorder provides a systematic framework to assist the implementation of well-researched interventions and to highlight areas in need of strategies for new treatment development. This early psychosis evidence map indicates that the bulk of research has focused on atypical antipsychotics in the treatment of the FEP or relapse prevention. However there is little research to date on other novel biological interventions, for example eicosapentaenoic acid or erythropoietin for neuroprotection and transcranial magnetic stimulation for treating hallucinations. There is also a lack of research on treating the cognitive deficits in the disorder across all stages of the illness. Neurprotective agents should be searched for and their effects on ameliorating cognitive deficits should be evaluated.

doi:10.1016/j.schres.2010.02.811

**Poster 51**

**COGNITION AND PSYCHOSOCIAL FUNCTIONING IN ADOLESCENTS WITH SCHIZOPHRENIA**

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**Background:** The predictive value of cognition on psychosocial outcome is one of the most replicated results in adults with schizophrenia (Green et al., 2004). Recently, it has been described that verbal memory, attention/vigilante and working memory performance are also good predictors of psychosocial functioning in adolescents with schizophrenia (Cervellione et al., 2007). But other authors have not found a significant relationship between verbal memory and psychosocial outcome (Landro et al., 2008). AIMS: (1) To analyze the cognitive and functional profile in a sample of adolescents with schizophrenia, (2) to analyze the predictive value of cognitive functions on patients’ psychosocial functioning.

**Methods:** Sample: 33 adolescent outpatients with schizophrenia spectrum disorders, clinical and pharmacological stabilized were included, and 33 healthy subjects matched for sex and age. Instruments: Neuropsychological battery of tests assessing IQ (Vocabulary and Block Design, WISC-IV or WAIS-III depending on age), memory (WMS-III), learning (RAVLT), processing speed (TMT-A, FAS), attention (Digits, WISC-IV/WAIS-III), working memory (Letter and Numbers, WISC-IV/WAIS-III), executive functions (TMT-B, WCST). We used the Spanish version of Life Skills Profile (LSP) scale to assess psychosocial functioning, and the PANNS and the CDS to assess clinical symptoms. Statistical analyses: multivariate analysis (MANCOVA) was used to assess global differences between patients and healthy subjects in cognitive variables and univariate analysis (ANOVA) were used to assess differences in functional variables, controlling for confounding variables. Multiple regression analysis (stepwise method) was used to identify the best predictors of LSP scores among cognitive and clinical variables.

**Discussion:** A generalized cognitive dysfunction was found among schizophrenic adolescents compared with healthy subjects, controlling for socioeconomic status and IQ differences between groups (λ Wilks = 0.683, p = 0.005). We also found a generalized functional impairment in LSP scores among patients compared with healthy subjects (F = 13.51, p = 0.001). Regression analysis entering all cognitive variables and controlling for confounders identified Processing Speed as the most predictive variable of psychosocial scores in adolescents with schizophrenia.

**Results:** Adolescents with schizophrenia showed a generalized cognitive and functional dysfunction compared with healthy subjects. Processing Speed emerged as the most predictive variable of the psychosocial scores. These results are consistent with recent studies in adolescent-onset (Cervellione et al., 2007) and adult-onset schizophrenia (Harvey et al., 2009; Bowie et al., 2008).

doi:10.1016/j.schres.2010.02.812

**Poster 52**

**HIGHER RATES OF PSYCHOPATHOLOGY IN THE CHILDREN AND ADOLESCENTS AT GENETIC HIGH RISK OF BIPOLAR DISORDER AND SCHIZOPHRENIA COMPARED TO HEALTHY CONTROLS: PRELIMINARY RESULTS**

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**Background:** Children of parents or with bipolar disorder or schizophrenia are at higher risk for developing psychiatric disorders than the general population. Higher rates of mood and disruptive disorders among bipolar offspring compared to healthy controls are the most replicated findings. On the other hand, studies of children of parents with schizophrenia also showed high rates of axis I disorders, specially externalizing disorders. Unfortunately, a limited number of papers have compared the rates of psychopathology between the young first-degree relatives of schizophrenia and bipolar disorder. The aims of the present study are: to examine the risk of psychopathology in youth at genetic risk for bipolar disorder (BPO) and schizophrenia (SZO) and compare them to offspring of healthy controls (HCO).

**Methods:** Child and adolescent first-degree relatives of bipolar (48 offspring), schizophrenia (17 offspring and 15 siblings) and healthy control (20 offspring), were assessed using the Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime version (K-SADS-PL) administered separately to parents and children. Children and adolescents were also evaluated with the Scale of Prodomal Symptoms (SOPS). Bipolar and Schizophrenia parents or siblings were assessed using the
Structured Clinical Interview (SCID-I) for DSM-IV axis I psychiatric disorder to confirm diagnoses. Also healthy control parents were assessed to confirm the absence of DSM-IV axis I diagnoses. Demographic and clinical variables were compared using chi-square tests or Fisher exact tests for categorical variables, and analysis of variance (ANOVA) for continuous variables, using Bonferroni for post-hoc analysis.

Results: First-degree young relatives of SZO and BPO had statistically significant higher rates of any Axis I psychiatric disorder (46.2% and 45.8%, respectively) as compared to first-degree of healthy control. For comparison of the three groups, diagnoses were regrouped as internalizing disorders (mood and anxiety disorder), externalizing disorder (ADHD, ODD, conduct disorder) and other (eating disorder, tic disorder and enuresis). Both genetic-high risk groups had statistically significant higher prevalence of internalizing and externalizing disorders compared to offspring of healthy controls. There were no statistically significant differences between rates of specific psychiatric disorders between BPO and SZO; however children at genetic high risk of SZO showed higher prevalence of externalizing disorders compared to children at genetic high risk of BPO and BPO young relatives showed more internalizing disorders than SZO relatives. Moreover, children at genetic high-risk of schizophrenia showed higher scores in the SAPS as compared to BPO and HCO groups.

Discussion: Our preliminary results are similar to those reported in literature for rates of psychopathology in BPO and SZO. There were no statistically significant differences among different Axis I diagnoses when comparing BPO and SZO. Moreover, SZO had more prodromal psychotic symptoms. Because of the small sample size we should be careful when interpreting these results.

doi:10.1016/j.schres.2010.02.813

Poster 53
INTER-RATER RELIABILITY IN THE ASSESSMENT OF PAEDIATRIC SCHIZOPHRENIA USING THE PANSS: TRAINING RESULTS FROM A RUSSIAN COHORT

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Background: The onset of schizophrenia is often in late adolescence or early adulthood though in some cases can be earlier with paediatric schizophrenia affecting approximately 2 in 1 million in the general population (Remschmidt, 2008). The assessment of schizophrenia in childhood or early adolescence demands a somewhat different style of interviewing technique but the core psychopathology is essentially similar to what may be seen in older patients: delusions, hallucinations and a range of other symptoms including social withdrawal and cognitive problems. The Positive and Negative Syndrome Scale (PANSS) is a primary measure in research used to assess these symptoms. In this study we looked at training data to determine if raters in this group were more or less likely to achieve similar reliability to that expected in adult samples. Because this was a Russian cohort and the materials were originally produced in English, we were also interested in potential linguistic or cultural effects as this has emerged as an important issue in the global standardization of research practices.

Methods: Two early adolescent aged patients with DSM-IV diagnosis of schizophrenia were rated by video using the PANSS in a training exercise with 30 Russian psychiatrists. All materials were translated into Russian and validated and scores were obtained by rating videos that were subtitled in Russian with transcripts available. Inter-rater reliability was obtained by using the intra-class correlation coefficient (ICC) statistic for total scale and for the positive, negative and general subscales.

Results: Raters achieved comparable inter-reliability to that reported in the literature for the rating of videos. There appeared to be little difference in ICCs for total scale and positive, negative and general subscales. The negative subscale was slightly less reliable in this group with .976 and .979 for pre and post training respectively, but this is still in the excellent range. Pre and post training ICCs for the positive subscale ICCs were .987 and .989, general .986 and .970 and total scale .987 and .976.

Discussion: A number of previous studies utilizing this methodology (rating from video) have reported ICCs in this range for the PANSS rating adults (e.g., Betsen et al., 1996; Garety et al., 2005; von Knorring & Lindstrom, 1995). Our data suggests that there does not appear to be a significant impact of rating child versus adult patients using the PANSS instrument with very high ICCs obtained in this small cohort of Russian psychiatrists. Linguistic and cultural considerations did not appear to impact overall reliability but may have had a limited effect on individual item reliability. Caution must be exercised in the interpretation of these results due to the limited sample size and because ICCs can be inflated by the reduction of information variance inherent in rating from video.

doi:10.1016/j.schres.2010.02.814

Poster 54
EXECUTIVE FUNCTION IMPAIRMENTS IN SCHIZOPHRENIA IN COMPARISON WITH NORMAL HEALTHY CONTROLS

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Background: Executive function deficits are prominent in schizophrenia and consensus is yet to be achieved on its relationship with severity of symptoms. This study compared the performance of patients with schizophrenia with that of healthy controls on a relatively new executive test battery, i.e. Cambridge Neuropsychological Test Automated Battery (CANTAB), to identify the specific impaired components of executive functioning. We then compared the performance of the patients in acute and remitted states of schizophrenia by controlling for the severity of psychopathology.

Methods: We recruited 54 outpatients with schizophrenia from Boramae Medical Center and 33 healthy controls from the
Background: All participants completed the Beck Anxiety Inventory (BAI) and subtests of CATBAB consisting of Choice Reaction Time (CRT: attention ability), Intra/Extra Dimensional Set Shift (IED: attentional set shifting ability), Stop Signal Test (SST: response inhibition), and Spatial Span (span length). They were also tested with short form of Korean Wechsler Adult Intelligence Scale (K-WAIS) to ensure the basic competency in performing the above tasks. The patient groups were also evaluated with 8-item PANSS and then were divided into the active and remitted groups according to Andreasen’s remission criteria (Andreason et al., 2005). Analysis of variance, t-test, and chi-square test were conducted to compare the demographic and neuropsychological variables, and analyses of covariance (ANCOVA) were further conducted where appropriate.

Results: No participant received an IQ score below 80, hence no one was excluded in the analysis. The three groups showed no significant differences in terms of sex and age, but they significantly differed in years of education and the level of anxiety, as measured by the BAI. The active and remitted groups were similar in duration of illness and age of onset, but significantly differed in the PANSS and the BAI total scores. We analyzed the performance of the three groups on the subtests of CANTAB, and significant differences in CRT mean reaction time, IED total errors, adjusted total errors, pre-extradimensional(Pre-ED) errors, and SST mean correct reaction time and stop signal reaction time(SSRT). When we further conducted the ANCOVA designating the years of education as the covariate, such differences remained significant except for IED adjusted total errors. When BAI was designated as the covariate, on the other hand, IED adjusted total errors and Pre-ED errors became insignificant, while other significant differences were maintained. In comparisons between the combined groups of schizophrenia and healthy controls, the patient group showed lower levels of performance on only the CRT mean reaction time and IED total error, after controlling for years of education and BAI. Lastly, between the schizophrenia groups, no significant differences were found in any of the CANTAB measures when the PANSS total score was entered as the covariate.

Discussion: Our results suggest that differences in executive function exist between the patients with schizophrenia and healthy controls, which can be largely attributed to the relatively poor performance of the patients in active state. Such impairments in executive function appear to be specific, rather than general, as demonstrated by ANCOVA results. Furthermore, the impairments in executive functions, such as inhibitory control deficit or slower inhibitory processes, may be largely affected by symptom severity and illness state in schizophrenia, as the differences in executive functioning measures between the active and remitted patient groups became insignificant when the severity of psychopathology was controlled.

doi:10.1016/j.schres.2010.02.815

Poster 55
NEUROCOGNITIVE FUNCTIONING IN SCHIZOPHRENIA SPECTRUM DISORDERS: IS THERE A DIFFERENCE BETWEEN REMITTED AND NON-REMITTED PATIENTS?

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Background: Next to positive and negative symptoms neurocognitive impairments are considered to be core features of schizophrenia. Evidence has mounted that some patients experience symptomatic remission and the question arises whether there would be a relationship between the patients’ remission status and cognitive functioning. Accordingly, the purpose of the present study was to identify neurocognitive variables associated with symptomatic remission from schizophrenia.

Methods: We performed a cross-sectional study including outpatients with schizophrenia or schizoaffective disorder between the ages of 19 and 65. All subjects had a duration of illness of over two years. At the time of the interviews, patients had been clinically stable with a fixed medication regimen for a period of at least 6 months. The diagnostic criteria of a schizophrenic or schizoaffective disorder according to ICD 10 served as a basis for study inclusion after patients had consented in writing. Psychopathological symptoms were rated by means of the Positive and Negative Syndrome Scale (PANSS). Symptom remission was assessed by using the concept defined by Andreasen et al. Premorbid intelligence was measured by using the Mehrfachwahl-Wortelsatz-Test-B (MWT-B). To assess neurocognitive functioning the following tests were used: Wisconsin Card Sorting Test (WCST: executive functioning), verbal fluency (subjects were asked to generate as many words as possible within the category of animals and as many words as possible that start with “S” in each of two 60-second trials), Münchener Gedächtnistest (MGT: verbal learning and memory), Test for Attention Performance (TAP: alerterness, optical vigilance, working memory), Benton Visual Retention Test (BVRT: visual memory).

Results: Out of 140 patients included into the study (60% males), 62 (44.3%) were symptomatically remitted. Their mean age was 40.2±10.3 years, and the mean education was 12±3.7 years. Mean age, education, and sex distribution were comparable in remitted and non-remitted patients. The two groups did not differ significantly with respect to premorbid intelligence, executive functioning, verbal learning and memory, and working memory. However, remitted patients showed significantly higher values on tests of verbal fluency, alertness, and optical vigilance.

Discussion: We found evidence for a pattern of cognitive dysfunction associated with symptomatic remission from schizophrenia. Specifically, patients who met the operational criteria for remission according to Andreasen et al. performed better than non-remitted, but stable, outpatient on tests of verbal fluency, alertness, and optical vigilance. Our data highlight the importance of cognitive performance as one possible predictor of remission and emphasize the necessity of providing psychological interventions focusing especially on the above mentioned cognitive domains in order to increase the likelihood of remission.

doi:10.1016/j.schres.2010.02.816

Poster 56
EXECUTIVE DEFICITS IN FIRST EPISODE PSYCHOSIS ACCURATELY PREDICT 90% OF THE FINAL DIAGNOSIS OF SCHIZOPHRENIA: A LONGITUDINAL STUDY

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Background: The predictive value of cognitive deficits in schizophrenia for the course of clinical symptoms and related variables...
remains unclear. Specifically, previous studies have failed to prove the longitudinal predictive value of cognition in determining the final diagnoses of the first episode psychosis (FEP) samples analyzed.

**Methods:** Eighty-three FEP patients were recruited and followed-up during a 2-year follow-up period after onset. Assessment included clinical interview, psychiatric evaluation (PANSS, Young Mania Scale, MADRS Depression Scale) neurocognitive (attention, processing speed, memory, language, executive functions) and functional assessment.

**Results:** Logistic regression models revealed that executive dysfunction correctly classified patients with schizophrenia (87%), from patients with bipolar disorder (81.3%), and other psychoses (72.4%). The prediction was stable despite the inclusion of positive, negative, affective symptoms, and other cognitive tests into the model. Just Wisconsin Card Sorting Test- categories completed and percentage of perseverative errors, correctly classify up to 79.4% of patients.

**Discussion:** These results showed that executive functioning, as measured with Wisconsin Card Sorting Test, may be a promising tool to use in basic clinical approach to FEP and schizophrenia. As far as the authors are aware, this is the first attempt to assess the longitudinal predictive value of neurocognitive performance and clinical symptoms on the clinical diagnosis after the FEP. Our results support Keefe et al’s suggestion (2007, 2008), of the importance of including cognition as a part of the diagnostic criteria for schizophrenia.

doi:10.1016/j.schres.2010.02.817

**Poster 57**

**THEORY OF MIND AND EMPATHY: THE TWO SIDES OF THE SAME COIN?**

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**Background:** Theory of Mind (ToM) is the ability to attribute mental states to others; empathy, the ability to infer emotional experiences: both are important processes in social cognition and every day life for an adequate understanding and managing of the social world complexity. Recent neuroimaging research as well as studies on clinical samples lacking ToM and/or empathy provided evidence for a common, or partially overlapping neural basis of mentalizing and empathy, engaging common as well as distinct neuronal networks. The relationship between ToM and empathy has yet however to be determined. The aim of this study is the investigation of the relationship between the two constructs studying patient groups with deficit in ToM and/or empathy such as subjects with schizophrenia and bipolar spectrum disorder.

**Methods:** Twenty subjects with schizophrenia and 20 with bipolar disorder according the DSM-IV-R criteria have been recruited. Symptomatology has been evaluated by using the Positive and Negative Symptoms Scale (PANSS). ToM evaluation was mad by Visual jokes for evaluation of Irony Stratta et al., 2007. Two sets of jokes have been used: a ‘Physical set’ of slapstick humour that did not require ToM capabilities to understand the joke contained within the picture, and a ‘ToM set’ in which appreciation of the mental states of the characters (i.e. false belief and deception) is required. Empathy evaluation. Empathy Quotient short form (EQ-short) containing 40 empathy and 20 filler/control items (Baron-Cohen & Wheelwright, 2004).

**Results:** Schizophrenics show poorer performance in both tasks. No correlation has been found between ToM and empathy evaluations; furthermore subjects with more empathic ability show poorer irony comprehension.

**Discussion:** The data suggest that the two constructs are independent, with more difficulty in attributing mental states to others when better is empathic ability to infer emotional experiences. A balance between rational (ToM) and emotional inferences could be needed for a good social functioning.

doi:10.1016/j.schres.2010.02.818

**Poster 58**

**COGNITIVE DEFICITS AS INTERMEDIATE PHENOTYPE IN SCHIZOPHRENIA**

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**Background:** Cognitive deficits have been demonstrated both in patients with schizophrenia and in their unaffected first-degree relatives, suggesting that it might be considered as a familial vulnerability marker. Substantial impairment have been described for short term memory, attention, working memory, executive function. Therefore cognitive impairment has been suggested as a endophenotype We used the neuropsychological battery for estimate the principals schizophrenia cognitive dysfunctions order to determine which components are impaired in both patients and their siblings, possibly reflecting shared genetic effects.

**Methods:** We studied 184 subjects. 60 patients with schizophrenia: 36 males; mean ± SD; age = 33.6 ± 9.5 years; TIB (Intelligence Short Test, premorbid IQ) = 106.3 ± 9.56; parental socioeconomic status (Hollingshead Scale) = 30.1 ± 16.1; handedness (Edinburgh Scale) = 0.7 ± 0.4. 54 unaffected siblings: 30 males; mean ± SD; age = 35.8 ± 9 years; TIB (Intelligence Short Test, premorbid IQ) = 107.7 ± 9.1; parental socioeconomic status (Hollingshead Scale) = 28.3 ± 16.2; handedness (Edinburgh Scale) = 0.7 ± 0.4. 70 normal controls: 31 males; mean ± SD; age = 32.9 ± 7.2 years; TIB (Intelligence Short Test, premorbid IQ) = 113.7 ± 6; parental socioeconomic status (Hollingshead Scale) = 33.3 ± 13.4; handedness (Edinburgh Scale) = 0.7 ± 0.4. Subjects underwent a set of neuropsychological tests assessing WM (N-back), sustained attention (Continuous Performance Test, CPT), executive function (Wisconsin Card Sorting Test, WCST), cognitive flexibility (Trail Making Test A-B) and we calculated a Z score for all subjects.

**Results:** There was no significant differences between diagnostic groups in any socio-demographic variables. Consistent with previous reports healthy siblings had an average performance at the composite score which was in between that of healthy controls and that of patients with schizophrenia. Moreover our results demonstrate a diagnosis effect on working memory performance and TMT score where siblings had an intermediate performance between that of schizophrenic patients and controls.
Discussion: These results demonstrate a significant evidence of potential susceptibility of siblings to cognitive impairments suggesting an association with genetic predisposition to schizophrenia. Moreover this study suggests the opportunity of using WM and cognitive flexibility as a neurocognitive endophenotype for investigation in schizophrenia research.

doi:10.1016/j.schres.2010.02.819

Poster 59
USING SCHIZOTYPY TO INVESTIGATE SEMANTIC MEMORY DEFICITS IN SCHIZOPHRENIA

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Background: Semantic memory abnormalities are argued to be a cardinal feature of schizophrenia, with research suggesting that symptoms arise from a disturbance in the organisation of knowledge. One problem with this literature has been inconsistent finding using a semantic memory assessment technique called semantic priming (SP). These inconsistencies have been attributed to a number of confounding factors that limit research with symptomatic clinical patients, including illness duration and medication use. Recently analogue studies, using persons with high schizotypy, have aimed to overcome these confounding factors. This presentation presents data from three analogue studies investigating semantic memory in high schizotypy.

Methods: Study 1 examined SP in 26 high and 32 low scorers on the OLIFE schizotypy scale. Study 2 correlated SP with OLIFE scores in 53 students. Study 3 compared 24 high and 30 low OLIFE scorers on a large battery of semantic memory measures.

Results: Study 1 and 3 established that semantic memory abnormalities are present in high schizotypes in SP and one other implicit semantic memory measure (semantic categorisation). Study 2 showed that the correlational analyses associated priming deficits with cognitive disorganisation scores. This is the analogue scale for thought disorder.

Discussion: Unlike patients with schizophrenia high schizotypes do not have globally impaired semantic memory. High schizotypes show subtle abnormalities on implicit semantic memory measures and not on explicit measures. Significantly these abnormalities were related to cognitive disorganisation and possible thought disorder. Semantic memory deficits in high schizotypes may be akin to those in the prodromal phase of schizophrenia.

doi:10.1016/j.schres.2010.02.820

Poster 60
NPAS3 AND SOX FAMILY GENES: TRANSCRIPTIONAL CONTROL OF NEURONAL PROLIFERATION AND DIFFERENTIATION AND ITS RELATION TO PSYCHIATRIC ILLNESS

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Background: Neuronal basic helix-loop-helix PAS domain transcription factor 3, NPAS3, is implicated in schizophrenia and bipolar disorder susceptibility by cytogenetics, GWAS and a knockout mouse model. Studying NPAS3’s established role in adult hippocampal neurogenesis may provide a biological mechanism linking neurogenesis dysfunction to psychiatric disorders. SOX family transcription factors are known to play a role in neural progenitor proliferation/differentiation.

Methods: To explore the transcriptional network these genes control, we over-expressed full length NPAS3 (FLNPAS3) and truncated NPAS3 (delta NPAS3) and other SOX genes in human kidney cell line HEK293 to identify downstream target genes.

Results: There were five key findings: (1) NPAS3 strongly activates VGF, a gene linking defective neurogenesis with depression in a mouse model, (2) NPAS3 regulates several SOX genes, including SOX11, and displays a similar target activation profile to SOX5/SOX6, (3) NPAS3, like NPAS2, is implicated in energy homeostasis, repressing hypoxia genes encoding most enzymes involved in glycolysis, (4) NPAS3 regulation appears to be sensitive to circadian time-point, and (5) SOX11, which has a key role during neuronal differentiation, activates expression of a histone gene cluster on chromosome 6 within the region implicated by recent schizophrenia GWAS. Q-PCR confirmation will be presented along with immunofluorescence findings of NPAS3, SOX11 and target proteins in hippocampus. We will also report findings on how these influence the time-course of neural precursor cell differentiation.

Discussion: NPAS3 targets have roles in many different cellular processes and are regulated in the context of circadian and hypoxia regulation mediated through interactions among the bHLH transcription factors. How this relates to neurogenesis and psychiatric illness is the focus of ongoing research. These data help unravel neurogenesis pathways and how they impact on psychiatric illness aetiology.

doi:10.1016/j.schres.2010.02.821

Poster 61
FAMILIAL CO-SEGREGATION OF COGNITIVE PERFORMANCE AND NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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Background: Impaired cognitive functioning is a hallmark of schizophrenia and an important indicator of functional outcome. Previous meta-analyses have shown an association between negative symptoms and cognitive performance. However the origin of this association remains unknown. This study investigated the association between neurocognitive performance (trait 1) and negative symptoms (trait 2) across genetically related persons (patients and first degree relatives) to find out whether a shared liability may underlie these traits. Guided by previous work a shared aetiology between negative symptoms and speed of processing in particular was hypothesized.

Methods: The study is part of the Genetic Risk and Outcome of Psychosis (GROUP) project, a multisite, longitudinal, naturalistic cohort study examining the 6 year course of patients with non-affective psychotic disorders, their siblings and healthy controls. At baseline, 1040 patients with a diagnosis of non-affective psychosis and 1030 siblings of these patients completed a cognitive test battery covering verbal learning, sustained attention, executive function, and WAIS III abbreviated (indexing
Neurological soft signs in all subscales were recognized in schizophrenic patients, but not normal people. In ten neurological soft signs (finger-thumb tapping in right hand, finger-thumb opposition in right hand, finger-thumb opposition in left hand, disdiadochokinesia in right hand, disdiadochokinesia in left hand, ozeretsky, fist-edge-palm in right hand, fist-edge-palm in left hand, finger agnosia in right hand, go/no-go), more schizophrenic patients significantly exhibited their signs than normal people. There was no significant relationship between the duration of illness and total score of neurological soft signs. There was no significant relationship between the daily medication dosage and total score of neurological soft signs. There was also no significant relationship between age and total score of neurological soft signs in both normal people and schizophrenic patients.

Discussion: This study suggests normal frequency of neurological soft signs over broad range of age in Japanese people. In addition, it suggests that patients with schizophrenia show more neurological soft signs than normal controls. There was no significant relationship between the duration of illness/the daily medication dosage and total neurological soft sign in schizophrenia. It may mean that both severity of illness and medication do not affect neurological soft signs. Further studies need to investigate the ability of neurological soft signs to discriminate between patients with schizophrenia and normal controls, and more detail analysis in more patients.

doi:10.1016/j.schres.2010.02.823

Poster 62
STUDY OF NEUROLOGICAL SOFT SIGNS IN JAPANESE SCHIZOPHRENIC PATIENTS

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Background: Neurological soft signs are minor neurological abnormalities in sensory and motor performance identified by clinical examination. The first purpose of this study attempted to examine the prevalence and type of neurological soft signs in Japanese normal people. The second aim was to examine the prevalence and type of neurological soft signs of schizophrenic patients based on the prevalence and type of neurological soft signs in the normal people. The third aim was to examine the relationship between the duration of illness, age and neurological soft signs.

Methods: Participants were 79 normal native Japanese people, aged 18-75 (22 males, 57 females) and 34 Japanese patients diagnosed as schizophrenia using ICD-10 diagnosis criteria, aged 21-84 (18 males, 16 females). Average duration of illness was 32.3 years (SD: 17.3, range: 1 month to 66 years). The mean daily medication dosage, which was converted to risperidone equivalent dosage, was 5.5(SD: 7.9) mg. Neurological soft signs were evaluated using short version of the Cambridge Neurological Inventory, including motor coordination, sensory integration, and disinhibition. The subscales have 25 neurological soft signs. Scoring was made according to standardized anchor points to indicate ‘normal’ response (0) or ‘abnormal’ response (1).

Results: The cross-trait, cross-sibling analyses revealed that speed of processing (β -0.10 p<0.000), attention reaction time (β -0.09 p<0.005) and working memory (β -0.06 p<0.03) in siblings were significantly associated with PANSS negative symptoms scores in the patients, indicating a familial co-segregation of these traits. Associations with positive symptoms were weak and non-significant. In addition the association between cognitive measures in siblings and patients (cross-sibling within-trait) were, with the exception of executive function, significant for all domains (β's range -0.41 -0.08 all p<0.01), indicating a familial clustering of cognitive measures. The results of the cross-trait, within-patient analyses showed a significant association between all cognitive domains (but not executive function) and negative symptoms (β's -0.21 -0.08 all P<0.01). Speed of processing had the highest effect-size.

Discussion: The finding that neurocognitive performance and negative symptoms co-segregate in families, suggests that these traits share a common genetic liability. The cross-trait, cross-sibling design rules out confounding by illness related factors. The Symbol Digit Coding test (speed of processing) proved to be the most sensitive measure, with the highest predictive value for negative symptoms.

doi:10.1016/j.schres.2010.02.822

Poster 63
ADDRESS UNKNOWN: HOW A STORY REVEALS A THEORY OF MIND DEFICIT IN SCHIZOPHRENIA

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Background: The concept of Theory of Mind (ToM) refers to the cognitive capacity to represent one's own mental states and those of others. Few circumstances enable one to evaluate ToM with an ecological task. We tried to analyze the difficulties that SCZ patients have when they are asked to do some reading at home.

Methods: We used Address Unknown, a novella written by K. Kressmann Taylor. This brutal drama of betrayal and vengeance consists of the letters that art dealers and business partners Max Eisenstein, a German Jew living in USA, and Martin Schulse, a German during the early 1930s. It captures the growing alienation that the two one-time friends experience as the second is swept up in the patriotic frenzy accompanying Hitler’s rise to power. Then I asked patients with schizophrenia (N=21) questions, examining their understanding of the story and awareness of the brutal dénouement, which is linked to ToM: - Are the two people who are writing to each other still friends?(1 to 7: yes, a little, neutral, no longer, hate each other, want each other dead, ready to kill each other) - Does one of the characters fear the other one? (1 = no; 2=yes).Why does Max keep writing?: Out of affection, - Does the truth about the story become visible? (1= no; 2=yes). Do you think that this story is well written? (1= no; 2=yes). Is the story well written? (1= no; 2=yes). Can a writer write a story like this? (1= no; 2=yes). What do you think of the plot of this story? (1= no; 2=yes). Can a lover lose dignity in a story? (1= no; 2=yes). Do you think that the plot of this story is well written? (1= no; 2=yes). What do you think of the plot of this story? (1= no; 2=yes).

Results: Both groups had read the story and had a good idea of its context and characters. The answers were compared to control population. It is impossible to understand the plot of this epistolary novella and find it interesting unless one has the capacity to attribute mental states to other people. The answers to the questions about ToM show strong and significant differences.
between groups for the variables “interesting,” $t(38) = 7.78$ $p < .001$; “hate-friendship,” $t(29.19) = 7.20$ $p < .001$; “fears the other,” $t(31.87) = 5.70$, $p < .001$; “affection,” $t(27.10) = -7.72$, $p < .001$; and “hated,” $t(10.23) = 32.60$, $p < .001$.

**Discussion:** The ToM capacity appears to be lacking in the SCZ patients. The problem understanding the issue of someone else’s mental state also means that SCZ patients do not find this story very interesting. Simply reading a 20-page novella, became a cognitive task, with a good ecological component.

doi:10.1016/j.j.schres.2010.02.824

**Poster 64**
**A SELF ADMINISTERED "ECOLOGICAL" QUESTIONNAIRE (BRIEF-A) PROVIDES A SENSITIVE MEASURE OF EXECUTIVE DEFICITS IN SCHIZOPHRENIC SUBJECTS**

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**Background:** Cognitive deficits are considered core symptoms of schizophrenia and have been found to correlate with the functional outcome. Executive functions are among the most impaired cognitive domains. Cognitive characteristics are usually measured with neuro-cognitive tests (objective tasks) or cognition questionnaires. In schizophrenic patients cognitive questionnaires have been seldom used and have been often considered to be less sensitive to the deficits of these patients. However, objective tasks have also limitations such as: practice effect, low test-retest reliability, administration time and, most of all, lack of ecological relevance (i.e. unrelated to subjects’ everyday functioning). For these reasons, the use of complementary measures has been advocated Niendam et al. (2007) found that the Behavioral Rating Inventory of Executive Functioning (BRIEF - a questionnaire that assesses daily living behaviours associated with executive dysfunction) was, in its informant form, sensitive to deficits seen in adolescents at risk for psychosis. The aim of the present study is to investigate the ability of the self administered form of the BRIEF-A (A standing for adult version) to identify executive deficits in patients with schizophrenia.

**Methods:** Subjects: The BRIEF-A has been administered to 31 ambulatory schizophrenic subjects and 34 controls. Schizophrenic subjects were in full or partial remission for at least one month. Clinical assessment: We used the DIGS (Diagnostic Interview for Genetic Studies) to confirm diagnosis in patients and absence of any, past or present, DSM IV axis I diagnosis in controls. In schizophrenic subject, we assessed clinical symptoms with the any, past or present, DSM IV axis I diagnosis in controls. In schizophrenic subject, we assessed clinical symptoms with the any, past or present, DSM IV axis I diagnosis in controls. In schizophrenic subject, we assessed clinical symptoms with the any, past or present, DSM IV axis I diagnosis in controls.

**Results:** To calculate the group effect on BRIEF-A scores, we investigated the ability of the self administered form of the BRIEF-A to identify executive deficits in schizophrenic patients with schizophrenia.

**Discussion:** The differences observed are comparable with (or greater than) the differences reported in similar studies using objective tasks of executive functions (range of the estimated effect 0.8 to 1.0) or other cognitive functions (0.52 to 1.57) (Dickinson et al., 2007). Thus, our findings show that a self report instrument could provide sensitive measures of executive deficits in subjects with schizophrenia. This type of measures might be a useful addition to objective measures because it allows to explore different aspects of cognition and to overcome some of the limitations of the objective tasks. Further research is needed to address limitations of this study (e.g. relatively small sample sizes) and to explore relationship between the subjective and objective measures of executive functions in schizophrenic subjects.

**References**


doi:10.1016/j.j.schres.2010.02.825

**Poster 65**
**SOCIAL COGNITION IN “ULTRA HIGH RISK” (PUTATIVE PRODROMAL) AND FIRST EPISODE PSYCHOSIS COHORTS: PRELIMINARY FINDINGS ON DEGREE OF IMPAIRMENT**

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**Background:** Social cognitive skills have been shown to be impaired in those individuals with schizophrenia and in first episode psychosis (FEP) (Bertrand et al., 2007). Particular social cognition skills such as Theory of Mind (ToM) also appear to be impaired in individuals deemed at particular high risk for developing psychosis (Chung et al., 2008) but the degree of impairment relative to FEP has not been investigated. Neither has the performance on multiple domains of social cognition in "at risk" groups. We aimed to investigate two well established domains of social cognition in FEP and an "at risk" for psychosis group compared to healthy controls.

**Methods:** An established clinically "at risk" for psychosis population (known as “Ultra High Risk” or UHR) and FEP patients were recruited from a youth mental health service in Melbourne; healthy controls from the general community within the service catchment area. Two domains of social cognition were assessed in the three groups. ToM was assessed using the Hinting Task and emotion recognition (for both faces and voices) using the adult version of the Diagnostic Assessment of Non Verbal Accuracy (DANVA2). We also measured social functioning, neuropsychological abilities and psychopathology. We analysed the differences in the groups using Analysis of Variance (ANOVA) and a general linear model with IQ as a covariate in the analysis.

**Results:** We have currently recruited 20 UHR, 39 FEP patients and 21 controls to the study. Preliminary analysis shows that ToM performance as assessed by the hinting task is significantly worse in FEP than controls, with UHR’s having an intermediate degree of impairment (mean score: FEP 15.9, UHR 16.9, controls...
First-rank (passivity) symptoms describe a loss of clear boundaries between the self and others, or the perception that one’s thoughts and actions are “made” or controlled by others. Contemporary neuropsychiatric models propose that passivity symptoms result from deficits in internal forward model representations, although it is becoming clear that forward model mechanisms do not have unique access to representations about the self. Here, we present new empirical evidence from our group in which we conducted neurocognitive and neurophysiological assessments of patients with passivity symptoms, and an investigation into their social functioning.

Methods: 32 patients with, and 48 patients without, passivity symptoms took part in our studies, which included a neuropsychological battery. Patients were assessed with the clinician-rated Psychological Impairments Rating Schedule to examine patients’ non-verbal interaction skills.

Results: The results show that passivity symptoms were not associated with greater cognitive impairments suggesting that they do not arise because of compromised intellect. The neuropsychological investigations showed that patients with passivity were impaired on the P300 and self-correction measures on the antisaccade task, consistent with the proposal of deficits in sensory-motor body representations which lead to pivotal disturbances in body is experienced.
Background: Biases in cognition such as Jumping to Conclusions (JTC) and Verbal Self-monitoring (VSM) are thought to underlie the formation of delusions and hallucinations, and are evident in people at high risk of psychosis and in patients with schizophrenia. While there is evidence that the severity of both these biases is related to the intensity of psychotic symptoms cross-sectionally, the extent to which they represent a state or a trait dysfunction, and how they relate to one another and to clinical outcome, is unknown. A powerful means of addressing these issues is to examine these biases using a prospective design. The aim of the present study was to examine whether serial measures of these cognitive impairments predicted clinical outcome in people with prodromal signs of psychosis.

Methods: Twenty-three participants with an At Risk Mental State (ARMS) for psychosis were assessed at clinical presentation and when followed up 31 months later. Participants performed a modified version of the Beads (Jumping to Conclusions; JTC) task, a Verbal Self-Monitoring (VSM) task, and a working memory task (2-back). Task performance at baseline and the longitudinal change in performance over time were related to progressive changes in symptom severity and level of function, and to the incidence of psychosis.

Results: Baseline JTC task and VSM task performance were correlated ($r = 0.497, p = 0.03$) and change in JTC performance over time correlated with change in VSM task performance ($r = 0.595, p = 0.007$) as well as change in working memory performance ($r = -0.78, p = 0.013$). JTC performance was correlated with symptom severity in the ARMS (total Peters Delusional Index PDI) at baseline, ($r = -0.33, p = 0.019$) and at follow up ($r = -0.582, p = 0.037$). Four of 23 participants (17%) developed psychosis during the follow up period, while another 7 (30%) recovered from the ARMS, and 9 (39%) made a functional recovery (GAF>75). Normal JTC performance at baseline was associated with functional recovery ($p = 0.025$) and remission from the ARMS ($p = 0.035$) at follow up. Neither baseline performance nor change in performance on either task predicted transition to psychosis.

Discussion: While there have been previous longitudinal studies of neuropsychological performance in the ARMS, the present study is the first to have examined tasks that engage cognitive biases that have been specifically related to the development of psychotic symptoms. Our data indicate that the JTC and VSM biases are in fact related, suggesting they may engage a common underlying process that is impaired in the ARMS - both paradigms engage executive functions, and require the subject to make a decision under uncertain conditions. Furthermore, performance on these tasks predicts symptomatic and functional outcome in the ARMS; the absence of an association between these cognitive biases and the incidence of psychosis may reflect limited statistical power.

doi:10.1016/j.schres.2010.02.829

Poster 69
ARE COGNITIVE IMPAIRMENTS IN PATIENTS WHO ONLY SUFFER FROM DELUSIONS THE SAME AS SCHIZOPHRENIA PATIENTS? AN EXPLORATORY STUDY

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Background: The cognitive processes associated with delusions have been investigated, albeit generally within schizophrenia patients. Although the cognition of patients with delusional disorder has been examined in relation to that of schizophrenia patients, the studies are few and involved a heterogeneous schizophrenia group. Due to the diversity of symptom profiles within schizophrenia, previous studies prohibited a systematic examination of the associations between cognition and particular psychotic symptomatology.

Methods: Each patient completed a structured clinical interview, an extensive neuropsychological evaluation, and a neurological examination. After evaluation, a group of delusional patients for whom delusions were the only psychotic symptom ($n = 10$) were discriminated from the larger sample ($n = 780$) of psychotic patients based on specific symptomatology, as were two distinct groups of schizophrenia patients. The first schizophrenia group included patients who experienced hallucinations, but not thought disorder ($n = 88$). The second schizophrenia group included patients with thought disorder ($n = 45$). Unrelated healthy controls ($n = 629$) without a history of psychiatric illness or substance abuse were included as a normative comparison group.

Results: All patients demonstrated significantly impaired performance relative to controls on the Digit Symbol Substitution test of the WAIS and on verbal tests of episodic memory, fluency, and learning. However, on measures of estimated IQ (WAIS) and across cognitive domains measuring working memory (verbal and spatial) and reasoning/card sorting ability the performance of delusional patients did not differ from controls ($p>.1$); performance which contrasted that of schizophrenia patients. The performance of schizophrenia patients with hallucinations - but no thought disorder - was significantly lower than on nearly all tests ($p<.01$). Relative to delusional patients, the performance of this schizophrenia group was significantly lower on measures of working memory ($p<.05$) and processing speed ($p<.05$); furthermore, the estimated IQ (WAIS) of this schizophrenia group was significantly lower than the estimated IQ of delusional patients ($p<.01$). Additionally, the performance of schizophrenia patients with thought disorder – relative to delusional patients – was significantly impaired on all tests ($p<.05$).

Discussion: In our sample, cognition of delusional patients was relatively preserved; significant impairments were only observed on measures of processing speed, and on measures of verbal fluency and verbal memory. Schizophrenia patients were additionally impaired across several other cognitive domains, including working memory. These results reveal the cognitive profile of delusional patients notably differs from that of schizophrenia patients. Moreover, our results suggest that in the absence of other psychotic symptoms, delusions are associated with impaired temporal and temporal-frontal reliant cognition, whereas prefrontal reliant cognition is preserved - contrasting that of schizophrenia patients.

doi:10.1016/j.schres.2010.02.830

Poster 70
NEUROPSYCHOLOGICAL CHANGES OVER ONE YEAR IN YOUTH AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Both cross-sectional and longitudinal studies of individuals who eventually develop schizophrenia suggest a possible progression of neuropsychological (NP) impairment immediately preceding or accompanying illness onset. However, minimal data are available during the prodromal stage to clarify the timing or specific nature of such a decline.

Methods: We assessed NP functioning across six cognitive domains in a sample of 58 clinical high risk (CHR) youth relative to 32 demographically similar healthy comparison (HC) participants. Linear regression of HC one year scores was used to predict one year performance for CHR from baseline scores and relevant demographic variables. We used raw scores and MANOVAs of the standardized residuals to test for progressive impairment over time and possible illness progression.

Results: The CHR sample as a whole demonstrated NP functioning at one year that was significantly below predicted levels. Effects were largest and most consistent for a failure of normative improvement over time on tests of executive function. Using the highest level of positive symptom rating on the Structured Interview of Prodromal Syndromes (SIPS) as an indicator of possible increased risk or proximity to illness, we found a significantly greater discrepancy between observed and predicted one year performance in those presumably closest to illness onset. CHR who developed severe and psychotic level symptoms after baseline (n=10/58) demonstrated significantly greater discrepancy on verbal memory tests at one year than CHR who did not develop this level of symptoms.

Discussion: Findings support the presence of progressive NP impairment during the prodrome to psychosis that appears to be greatest for those at highest risk or seemingly closest to illness onset. However, much of the cognitive impairment associated with schizophrenia may be present even prior to the full expression of psychotic symptoms, at least in help-seeking CHR samples.

doi:10.1016/j.schres.2010.02.831

Poster 71
GENDER DIFFERENCES IN NEUROPSYCHOLOGICAL PERFORMANCE IN PATIENTS WITH FIRST EPISODE OF PSYCHOSIS

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Background: Although there are several studies examining neuropsychological performance in first onset psychosis, an unresolved question involves whether there are gender differences in cognitive performance in schizophrenia and other psychotic disorders.

Methods: We compared neuropsychological tests performances of males and females who had a consensus ICD-10 diagnosis of schizophrenia (M = 50; F = 28), bipolar/mania (M = 15; F = 22), depressive psychosis (M = 16; F = 23) with those of 177 healthy controls (M = 78; F = 98). Data was collected on six cognitive domains: (1) memory (verbal and visual) (2) WAIS-R academic verbal abilities (3) attention, concentration and mental speed (4) executive functions and working memory (5) language, and (6) visual constructive/perceptual abilities. Premorbid intelligence (NART), current full-scale IQ, performance IQ and verbal IQ were also assessed.

Results: There was strong evidence for disorder specific gender differences in neuropsychological performance. Females with psychotic depressive disorder performed worse than males. Differences in neuropsychological performance between males and females with bipolar/manic disorder were restricted to language. By contrast in the schizophrenia group, females performed worse than men on the majority of measures but the differences were not significant. Symptoms dimensions did not contribute to observe gender differences.

Discussion: In our epidemiological study, gender related factors appear to modulate the severity of cognitive deficits in depressive psychosis patients.

doi:10.1016/j.schres.2010.02.832

Poster 72
MOTOR PERFORMANCE IN PATIENTS WITH SCHIZOPHRENIA AND SCHIZOPHRENIA SPECTRUM DISORDERS AFTER FIRST PSYCHOTIC EPISODE

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Background: Existing evidence suggests that psychomotor impairment is a prominent feature of schizophrenia which may already be present long before the onset of psychosis. Schizophrenia spectrum disorders are generally characterized by brief psychotic and/or affective episodes, usually with favourable outcomes and with less cognitive deteriorations. However, so far no study has directly compared psychomotor impairment in first episode schizophrenia to psychomotor impairment in schizophrenia spectrum disorder patients. We use a test developed by A.R. Luria, whose concept of higher cortical functions as compound dynamic systems includes a systematic qualitative analysis of core symptoms and accompanying deficits such as kinetic apraxia. The central postulate of the concept is that the organization of movements in time, the programming of movements, and the exertion of control over performance of the movement program require the integration of frontal and premotor cortical areas.

Methods: A Fist-Edge-Palm test neurocognitive battery based on the systematic approach of A.R. Luria was used to describe performance decrements in the conjugate motor probe in 57 first episode patients with schizophrenia (F20.0, F20.2, F20.3, F20.6; mean age 23.89 ± 5.86 years, 38% female, 13.92 ± 1.81 years of education), 32 first episode patients with schizophrenia spectrum disorders (schizotypal disorder F21; schizoaffective disorder, F25; mean age 25.5 ± 9.51 years, 56% female, 13.03 ± 2.17 years of education) and 51 normal controls (mean age 28 ± 6.5 years, 68% female, 13.4 ± 0.9 years of education). Most patients (N = 80) were receiving monotherapy with atypical antipsychotics, and 9 received combination treatments. 67.53% and 69.19% of patients with schizophrenia and schizophrenia spectrum, respectively, had received neuroleptics for on average 3 weeks, and 11 patients (7 schizophrenia patients and 4 schizophrenia spectrum disorder patients) were drug naive. For the Fist-Edge-Palm test, categorical ratings were performed on a 4-point rating scale (0 — no mistakes, 1—slow correct performance with single mistakes while speeding-up, 2—occasional errors, 3 — stable errors without correction).
Results: Performance in the Fist-Edge-Palm test was seen to decrease by 0.836 SD in schizophrenia patients as compared to healthy controls (z = 7.42, p < 0.001) (see Fig. 1). Comparison between schizophrenia patients and schizophrenia spectrum groups showed worse performance in patients with schizophrenia (z = 2.30, p = 0.020). Qualitative analysis confirmed that all patients were more likely to show difficulties in assimilation of the task program even with verbalization of hand positions. All patients also experienced deautomatization. Over 75% of patients exhibited scores of 1 and 2. In controls, we only found single mistakes (17%) when subjects were asked to go faster. However, no correlations between test performance, symptom severity, and medication were detected.

Discussion: This study shows that Luria’s concept of conjugate motor performance can be used to demonstrate a higher degree of impairment in first episode schizophrenia patients compared with first episode schizophrenia spectrum disorder patients, who in turn performed worse than healthy controls matched for age and years of education. Furthermore, the differences in test results were not associated with positive or negative symptoms in schizophrenia patients, suggesting that complex motor performance is specifically impaired in schizophrenia patients.

doi:10.1016/j.schres.2010.02.833

Poster 73
VERBAL EPISODIC MEMORY IN FIRST EPISODE AND AT RISK MENTAL STATE FOR PSYCHOSIS PATIENTS COMPARED TO DEPRESSIVE PATIENTS AND HEALTHY CONTROLS

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Background: The Early Detection of Psychosis Clinic in Basel identifies patients in an “at risk mental state for psychosis” (ARMS) based on clinical signs with the aim to further improve the detection of patients in the prodromal phase of psychosis. Many clinical signs of the prodromal phase of schizophrenia are unspecific and can also occur in depressive disorders. A promising approach to improve the specificity of differential diagnosis is the evaluation of typical cognitive patterns. Many studies have shown that episodic memory deficits are present in the early phase of schizophrenia. In the present study we evaluated verbal episodic memory of first episode (FE) patients, ARMS patients that convert to psychosis (ARMS-T) and ARMS that do not (ARMS-NT) compared to depressive (DC) and healthy controls (HC). Our hypothesis was that FE patients are most severely impaired in verbal episodic memory, followed by ARMS-T; DC were expected to be less impaired than the other groups of patients and ARMS-NT patients to be ranged between DC and ARMS-T.

Methods: 41 HC, 30 DC, 42 FE, 26 ARMS-NT and 14 ARMS-T were assessed with parameters of the California Verbal Learning Test (CVLT). Overall memory function was tested with MANOVA. Comparisons of patients with HC were made using linear regression models. We used ANOVAS with Helmer contrasts to evaluate the expected order of performance in memory functions in patients (HC>DC>ARMS-NT>ARMS-T>FE). Potential confounding factors age, gender, education, medication and use of cannabis were controlled.

Results: Overall the memory functions differed among groups (MANOVA, p < .01). DC and ARMS-NT were not significantly impaired in any tested parameter compared to HC. FE patients were significantly impaired in all test parameters (p’s < .05) except for the first learning trial where they showed a trend (p = .08). ARMS-T showed significant impairments in the sum of learning trials (p = .05), the second (p = .06), third (p = .06) and fourth (p = .05) learning trials and the long delay cued recall (p = .04). Helmert contrasts confirmed the expected order in severity (HC>DC>ARMS-NT>ARMS-T>FE) in all tested parameters (p’s < .05) except for the first learning trial where a trend (p < .06) was observed.

Discussion: The expected order in severity of memory dysfunction (HC>DC>ARMS-NT>ARMS-T>FE) could be confirmed. DC had preserved memory functions in all test parameters while ARMS-T showed impairment in learning trials and long delay cued recall. These parameters might be helpful in the differential diagnosis between ARMS-T and depressive patients.

TEST

doi:10.1016/j.schres.2010.02.834

Poster 74
A SNAP25 PROMOTER VARIANT IS ASSOCIATED WITH SCHIZOPHRENIA AND A DISTURBED SNAP25/SNAP25A EXPRESSION RATIO IN PATIENTS

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Background: The implication of genetic factors in schizophrenia is now well established (Cardno et al, 1999). Abnormalities in neural connections and the neurotransmitter system appear to be involved in the pathophysiology of schizophrenia. The synaptosomal-associated protein SNAP25, a presynaptic plasma membrane protein essential for the triggering of vesicular fusion and neurotransmitter release (Sorensen et al., 2003), expression may be decreased in schizophrenia (Fatemi et al., 2001). It is therefore a good candidate gene in this disease.

Methods: We genotyped 7 tagging SNPs in SNAP25 in a sample of 288 schizophrenic patients consecutively admitted to three French university-affiliated psychiatry departments and 137 unaffected controls. All the subjects were interviewed by trained psychiatrists, using the French version of the Diagnostic Interview for Genetic Studies. Only controls, with no personal or family (first degree) history of axis I psychiatric disorders were included. All patients and controls were Caucasian of French descent. In addition, we analyzed the expression level of the two SNAP25 isoforms in 30 schizophrenic patients and 30 controls brains. All RNA, cDNA and DNA were donated by the Stanley Medical Research Institute, as part of the Array Collection that consisted of samples from the dorsolateral prefrontal cortex (Brodman’s area 46).

Results: We showed that one variant (rs6039769), located in the promoter region, was associated with schizophrenia (Genotype association analysis: p = 0.004) with a recessive model explaining the best this association (Recessive model analysis:
Comparing schizophrenic patients and controls brains, no difference in expression level was observed neither for SNAP25a nor for SNAP25b. In schizophrenic patients we found a significant difference comparing the ratio SNAP25b/SNAP25a in each genotype group for the rs6039769 variant (p = 0.04). The A/A genotype carriers had a much lower ratio than the A/C and C/C genotypes carriers. We found similar results using ANOVA with Postmortem interval, Refrigerator Interval, Brain pH and Sex as covariates. This association was not found in controls.

**Discussion:** This SNAP25b/SNAP25a ratio is known to be modified and inverted at the teenage, a high risk period for schizophrenia onset. We hypothesize that the inversion of this ratio could be impaired by the presence of genetic variants in the SNAP25 gene. This impairment might be implicated in schizophrenia physiopathology. Further analyses of this gene, as well as analysis of genes encoding for the SNAP25 protein partners, are required to understand the impact of such molecular mechanisms in schizophrenia.

**References**


**Poster 75**

**ASSOCIATION BETWEEN THE SELENBP1 GENE AND SCHIZOPHRENIA IN A JAPANESE POPULATION**

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**Background:** The selenium binding protein 1 (SELENBP1) gene is considered as a candidate gene which contributes the pathogenesis of psychiatric disorder. A previous study showed that the expression of the SELENBP1 gene was increased both in the blood and brain of the patients with schizophrenia by microarray. They also demonstrated that SELENBP1 mRNA was up-regulated in schizophrenia brains using quantitative PCR. In the present study, we investigated the association between the LIF gene and the patients with schizophrenia in a Japanese population.

**Methods:** Subjects were comprised of 487 patients with schizophrenia and 470 age- and gender-matched healthy controls. We genotyped the four single nucleotide polymorphisms (rs1078804, rs2800953, rs744459 and rs2769265) of the SELENBP1 gene. Genotyping was performed by TaqMan technology on a Stratagene Real Time QPCR System Mx3000P.

**Results:** Rs1078804 showed monomorphism in the present Japanese population. We found a significant association between hebephrenic schizophrenia and genotypic frequency of rs2800953 (P = 0.037) and between paranoid schizophrenia and allelic frequency of rs2800953 (P = 0.048). But, there were no significant differences in genotypic or allelic distribution both of rs744459 and rs2769265 between schizophrenia and control. Estimation of the pairwise LD between the three polymorphisms of the SELENBP1 gene revealed that rs744459 and rs2769265 showed strong LD. We then analyzes the haplotype distribution which showed no significant differences between schizophrenia and control.

**Discussion:** The present study suggested that the SELENBP1 gene may contribute the susceptibility to schizophrenia. Recently, Kanazawa et al. reported that rs2800953, one of four haplotype-tagging SNPs, and two different two-marker haplotypes showed nominally significant association with the patients of schizophrenia in a Han Chinese population. Our result in Japanese patients is consistent with their result which showed a significant association of the rs2800953 of the SELENBP1 gene but failed to replicate the association of two different two-marker haplotypes. Our sample showed monomorphism at rs1078804 of the SELENBP1 gene and did not show a strong LD between the four polymorphisms except for rs744459 and rs2769265. The differences may due to the population differences or our sample size was not enough large to compare. Further studies by examining of additional polymorphisms in large sample populations are necessary to understand the physiological roles of the SELENBP1 gene.

doi:10.1016/j.schres.2010.02.835

**Poster 76**

**NO ASSOCIATION ANALYSIS BETWEEN SHC3 AND SCHIZOPHRENIA IN A JAPANESE POPULATION**

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**Background:** Src homology 2 domain containing transforming protein 3 (SHC3) is one of the Shc-like adaptor protein family, which serve to link a number of tyrosine kinase receptors with multiple intracellular signaling cascades, and expressed pre-dominantly in the mature neurons of the central nervous system (CNS). The animal study suggested that SHC3 involve in the regulation of NMDA receptor function in hippocampus and affect learning and memory. In addition, recent genetic study reported significant association between SHC3 and nicotine dependence. The roles of SHC3 in human brain may contribute to the symptomatology of patients with schizophrenia. Therefore, we conducted gene-based association study between SHC3 and schizophrenia in a Japanese population.

**Methods:** The subjects in the association analysis were 726 schizophrenia patients and 758 healthy controls. We consulted HapMap database and selected 10 tagging SNPs using tagger program by haploview software. SNPs genotyping was used by TaqMan assays. Genotype deviation from the Hardy-Weinberg equilibrium (HWE) and allele/genotype-wise analysis was evaluated by the chi-square test. Haplotype frequencies were estimated and log likelihood ratio tests were performed for
global p-values with the COCAPHASE program. Written informed consent was obtained from each subject. This study was approved by the ethics committees at Fujita Health University, Nagoya University Graduate School of Medicine.

**Results:** Genotype frequencies of subjects and controls did not deviate significantly from HWE. There was no significant association between all tagging SNPs and SHC3 in the allele/genotype and haplotype-wise analysis.

**Discussion:** In conclusion, we suggest that SHC3 is unlikely to contribute to susceptibility to schizophrenia in the Japanese population. However, it will be necessary to validate or replicate our association in other, larger population samples and to evaluate between rare variants with functional and schizophrenia.

doi:10.1016/j.schres.2010.02.837

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**Poster 77**

**INFLUENCE OF GENETIC VARIATIONS OF FTO AND SH2B1 GENES ON WEIGHT GAIN INDUCED BY ANTIPSYCHOTICS**

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**Background:** Weight gain is one of the major side effects of antipsychotic drugs. The mechanism underlying antipsychotic-induced weight gain remains unclear. The great differences between individuals suggest that genetic factors could play a significant role in this process and make some patients more susceptible to weight increase. In recent genome-wide association (GWA) studies variants of FTO and SH2B1 genes have been strongly associated with obesity in general population. The aim of this study was to determine whether weight increase during the first year of antipsychotic treatment was influenced by the rs9939609 single nucleotide polymorphism (SNP) of fat mass and obesity associated (FTO) gene and the rs7498665 of (SH2B adapter protein 1) SH2B1 gene.

**Methods:** We carried out a prospective study on 239 first episode psychiatric patients. Weight measurements were obtained prior to starting medication and after one year. Patients were genotyped for rs9939609 using Mass-array iPLEX system and rs7498665 was genotyped using SNPlex multiplex system. Analyses of covariance were carried out to determine the association between weight gain and genotypes. The sample size of our study, based on an additive model, provides 80% power to detect an effect of ≥ 2.8 kg, assuming an α = 0.05 and a MAF> 30% (Quanta program).

**Results:** 85% of the patients completed the follow-up at 1 year. Rs9939609 was successfully genotyped in 84.9% and rs7498665 in 93% of the samples. At baseline, patients with the AA risk genotype of the FTO rs9939609 variant had higher body mass index (BMI) than the AT/TT group (24.2 ± 3.8 vs 22.8 ± 3.3; F = 5.744; p = 0.018) as described in previous studies. After one year of antipsychotic treatment the magnitude of weight increase was similar in the three genotype groups. No association was found between rs7498665 and BMI at baseline or weight gain during the first 12 months of antipsychotic therapy.

**Discussion:** It appears that genetic variations in FTO and SH2B1 genes that have been consistently associated with obesity in different populations do not have a relevant clinical influence on weight gain induced by antipsychotics.

doi:10.1016/j.schres.2010.02.838

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**Poster 78**

**THE EFFECT OF THE COMT VAL158MET POLYMORPHISM ON COGNITIVE STABILITY AND COGNITIVE FLEXIBILITY**

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**Background:** Dopamine in prefrontal cortex (PFC) modulates core cognitive processes, notably working memory and executive control. Dopamine regulating genes in PFC - specifically Catechol-O-Methyltransferase (COMT) Val158Met - are crucial to understanding the molecular genetics of cognitive function and dysfunction. A popular mechanistic account of the COMT-Val158Met effect associates the Met allele with increased tonic dopamine transmission underlying maintenance of relevant information, and the Val allele with increased phasic dopamine transmission underlying the flexibility of updating new information. We tested the explanatory capability of this hypothesis by predicting that Val carriers would display poorer performance when the maintenance component was taxed, while Met carriers would be less efficient when rapid updating was required.

**Methods:** Using a parametric Stroop task that manipulated level of required cognitive stability and flexibility, we examined performance of patients with schizophrenia (n = 67) and healthy controls (n = 186) genotyped for the Val/Met variation.

**Results:** In both groups we found a Met advantage for tasks requiring cognitive stability but also a high level of cognitive flexibility, but no COMT effect when a moderate level of cognitive flexibility was required.

**Discussion:** Our results do not support a simple stability/flexibility model of dopamine COMT Val/Met effects and underscore the need for a more sophisticated experimental operationalization of these cognitive components.

doi:10.1016/j.schres.2010.02.839

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**Poster 79**

**INTERACTIVE EFFECTS OF COMT AND MTHFR MODERATE STRESS SENSITIVITY IN PSYCHOSIS**

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Background: COMT has long been considered as a possible candidate gene for schizophrenia. Previous studies indicated a possible trade-off effect of COMT with increased COMT activity (Val/Val genotype) resulting in compromised cognition but increased resilience to stress, and decreased COMT activity (Met/Met genotype) resulting in improved cognition but greater reactivity to stress. Part of the phenotypic variability associated with COMT Val158Met has been proposed to be caused by variations in genes that collaborate with COMT, or modify COMT function. A strong candidate gene is the gene encoding for methylenetetrahydrofolate reductase (MTHFR). MTHFR catalyzes the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate in the one-carbon metabolism, which has an important role in DNA methylation. The two common functional polymorphisms, C677T and A1298C, both result in reduced MTHFR enzyme activity. We hypothesized that interaction between MTHFR and COMT Val158Met would predict psychotic reactivity to stress in patients with non-affective psychotic disorder.

Methods: A sample of 98 patients with non-affective psychotic disorder and 118 controls were genotyped for MTHFR C677T, MTHFR A1298C, and COMT Val158Met (rs48180, rs1801131, and rs1801133). Psychotic reactivity to daily life stressors was measured with the experience sampling method.

Results: MTHFR C677T genotype moderated the interaction between COMT Val158Met genotype and stress in patients (p<0.0001), but not in controls (p=0.68). Carriers of MTHFR 677 T-allele and COMT Met/Met displayed the largest psychotic reactivity to daily life stressors.

Discussion: The results indicate for the first time that MTHFR modulates the effect of COMT genotype on psychotic reactivity to daily life stress, and that this may selectively occur in patients. These findings are in line with an earlier finding on moderation of MTHFR on COMT effects on cognition in schizophrenia patients and increase our understanding of the molecular mechanisms underlying COMT’s trade-off effects. Although replication of our findings is warranted, the data suggest that MTHFR-dependent molecular processes, such as the one carbon metabolism and DNA methylation, affect functioning of COMT in schizophrenia.

Poster 80

FOXP2 AND SCHIZOPHRENIA

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Background: Schizophrenia is considered a disease that only affects humans. Taking this into account, previous works have reported signals of positive selection specific to the human lineage for schizophrenia-associated genes. In the FOXP2 gene, there are two important features that contribute to consider this gene a likely candidate gene for schizophrenia vulnerability: FOXP2 is the first gene related to a language disorder; and it has been subject to positive selection in the human lineage.

Methods: We analyzed 27 SNPs located in the region of FOXP2 in a cohort of 293 patients with schizophrenia and 340 controls. In a subsample, the potential expansion of three trinucleotide tracts in FOXP2 was also screened. Methylation analysis of a CpG island located in the first exon of the gene was performed in post-mortem brain samples, as well as qRT-PCR analysis.

Results: A significant association was found for SNP rs2253478 and the Poverty of speech (p=0.038 after Bonferroni correction). Significant associations were also found for rs7803667/ta rs10447760/crs923875A/rs2396722c/rs2396753A haplotype, and for allelic frequencies of rs2396753 and rs17137124, when patients with auditory hallucinations were compared with controls. In methylation and expression analyses, differences between patients and controls were found in samples from the parahippocampal gyrus.

Discussion: Our data provide evidence of the association of a polymorphism in FOXP2 and one of the common language deficits in patients with schizophrenia. Our results are consistent with the hypothesis that FOXP2 plays a role in the vulnerability to schizophrenia through its implication in language deficits.

doi:10.1016/j.schres.2010.02.841

Poster 81

PLASMA LEVELS AND GENETIC POLYMORPHISMS OF INTERLEUKIN 6 AND INTERLEUKIN 10 IN SCHIZOPHRENIA

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Background: A number of studies suggest that immune system dysregulation plays a role in the pathogenesis of schizophrenia. Alterations of the cytokine levels in serum or plasma, such as elevated interleukin 6 (IL-6), represent a common finding in schizophrenia. Genetic studies have also been carried out, some showing association of the interleukin (IL) gene polymorphisms with schizophrenia. However, the genetic findings are inconsistent across studies, and it remains to be elucidated whether the cytokine imbalance in schizophrenic patients is genetic or acquired. We measured plasma cytokine levels (IL-2, IL-4, IL-6, IL-10, tumor necrosis factor, interferon-gamma, IL-17A) in subjects with schizophrenia and examined whether the plasma levels were associated with genetic polymorphisms.

Methods: A total of 113 schizophrenic patients (mean age 39, 55 males) and 113 controls matched for age and sex (mean age 39, 55 males) were recruited for this study. All subjects were biologically unrelated Japanese. Plasma levels of IL-6 and IL-10 were determined by a BD(TM) Cytometric Bead Array (CBA) system using BD FACSCanto II. Data analysis was done by the FCAP Array software. Seventeen tagging single nucleotide polymorphisms (SNPs) of the IL-6, IL-6 receptor (IL-6R), IL-10, and IL-10 receptor (IL-10R) genes were selected and genotyped by using Taqman 5’ allelic discrimination assay.

Results: Significantly increased plasma levels of IL-6 (p=0.006) and IL-10 (p<0.0001) were found in schizophrenic subjects compared with controls. No significant difference in any of the allele frequencies of the examined genes was found between schizophrenics and controls. However, individuals carrying the Asp358 allele of the IL-6R gene were significantly more common in schizophrenics than in controls (p=0.03). The mean plasma level of IL-6 in the control group was highest in Ala358 homozygotes and lowest in Asp358 homozygotes (p=0.016, Kruskal Wallis test), but such an association was not observed in subjects with schizo-
Background: A major hypothesis is that tardive dyskinesia (TD) is a pharmacogenetic disease presenting interaction of conventional antipsychotic exposure with individual genetic variation mediates risk. Several results in the literature relate glial cell line antipsychotic exposure with individual genetic variation mediates pharmacogenetic disease presenting interaction of conventional antipsychotics. TD was assessed using Abnormal Involuntary Movement Scale (AIMS) or Hillside Simpson Dyskinesia Scale (PDGFRA, PDGFRB and adaptor protein SHB). Considering evidences of GDNF effect on Parkinson’s disease and dopaminergic neuron survival as well as GDNF alpha-receptor 2 (GFRA2) molecular findings, we hypothesized that variants in GFRA2 gene could play a role in the genetic susceptibility of TD.

Methods: Local Ethics Committees have approved this protocol and Consent Form was obtained from all subjects. Two hundred and sixteen subjects were recruited from the Centre for Addiction and Mental Health, Case Western Reserve and the Hillside Hospital. All subjects presented Caucasian ethnic Background and sixteen subjects were recruited from the Centre for Addiction and Mental Health that were African-American. All patients had at least 1 year of cumulative treatment with typical antipsychotics. We observed significant power in our sample to detect the positive associations. Ethnic population stratification does not seem to be an important limitation in this study as the results are reproducible if excluded the African-American Background subjects. Several results in the literature relate GDNF signalling pathway with neuroprotective effects in, at least, central dopaminergic neurons and spinal motoneurons. Although there is no reported functionality for the variants evaluated in this study, this study further support an effect of GDNF pathway in neurological conditions.

Discussion: Our results implicate GFRA2 polymorphic variants with reduced risk for developing TD in schizophrenia subjects taking antipsychotics. We observed significant power in our sample to detect the positive associations. Ethnic population stratification does not seem to be an important limitation in this study as the results are reproducible if excluded the African-American Background subjects. Several results in the literature relate GDNF signalling pathway with neuroprotective effects in, at least, central dopaminergic neurons and spinal motoneurons. Although there is no reported functionality for the variants evaluated in this study, this study further support an effect of GDNF pathway in neurological conditions.

Results: There were significantly more males in the patient group (80 v. 54% male, p<0.0001) and the unstandardised residual of brain volume corrected for age, sex and intracranial volume was significantly lower in the patient group (-11.0 v. 11.7, p<0.0001). FGF14 SNPs are overrepresented in the list of highest main effects (brain volume regardless of disease status). From this large gene we used 91 SNPs. It has previously been implcit in movement disorders in mice. In the list of highest interaction effects (brain volume difference in patients) 3 out of 5 SNPs are related to platelet derived growth factor function (PDGFRA, PDGFRB and adaptor protein SHB).

Discussion: After correction for 83 genes several trends are noticeable, but no significant results were found. Although this is a relatively large sample of genotyped subjects with MRI scans, we cannot draw firm conclusions. Therefore a replication of the top SNPs in an independent sample is needed to determine the effects of FGF genes on brain volume in schizophrenia patients and controls.

doi:10.1016/j.schres.2010.02.843

Poster 83
FIBROBLAST GROWTH FACTORS AND BRAIN VOLUME IN SCHIZOPHRENIA PATIENTS AND HEALTHY CONTROLS

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Background: There is convincing evidence for an involvement of fibroblast growth factors (FGFs) in schizophrenia (Terwisscha van Scheltinga et al., 2009). FGFs regulate growth, maintenance and repair of neuronal tissue. This makes the genes in the FGF system plausible candidate genes for the smaller brain volume seen in schizophrenia patients and their relatives relative to control subjects. We use total brain volume as an endophenotype of schizophrenia, since it has a 90% heritability, can be reliably measured, cosegregates with illness in families and is relatively independent of clinical state (van Haren et al., 2008).

Methods: Using online genomic databases 1231 SNPs in 22 FGFs, 5 FGF receptors and 56 interacting genes were selected and genotyped using the Illumina HumanHap550 beadchip. A 1.5T MRI scan of the brain was acquired for 169 schizophrenia cases and 159 healthy controls. Total brain volume was estimated and corrected for age, sex and intracranial volume. A linear regression analysis was performed, using disease status as an independent variable.

Results: There were significantly more males in the patient group than in the control group (80 v. 54% male, p<0.0001) and the unstandardised residual of brain volume corrected for age, sex and intracranial volume was significantly lower in the patient group (-11.0 v. 11.7, p<0.0001). FGF14 SNPs are overrepresented in the list of highest main effects (brain volume regardless of disease status). From this large gene we used 91 SNPs. It has previously been implicated in movement disorders in mice. In the list of highest interaction effects (brain volume difference in patients) 3 out of 5 SNPs are related to platelet derived growth factor function (PDGFRA, PDGFRB and adaptor protein SHB).

Discussion: After correction for 83 genes several trends are noticeable, but no significant results were found. Although this is a relatively large sample of genotyped subjects with MRI scans, we cannot draw firm conclusions. Therefore a replication of the top SNPs in an independent sample is needed to determine the effects of FGF genes on brain volume in schizophrenia patients and controls.

doi:10.1016/j.schres.2010.02.844
**Poster 84**

ASSOCIATION STUDY OF CNVS WITH BRAIN VOLUME AND BRAIN VOLUME CHANGE OVER 5 YEARS IN SCHIZOPHRENIA PATIENTS AND HEALTHY CONTROLS


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**Background:** Genetic studies of schizophrenia have revealed that not only common risk alleles contribute to this disease, but also rare copy number variations (CNVs). CNVs are duplicated or deleted chromosome regions that may disrupt genes or alter gene expression. Novel CNVs were shown to be more frequent in schizophrenia patients (15%) and childhood-onset schizophrenia patients (20%) than in healthy controls (5%) (Walsh et al., 2008). We use total brain volume as an endophenotype of schizophrenia, since it is associated with this illness and has a 90% heritability. Moreover, it can be reliably measured, cosegregates with illness in families and is relatively independent of clinical state (van Haren et al., 2008). CNVs are thus more common in schizophrenia patients, and these patients have smaller brain volumes. We therefore hypothesized that CNVs are more common, and disrupt more genes, in (1) patients with small brain volumes compared to patients with larger brain volumes or healthy controls, and (2) in patients with a large average brain volume change over a 5 year period, which also has a high heritability (66%) (Brans et al., 2008).

**Methods:** A 1.5T MRI scan of the brain was acquired for 179 schizophrenia patients and 175 healthy controls. Total brain volume was estimated and corrected for age, sex and intracranial volume, saving the unstandardized residuals. For 64 patients and 65 controls a 5-year follow-up MRI scan was available. Mean brain volume change per year was calculated. Subjects were genotyped using the Illumina HumanHap550 beadchip. CNV data were derived from the SNP data using QuantSNP. Deviations in B allele frequencies (ratio of intensity of fluorescent signals from one alleleic probe to another) for at least 20 consecutive SNPs were counted as CNVs (either deletion or duplication). Refseq genes within 50 kb of the CNV borders were counted. Brain expression of these genes was estimated using expressed sequence tag data of brain tissue available in the UCSC browser. A linear regression analysis was performed with the 

**Results:** The number of CNVs (ranging 0-8; mean 2.32), the number of CNVs affecting genes (0-6; mean 1.2), the number of genes affected by CNVs (0-43; mean 3.11) and the number of brain expressed genes affected by CNVs (0-27; mean 1.47) were used as genotypic measures. None of these showed a significant correlation with brain volume or with brain volume change over five years in the total group, nor in the patient and the control subgroups.

**Discussion:** Analyzing a quantitative endophenotype is expected to have more power than a case-control analysis in the dissection of complex disorders. However, MRI data are usually more difficult to obtain than case-control status, which results in relatively small sample sizes. Our data suggest that common CNVs do not exert major effects on brain volume or brain volume decline in schizophrenia. We cannot rule out small effects, and a replication should be performed before definitive conclusions can be drawn.

**Poster 85**

PRELIMINARY ASSOCIATION OF ESR1 GENETIC VARIATION WITH SCHIZOPHRENIA AND WORKING MEMORY PERFORMANCE

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**Background:** Estrogen receptors alpha (ESR) are involved in cognitive functions like working memory, and may play a role in modulation of pathophysiology in schizophrenia. Earlier evidence suggests that SNPs in the gene coding for ESR (ESR1) are associated with binding affinity and mRNA expression as well as with schizophrenia. Consistently, previous studies have demonstrated a reduction in hippocampal and cortical ESR1 mRNA, in patients with schizophrenia. Aim of the present study was to investigate the association between 4 ESR1 SNPs and their haplotypes with working memory performance (N-Back) and diagnosis of schizophrenia.

**Methods:** 284 subjects, 123 healthy controls (68 F and 55 M, mean age ± SD, 27.8 ± 7.5) and 161 patients with schizophrenia (42 F and 119 M, mean age ± SD, 33.7 ± 9.9) were recruited and genotyped for ESR1 rs2228480, rs3798577, rs827421, and rs988328. All genotypes were in Hardy-Weinberg equilibrium (p > 0.1). Working memory was evaluated with the N-Back task which provides increasing cognitive loads (1- and 2-Back). Performance data were recorded in terms of correct responses (accuracy). Stepwise linear regression analyses were performed in HelixTree to evaluate the association between ESR1 SNPs, haplotypes and the phenotypes of interest in the overall sample, and separately in female and male groups.

**Results:** In the overall sample, the major allele (G) of ESR1 rs2228480 was associated with diagnosis of schizophrenia (p = 0.04) and reduced working memory performance (1-back: p = 0.03 and 2-back: p = 0.06). In the female group we also found that the G allele was associated with diagnosis of schizophrenia (p = 0.03) and reduced working memory performance (1-back: p = 0.04; 2-back: p = 0.001). Moreover, in this latter group the GGAG haplotype resulted associated with diagnosis of schizophrenia (p = 0.0002) while the GGA haplotype was associated with reduced performance at 1-back (p = 0.0031). Finally, in the male group we found only an association of the GGA haplotype with diagnosis of schizophrenia (p = 8.59-5; OR = 5.09).

**Discussion:** Even though the number of subjects included in the present study is relatively small and requires replication, our data suggest that these ESR1 SNPs and haplotypes may be over-represented in patients with schizophrenia, and may affect working memory performance.

**Poster 86**

DISC1 CONDITIONED GENOME-WIDE ASSOCIATION STUDY OF PSYCHOSIS PRONENESS IN A LARGE FINNISH BIRTH COHORT

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Background: DISC1 is currently one of the most promising candidate genes for schizophrenia and other major mental illnesses. We have previously detected association between DISC1 and measures of social and physical anhedonia in the large birth cohort of Northern Finland 1966 (NFBC66). In the present study, we performed a genome-wide association study conditioned on these previously recognized DISC1 variants in this same cohort, for the outcome measures Revised Social Anhedonia Scale and Revised Physical Anhedonia Scale (PHAS). With these genetically more homogeneous stratified samples we are more likely to recognize variants of small effect size that are related to psychosis proneness and potentially interact with DISC1. This approach of using quantitative phenotypes assessed in large population cohorts can be a powerful way of identifying genes that predispose to related clinical disorders, in this case psychosis.

Methods: We utilized the large birth cohort collected in Northern Finland 1966 (NFBC66). From the original sample (N = 12 058), 4561 individuals attended a 31-year follow up and provided data for the present study. The sample has been genotyped using the Illumina Infinum Assay and HumanHap 370 K marker set. For the statistical analyses, the sample was stratified based on the DISC1 variants. Carriers of risk and protective DISC1 variants were analyzed separately (N = 3 054 and N = 962 respectively). The remaining individuals not carrying either of the variants were analyzed as one group (N = 545).

Results: No markers were significant at the genome-wide level. However, suggestive evidence for association with biological relevance to psychosis and the DISC1 pathway was noted. The regions of interest were chromosomes 2q21.3 (risk model, best P = 1.84E-06) and 12q24.21 (neutral model, best P = 2.24E-06) for PHAS. Located at these loci are the LCT gene and hsa-mir-620 microRNA, respectively. Additional Gene Ontology (GO) analysis demonstrated that PHAS is associated with genes enriched in estrogen related pathways (risk model, GO term: response to estrogen stimulus, P = 0.00017, permuted P = 0.0037).

Discussion: Recently, W. Hennah and D. Porteous reported variants in DISC1 and DISC1 binding partners, PDE4B, PDE4D, NDE1, and NDE1, having a significant impact on expression levels of numerous genes, including LCT, involved in DISC1 related pathways. Intriguingly, carbohydrates that include galactose (produced by LCT) have been implicated in neuronal development, learning and memory. The microRNA hsa-mir-620 has a significant enrichment of predicted target sites in, and therefore is thought to regulate the expression of, genes involved in nervous system development. It is also predicted to target LCT. Our findings are suggestive of the potential complex genome wide interplay between variants that increase risk to psychosis with DISC1 proving to be the key to these discoveries.

doi:10.1016/j.schres.2010.02.847

Poster 87
COGNITIVE PERFORMANCE IN THE SCHIZOPHRENIA SPECTRUM: THE INFLUENCE OF COMT AND BDNF POLYMORPHISMS

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Background: Individuals with schizophrenia and other psychotic disorders often manifest signs of cognitive impairment prior to the onset of their illness and some aspects of cognitive disturbance worsen with the onset of psychosis. Recent findings from genetic research indicate that vulnerability is likely a result of many genes with additive and interactive effects, and that there are nonspecific genetic vulnerabilities to psychosis, such that schizophrenia and affective psychoses share some etiologic factors. Studies demonstrate that polymorphisms in the Catechol-O-Methyltransferase (COMT) and Brain-Derived Neurotrophic Factor (BDNF) genes influence cognition, and these variants have also been proposed to be involved in the pathogenesis of schizophrenia. Although findings on the relation of cognition with polymorphisms in the COMT and BDNF genes are mixed, the relation of these genes with dopamine neurocircuitry, and prefrontal cortex and medial temporal lobe function make them strong candidates for investigating the association between genes and cognitive function. Based on this literature, we hypothesized, first, with regard to the COMT Val108/158Met polymorphism, that Val carriers would have lower cognitive performance compared to individuals homozygous for the Met allele. Second, for the BDNF Val66Met polymorphism, Met carriers were expected to have lower cognitive performance, particularly in the domain of working memory compared to individuals with a homozygous Val genotype. Third, it was hypothesized that COMT Val108/158Met and BDNF Val66Met interact to affect cognition.

Methods: Study participants included a sample of 64 adolescents (diagnosed with schizotypal personality disorder, other personality disorders, or no psychiatric diagnoses) and 90 adults (diagnosed with schizophrenia, schizoaffective disorder, psychosis not otherwise specified, or no diagnoses) drawn from two independent studies originally designed to investigate other research questions. Subtests of the Wechsler Memory Scale, 3rd Edition (WMS-III) measuring immediate and delayed verbal memory, as well as working memory were administered to all participants. DNA was extracted through saliva samples collected from each participant using Oragene DNA Self-Collection kits from DNAGenotek.

Results: Investigation of genetic effects across the entire sample revealed a trend-level main effect of COMT Val108/158Met on cognitive performance. However, further analysis across samples revealed a significant sex-specific main effect of the COMT polymorphism on immediate and delayed memory for female participants, with Met/Met individuals showing better performance than Val/Val individuals. This effect was not found for male participants. After statistically controlling for self-reported race, diagnosis, and recruitment site, male participants demonstrated a main effect of the BDNF polymorphism on immediate and delayed memory, such that carriers of the Val allele showed better performance. Male participants also demonstrated a significant interaction between COMT Val108/158Met and BDNF Val66Met on working memory. Those with the COMT Met allele and the BDNF Val allele manifested the highest level of performance.

Discussion: Results from the current analysis highlight the complex nature of genetic effects. Specifically, findings suggest that genetic polymorphisms may have differential effects on cognition in men and women. Multiple factors influence the effects of genes on cognition and future studies should continue to investigate the multiple contributions to impaired cognition in psychosis.

doi:10.1016/j.schres.2010.02.848
Poster 88
COMT GENOTYPE AND MEMORY PERFORMANCE IN SCHIZOPHRENIA

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Background: The Val158Met single nucleotide polymorphism of the catechol-O-methyltransferase (COMT) gene on chromosome 22 influences dopamine catabolism and is related to cognitive impairment in schizophrenia. Previous research has found that the Met allele is associated in a dose-response fashion with better performance on most neuropsychological tests.

Methods: We assessed 138 outpatients with schizophrenia-spectrum disorders (65% men; 59% Caucasian; mean age = 49; mean years of education = 13) with a blood draw and a comprehensive neuropsychological, functional, and clinical battery. Participants with the Val/Val (n = 49), Val/Met (n = 57), and Met/Met (n = 32) genotypes did not differ on demographic variables, diagnosis, type or dosage of antipsychotic medication, or duration of psychosis.

Results: Spearman correlations between the “dose” of the Met allele (0, 1, or 2 Met alleles) and the neuropsychological, functional, and clinical variables demonstrated that a higher number of Met alleles was associated with better estimated premorbid intellectual functioning (r = .20, p = .026), verbal memory (r = .18, p = .036), visual memory (r = .17, p = .047), and working memory (r = .17, p = .045). Met carriers significantly outperformed noncarriers on measures of premorbid intellectual functioning (t = 2.25, df = 136, p = .025), verbal memory (t = 2.13, df = 136, p = .035), and visual memory (t = 2.09, df = 119.34, p = .042).

Discussion: The Met allele appears to be associated with better performance in premorbid intellectual functioning, delayed verbal and visual recall, and working memory, explaining 3-4% of the variance in these abilities. Associations between COMT genotype and functional capacity or psychiatric symptom severity were not statistically significant. Because the Val158Met polymorphism typically explains a small amount of variance in cognitive performance and given the size of the current sample, these results need to be replicated with a larger sample and other variants should be considered to further understand genetic contributions to cognition.

doi:10.1016/j.schres.2010.02.849

Poster 89
DISRUPTED IN SCHIZOPHRENIA 1 GENOTYPE AND RESPONSE TO ANTIPSYCHOTICS IN FIRST EPISODE PSYCHOSIS

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Background: Currently there is substantial evidence supporting DISC1 as one of the main candidate genes for schizophrenia. Moreover, variations in several DISC1 polymorphisms have been associated in schizophrenic patients to brain structure abnormalities, altered brain activation, cognitive impairment, and clinical severity. The biological function of the DISC1 is not completely understood. However, there is strong evidence showing that DISC1 interacts with a range of proteins forming the DISC1-Interactome. Through its interactions with these proteins, DISC1 gets involved in neurodevelopment and neuronal signalling processes, but also in glutamate transmission. And since the glutamate system has been proposed as one of the mechanism of actions for antipsychotic drugs, the DISC1, through its interaction with proteins of the glutamate system might be involved itself in processes of treatment response. Recent studies support this hypothesis. Therefore it has been shown that chronic treatment with antipsychotics increased the expression of DISC1 mRNA in cortex and hippocampus. Moreover, some psychiatric drug target genes that display DISC1 pathway mediated differential expression. Therefore we aimed to study if variations in a DISC1 polymorphism were associated to variations in treatment response.

Methods: We studied a sample of 213 Caucasian drug-naive patients experiencing a first episode of non-affective psychosis (DSM-IV). Response to antipsychotics was defined according to three symptom scales. Response was assed at 6 weeks (short-term) and at 1 year (long-term) of entering the treatment program. BPRS Response was defined as a decrease of at least 40% in BPRS. SANS response and SAPS Response: Patients had to fulfill the three following criteria: i) Decrease of at least 40%; ii) Total score below 8; iii) Non of the scale Items being equal or above 4. Genotyping was accomplished by automatic genotyping using ABI 3700 technology. All statistical analyses were carried out using the statistical software package SPSS 15.0 for Windows. When studying possible associations between Ser704Cys genotype and response to antipsychotic treatment, Chi square analyses were carried out. Statistical significance was established at p < 0.05.

Results: Patients were in Hardy-Weinberg equilibrium. Rs821616 genotype and allelic frequencies were calculated, being as follows: AA = 66.8%; AT = 42.7%; TT = 50.7% and A = 0.28; T = 0.72 respectively. None of Ser704Cys DISC1 genotypes modulated significantly the risk of psychosis when comparing the sample of psychotic patients with the control group. Our results showed no statistical association between the Ser704Cys polymorphism and response to antipsychotic treatment using any of the response definitions, neither at short-term (6 weeks) nor at long-term (1 year).

Discussion: Our study showed that Ser704Cys DISC1 genotype is not a marker of response in psychosis. However, this result is not completely unexpected as we can only understand the treatment response as a complex process in which multiple proteins are involved in multi-interactions. Therefore, it would be difficult to find a single polymorphism causing such a modulation on the treatment response to antipsychotics. It is more likely that the pharmacogenetic processes will be explained using more complex models such as the “Synaptic Theory of Schizophrenia” proposed by Harrison and Weinberger, in which the risk of psychosis –and why not, the response to antipsychotics- would be mediated by the convergence of several susceptibility genes’ effects on synaptic processing in brain microcircuits, mainly on the glutamate synapse.

doi:10.1016/j.schres.2010.02.850

Poster 90
AKT1 GENE IS ASSOCIATED WITH ATTENTION AND BRAIN MORPHOLOGY IN PATIENTS WITH SCHIZOPHRENIA

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Background: The AKT1 gene is located on chromosome 17q23.3 and encodes for the serine/threonine kinase AKT1. Recent studies have shown that the AKT1 gene is associated with attention and brain morphology in patients with schizophrenia. However, the biological function of the AKT1 is not completely understood. Therefore, we aimed to study if variations in a AKT1 polymorphism were associated to variations in attention and brain morphology.

Methods: We studied a sample of 213 Caucasian drug-naive patients experiencing a first episode of non-affective psychosis (DSM-IV). Response to antipsychotics was defined according to three symptom scales. Response was assed at 6 weeks (short-term) and at 1 year (long-term) of entering the treatment program. BPRS Response was defined as a decrease of at least 40% in BPRS. SANS response and SAPS Response: Patients had to fulfill the three following criteria: i) Decrease of at least 40%; ii) Total score below 8; iii) Non of the scale Items being equal or above 4. Genotyping was accomplished by automatic genotyping using ABI 3700 technology. All statistical analyses were carried out using the statistical software package SPSS 15.0 for Windows. When studying possible associations between Ser704Cys genotype and response to antipsychotic treatment, Chi square analyses were carried out. Statistical significance was established at p < 0.05.
Background: The v-akt murine thymoma viral oncogene homolog 1 (AKT1) has a function of regulating intracellular signaling pathways in the central nervous system. The association between genetic variations of the AKT1 gene with schizophrenia has been reported in various ethnicities. Of the genetic variations in the AKT1 gene, a single nucleotide polymorphism (SNP; rs2494732) was associated with schizophrenia and response to antipsychotic medication in Japanese population. A strategy for characterizing the role of genes in complex human behaviors such as psychosis is to study genetic association at the level of brain structure and function. In the present study, we examined the association between the SNP (rs2494732) in the AKT1 gene and memory performance and also between the SNP and brain morphology in an Asian population.

Methods: Genotyping of rs2494732 was carried out using TaqMan assays. Then, we examined the association between the SNP and memory performance, attentional performance and GM volume between the A allele carriers and the G allele homozygotes. The memory performance was measured by the Wechsler Memory Scale-Revised (WMS-R) (86 cases and 117 controls). Attentional performance was measured by using the Continuous Performance Test (CPT) (52 cases and 117 controls). Neuroimaging analysis was administered to subjects with brain magnetic resonance imaging (MRI) (55 cases and 159 controls). All images were processed with voxel-based morphometry (VBM) by using Statistical Parametric Mapping 5 (SPMS). Statistical analysis was carried out by using SPSS for Windows version 10. Statistical significance was defined as $p<0.05$. Written informed consent was obtained for all subjects after the procedures had been fully explained. This study was carried out in accordance with World Medical Association's Declaration of Helsinki and approved by the Research Ethical Committee of Osaka University.

Results: The attention/concentration scores of the WMS-R in individuals with the A allele, which was enriched in patients with schizophrenia compared with controls, were significantly lower than those in individuals with the G/G genotype. There was no significant association between any other domain score and this SNP. We confirmed the association of the SNP with attentional performance by the CPT. Lower score was found in A allele carrier patients with schizophrenia. Furthermore, A allele carriers in patients with schizophrenia showed smaller GM volume in the right inferior parietal lobule, which has been reported as a region associated with attentional performance. Our results suggest that the genetic variation of AKT1 might be associated with attentional performance and brain morphology in patients with schizophrenia.

Discussion: This is the first report demonstrating an association between rs2494732 in AKT1 and neuropsychological parameters and GM volume in an Asian population. The risk SNP has an impact on the smaller GM volume in right inferior parietal lobule, which might be associated with lower memory and attentional performance in schizophrenia. The mechanisms underlying the effect of rs2494732 in AKT1 on cognitive function are unclear; however, several studies suggested the involvement of AKT-GSK3β signaling pathway. Further studies are needed to elucidate an underlying genetic vulnerability to neurobiological traits in schizophrenia.
Methods: We have used magnetic resonance imaging (MRI) and voxel-based morphometry methods to compare the gray (GM) and white matter (WM) density between patients respectively respon- der and non-responder to atypical antipsychotics. Clinical response was both retrospectively and prospectively assessed. In total, 30 schizophrenia patients and 31 controls, not previously included in any report from our group, were recruited. Of them, 20 were considered responders and 10 non-responders to treatment with risperidone or olanzapine. Illness duration, sex, age and socio-economic level did not differ between patient groups.

Results: In comparison to controls, both groups of patients showed a significant increase in dorsal basal ganglia portions, as well as a decrease in anterior cerebellar vermis. Resistant patients, in addition, showed a significant GM decrease in anterior cingulate (BA 24), insula (BA 13) and orbitofrontal (BA11) cortices. The direct comparison between both groups of patients showed a significant decrease in orbit and insular GM in the resistant group. Concerning the WM, both groups showed a significant decrease in the anterior portion of the corpus callosum in comparison to the healthy controls. Besides, they showed a significant increase in left inferior temporal WM.

Discussion: GM distribution may relate to the response to atypical treatment in schizophrenia.

doi:10.1016/j.schres.2010.02.853

Poster 93
GLUTAMATE RECEPTOR DELTA 1 (GRID1) GENETIC VARIATION AND BRAIN STRUCTURE IN SCHIZOPHRENIA

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Background: Genetic variation in the gene encoding the glutamate receptor delta 1 (GRID1) has recently been shown to confer increased risk for schizophrenia in three independent large samples. GRID1 encodes for a new family of glutamate receptors, which operate as modulators of glutamatergic transmission rather than forming ion channels, and constitute a class of their own within the glutamate receptor family. GRID1 is known to be expressed in several brain areas in humans, including amygdala, hippocampus, and thalamus.

Methods: We analysed high-resolution magnetic resonance imaging (MRI) data (1.5 Tesla; T1-weighted images with 1×1×1 mm voxel resolution) from 62 patients with DSM-IV schizophrenia (18 female, 44 male; mean age 31.7 years, SD 11.5; age range 18-58 years) and 54 healthy controls (35 female, 29 male; mean age 29.5 years, SD 9.9; age range 18-58 years). Images were analysed using voxel-based morphometry using the standardised VBM5 protocol (http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5/), which involves Hidden Markov Random Fields to increase signal-to-noise ratio. From a number of GRID1 single nucleotide polymorphisms (SNP), we selected the rs3814614 marker (within the GRID1 promoter region), which was identified as a risk factor in the German GRID1 study sample, to form sub-groups with each sample. In addition to the regional analyses obtained with VBM, we also analysed total brain grey matter and white matter (determined as number of voxels in the segmented images) to assess potential global effects.

Results: There were no effects of genotype or group X genotype interactions on total brain grey matter or white matter, as estimated from total number of segmented voxels for each tissue type. In healthy subjects, we identified a significant effect of rs3814614 genotype in the anterior thalamus (bilaterally), superior prefrontal cortex, and orbitofrontal cortex, in all cases with T allele homozygotes showing higher grey matter density. We did not see this association within the schizophrenia sample, where rs3814614 variation was only associated with grey matter reduction in TT risk allele homozygotes in medial parietal cortex and increased grey matter in right medial cerbellum. This dissociation was confirmed in post hoc testing of group by genotype interaction. For white matter, we did not observe significant effects of genotype in healthy controls, and only minor effects of genotype within schizophrenia patients in the posterior temporal lobe white matter.

Discussion: Our data show that GRID1 rs3814614 genotype is related to grey matter variation in prefrontal and anterior thalamic brain areas in healthy subjects, but not in schizophrenia patients. While this indicates a potential role of GRID1 genetic variation in thalamocortical functioning, the lack of correlation in schizophrenia might relate to dysfunction of thalamo-prefrontal projections, which might constitute an important pathophysiological feature in schizophrenia. This study was supported by a grants of the EU (EUTwinsS network; RTN, F6P), the IZKF (University of Jena), and BMBF.

doi:10.1016/j.schres.2010.02.854

Poster 94
P53 GENETIC VARIABILITY IS ASSOCIATED WITH FRONTAL WHITE MATTER VOLUME IN SCHIZOPHRENIC PATIENTS

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Background: Evidence for abnormalities in white matter (WM) tracts and WM volumes in schizophrenia (SZ) has been confirmed by recent reviews (Ellison-Wright et al., 2009). Likewise post-mortem studies (prefrontal/temporal cortices) have revealed a reduced expression of oligodendrocyte/myelination genes in SZ (Mikus et al., 2008). P53 protein has a central role in the control of apoptotic processes (Vazquez et al., 2008) and a deep involvement in oligodendrocyte development and myelination in CNS (Billon et al., 2004; Li et al., 2008). TP53 gene polymorphisms may account for variability in i) WM features and ii) biochemical markers of neuronal activity and myelin turnover.

Methods: We probed Arg and Ins16bp polymorphisms at TP53 gene were analyzed in 20 DSM-IV schizophrenic patients. T1/T2-weighted sequences were acquired using a 1.5T Philips Gyroscan system, Scans were transformed into Talairach space and segmented into GM, WM and CSF using Statistical Parametric Mapping under a ROI analysis. MRI data were adjusted for age and brain volume using regression parameters from a healthy control group (n = 45). Proton magnetic resonance spectroscopy (1H MRS) was used to examine NAA, Cr and Cho levels in the dorsolateral-prefrontal cortex (DLPFC).
Results: Pro/Arg heterozygous for the Pro72Arg polymorphism showed a generalized deficit in whole-brain WM as compared to Pro/Pro homozygous (Mann-Whitney U = 22, z = -2.006, p = 0.045). This WM deficit was especially prominent in right frontal lobe (Mann-Whitney U = 16, z = -2.469, p = 0.012). Pro72Arg subjects showed decreased NAA/Co ratio levels in right frontal lobes and NAA/Co ratio in DLPEC. Whether this effect arises from apoptotic processes or from an altered myelination is a consequence of a disturbed oligodendrocyte development warrants further research.

Acknowledgements: Supported by Fundación “La Caixa” (99-111-00; 99-042-00), Instituto de Salud Carlos III, CIBER-Salud Mental (CIBERSAM) and Spanish Ministry of Science and Innovation (SAF2008-05674-C03-01).

doi:10.1016/j.schres.2010.02.855

Poster 95
WHITE MATTER TRACTS AS PREDICTORS OF TREATMENT OUTCOME
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Background: The caudate volume is a structure often implicated in the pathogenesis of schizophrenia. This structure also regulates a number of cognitive functions. However, only few studies have investigated the correlation of cognitive functioning with caudate volume in patients with psychosis. To investigate caudate volume in first episode psychosis patients and healthy controls and to examine the relationship between caudate volume and cognitive functioning.

Methods: 95 first episode psychosis patients (60 males, 35 females; mean age (27.49) ± 7.8; 47 schizophrenia, 29 Affective disorders, 18 Other) and 91 healthy controls (54 Males, 37 females; mean age (30.2) ± 8.72) were scanned using a 1.5 Tesla scanner. Caudate volume was estimated with the software MEASURE. Executive functioning, verbal memory, general intellectual ability and IQ were examined. Analyses of (Co)variance (ANCOVA) were conducted with age and whole brain volume as covariate's on the caudate volume, diagnosis and pharmacological data. Caudate volume was then correlated with neuropsychological scores.

Results: Patients had larger caudate volume than healthy controls, albeit only at trend level (p = 0.069). Within the patient group, there was a positive correlation between caudate volume and performance on the Ravens task (p = 0.008) and the trail making task (p = 0.006).

Discussion: These data suggest that a smaller caudate volume in schizophrenia is associated with a poorer performance in tests of general intellectual ability and executive function.

doi:10.1016/j.schres.2010.02.856

Poster 96
CORTICAL THICKNESS AND SUBCORTICAL VOLUMES IN SCHIZOPHRENIA AND BIPOLAR DISORDER
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Results: Pro/Arg heterozygous for the Pro72Arg polymorphism showed a generalized deficit in whole-brain WM as compared to Pro/Pro homozygous (Mann-Whitney U = 22, z = -2.006, p = 0.045). This WM deficit was especially prominent in right frontal lobe (Mann-Whitney U = 16, z = -2.469, p = 0.012). Pro72Arg subjects showed decreased NAA/Co ratio levels in right frontal lobes and NAA/Co ratio in DLPEC. Whether this effect arises from apoptotic processes or from an altered myelination is a consequence of a disturbed oligodendrocyte development warrants further research.

Acknowledgements: Supported by Fundación “La Caixa” (99-111-00; 99-042-00), Instituto de Salud Carlos III, CIBER-Salud Mental (CIBERSAM) and Spanish Ministry of Science and Innovation (SAF2008-05674-C03-01).

doi:10.1016/j.schres.2010.02.855

Background: Schizophrenia and bipolar disorder are severe psychiatric diseases with partly overlapping symptomatology. Widespread brain morphological abnormalities, including cortical thinning and subcortical volume reductions, have been demonstrated in schizophrenia but it is unclear whether similar abnormalities are present in bipolar disorder. The purpose of this study was to compare cortical thickness and subcortical volumes in schizophrenia and bipolar disorder, in order to assess differences and similarities in cortical and subcortical brain structure.

Methods: We analyzed MRI images from a sample of 173 patients with schizophrenia spectrum disorder, 139 patients with bipolar disorder (type 1 and 2), and 207 healthy control subjects. Cortical thickness was compared between the groups in multiple locations across the continuous cortical surface. Subcortical volumes were compared on a structure-by-structure basis.

Results: Both patient groups showed substantial subcortical volume reductions bilaterally in the hippocampus, in the left thalamus, right nucleus accumbens, left cerebellar cortex, and the brainstem, along with substantial ventricular enlargements. There was no significant difference between schizophrenia and bipolar disorder in these structures; however, the effect sizes were consistently larger in the schizophrenia group. In the cortex, there was widespread, bilateral thinning in schizophrenia compared to healthy controls, in frontal, temporal, and occipital regions. There were a few, comparatively small, right hemisphere regions where bipolar disorder showed cortical thinning compared to controls; one in the superior frontal gyrus, one in the entorhinal cortex, and one in the occipitotemporal junction. However, comparing the subgroup of patients with bipolar disorder 1 to healthy controls, there was substantial, bilateral cortical thinning in the superior frontal lobes. Although there was no significant difference between schizophrenia and bipolar disorder in the cortex, the effect sizes were consistently larger in the schizophrenia group.

Discussion: The overlapping patterns of subcortical volume reductions are consistent with a common subcortical pathophysiology for bipolar disorder and schizophrenia. Cortically, there was a larger discrepancy between findings in the schizophrenia and bipolar disorder groups. Although direct comparisons between the groups failed to yield statistically significant results, the healthy controls vs. bipolar disorder comparisons did not yield any findings in the left hemisphere, and somewhat limited findings in the right hemisphere, suggesting that bipolar disorder falls between healthy controls and schizophrenia. This is consistent with the effect sizes in these groups. Bipolar disorder type 1 showed cortical thinning more similar to that seen in the schizophrenia group; however, in contrast to schizophrenia, the inferior frontal, lateral and medial occipital, and most of the temporal lobes were not significantly affected.
Poster 97
INSULAR CORTEX THINNING IN FIRST EPISODE SCHIZOPHRENIA PATIENTS, CORRELATIONS WITH CLINICAL VARIABLES, SYMPTOMATOLOGY AND COGNITIVE FUNCTIONING

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Background: The thickness of the cortical mantle is a relevant measure by which to identify anomalies in the structure of the cerebral cortex (Sowell et al., 2003) and may provide important information about brain development (Rockel et al., 1980). Overall and regional cortical thinning has been observed at the first break of schizophrenia. Due to its anatomical location and wide interconnectivity with cortical and limbic areas the insula might be of great interest in the investigation of psychiatric disorders of neurodevelopmental origin (Jang et al., 2006).

Methods: We investigated insular thickness anomalies in 118 first episode schizophrenia patients and 83 healthy subjects. Magnetic resonance imaging brain scans (1.5 T) were obtained, and images were analyzed by using BRAINS2. The insular cortex was manually outlined without knowledge of the diagnosis. The drawing was performed using a previously published method (Crespo-Facorro et al., 2000; Kim et al., 2003). All measures of insular cortex thickness were subjected to analysis of covariance, with diagnosis and gender as the between-groups factor and age as the covariate. Pearson’s product moment correlation coefficients with age as the covariate were calculated to examine the relationships between morphological measurements and clinical and cognitive variables. Throughout, a two-tailed alpha-level of 0.05 was used for statistical testing.

Results: Significant differences were found between groups in age (F = 3.99, P = 0.047). There were no significant differences between patients and healthy subjects with regard to any other demographic variable. Schizophrenia patients demonstrated a significant right insular thinning (F = 5.54; d = 0.40; P = 0.020). Group by gender interactions were found for left insular thickness (F = 4.71; P = 0.031). Post-hoc comparisons revealed that male schizophrenia patients had a significant left insular thinning (P = 0.015) compared to healthy male subjects. There were no significant associations between insular thickness the severity of symptoms at baseline and cognitive measurements and premorbid variables (all r’s <0.16 and P’s >0.080).

Discussion: In the present study, we observed gross significant differences in insular thickness between first episode schizophrenia patients and healthy volunteers. The fact that insular thinning is already present at early phases of the illness and is independent of intervening variables offers evidence for the potential of these changes to be a biological marker of the illness. Further studies are warranted to elucidate the influence of different neurobiological mechanisms (cellular shrinkage, reduction in dendritic arborization, and disruptions in white matter bundles) associated with reduced insular thickness in schizophrenia.

doi:10.1016/j.schres.2010.02.858

Poster 98
MULTIMODAL IMAGING REVEALS CONVERGENT EVIDENCE OF MEDIAL PREFRONTAL CORTEX PATHOLOGY IN SCHIZOPHRENIA

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Background: Neuroimaging studies have found evidence of both brain structural and brain functional abnormality in schizophrenia. However, changes have been identified in many different areas and the findings are not consistent across techniques. It has been suggested that further understanding of brain pathology in schizophrenia will depend on integration of findings from voxel-based structural techniques with those from functional imaging and white matter imaging using DTI.

Methods: We applied a whole brain multimodal imaging approach combining VBM, fMRI and DTI/tractography to 32 chronic schizophrenic patients and matched healthy controls. For each analysis we used a conservative threshold of p = 0.01, in order to minimise false positive findings arising from the analysis of several modalities and from different sets of images. This corresponds to an overall false discovery rate of 0.03.

Results: At this threshold, structural and functional imaging revealed overlapping regions of abnormality in the medial frontal cortex. DTI revealed prominent abnormality in the anterior corpus callosum, and tractography of representative seed regions indicated that these fibres projected to the medial frontal cortex. There was also evidence of convergent abnormality in the dorsolateral prefrontal cortex, although here the laterality was less consistent across techniques.

Discussion: Three different imaging techniques converge on the medial frontal cortex as site of abnormality in schizophrenia. This region corresponds to the anterior midline node of the default mode network, a brain system which is believed to support internally directed thought, a state of watchfulness, and/or the maintenance of one’s sense of self, and which is of considerable current interest in a range of different neuropsychiatric disorders.

doi:10.1016/j.schres.2010.02.859

Poster 99
GREY MATTER DEFICITS IN CHRONIC PSYCHOSIS NOT PRESENT AT FIRST EPISODE

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Background: Abnormalities in grey matter that have been replicated in a number of studies include frontal, temporal and subcortical regions, such as the basal ganglia, thalamus and hippocampal complex. However, the effects of illness course and medication exposure on these structural changes have proven more difficult to disentangle. One strategy in deciphering etiological factors is to investigate changes in the medial frontal cortex, although the findings are not consistent across techniques. It has been suggested that further understanding of brain pathology in schizophrenia will depend on integration of findings from voxel-based structural techniques with those from functional imaging and white matter imaging using DTI.

Methods: Voxel-based morphometry was used to compare grey matter in individuals experiencing either their first-episode (n = 40) or later episodes of psychosis (n = 47) with those of healthy controls (n = 60). Illness severity was assessed using the Positive and Negative Symptom Scale (PANSS). Medication exposure was estimated using chlorpromazine equivalents.
Results: Chronic psychosis was associated with grey matter deficits bilaterally in the insular cortices, and in the superior frontal gyrius and left caudate relative to the healthy group. No significant differences were detected between the first-episode and either the chronic psychosis or healthy control groups. Grey matter deficits did not appear to be related to the severity of positive, negative, general or total illness symptoms, the age of illness onset or medication exposure.

Discussion: Grey matter deficits observed later in illness course may not be present to the same extent at the time of first episode of psychosis. However, this would warrant further investigation using small volume correction applied to examine regions strongly implicated in the pathophysiology of schizophrenia including frontal cortical regions. Our findings are in line with those of the previous literature in identifying reduced grey matter in schizophrenia in frontal and temporal cortical regions.

doi:10.1016/j.schres.2010.02.860

Poster 100
MAPPING RELIABILITY OF MULTICENTER MRI: CORTICAL THICKNESS AND Voxel-BASED MORPHOMETRY

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Background: Multicenter structural MRI studies can have greater statistical power to detect disease effects or heritabilities of brain tissue than single-center studies. However, across-center differences in contrast sensitivity, spatial uniformity, etc., may lead to tissue classification or image registration differences that could reduce or wholly offset the enhanced statistical power of multicenter data. Prior work has validated volumetric multicenter MRI, but robust methods for assessing reliability and power of multisite analyses with voxel-based morphometry (VBM) and cortical thickness measurement (CORT) are not yet available.

Methods: We developed quantitative methods to investigate the reproducibility of VBM and CORT to detect group differences and estimate heritability when MRI scans from different scanners running different acquisition protocols in a multicenter setup are included. The method produces brain maps displaying information such as lowest detectable effect size (or heritability) and effective number of subjects in the multicenter study. We applied the method to a five-site multicenter calibration study using scanners from four different manufacturers, running different acquisition protocols.

Results: The reliability maps showed an overall good comparability between the sites, providing a reasonable gain in sensitivity in most parts of the brain. In large parts of the cerebrum and cortex scan pooling improved heritability estimates, with ‘effective-N’ values up to the theoretical maximum. For some areas, ‘optimal-pool’ maps indicated that leaving out a site would give better results. The reliability maps also reveal which brain regions are in any case difficult to measure reliably (e.g., around the thalamus).

Discussion: These tools will facilitate the design and analysis of multisite VBM and CORT studies for detecting group differences and estimating heritability. The comparability between scans from the five sites of the analyzed multicenter study is good, especially in the cortical areas. Combining MRI data from these different sites will result in improved statistical power, allowing smaller effects to be discovered.

doi:10.1016/j.schres.2010.02.862

Poster 101
DIFFUSION TENSOR IMAGING OF THE CINGULUM BUNDLE IN FIRST EPISODE SCHIZOPHRENIA

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Background: The cingulum bundle is the major white matter tract connecting the cortex and limbic system, and has been observed to be abnormal in patients with chronic schizophrenia. The cingulum bundles of 19 patients with first episode schizophrenia (FESZ) and 20 controls (NC) were examined using diffusion tensor imaging on a 3T MRI scanner.

Results: Fractional anisotropy (FA) abnormalities were not significant between FESZ and NC. However, both Axial and Radial diffusivity were abnormal on both the left (FA: t(37) = 0.763, p = 0.450, Cohen’s d = 0.244; Axial: t(37) = 4.245, p < 0.001, Cohen’s d = 1.360; Radial: t(37) = 2.235, p = 0.032, Cohen’s d = 0.716), and the right side (FA: t(37) = 1.626, p = 0.113, Cohen’s d = 0.521; Axial: t(37) = 4.164, p < 0.001, Cohen’s d = 1.334; Radial: t(37) = 2.762, p = 0.009, Cohen’s d = 1.685) in FESZ compared to NC. However, both Axial and Radial diffusivity contribute to the change in overall white matter health and organization measured by FA. Results further suggest that the underlying pathology in FESZ in the cingulum bundle involves abnormalities in both axon integrity and myelination. This is consistent with abnormal myelin development that results in partial degeneration of the underlying axons.

Discussion: These results suggest that both axial and radial diffusivity contribute to the change in overall white matter health and organization measured by FA. Results further suggest that the underlying pathology in FESZ in the cingulum bundle involves abnormalities in both axon integrity and myelination. This is consistent with abnormal myelin development that results in partial degeneration of the underlying axons.

doi:10.1016/j.schres.2010.02.862

Poster 102
CEREBRAL WHITE MATTER CHANGES ON COMBINED STRUCTURAL MRI AND DIFFUSION TENSOR IMAGING IN FIRST EPISODE SCHIZOPHRENIA

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Background: Previous studies have revealed volumetric abnormalities of white matter in patients with schizophrenia but the corresponding white matter dysconnectivities are less studied in tandem. The aim of this study is to examine white matter integrity
in the region of white matter volume deficit in patients with first-episode schizophrenia (FES).

**Methods:** A cross-sectional, case-control design was adopted and we used empirically-defined region of known white matter volume deficit to interrogate diffusion tensors. The participants included 103 subjects comprising of 39 patients with FES and 64 age-, sex-, and handedness-matched healthy controls. The neurocognitive domains assessed included intelligence, attention, executive functioning, verbal and spatial working memory. The main outcomes were gray and white-matter partial volumes, fractional anisotropy, trace and geometric diffusion indices.

**Results:** Structural voxel-wise analyses revealed that patients with first episode schizophrenia had lower gray matter volumes in bilateral hippocampi ($P<.01$) and lower white matter volume in the right temporal-occipital region ($P<.005$) corresponding to the inferior longitudinal fasciculus. Further analyses of diffusion anisotropy in the right temporal-occipital region revealed lower planar anisotropy, $c_p$, and higher linear anisotropy, $c_l$ ($P = 0.012$) in patients with first episode schizophrenia. However, no differences were found for fractional anisotropy and trace in the implicated white matter region between the two groups. Patients performed poorer in digit span, spatial working memory and executive functioning, compared to healthy controls.

**Discussion:** To the best of our knowledge, this is the first study to employ geometric diffusion measures in interrogating the nature of diffusion tensor in schizophrenia. We confirmed previous findings of white matter volume deficit in the region of inferior longitudinal fasciculus. The presence of changes in geometric diffusion indices in the implicated white matter region suggests that pathophysiological processes which underlie cerebral white matter volume reduction may not be reflected by changes in fractional anisotropy. Further research is needed to better understand the nature of these white matter changes and its progression in schizophrenia over time.

doi:10.1016/j.schres.2010.02.863

**Poster 103**

**ALTERATIONS IN WHITE MATTER MICROSTRUCTURE ASSOCIATED WITH THE ONSET OF PSYCHOSIS**

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**Background:** The At Risk Mental State (ARMS) refers to a group of symptoms associated with a very high risk of developing psychosis: 25–33% of ARMS subjects become psychotic within 1–2 years. Diffusion Tensor Imaging studies indicate that schizophrenia is associated with reduced integrity in the frontal, cingulate, parietal and temporal white matter, but the extent to which vulnerability to psychosis is associated with abnormalities of structural connectivity is unclear. We addressed this issue through cross-sectional and longitudinal comparisons of diffusion tensor imaging data acquired from subjects with an ARMS.

**Methods:** Thirty–one individuals meeting PACE criteria for the ARMS and 34 healthy volunteers were studied using a 1.5T MRI scanner. Diffusion weighted data were acquired using a multi-slice, whole brain, peripherally gated echo-planar imaging (EPI) sequence, optimized for precise measurement of the diffusion tensor in the brain. At each slice location 7 images without diffusion weighting gradients and 64 diffusion-weighted images ($b$-value $= 1300\text{ s mm}^{-2}$) with gradient directions uniformly distributed in space were acquired. ARMS and first episode subjects were scanned at clinical presentation. Twenty-two of the ARMS subjects and 14 controls were re-scanned using identical methods after a mean interval of 28 months. Five of these 22 ARMS subjects had developed schizophrenia, defined according to DSM-IV criteria, in the 2 years subsequent to scanning. Between-group differences in fractional anisotropy were evaluated longitudinally and cross-sectionally using a non-parametric voxel based analysis. Results were localised using the ICBM-DTI-81 white matter labels atlas and values of fractional anisotropy (FA), mean and radial diffusivity and three eigenvalues extracted.

**Results:**

Baseline analyses:

In relation to healthy volunteers, the ARMS group showed a reduction of FA in the left external capsule, in the posterior limb and in the retrolenticular portion of the left internal capsule, the left superior and posterior corona radiata, the left posterior thalamic radiation, and the left superior longitudinal fasciculus. The ARMS group, the subgroup who later developed psychosis had reduced FA values in the right anterior corona radiata compared to those who did not.

Longitudinal analyses:

Within the ARMS group, in subjects who later developed psychosis compared to those who did not, there was a longitudinal reduction in FA in the genu and body of the corpus callosum, the superior and posterior corona radiata and superior longitudinal fascicle bilaterally, the left anterior corona radiata, and the right external capsule, posterior limb of the right internal capsule and the right superior fronto-occipital fasciculus.

**Discussion:** These results suggest that abnormalities in white matter tracts linking the frontal, parietal and temporal lobes are evident in people at high risk of psychosis. Within this group, the later onset of psychosis was particularly associated with reduced integrity in the major pathways between cortical areas, and between cortical and subcortical regions.

doi:10.1016/j.schres.2010.02.864

**Poster 104**

**A FOLLOW-UP MRI STUDY OF THE SUPERIOR TEMPORAL SUBREGIONS IN SCHIZOTYPAL DISORDER AND FIRST-EPISODE SCHIZOPHRENIA**

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**Background:** While longitudinal magnetic resonance imaging (MRI) studies have demonstrated progressive gray matter reduction of the superior temporal gyrus (STG) during the early phases of schizophrenia, it remains unknown whether patients with schizotypal features exhibit similar STG changes.

**Methods:** In this study, longitudinal MRI data were obtained from 18 patients with first-episode schizophrenia, 13 patients with schizotypal disorder, and 20 healthy controls. The volumes of the STG and its
subregions [planum polare (PP), Heschl gyrus (HG), planum temporale (PT), rostral STG, and caudal STG] were measured on baseline and follow-up (mean: 2.7 years) scans and were compared across groups.

**Results:** At the baseline, both the schizophrenia and schizotypal patients had smaller left PT and left caudal STG than the controls. In a longitudinal comparison, the schizophrenia patients showed significant gray matter reduction of the STG over time (left: -2.3%/year; right: -1.5%/year) compared with the schizotypal patients (left: -0.6%/year; right: -0.3%/year) and controls (left: 0.0%/year; right: -0.1%/year) without a prominent effect of subregion or type of antipsychotic (typical/atypical). In the schizophrenia patients, greater annual volume reductions of the left PT and bilateral caudal STG.

**Discussion:** Our findings suggest that the left posterior STG subregions are commonly reduced in diseases of the schizophrenia spectrum; whereas, schizophrenia patients exhibit further progressive STG changes associated with overt psychosis in the early years of the illness.

doi:10.1016/j.schres.2010.02.865

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**Poster 105**

**GLOBAL AND REGIONAL CORTICAL THINNING IN FIRST-Episode SCHIZOPHRENIA PATIENTS: RELATIONSHIPS WITH CLINICAL AND COGNITIVE FEATURES**

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**Background:** Imaging and neuropathological evidence indicate that schizophrenia is associated with cortical structural abnormalities. The thickness of the cortical mantle is a sensitive measure for identifying alterations in cortical structure.

**Methods:** We investigated regional changes in cortical thickness in a large and heterogeneous sample of schizophrenia spectrum patients (N=142) at their first break of the illness and healthy controls (N=83). Magnetic resonance imaging brain scans (1.5 T) were obtained and images were analyzed by using BRAINS2 to obtain quantitative measures the cerebral surface anatomy. The contribution of sociodemographic, cognitive and clinical characteristics was controlled.

**Results:** Schizophrenia patients demonstrated a significant decrease in total cortical thickness (F = 17.55; d = 0.62; P < 0.001) and in frontal, temporal and parietal cortices (all P’s <0.001; d’s >0.53). There were no significant associations between the severity of symptoms at baseline and premorbid variables and any of the cortical thickness measurements (all r’s <0.19 and P’s >0.05). A weak significant negative correlation between attention and parietal cortical thickness (r = -0.22; p = 0.032) was found in patients. We did not find significant group-by-gender interactions for any of the brain structures analyzed (all P’s >0.15). No significant effect of schizophrenia in age-related cortical thickness variations was observed. Thus, cortical thinning is independent of gender, age, age of onset and duration of the illness and does not seem to significantly influence clinical and functional symptomatology.

**Discussion:** Significant cortical thinning at the time of the first break of the illness supports a primary neurodevelopment disorder affecting the normal cerebral cortex development in schizophrenia.

doi:10.1016/j.schres.2010.02.866

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**Poster 106**

**CORTICAL THICKNESS IN SCHIZOPHRENIA AND BIPOLAR DISEASE: A TWIN MRI STUDY OF DISEASE-SPECIFIC AND COMORBID ENDOPHENOTYPES**

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**Background:** Recently, genetic findings have shed a different light on the traditional dichotomy between schizophrenia and bipolar disease. Lichtenstein et al. (The Lancet, 2009) found substantive heritabilities for both diseases (schizophrenia: 64%, bipolar disease: 59%), which for the larger part were due to comorbid genetic factors (52% of total genetic variance in schizophrenia, 69% in bipolar disease). This calls for a search for inheritable brain-related traits that show similar alterations in patients with schizophrenia and with bipolar disease. Here we report on differences and similarities in cortical thickness in both types of patients.

**Methods:** Data are presented on cortical thickness, measured on a 1.5 Tesla MRI scanner, collected in a large twin sample of discordant schizophrenic (MZ/DZ: 13/13), concordant and discordant bipolar (22/24) and healthy control twin pairs (44/39), adding up to a total of 313 participants.

**Results:** A number of brain areas were affected alike in both diseases: both types of patients showed a thinner cortex in the parahippocampal gyrus and in the right orbitofrontal area, and a thicker cortex in the temporoparietal cortex (Wernicke’s area) and left superior motor cortex. In general, these comorbid effects were caused by genetic factors. In contrast to these similarities, large parts of the cortex were affected differently in schizophrenia vs. bipolar patients: schizophrenic patients showed a thicker right parietal cortex than controls which was accounted for by genetic factors, bipolar patients showed a thinner right parietal cortex than controls, which seemed to be due to unique environmental influences.

**Discussion:** In conclusion, depending on the specified brain area, cortical thickness can be regarded as a promising endophenotype for the genetic comorbidity as well as for the disease-specific alterations in brain structure of these psychosis-related diseases.

doi:10.1016/j.schres.2010.02.867

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**Poster 107**

**AUTOMATIC CLASSIFICATION OF MAGNETIC RESONANCE SCANS IN FIRST EPISODE SCHIZOPHRENIA: AN EXPLORATORY INVESTIGATION USING LINEAR SUPPORT VECTOR MACHINES**

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Background: Diagnoses of all forms of psychosis, including schizophrenia, are descriptive, generated from assessment schedules, such as the SCAN, SADS-L, and DSM-IV, and from clinical and behavioral observation. Although quantitative, objectively measurable markers, known as endophenotypes, have begun to be identified (Allen et al., 2009), diagnostic applications have yet to be developed. MRI structural abnormalities are among the most promising markers (Prasad and Keshavan, 2008). Classification using structural scans may be useful for early diagnosis of individuals at high risk and may help to better refine the classification of psychiatric disorders by decreasing heterogeneity of diagnoses and enhancing etiologic validity.

Methods: We aimed to identify which parameters of T1-weighted MRI scans of patients with first episode (FE) schizophrenia may be useful for generating a diagnostic model using support vector machine (SVM) classification. In SVM classification of images, a similarity measure known as a kernel matrix is created by pair wise multiplication of images. Individual images are handled as points in a high dimensional feature space and images of high similarity cluster into subspaces. An SVM classifies the images into two groups by identifying an optimal separating hyperplane (OSS), defined by the most ambiguous voxels, termed the support vectors, which maximizes the distance between groups. The OSS encompasses learned differences between groups which are used to designate disease status to each image. VBM groups. The OSH encompasses learned differences between groups termed the support vectors, which maximizes the distance between separating hyperplane (OSH), defined by the most ambiguous voxels, SVM classifies the images into two groups by identifying an optimal images. Individual images are handled as points in a high dimensional classification. In SVM classification of images, a similarity measure known as a kernel matrix is created by pair wise multiplication of images. Individual images are handled as points in a high dimensional feature space and images of high similarity cluster into subspaces. An SVM classifies the images into two groups by identifying an optimal separating hyperplane (OSS), defined by the most ambiguous voxels, termed the support vectors, which maximizes the distance between groups. The OSS encompasses learned differences between groups which are used to designate disease status to each image. VBM preprocessing in SPMB was applied to generate whole brain gray matter (GM), white matter (WM), cerebrospinal fluid (CSF), and Jacobian determinant maps from T1 images of 62 brains of patients with FE schizophrenia and 63 matched controls. Linear SVM analyses with leave-one-out cross validation were performed using kernel matrices generated from whole brain tissue maps with varied smoothing and combinations of these maps (e.g. GM + WM), as well as regions of interest of putative abnormality.

Results: The best accuracy achieved for any image kernel (69.7%) was obtained for the superior temporal pole (using the Jacobian determinant, smoothed 4 mm FWHM). We also achieved moderate accuracies (63%) with unsmoothed CSF maps. In general, CSF; WM, and Jacobian determinants were more classifiable than GM maps, which was unexpected given the plethora of ROI and VBM studies reporting volumetric deficits in GM regions in schizophrenia. In the masked analysis, the image kernels with most consistently significant accuracies/AUCs over all levels of smoothing were: (GM) superior medial frontal gyrus, (WM) anterior cingulate, superior frontal and middle frontal gyrus, and (Jacobians) caudate and temporal pole, and over all tissue types, smoothing, and ROIs were: anterior cingulate, caudate, and superior medial frontal gyrus.

Discussion: This is the first SVM study that classifies MRI scans of FE brains using VBM preprocessing. The only other SVM study of FE brains used structure-specific transformation parameters in a small image set (Pohl and Sabuncu, 2009). Although we did not achieve the high accuracies found in SVM classifications using other techniques in chronic (Fan et al., 2008, Fan et al., 2007, Fan et al., 2005, Davatzikos et al., 2005) and FE schizophrenia (Pohl and Sabuncu, 2005), we have identified image parameters that may be relevant to the diagnosis of FE schizophrenia from T1 images using VBM techniques. We are currently completing SVM analyses of magnetization prepared images, which may be more sensitive to neuroaxonal and myelin pathology (Price et al., 2010).

Results for psychotic individuals were not related to medication use. These changes cannot be attributed to (antipsychotic) medication use and as such reflect a pathophysiological process related to clinical manifestation of psychosis.

doi:10.1016/j.schres.2010.02.869

Poster 109

DISRUPTED THEORY OF MIND NETWORK PROCESSING IN RESPONSE TO IDEA OF REFERENCE EVOCATION IN SCHIZOPHRENIA

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Background: Idea of reference is the most common symptom of psychosis and a precursor to developing persecutory delusions. Recent studies have reported dysfunction in the theory of mind network consisting of the medial prefrontal cortex and the superior temporal sulcus in patients with schizophrenia. This study examined the neural pathophysiology of persecutory delusion by eliciting self-referential processing in the theory of mind network in patients with schizophrenia.

Methods: Functional magnetic resonance imaging was conducted on 14 schizophrenic inpatients with idea of reference and 15 healthy participants while viewing video vignettes of referential conversations, non-referential conversations, or no conversations between two persons.

Results: In contrast to healthy controls, patients showed attenuated superior temporal sulcus activation to social perception of conversa-
Poster 110
EFFECT OF BDNF MET66VAL POLYMORPHISM ON HIPPOCAMPAL STRUCTURE AND FUNCTION: A META-ANALYSIS
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Background: The Met-variant of the rs6265 single nucleotide polymorphism (SNP) of the Brain-derived neurotrophic factor (BDNF) gene has been linked with reduced activity-dependent secretion of BDNF in the hippocampus, that follows from impaired intracellular trafficking of the precursor peptide pro-BDNF. It is thought that this might result in subtle abnormalities of hippocampal structure and function in otherwise healthy risk-allele carriers. We used a meta-analytic approach to investigate the effect of the Val66Met-polymorphism in the BDNF gene on hippocampal structure and function. In order to analyze the effects on hippocampal structure, we employed MRI-based measures of hippocampal structure. To analyze the effects on hippocampal function we used two complementary parameters that together may be considered a reliable measure: episodic memory performance and hippocampal BOLD activity as measured by fMRI during episodic memory tasks. The meta-analytic approach enabled us to evaluate the effect of the genetic variation after controlling for potential confounding factors such as diagnostic group, laterality, age, gender or ethnicity.

Methods: The PubMed database was searched for studies reporting effects of the Met66Val-polymorphism on hippocampal grey matter volume, performance in episodic memory tasks or hippocampal activation. Studies published until the 5th of September 2009 were included in the present meta-analysis. The individual effect-size of each study was entered into a fixed-effects model to compute an overall effect-size. A random-effects model was used to re-analyze the results in case first-level analyses revealed heterogeneous effect sizes. Egger’s test was performed to exclude the possibility of publication bias following visual inspection of the Funnel plots of the selected studies for symmetry. A meta-regression analysis was carried out to examine the source of heterogeneity in effect-sizes and the influence of confounding factors.

Results: Sixteen studies and 25 independent samples (total n = 1582 subjects) examining the effect of BDNF on hippocampal volume were found. The random-effects analysis led to a significant summary effect-size of d = 0.167 (Z = 2.30, p < 0.02). A meta-regression analysis revealed no significant effects of year of publication, gender, ethnicity, diagnostic group and mean age on the effect-size (all p > 0.1). For the meta-analysis of the effect of BDNF on episodic memory performance, 9 studies examining 11 independent samples (total n = 3242 subjects) were selected. A random-effects model revealed a significant summary effect size of d = 0.22 with a significant between study heterogeneity (p = 0.0001) but no evidence for a publication bias. Six studies examining 7 independent samples (total n = 207 subjects) were included in the meta-analysis of the effect of BDNF on hippocampal activation. A random-effects model revealed a summary effect-size of d = 1.66 with significant heterogeneity between studies (p = 0.0001) but no evidence for a publication bias.

Discussion: These results suggest that the theory of mind-related medial prefrontal-superior temporal network may be dysfunctional during non-referential and referential social context processing. Additionally, our findings suggest that dysfunction in referential processing by the superior temporal sulcus may be related to idea of reference in patients with schizophrenia.

doi:10.1016/j.schres.2010.02.870

Poster 111
WHY PROTOCADHERIN11XY (PCDH11XY) AND NO OTHER GENE WILL EXPLAIN THE SEX DIFFERENCES IN PSYCHOSIS
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By contrast with differences in the reproductive system differences in secondary sexual characteristics are taken as an index of sexual selection and are species-specific. Darwin had an intuition that sexual selection and human evolution were linked, and a general relationship between sexual selection and speciation has been postulated by a number of recent authors. In particular HEH Paterson proposes that what defines a species is the mate recognition system and this must depend on the establishment of a species-specific sex difference.

At least four sex differences in psychosis require explanation: 1) earlier ages of onset in males, 2) an excess of later onset schizophrenia and paraphrenic illnesses in females 3) sex differences in the fibre content of the corpus callosum (increased in males, decreased in females) 4) the sex difference along the counter-torque axis in bipolar illness (male patients have greater and female patients lesser volume than same-sex controls along the left frontal to right occipital axis). What variable is relevant to these sex differences and also to the human specific capacity for language that is the basis that the symptoms of psychosis?

A single variable, degree of lateralisation, predicts verbal and non-verbal ability in a way that no other genetic factor has been shown to do. It is relevant to sexual preference. Here is a dimension of variation that is human specific, separates the two sexes, and arguably constitutes the basis of the human mate recognition system including the capacity for language.

Species-specific sex differences cannot be accounted for by hormones but are attributable to sex linked, particularly X and Y linked genes. In this class one gene pair, Protocadherin 11XY stands out as having been established at the origin of the hominin lineage, and being subject to subsequent change in both X and Y sequences in a way that is highly likely to influence protein structure. There is a strong case from sex chromosome aneuploidies that it is a determinant of lateralisation. This gene pair therefore can account
Poster 112
BRAIN ACTIVATION PATTERNS DURING RTMS TREATMENT OF SCHIZOPHRENIA

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Background: Negative symptoms are regarded as the most persistent and disabling component of schizophrenia. The possibility of influencing them by means of antipsychotics remains problematic. Repetitive transcranial magnetic stimulation (rTMS) presents a new opportunity for influencing negative schizophrenic symptoms. A theoretical justification of the effect of rTMS on negative schizophrenic symptoms can be seen in the fact that high-frequency rTMS has an activating impact on cortex neurons. The negative correlation between activity of the frontal cortex and severity of negative symptoms has been proved repeatedly. Another important fact is that dopamine can be released in the mesolimbic and mesostriatal brain systems by high-frequency stimulation of the frontal cortex.

Methods: Twenty four schizophrenic patients on stable antipsychotic medication with prominent negative symptoms were included in the trial. They were divided into two groups: twelve of them were treated with effective rTMS and twelve with ineffective “sham” rTMS. The ineffectiveness of the sham rTMS was achieved through placebo coil. Stimulation was applied to the left dorsolateral prefrontal cortex. The stimulation frequency was 10 Hz. Stimulation intensity was 110% of the motor threshold intensity. Each patient received 15 rTMS sessions on 15 consecutive working days. Each daily session consisted of 15 applications of 10-second duration and 30-second intervals between sequences. There were 1500 stimuli per session. fMRI investigation was done before and after rTMS course with verbal fluency task as cognitive paradigm to assess brain activity changes.

Results: During real rTMS treatment a statistical significant decrease of negative symptoms was determined. In sham rTMS treatment a decrease of negative symptoms was also identified, but to a lesser extent than in real rTMS. Mutual comparison revealed a greater decrease of negative symptoms in favor of real rTMS in contrast to sham rTMS. However, there was no significant distinction between activated brain areas during VFT before and after rTMS as in real as in sham group.

Discussion: The augmentation of antipsychotics with high-frequency rTMS applied above the area of the left prefrontal cortex causes a significant reduction in the intensity of the negative symptoms of schizophrenia. The improvement of negative symptoms of schizophrenia and cognitive performance during VFT in real rTMS course was not followed by the increase of corresponding neuronal activation (DLPFC). This work was supported by the Internal Grant Agency of the Ministry of Health (Project No. 9890-4) and by the Ministry of Education, Youth and Sports of Czech Republic (Project MSM 0021622404).

doi:10.1016/j.schres.2010.02.873

Poster 113
INTERACTION BETWEEN DRD2 GENE AND PREFRONTAL CORTEX ACTIVITY DURING DIFFERENT WORKING MEMORY PHASES

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Background: Dopamine D2 receptors are involved in modulation of the cortico-striato-thalamo-cortical circuit during working memory (WM) processing (Williams and Goldman-Rakic, 1995; Robbins, 2000). Consistently, recent studies have indicated that an intronic single nucleotide polymorphism in the D2 gene (DRD2 rs1076560, G>T) is associated with WM performance and differential cortical activity during WM tasks (Zhang, 2007; Bertolino, 2009). On the other hand, WM is not a unitary construct and involves distinct cognitive subprocesses, such as encoding, maintenance, and retrieval. In this fMRI study, we used an event-related design to investigate DRD2 rs1076560 association with prefrontal activity during these subprocesses within WM.

Methods: 50 healthy subjects, genotyped for DRD2 rs1076560 (G/G=39; G/T=11, matched for a series of demographical variables) underwent BOLD-fMRI at 3 tesla while performing a modified version of the Sternberg Task implying different load of WM subprocesses. SPM5 random-effects models were used for statistical analysis (p<0.05, small volume corrected).

Results: ANOVA revealed an effect of WM subprocesses on prefrontal cortex activity, with greater involvement of the dorso-lateral prefrontal cortex (DLPFC) during maintenance and of ventrolateral prefrontal regions (VLPFC) during encoding and retrieval. Furthermore, there was an effect of rs107650 genotype in both left DLPFC and bilateral VLPFC, with greater activity in GT relative to GG subjects. Moreover, there was an interaction between load, WM subprocesses and DRD2 genotype in a cluster in DLPFC. Inspection of signal change from this cluster suggested that GG subjects had greater activity during maintenance, while G/T individuals showed greater BOLD responses during retrieval. In addition, both genotype groups were associated with increasing DLPFC activity with greater cognitive load during maintenance and retrieval. However, during encoding, GT subjects had greater activity associated with the lower cognitive load.

Discussion: This study suggests that the lateral PFC is differentially involved in WM subprocesses. Moreover, it may indicate that DRD2 rs1076560 differentially affects the WM prefrontal circuit as a function of the WM subprocess involved. These data suggest that genetically determined D2 signaling within the cortico-striato-thalamo-cortical circuit affects prefrontal tuning efficiency in terms of regional activation and functional integration.

doi:10.1016/j.schres.2010.02.874

Poster 114
POWER SPECTRUM SCALE INVARIANCE OF FMRI TIME SERIES IDENTIFIES PREFRONTAL DYSREGULATION IN SCHIZOPHRENIA

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Background: Both theory and experimental evidence suggest that complex living systems self-organize and function close to the boundary of chaos, with erroneous organization to an improper
Poster 115
VERBAL THOUGHT GENERATION IN SCHIZOPHRENIA PATIENTS IS ASSOCIATED WITH ABERRANT ACTIVATION IN A NEURAL NETWORK INVOLVING TASK-POSITIVE AND TASK-NEGATIVE ASPECTS

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Background: Schizophrenia, particularly auditory verbal hallucinations (AVH), has been associated with impairments in source monitoring where patients tend to misattribute the source of an internal speech event to an external agent. Previous research has proposed that abnormalities in generating thoughts induce more vivid auditory sensations in schizophrenia patients through a failure of corollary discharge between the frontal and the temporal cortices (Frith, 1996). The patients are able to generate willed actions but cannot control the intentions behind it and therefore experience them as originating from an external source. This could account for source attribution errors, and at a higher threshold, could lead to AVH. In the present study, we investigated the neural underpinnings of a verbal thought generation (VTG) task using fMRI in 5 schizophrenia patients (DSM-IV; mean age = 33.8; sd = 7.53) and in 12 healthy controls (mean age = 25.9; sd = 7.08). The study sought to investigate the patterns of cerebral activation associated with generating thoughts in schizophrenia patients.

Methods: Two conditions were examined. In the first condition, participants were required to mentally generate a definition of a common word presented on the screen. In the second condition, they had to listen to the definition of a common word presented on the screen. An event-related fMRI protocol was used during two 9.25 minute scanning sessions in a 3T scanner.

Results: Statistical analyses were performed using constrained principal component analysis (CPCA) with a finite impulse response (FIR) model. During the mental generation task, activations (task-positive network) were observed for both groups in the anterior cingulate (BA 32) and in the left prefrontal (BA 47) gyri, while deactivations (task-negative network) included the posterior cingulate cortex (BA 31), the medial frontal gyrus bilaterally (BA10), and the bilateral angular gyrus (BA 39, 40). Importantly, this network showed less activation of the task-positive and more deactivation of the task-negative networks in schizophrenia patients relative to healthy controls. On the contrary, no group differences were detected in the listening only condition, with activations found within auditory superior temporal and dorsolateral frontal regions in both groups.

Discussion: These results suggest abnormalities in task-positive and task-negative networks associated with the generation of thoughts in schizophrenia, but these abnormalities were not found during listening. Given the hypothesized role of the above-mentioned regions in internal speech and self attributed mental processes (Buckner et al., 2008), these abnormalities might result in self referential misattribution which may play a part in the genesis of auditory verbal hallucinations.

doi:10.1016/j.schres.2010.02.875

Abstracts

Poster 116
NEURAL NETWORKS FOR EMOTIONAL DISCOURSE COMPREHENSION IN SCHIZOPHRENIA

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Background: In a previous study, we showed that patients with schizophrenia did not activate the medial part of the superior frontal gyrus (MFG) when listening to narration describing social interactions with cheating and deception. Considering that MFG is a part of the core network of theory of mind (TOM) processing we suggested that patients’ absence of recruitment of MFG was related to their impairment in social interactions. Here, we question whether patients present a deficit of recruitment while they are processing a task dealing with emotional speech understanding and known to involve the MFG, the left angular gyrus (LAG) and the temporal poles (TP) in healthy subjects.

Methods: Twenty outpatients with schizophrenia (DSM-IV) and thirty-nine healthy volunteers participated in the fMRI study (3T Philips). Both groups did not differ for gender (male: 16 patients and 25 controls), age (patients: 34.0 ± 7.6, controls: 30.5 ± 8.8 years old) and handedness (2 left-handers in patients and controls). Patients showed significant lower level of education than controls (education years, patients: 11.7±0.6, controls: 14.8±0.4, p = 0.0001). Participants performed 2 different tasks replicated twice (4 runs): 1- EMO: classification of 24 emotional sentences into one of three categories: happiness, anger, or sadness 2- NEU: classification of 24 neutral sentences according to sentences’ subject grammatical category: first, second, or third person. Subjects answered a post-session questionnaire in order to assess the strategy used to perform EMO. TOM strategy was considered whether participants imagined they took the place of the speaker or used their knowledge on social relationships. Functional data were analyzed and integrated in a statistical model with SPM5. A second-level random effect analysis was performed with Task (EMO and NEU) and Illness (patients and controls) factors.
Results: Correct answers (CA) and response times (RT) were not significantly different between patients and controls for EMO and NEU (CA EMO patients: 22.2 ± 2.3, controls: 23.3 ± 1.3; RT patients: 997 ± 335 ms, controls: 742 ± 266 ms). The proportion of participants reporting using TOM strategy to complete EMO did not differ between patients and controls (14 patients and 33 controls, p = 0.2). EMO minus NEU contrast revealed activations in the bilateral inferior frontal gyri (F3), bilateral TP, LAG and MF1. Patients minus controls contrast showed bilateral activations in the precentral and superior parietal gyri and the intra-parietal sulcus. Moreover, a significant Task x Illness interaction was found in M1 where only controls activated this region during EMO.

Discussion: A lack of MF1 activation was observed in patients while they did, as controls, use a TOM strategy and as they did not present any trouble to succeed the emotional sentence classification task. This area is known to be involved in various social cognition tasks. Consequently, this result reinforces the idea that this area could be implicitly involved in social cognitive processing and that its functional defect might be at the core of schizophrenic disorders and their impaired social interactions and communication.

doi:10.1016/j.schres.2010.02.877

Poster 117
RESTING-STATE NETWORK CORRELATES OF PSYCHOTIC SYMPTOMS IN SCHIZOPHRENIA

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Background: Schizophrenia has been associated with aberrant intrinsic functional organization of the brain but the relationship of such deficits to psychopathology is unclear. In this study, we investigated associations between resting-state networks and intrinsic functional organization of the brain but the relationship of schizophrenia with paranoid schizophrenia and sixteen matched healthy control participants.

Methods: We estimated whole-brain functional connectivity of multiple networks using a combination of spatial independent component analysis and multiple regression analysis. Five networks (default-mode, left and right fronto-parietal, left fronto-temporal and auditory networks) were selected for analysis based on their involvement in neuropsychological models of psychosis. Between-group comparisons and correlations to psychopathology ratings were performed on both spatial (connectivity distributions) and temporal features (power-spectral densities of temporal frequencies below 0.06 Hz).

Results: Schizophrenia patients showed aberrant functional connectivity in the default-mode network, which correlated with severity of hallucinations and delusions, and decreased hemispheric separation of fronto-parietal activity, which correlated with disorganization symptoms. Furthermore, the severity of positive symptoms correlated with functional connectivity of fronto-temporal and auditory networks. Finally, default-mode and auditory networks showed increased spectral power of low frequency oscillations, which correlated with positive symptom severity.

Discussion: These results are in line with findings from studies that investigated the neural correlates of positive symptoms and suggest that psychopathology is associated with aberrant intrinsic organization of functional brain networks in schizophrenia.

doi:10.1016/j.schres.2010.02.878

Poster 118
ALTERED COGNITIVE AND EMOTIONAL MODULATION OF BRAIN ACTIVITY IN SCHIZOPHRENIA

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Background: Everyday life and clinical experiences demonstrate strong interaction between the processing of emotion and cognition in the human behaviour. Reciprocal modulation and attenuation in medial and lateral prefrontal cortices (including the anterior cingulated cortex) may constitute the neurophysiologic basis for emotional-cognitive interaction as observed in both healthy and psychiatric subjects. Schizophrenia is among the most severe of psychiatric disorders, leading to impairments of affective and cognitive abilities. These dysfunctions affect each other mutually. In this study, we investigated the neural deficits of schizophrenia patients during the interaction of negative emotion and short-term memory.

Methods: Using functional magnetic resonance imaging (fMRI), we investigated BOLD-signal changes in 13 medicated schizophrenia outpatients and 10 healthy subjects during a short-term memory task involving photographs taken from the International Affective Picture System (IAPS). Each short-term memory trial consisted in the sequential presentation of two pictures and a simple question concerning one of the images. The pictures were grouped in 20s blocks depending of their emotional content (negative or neutral). These different experimental conditions were then compared to each other using classic linear modeling. This design allows studying the influence of negative emotional pictures on the short-term memory processes.

Results: During the neutral condition (i.e. visualisation and memorisation of two neutral pictures), schizophrenia patients exhibited higher frontal activity than control subjects, especially in the dorsal part of the anterior cingulate gyrus (dACC) and the dorso-lateral prefrontal cortex (dIPFC). When comparing negative and neutral conditions (i.e. memorisation of two negative pictures versus two neutral pictures), we observed lower activations in schizophrenia patients compared to healthy subjects in the rostral part of the anterior cingulate gyrus (rACC), the medial obito-frontal cortex and bilateral fronto-insular cortex (FIC).

Discussion: These results demonstrate that schizophrenia patients recruit the dIPFC and the dACC more intensely than healthy subjects during a short-term memory task (i.e. neutral condition). A stronger activity in these areas is likely to reflect an increased effort to appropriately complete the task in schizophrenia patients. However, with emotional pictures (negative condition), schizophrenia patients exhibited lower activity in a fronto-insular network, including medial prefrontal areas (rACC and orbito-frontal cortex), compared to healthy participants. Moreover, this lower frontal activity was associated with an increase of the patient reaction times.

doi:10.1016/j.schres.2010.02.879
Poster 119
SEVERITY DEMONSTRATED BY MULTIMODAL MORMOPHOMETRY AND FUNCTIONAL MR IMAGING IN AUDITORY HALLUCINATIONS

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Background: The aim of this study was to validate a multimodal (structural and functional magnetic resonance) approach previously used to study auditory hallucinations. Coinciding clusters in brain areas known to be linked to auditory hallucinations are hypothesized to correlate with clinical severity.

Results: The coincidence analysis showed areas with coexistence of gray matter reduction and emotional activation in the middle temporal gyrus (bilateral) and superior temporal gyrus (bilateral). Significant negative correlations between BPRS and PSYRATS scales were observed in schizophrenic patients. BPRS scores were negatively correlated in middle temporal gyrus (right), while negative PSYRATS correlation affected regions in both the superior temporal gyrus (left) and middle temporal gyrus (left).

Discussion: Our data identify the left superior and middle temporal gyrus as relevant areas for the study of auditory hallucinations. These results give support for the use of multimodal approaches, particularly a structural and functional magnetic resonance technique previously published by our group (Martí-Bonmatí et al., 2007) for identifying areas specifically linked to the pathogenesis of auditory hallucinations.

doi:10.1016/j.schres.2010.02.880

Poster 120
THE NEURAL CORRELATES OF SEVERE COGNITIVE IMPAIRMENT IN SCHIZOPHREinia

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Background: Cognitive impairment is an established finding in schizophrenia, and can be profound in some cases. Nevertheless, little is known about its relationship to the structural and functional brain abnormalities which also characterize the disorder.

Methods: We carried out structural MRI and voxel-based morphometry (VBM) in 25 cognitively impaired and 18 cognitively preserved schizophrenic patients, and also 31 matched controls. Presence of cognitive impairment was defined on the basis of performance below the 1st percentile on either the Rivermead Behavioural Memory Test (RBMT) or the Behavioural Assessment of Dysexecutive Syndrome (BADS), or below the 5th percentile on both. A subset of 18 cognitively impaired patients, 15 cognitively preserved patients and 30 controls also underwent fMRI during performance of a working memory task.

Results: No differences were found between cognitively intact and cognitively impaired patients in lateral ventricular volume or whole brain volume. Voxel-based morphometry also failed to reveal clusters of significant difference in grey matter volume. However, during performance of the n-back task, the cognitively impaired patients showed hypovolisation compared to the cognitively intact patients in a large area that included the dorsolateral prefrontal cortex, the supplementary motor area, the precentral, postcentral and supramarginal gyri and the insula bilaterally.

Discussion: Cognitively impaired schizophrenic patients show no more structural brain abnormality than in the disorder as a whole, but that their brain function is more compromised. This finding could have implications for cognitive remediation strategies in schizophrenia.

doi:10.1016/j.schres.2010.02.881

Poster 121
REDUCED CORTICAL THICKNESS IN FIRST EPISODE SCHIZOPHRENIA

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Background: Previous morphometric studies are suggesting altered cortical thickness mainly in prefronto - temporal regions in first episode schizophrenia. In an extension of these earlier studies, we used an entire cortex vertex wise approach and an automated clustering for the detection and exact quantification of cortical thickness alterations in first episode schizophrenia.

Methods: A group of 54 patients with first-episode schizophrenia according to DSM IV and 54 age and gender matched healthy control subjects were included. All participants underwent high-resolution T1- weighted MRIs scans on a 1.5 Tesla scanner. Cortical thickness was estimated as the distance between the gray-white matter border and the pial surface using an automated computerized algorithm (FreeSurfer Software). Statistical cortical maps were created to estimate differences of cortical thickness between groups based on this entire cortex analysis.

Results: Significant cortical thinning was observed in first-episode schizophrenia patients relative to controls in a number of cortical areas including the dorsolateral and frontopolar cortices, the anterior cingulate cortex, a ventrolateral-orbitofrontal cluster, as well as the superior temporal cortices and superior parietal lobe. Cortical thinning within these regions was on average 4.4-5.7% with strongest reductions in orbitofrontal regions (7.1%).

Discussion: The present findings suggest widespread reduction of cortical thickness, mostly in heteromodal cortices of frontotemporal networks to be present at an early stage of schizophrenia. Taken together, the present morphometric data in first-episode schizophrenia provide further evidence for potential neurodevelopmental deficits and disruption of cortical maturation in this disorder.

doi:10.1016/j.schres.2010.02.882

Poster 122
FUNCTIONAL MAGNETIC RESONANCE IMAGING OF INNER SPEECH IN SCHIZOPHRENIA

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Background: Cognitive deficits and disruption of cortical maturation in this disorder.
Background: Auditory verbal hallucinations in schizophrenia have been linked to defective monitoring of one's own verbal thoughts. Previous studies have shown that patients with auditory verbal hallucinations show attenuated activation of brain regions involved with auditory processing during the monitoring of inner speech. However, there are no functional magnetic resonance imaging studies explicitly comparing the perception of external speech with internal speech in the same patients with schizophrenia. The present study investigated the functional neuroanatomy of inner and external speech in both patients with schizophrenia and healthy control subjects.

Methods: Fifteen patients with schizophrenia and 12 healthy control subjects were studied using functional magnetic resonance imaging while listening to sentences or imagining sentences. The control subjects were studied using functional magnetic resonance imaging while listening to sentences or imagining sentences. The mean age of the patients was 34.7 years (SD 8.7). Mean duration of illness was 11.2 years (range 3–27). Mean score on the Positive and Negative Syndrome Scale (21) was 48.5 (SD 16.5, range 30–83). Patients were matched for age, sex, and handedness to a control group. The present study minimized the effects of acoustic scanner noise during the stimulus presentation through the use of a partially silent gap followed by a period of continuous image acquisition.

Results: The mean response time to complete the inner speech task was 2.62 seconds (SD 1.59) for control subjects and 2.28 seconds (SD 0.85) for patients. This difference was not statistically significant. The main effect of inner speech was associated with greater activation in the left inferior frontal gyrus and anterior cingulate gyrus compared with listening. Listening was associated with greater activation in the right superior temporal gyrus, left transverse temporal gyrus, and right inferior parietal lobule across both groups. Significant interactions between groups (control versus patients) and task (listening versus inner speech) were seen for the left superior temporal gyrus, as well as regions within the cingulate gyrus.

Discussion: The main finding was a significant interaction between group and task for the left superior temporal cortex. During the listening trials, the anticipated activation of the left superior temporal cortex was evident in control subjects and in schizophrenia patients, suggesting that listening to spoken sentences is not impaired in schizophrenia patients. Control subjects showed greater decrease in activation during inner speech compared with listening than patients. This provides evidence for defective self-monitoring of inner speech in schizophrenia patients. Failure to attenuate the activity in the temporal cortex may lead to the attribution of the verbal material as being of external origin, ultimately leading to auditory hallucinatory experiences.
REALITY MONITORING IN SCHIZOPHRENIA PATIENTS:

Twenty-four psychotic patients indicated the presence of AVH during 3T fMRI scanning by squeezing a hand-held balloon. A one sample T-test was performed to reveal group-wise activation during AVH. To enable analysis of brain activation 6 to 0 seconds preceding AVH a tailored ‘selective averaging’ method without any a priori assumptions concerning the haemodynamic response profile was performed. To control for motor related activation, fifteen control subjects squeezed a balloon at matched time intervals.

GROUP-WISE ANALYSIS DURING AVH

Results: Group-wise analysis during AVH revealed brain activation in bilateral, right more than left, language-related regions and bilateral motor-regions. Prominent deactivation preceding AVH was observed in the left parahippocampal gyrus. In addition, significant deactivation was found in the left superior temporal, right inferior frontal and left middle frontal gyri as well as in the right insula and left cerebellum preceding AVH. No significant signal changes were revealed prior to the matched balloon-squeezing in the control subjects.

Discussion: Auditory verbal hallucinations in psychotic patients are consistently preceded by deactivation of the parahippocampal gyrus. The parahippocampus has been hypothesized to play a central role in memory recollection; sending recognized information from the hippocampus to the association areas. Dysfunction of this region could trigger inadequate activation of right language areas during AVH.

doi:10.1016/j.schres.2010.02.885

NEUROPLASTICITY-BASED COGNITIVE TRAINING IMPROVES REALITY MONITORING IN SCHIZOPHRENIA PATIENTS: BEHAVIORAL AND FMRI ASSESSMENTS

Background: Prior research indicates that schizophrenia patients (SZs) are impaired at identifying themselves as the source of self-generated information (reality monitoring). They also show relatively decreased activation within the dorsal medial prefrontal cortex (dMPFC) compared to healthy comparison subjects (HCs) when engaged in this process (Vinogradov et al., 2008). In the present study, we investigated whether this deficit is amenable to a behavioral intervention.

Methods: Thirty one SZs and 15 HCs underwent an fMRI source-monitoring task. Fourteen SZs were then randomly assigned to 80 hours of computerized targeted-cognitive-training (TCT) that focused on training auditory, visual and social cognitive processes. The other fourteen SZs were assigned to a control condition of 80 hours of computer-games (CGs). All subjects repeated the task after the 16 week intervention period. Prior to scanning, subjects were presented with sentences, where the final target word was either supplied by the experimenter, or left blank for subjects to generate themselves. During scanning, subjects were presented with target words, and decided whether they were experimenter-presented or self-generated. BolD fMRI activity was measured on a 3T GE scanner (EPI; TR = 1 sec, 14 slices) before and after the 16 week intervention. Images were analyzed using SPM2.

Results: At baseline, SZs revealed significantly more impairments, compared to HCs, while recalling self-generated information (p <.0005). Whole-brain analyses focused on brain regions showing greater activation for correctly remembered self-generated items versus externally presented items (i.e., a self-referential effect). Across 15 HCs at baseline, the largest region that demonstrated this self-referential effect was dMPFC. Furthermore, as dMPFC activity increased across 15 HC, the more accurate they were at correctly identifying self-generated information (r =.48, p =.03). In contrast, at baseline, all SZs showed deactivation in bilateral frontal regions. Paired t-tests indicate that after 16 weeks of computer-games compared to baseline, CG patients showed increased activation only in bilateral occipital gyri (but not in dMPFC) during self-referential processing, and revealed no change on identifying either more self-generated items (t =.436, p =.66) or more externally-derived items (t =.423, p =.674), compared to baseline. In contrast, after 16 weeks of TCT exercises compared to baseline, TCT patients showed increased activation in the same dMPFC region that the HCs revealed during self-referential processing, and also showed significant improvement on correctly identifying more self-generated items (t =2.026, p =.049), as well as more externally-derived items (t =3.367, p =.002) compared to baseline.

doi:10.1016/j.schres.2010.02.886

THE NEURAL BASIS OF ASSOCIATIVE EMOTIONAL LEARNING IN SCHIZOPHRENIA AND THE RELATIONSHIP WITH ALEXITHYMIA

Background: Schizophrenia is characterized by deficits in emotional processing and regulation (Aleman & Kahn, 2005). Verbalizing of emotions is an important aspect of emotion regulation. To verbalize emotions it is crucial to make associations between feelings and words, which involves emotional memory. We investigated whether schizophrenia patients and controls show different brain activation during associative emotional learning. We also examined whether this was associated with alexithymia (or “no words for feelings”). We expected increased limbic activation in schizophrenia patients during emotional memory. Additionally, we expected schizophrenic patients to report lower verbalizing ability than the controls.

Methods: Seventeen schizophrenia patients and seventeen controls (matched on age, gender and education) performed an associative emotional learning task with emotional and neutral picture-word pairs during fMRI scanning. Participants had to indicate if the picture and word were associated and had to remember the pairs. After scanning they were tested for their memory of the picture-word pairs. They also filled in the Bermond-Vorst Alexithymia Questionnaire (BVAQ). Functional images were acquired with a 3T Philips scanner using echo-planar imaging (EPI). We created contrast images for each participant for the emotional vs. neutral picture-word pairs. We used t tests for group comparisons between patients and controls (SPM5).

Results: Patients demonstrated increased activation in bilateral superior temporal gyrus (STG), left amygdala/hippocampus (amy/
h Hipp) and in left cingulate gyrus (CG) in emotional compared to neutral picture-word pairs. Patients had a higher score on the cognitive component (i.e. were worse in verbalizing, analyzing and identifying emotions) of the BVAQ whereas on the emotional component, groups scored similarly. Patients remembered less picture–word pairs than controls.

**Discussion:** The areas of increased activation in patients have been related to emotional learning (amy/hipp), reduced emotion regulation (amy) and theory of mind (STG) during learning and associating emotional picture-word pairs. We suggest that the increases in activation reflect increased recruitment of neural resources to counter the difficulties that patients have in performing this task. This is consistent with the behavioral and questionnaire results in which patients reported more difficulties in verbalizing, analyzing and identifying their emotions and the fact that they remembered less pairs during the memory test after scanning.

doi:10.1016/j.schres.2010.02.887
activation in the left inferior parietal gurus (p = 0.047), bilaterally in the thalamus (p = 0.025), and a trend level in the striatum (p = 0.052).

**Discussion:** These preliminary analyses on a small sample suggest that the effort needed to complete the N-back task is the same in patients, independently of whether or not they will later respond to treatment. However, patients who later did not respond to treatment, showed decreased activation in the thalamus and striatal regions, both heavily involved with the dopaminergic system. This suggests that patients who are later categorised as non-responders may have a dopaminergic dysfunction which can be observed at baseline, and that could be considered a predictor of future response to treatment.

doi:10.1016/j.schres.2010.02.889

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**Poster 129**

**ALLELIC VARIATION IN NKCC1 IS ASSOCIATED WITH HIPPOCAMPAL AND DORSOLATERAL PREFRONTAL CORTEX ACTIVATION DURING WORKING MEMORY**

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**Background:** Schizophrenia is a disorder of complex heritability, but investigations into this complex genetic architecture can take advantage of decades of basic and clinical data implicating certain physiological systems implicated in the illness. For example, alterations in GABA-mediated neurotransmission are one such candidate system in schizophrenia. Early in brain development, GABA, the primary inhibitory neurotransmitter in the adult brain, is excitatory. The switch from excitation to inhibition is mediated by the relative expression of two genes, SLC12A2 (NKCC1) and SLC12A5 (KCC2) – both cation chloride cotransporters. Studies of gene expression have implicated a potential for alternate transcripts in the pathophysiology of schizophrenia (e.g., KCNH2 (Huffaker, 2009) and DISC1 (Nakata, 2009)). Our group has identified a significant association with the expression of the alternative transcript (NKCC1b (1

∼

27 (Δ21)) and the NKCC1 SNP rs3087889. Specifically, the (A/A) genotype predicted lower expression than both the T/A (p = 0.044) and T/T (p = 0.01) genotypes (Morita, in prep.). This SNP, together with two others at the 3' end of NKCC1, showed weak association to schizophrenia and to cognition in healthy subjects with AA genotype being risk associated. The aim of this study was to examine the effects of eight putative risk SNPs in the NKCC1 gene on neural activity underlying working memory (WM) in order to further understand the potential role of genetic variation in NKCC1 to schizophrenia risk.

**Methods:** We examined the association between NKCC1 and BOLD fMRI activity during WM in a sample of 225 Caucasian healthy volunteers studied at 3T (GE, Milwaukee, WI). Groups were matched for age, gender, WAIS-IQ, 2-back reaction time and 2-back performance (p > 0.05). We performed a second level random effects analysis using multiple regression for independent main effects of each SNP against all others and all possible interactions. Given the stronger relationship between the 3' UTR haplotypes and cognition, we created 4 SNP 3' UTR haplotypes using PHASE (Stephens, 2001) as described previously (Nichols et al. 2006).

**Results:** There were no differences between groups in either 2-back accuracy or reaction time based on genotype. Six out of eight SNPs demonstrated greater DLPCF inefficiency activation consistent with other risk genes and as seen in schizophrenic patients and their unaffected siblings – PFC inefficiency as defined by greater BOLD activation with no accompanying increase in accuracy or speed. Four of these positive SNPs lie on the 3' UTR end of the gene. Haploype analysis revealed that the healthy subjects carrying the risk haplotype showed significantly greater bilateral DLPFC activation and hippocampal activation relative to the non-risk group during the 2-back task.

**Discussion:** We found an association between allelic variation in NKCC1 and neurophysiology within the WM network. This association between expression of alternative transcripts of NKCC1 and allelic variation may confer genetic risk by effecting cortical information processing during higher order cognition in the DLPFC and hippocampus.

doi:10.1016/j.schres.2010.02.890

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**Poster 130**

**ALTERED BRAIN FUNCTION DURING WORKING MEMORY IN ADOLESCENTS AND YOUNG ADULTS AT GENETIC RISK FOR BIPOLAR DISORDER: PRELIMINARY FINDINGS**

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**Background:** First-degree relatives of persons with bipolar disorder (BD) have elevated risk for the illness and subtle cognitive deficits (possible endophenotypes). In our previous work, older adult relatives of BD exhibited hyperactivity in emotion circuitry during a working memory (WM) task, but there have been no published studies of this potential endophenotype in adolescent and young adult relatives.

**Methods:** Ten adolescent and young adult (age 13–28) unmedicated, non-ill first-degree relatives of persons with BD (RELS) and 10 healthy comparable controls performed a 2-back working memory (WM) task and a 0-back control task during fMRI. fMRI data were collected on a 1.5T scanner and analyzed using SPM-2. Mood was assessed on the day of scanning.

**Results:** The groups did not differ on any demographic, neuropsychological or in-scanner task performance variables. RELS failed to exhibit patterns of modulation during WM exhibited by controls (enhancement of cerebellar vermis and midbrain/pons activity, and suppression of OFC activity), and also showed activation patterns not seen in controls (hyperactivation of frontopolar cortex and suppression of amygdala/parahippocampus). Results remained significant after controlling for potential confounders. RELS did not exhibit correlations between performance, brain activity and mood seen in controls, and showed unique associations of brain activity and mood not seen in controls.

**Discussion:** During WM, young, unmedicated RELS of persons with BD exhibit altered modulation of activity in autonomic, emotion and reward circuitry, which, if replicated, may represent biomarkers of genetic risk for BD.

doi:10.1016/j.schres.2010.02.891

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**Poster 131**

**FUNCTIONAL CORRELATES OF THE NON SELF-SERVING ATTRIBUTIONAL BIAS – A PILOT STUDY**

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**Background:** Attributional bias is the tendency to attribute one’s own performance to the internal (stable and global) or external (unstable and specific) causes. Our hypothesis is that individuals with non-self-serving attributional bias (NSA) exhibit underestimation of their ability, making them particularly prone to underestimating their performance in the face of negative feedback and overestimating their performance in the face of positive feedback. Consequently, these individuals would be less likely to engage in effective behavior change. In a previous study, we found that individuals with NSA exhibit impaired hippocampal activation during learning, suggesting that this bias is related to neurophysiological changes associated with learning and memory (Williams et al., 2009).

**Methods:** We examined the neural correlates of learning and memory in individuals with NSA using functional magnetic resonance imaging (fMRI) during a 1-back working memory (WM) task in which participants learned to associate novel stimuli with positive or negative feedback. Participants were divided into high and low NSA groups based on a measure of attributional bias. fMRI data were collected on a 3T scanner and analyzed using SPM-2.

**Results:** Compared to high NSA individuals, low NSA individuals showed reduced hippocampal activation during the learning phase of the WM task, indicating that they may be less able to engage in effective behavior change due to impaired hippocampal activation.

**Discussion:** The results of this study suggest that NSA is associated with impaired hippocampal activation during learning, which may contribute to the difficulty these individuals have in effectively engaging in behavior change. Future studies should examine whether interventions that enhance hippocampal activation in individuals with NSA can improve their ability to engage in effective behavior change.
Background: Humans use causal attributions to infer the cause of events in their social world. Attributions may be internal (attributing the cause to oneself) or external (attributing the causation to another person or situational factors). Causal attributions typically used by a person are associated with psychological disorders (1,2). Some studies demonstrated an association between persecutory delusions and exaggerated externality when attributing causes for negative events while most attribution research has tested the link between depression or anxiety and an attenuated self serving bias (SSB) (3, 4). SSB is the tendency to excessively attribute positive events to internal and negative events to external causes. The few neuroimaging studies into SSB so far have been inconclusive (4).

Methods: Thirteen healthy, right handed men (26 ± 7 yrs, IQ: 113 ± 17) performed an event related attributional bias paradigm (80 visually presented statements based on the Internal, Personal, and Situational Attributions Questionnaire) while assessed with functional Magnetic Resonance Imaging (3 T). Per button press participants indicated whether they attributed the situation externally or internally. ANOVA was performed using SPSS (P < 0.01 at voxel level, Monte-Carlo-corrected P ≤ 0.05, ≥ 26 continuous voxels).

Results: The behavioural data demonstrated a significantly higher number of external (54.5 ± 6.7) compared to internal (24.9 ± 6.2) attributions irrespectively of the situations valence (positive vs. negative) [F(1, 12) = 68.8, p < 0.001]. Valence (positive/negative) however interacted with the attributional style, with a preponderance of positive events in the self attributed trials, whereas negative situations were overbalanced in the trials attributed to others [F(1, 12) = 18.6, p = 0.001]. The fMRI data revealed increased BOLD for the interaction representing a ‘non self serving bias’ (attributing negative events internally and positive events externally) bilaterally in the superior medial gyrus, middle cingulate cortex, right middle frontal gyrus, posterior cingulate cortex and angular gyrus and left superior frontal as well as medial gyrus. The self-serving condition itself did not lead to differential contrasts in brain activation.

Discussion: Behaviourally our sample showed a strong tendency to externalise (attributing all events rather to others than to oneself), which can also be interpreted as low self-responsibility. This tendency might have partially diluted the self-serving bias, as reflected functionally in the lack of any differential brain activation to the self-serving bias condition per se. However our subjects showed an increased brain activation in the frontal and cingulate cortex and the angular gyrus under non self-serving conditions, partly confirming previous work (4). This non self-serving attributional style has previously been associated with depression (3) where subjects demonstrate the tendency to attribute the causation of negative events to themselves and positive events to others. Our study therefore provides insight into the neural network subserving social cognition.

References


doi:10.1016/j.schres.2010.02.892
FUNCTIONAL CONNECTIVITY IN SCHIZOPHRENIA

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Background: The human brain is a complex network of interacting brain regions (Achard et al., 2006). Like people traveling back and forth between connected cities, brain regions continuously share and integrate information. In schizophrenia abnormalities in functioning and structure of anatomically distant brain areas are present; these may reflect a disruption of information integration. New advances in neuroimaging now enable the measurement of functional connectivity, believed to reflect neuronal synchronization between brain regions, and tend to be associated with cognitive functioning (Van den Heuvel et al., 2009). Here we examined whether global functional communication is disrupted in schizophrenia.

Methods: 3 Tesla resting-state fMRI was acquired in 20 patients and controls with chronic schizophrenia and 20 healthy comparison subjects, matched for age, gender and parental education levels. For each individual dataset, the level of voxel-wise correlation between the functional neuroimaging time-series was computed, reflecting the level of functional connectivity. Next, organizational properties of the resulting networks were computed, including measurements for amplitude of the low frequency spontaneous fluctuations (power of LFSF), total number of connections, local and global efficiency (Van den Heuvel et al., 2008).

Results: In the overall organization of functional connectivity between brain regions (both local and global organization), no significant difference was found between patients and controls. Although this of course could be related to the low n, these results tend to suggest that schizophrenia does not involve a wide spread dysfunctional communication between brain regions. However, interestingly, looking at region specific effects, patients showed significant lower LFSF power in the left and right inferior frontal gyrus (T = 3.94, p < 0.05) and inferior parietal gyrus (T = 5.63, p < 0.05).

Discussion: At first glance, overall organization of functional connectivity in schizophrenia seems to be unchanged, observed by similar organization measures as in healthy controls. However, this does not mean that local networks are unaffected. At a more detailed voxel level, patients showed a decreased LFSF power in frontal and temporal regions, regions that are commonly reported to show neurodegenerative effects and structural disconnection effects in schizophrenia (Hulshoff Pol et al., 2001; Mandl et al., 2008), marking less spontaneous neuronal activation in high order brain regions and suggesting local disorganization. Currently, larger groups of patients are examined and correlations with clinical values are assessed.

doi:10.1016/j.schres.2010.02.894

AUDITORY VERBAL HALLUCINATIONS ARE RELATED TO DECREASED BETA-BAND POWER IN THE ANTERIOR SUPERIOR FRONTAL GYRUS – AN MEG STUDY

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Background: FMRI experiments have shown increases in activity in language-related cortical areas during auditory verbal hallucinations, including Broca's and Wernicke's areas. However, scanner noise may interact with hallucination-related brain activity, and blood oxygen level-dependent activity is an indirect measure of neuronal activity. In contrast, magnetoencephalography (MEG) provides no scanner noise and directly measures postsynaptic neuronal activity, providing an appropriate method to investigate the neural correlates of auditory verbal hallucinations. Thus far, MEG studies investigating auditory verbal hallucinations have consisted of very small sample sizes (N = 1; N = 1 and N = 3). The present study is the first MEG study investigating this phenomenon in a larger sample.

Methods: Twelve patients with a psychotic disorder (paranoid schizophrenia: 10; psychosis non-otherwise-specified: 2) who intermittently experienced auditory verbal hallucinations indicated their hallucinations by button-press while laying in a 151-channel MEG-scanner for 30 minutes. For each individual, artifact-free segments in the hallucinatory state and in the non-hallucinatory state were selected. To account for the heterogeneity in hallucination-length and –number, and to include as much data as possible, length and number of the selected segments were maximized on an individual basis. These data were contrasted using synthetic aperture magnetometry (SAM), a recently developed method for source localization. As a control condition, patients performed a self-paced button-press task.

Results: In the hallucination experiment, SAM imaging revealed a statistically significant decrease in beta-band neuronal synchronization in the bilateral superior frontal gyrus during the hallucinatory state. In addition, significant decreases in synchronization in the beta and gamma frequency bands were observed in the left motor cortex. In the control experiment, an increase in synchronization in the alpha band in the right motor cortex as well as decreases in synchronization in the beta and gamma bands in the left motor cortex were observed.

Discussion: In this study, a change in beta-band activity in the anterior superior frontal gyrus was observed during auditory verbal hallucinations. This brain region is often considered to be part of the dorsolateral prefrontal cortex, a brain area implicated in selective attention, working memory and meta-cognitive processes. Aberrant activation of this region in schizophrenia has consistently been shown in neuroimaging experiments, including an MEG study (N = 3) in which patients showed aberrant beta-band activity during auditory verbal hallucinations. These findings suggest that higher cognitive functioning deficits are related to the experience of auditory verbal hallucinations. However, more research will be needed to elucidate the exact relationship between the anterior superior frontal gyrus and auditory verbal hallucinations in psychotic patients.

doi:10.1016/j.schres.2010.02.895

DECREASED LANGUAGE LATERALIZATION IN MEDICATION NAIVE SCHIZOPHRENIA

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Background: Lateralization refers to differences between hemispheres regarding structure and function. Functional lateralization can be calculated based on functional MRI data and is expressed by the lateralization index (LI), showing the relative contribution of the
hemispheres during a task. A positive LI represents left-hemisphere dominance, whereas a negative value indicates right-hemisphere dominance. Evidence is accumulating to suggest that patients with schizophrenia show aberrant language lateralization. While language functioning in healthy controls is mediated predominantly by regions in the left hemisphere and is thus characterized by a positive LI, the LI is decreased in patients. It is, however, unclear at what stage of the illness this abnormal lateralization arises, and whether it is affected by medication. Using fMRI, we investigated whether language lateralization is already different in medication naive schizophrenia patients in their first episode of illness.

**Methods:** We included first episode schizophrenia patients who had never had antipsychotic medication (SZ, n = 35) and compared them to matched healthy subjects (HC, n = 43). Subjects performed 3 tasks which have been shown to activate language areas: a paced verb generation task, an anotnym generation task, and a semantic decision task (1, 2). Regions of interest (ROIs) were selected based on their known involvement in language processing (3) and created using the AAL-atlas (4). This resulted in 8 ROIs per hemisphere. fMRI data were analysed and pre-processed using SPM5. Activation levels for language processing, expressed in b-values, were obtained. Subsequently, the LI was calculated for each ROI and each subject, based on the magnitude of activation change. To prevent a bias caused by activation level differences between groups, we applied a dynamic threshold (5). A repeated measures ANOVA with ROI (8 levels) as within-subjects factor and group (2 levels) as between-subjects factor was conducted to investigate effects of group on lateralization indexes. Post-hoc t-tests, corrected for multiple comparisons, were performed to investigate in which ROIs lateralization was significantly different between groups.

**Results:** There was an effect of group (F(1,76) = 14.68, p < 0.000) on lateralization, with SZ (LI = 0.62) showing less lateralization than HC (LI = 1.46). This was due to a reduced left sided activation in SZ compared to HC (SZ:3.059 vs. HC:3.66, t (76)=-2.04, p=.045). The LI was significantly decreased in patients. It is, however, unclear at what stage of the illness this decreased lateralization arises, and whether it is affected by medication. Using fMRI, we investigated whether language lateralization is already different in medication naive schizophrenia patients in their first episode of illness.

**Discussion:** Here, we compared brain activation during WM between patients and healthy controls matched for performance. The reduced WM capacity in patients, as observed by a smaller memory set size, was paralleled by reduced activation in bilateral putamen and VLPFC. As all patients were on antipsychotics with low impact on the striatal DA system (e.g. clozapine, quetiapine, olanzapine), respectively received low daily antipsychotic doses, this reduced activation in the putamen is not likely to be an artefact of medication. We are currently including more patients to increase statistical power. Furthermore, we will extend this study to include healthy siblings of patients, in order to investigate the effect of genetic factors on WM activation. Finally, we plan to run connectivity analyses (DTI, PPI, DCM) to test for changes in fronto-striatal connectivity beyond activation level differences.

**Acknowledgements:** This study was supported by grants to M.V. from the Boehringer Ingelheim RLD, the Stichting MAPE, the ECVN, the Amsterdam University Medical Centre, the ZonMW and the Netherlands Organization for Health Research and Development (ZonMw). We would like to thank the patients and their families for their participation.

**References:**

(5) Zerrin Atakan 1, Philip K. McGuire 1

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**Poster 136**

**EVIDENCE FOR DECREASED FRONTO-STRIATAL FUNCTIONING IN SCHIZOPHRENIA DURING WORKING MEMORY**

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**Background:** Functional magnetic resonance imaging (fMRI) studies on working memory (WM) tasks in schizophrenia patients have shown conflicting results regarding frontal lobe activation. Both hyper- and hypo-activation of the prefrontal cortex (PFC) have been reported. This inconsistency may be due to several factors of which the cognitive tasks used, the cognitive load, and the effects of medication are probably the most important. In addition to PFC, the basal ganglia are also thought to be of importance, especially during encoding and maintenance, by mediating cortico-basal ganglia-cortical interactions. The goal of the present study was to determine the neural activation pattern of WM in schizophrenia patients matched for performance compared to controls.

**Methods:** 14 schizophrenia patients on atypical antipsychotic medication and 14 matched healthy controls performed a Sternberg verbal WM task consisting of high and low WM load trials. During each trial a memory set was presented for 4 seconds, followed by a maintenance period (0.5 or 3.5 s) and final presentation of a probe letter. Subjects had to indicate whether or not this probe letter was part of the memory set. Prior to scanning, the size of the memory set for the high load condition was determined individually in a practice session. The aim of this session was to determine the maximal set size in which subjects would perform at 90 percent accuracy. The time between memory set and probe, as well as between subsequent trials was varied in such a way as to minimize multi-collinearity between task regressors. This allowed us to separate the fMRI response during encoding, maintenance and retrieval. fMRI data were acquired on a 3.0 T scanner and preprocessed and analysed using SPM5.

**Results:** Controls performed at 87.4% (± 4.8) and 93.1% (± 6.5) accuracy level on the high versus low WM trials, respectively. Patients performed at 82.6% (± 10.1; p = 0.13) and 90.7% (± 8.0; p = 0.27), respectively. However, the average memory set size differed (p = 0.002), with patients using on average 5 letters (± 1.1) and controls 6 (± 1.0) letters. In controls, activation during high WM load trials was increased compared to low WM trials in the left dorsolateral prefrontal cortex (DLPFC), the supplementary motor area (SMA) extending into the anterior cingulate cortex (ACC), bilateral superior parietal cortices and bilateral putamen. As compared to controls, patients showed significantly reduced activation in left ventrolateral prefrontal cortex (VLPFC), bilateral inferior parietal cortices and bilateral putamen. During encoding and maintenance, controls showed greater activation in bilateral putamen and left VLPFC compared to schizophrenia patients. Finally, retrieval was associated with increased activation in left SMA and left DLPFC in controls but not in patients.

**Discussion:** Here, we compared brain activation during WM between patients and healthy controls matched for performance. The reduced WM capacity in patients, as observed by a smaller memory set size, was paralleled by reduced activation in bilateral putamen and VLPFC. As all patients were on atypical antipsychotics with low impact on the striatal DA system (e.g. clozapine, quetiapine, olanzapine), respectively received low daily antipsychotic doses, this reduced activation in the putamen is not likely to be an artefact of medication. We are currently including more patients to increase statistical power. Furthermore, we will extend this study to include healthy siblings of patients, in order to investigate the effect of genetic factors on WM activation. Finally, we plan to run connectivity analyses (DTI, PPI, DCM) to test for changes in fronto-striatal connectivity beyond activation level differences.

**Acknowledgements:** This study was supported by grants to M.V. from the Boehringer Ingelheim RLD, the Stichting MAPE, the ECVN, the Amsterdam University Medical Centre, the ZonMW and the Netherlands Organization for Health Research and Development (ZonMw). We would like to thank the patients and their families for their participation.

**References:**

Background: Cannabis is the world’s most commonly used illicit substance. Whilst its effects on perception are well documented, little is known about the neural basis of these effects and how they are modulated by two of cannabis sativa’s most abundant active ingredients, Delta-9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD). We used fMRI to assess the effects of THC and CBD on brain activation during a simple visual and auditory stimulation paradigm in healthy volunteers.

Methods: Fourteen right handed male subjects who had used cannabis at least once but less than 15 times attended scanning sessions on 3 occasions. Identical 10 mg THC, 600 mg CBD and placebo capsules were allocated in a balanced double blinded pseudorandomised crossover design. Measures of plasma levels of each substance, physiological parameters and measures of psycho-pathology, anxiety, intoxication and mood were taken at baseline and at regular intervals following ingestion of substances.

Results: Ingestion of THC and CBD led to reliable increases in plasma levels of each substance and for THC concomitant increases in anxiety, intoxication and positive psychotic symptoms; CBD and placebo caused no significant symptoms. As expected, visual and auditory stimulation led to robust activations in occipital and temporal cortices respectively under placebo conditions. Administration of THC led to decreased activation in primary auditory cortex relative to placebo in the auditory task but increased activation in primary visual cortex, with the additional recruitment of other visual areas, in the visual task. CBD led to an increase in activation in right temporal activation during auditory stimulation and right occipital activation during visual stimulation. THC and CBD had opposite effects in the posterior superior temporal gyrus, the right sided homologue to Wernicke’s area, during auditory stimulation. Moreover, THC mediated attenuation of activation in this area (cluster maximum -61, -15, -2) during auditory stimulation correlated with concomitant rise psychotic symptoms ($r = -0.534$, $p = 0.049$). In the visual task CBD enhanced visual responsiveness in widespread extrastriate regions compared to THC.

Discussion: Single acute doses of THC and CBD significantly modulate brain function in areas that process auditory and visual information. The data also indicate that the different psychoactive constituents of cannabis have dissociable quite different effects on sensory processing, often in opposite directions. In the right sided homologue to Wernicke’s area the effects of THC were opposite to those of CBD and correlated with the concurrent increase in psychotic like symptoms; this region is thought to play a role in resolving ambiguous and affect laden meanings in language. These results are the first to demonstrate how two different constituents of cannabis (THC and CBD) act on the sensory cortices and how these effects are associated with the induction of psychosis like symptoms. This has important implications in furthering our understanding of the mechanisms of the actions of cannabis and the symptoms of psychosis.

doi: 10.1016/j.schres.2010.02.899

**Poster 138**

**GLUTAMATE IN SCHIZOPHRENIA - A REVIEW**

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Background: Schizophrenia is characterized by decreased brain volumes, which might be explained by reduced neuropil (Harrison, 1999; Wright et al., 2000). This suggests changes in synaptic organization, NMDA-receptor mediated glutamatergic neurotransmission, in particular hippocampal glutamatergic pathways, might be prominently involved (Harrison, 2004; Harrison and Weinberger, 2005). It is hypothesized that in schizophrenia, NMDA-receptor hypofunction leads to excessive release of glutamate, which results in molecular and behavioral abnormalities (Olney, 1995). Glutamatergic neurotransmission is thus likely to be of major importance in the disease mechanism. To investigate the role of glutamate in schizophrenia, we reviewed human in vivo 1H magnetic resonance spectroscopy (1H-MRS) studies published on this topic.

Methods: We conducted a PubMed search for articles reporting on glutamate levels in schizophrenia. Studies were included if they (1) were in vivo 1H-MRS studies of glutamate concentrations in schizophrenia, (2) compared patients with a healthy control group and (3) did not use any interventions. We were able to obtain 16 articles that met these criteria.

Results: Most articles report on chronically ill patients (Chang et al., 2007; Luktenhoff et al., 2008; Ohmann et al., 2005, 2007; Öngür et al., 2008; Rüsch et al., 2008; Tajoshi et al., 2009; Tebartz van Elst et al., 2005; Théberge et al., 2003; Wood et al., 2007), a few studies examined high risk adolescents (Stone et al., 2009; Tibbo et al., 2004; Yoo et al., 2009) and first-episode patients (Ohmann et al., 2005, 2007; Théberge et al., 2002, 2007; Wood et al., 2008). Prefrontal glutamine, a glutamate precursor, appears to be upregulated in early disease stages, but no changes were reported on glutamate levels. As the disease progresses, prefrontal glutamine and glutamate levels may decrease below normal. In the thalamus, glutamine also seems to be increased in first-episode patients, but again glutamine remains unchanged. Glutamate and glutamine in the hippocampus remain at normal levels. In general, glutamatergic alterations in schizophrenia cannot be explained by severity of symptoms, illness duration or medication intake.

Discussion: The increased glutamine levels together with unchanged glutamate levels in schizophrenia may indicate increased glutamatergic activity; alternatively, it can be a marker of abnormal glutamine-glutamate conversion. Decreased prefrontal glutamatergic levels suggest reduced synaptic activity later on in the disease. Changes in hippocampal glutamatergic activity in schizophrenia were generally not reported in the reviewed studies. Further research is needed to fill the gaps in knowledge about glutamatergic neurotransmission during the course of schizophrenia.

doi: 10.1016/j.schres.2010.02.899
Poster 140
INTERACTION BETWEEN HIPPOCAMPAL GLUTAMATE AND STRIATAL DOPAMINE – RELATIONSHIP TO SUBSEQUENT ONSET OF PSYCHOSIS

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Background: Excess striatal dopamine activity in schizophrenia is thought to arise secondary to dysfunctional glutamatergic transmission. Whilst imaging studies have provided substantial evidence for both glutamatergic and dopaminergic abnormalities in schizophrenia, the relationship between these two neurochemical systems has yet to be directly investigated in humans. Subjects with attenuated psychotic symptoms (an At Risk Mental State – ARMS), have a 400 fold increased risk of transition to a psychotic disorder. Previous neuroimaging studies in the ARMS have separately shown that it is associated with alterations in hippocampal structure and function, striatal hyperdopaminergia, and reduced regional glutamate levels.

Methods: We recruited 16 subjects with prodromal symptoms of psychosis, who met criteria for the ARMS, and 12 healthy control subjects. All the ARMS subjects had attenuated psychotic symptoms (abnormal beliefs, perceptions or speech). Subjects were assessed at the time of scanning with the Comprehensive Assessment of At Risk Mental States (CAARMS). We acquired 1H-MRS data using a Point Resolved Spectroscopy (PRESS) sequence (Echo Time = 30 ms) from the left hippocampus on a General Electric 3 T MR scanner. Waterscaled metabolite levels were determined using LCModel, and corrected for tissue content of the spectroscopy volume. PET data were acquired for all subjects following injection of [18F]DOPA on an ECAT/EXACTID 966 PET tomograph. Data were spatially normalized to the Montreal Neurological Institute (MNI) template, and left striatal [18F]DOPA uptake constant Ki values were calculated using cerebellum as the reference region. Group differences in the relationship between striatal [18F]DOPA uptake and hippocampal glutamate were determined using a general linear model to examine the group by covariate interaction (group-mean centered hippocampal glutamate) interaction, with striatal [18F]DOPA Ki as the dependent variable. In ARMS subjects, relationships between left striatal [18F]DOPA uptake and left hippocampal glutamate and the three main CAARMS outcome measures (severity of abnormal thought content, abnormal perceptions and speech abnormalities) were explored using linear regression with model simplification by backwards elimination. The relationship of dopamine and glutamate to transition was investigated by logistic regression.

Results: There was a significant group difference in the relationship between striatal [18F]DOPA Ki and hippocampal glutamate (F2,25 = 3.377; p = 0.05), with a significant negative correlation in ARMS subjects (r = -0.538, p < 0.05), but no correlation in controls (r = 0.046; p = 0.887). Subsequent to scanning, four of the ARMS sample underwent transition to frank psychosis. In this subgroup, there was a trend for the interaction between [18F]DOPA Ki and hippocampal glutamate (p = 0.08) to predict the later onset of psychosis. Linear regression of [18F]-DOPA Ki on CAARMS symptoms in ARMS subjects showed a significant correlation with attenuated delusions after model simplification (F1,14 = 6.268, p = 0.025). Hippocampal glutamate levels in ARMS subjects were inversely correlated with abnormalities of speech production at trend level (F1,14 = 4.215, p = 0.06).

Discussion: These findings provide the first in vivo evidence that the coupling between hippocampal glutamate and striatal dopamine activity is abnormal in people with prodromal signs of psychosis, and that the relationship between these two neurotransmitters might be a marker for increased risk of transition to a full-blown psychotic disorder. These data also support the hypothesis that dopamine and glutamate dysfunction in psychosis are related to different types of psychotic phenomena.
aim of this study was therefore to examine theta-gamma power cross spectral phase coherence (CSPC) in this patient group.

**Methods:** EEG data was collected during the performance of a go-no-go task in a sample of sixteen patients with schizophrenia and seventeen healthy controls. Patients and controls were matched on age and parental socioeconomic status. Independent component analysis was used to extract a stimulus locked fronto-central and posterior component on bandpass filtered data from each subject. Phase coherence was then measured using a wavelet decomposition between the signal at 6 Hz and power at all frequencies between 6 and 50 Hz for each time point in the epoched data, both between and within the two independent components. Statistical comparisons were thresholded using the false discovery rate (FDR) because of the multiple comparisons in the time-frequency plane.

**Results:** Two components matched on spatial location and ERP were reliably obtained from all study participants. Both components showed a consistent event related spectral perturbation (ERSP) with peak power changes occurring earlier in the posterior component, and a greater ERSP in the nogo condition. Stimulus locked increases in cross spectral theta-gamma CSPC were also seen in both components (FDR corrected p < 0.05). There was no effect of diagnosis on ERSP. However, the CSPC was reduced in the posterior component, and between components in the patient group (FDR corrected p < 0.05).

**Discussion:** In the controls there was a sequence of coherence between theta and gamma power both within and between components following stimulus presentation prior to the button press, and a subsequent fronto-central gamma power increase. This was significantly attenuated in the patient group, suggesting reduced communication both within and between the two regions reflected by the independent components. It is likely this communication reflects the interaction between top-down and bottom-up elements to information processing in evaluating the stimulus prior to making the response. Whilst the source of theta measured at the surface remains unclear, it is likely that a significant component arises from the medial temporal lobe and reflects resonance between hippocampus, cingulate and more superficial neocortical structures. These findings suggest a further mechanism for dysconnectivity in schizophrenia, and may reflect abnormalities in binding between hippocampus and neocortical areas. This also provides a new model for the genesis of positive symptoms in the disorder.

**Poster 142**

**ELECTROPHYSIOLOGICAL CORRELATES OF WORKING MEMORY IN ADOLESCENTS AT-RISK OF PSYCHOSIS AND MATCHED CONTROLS**

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**Background:** The presence of psychotic symptoms in adolescence has been identified as a potential risk marker for the development of schizophrenia in adulthood. It is considered that working memory may represent a neurocognitive trait marker for schizophrenia, as it is considerably impaired throughout the illness, it involves neural circuits deemed dysfunctional in the disorder and has been associated with negative symptoms (Wood et al., 2003). The present study aimed to investigate the electrophysiological correlates of working memory in adolescents considered symptomatically at-risk of developing psychosis and a group of healthy controls.

**Methods:** Participants were recruited from 8 primary schools in north Co. Dublin. Participants were screened for psychotic symptoms in schools using a 7-item Adolescent Psychotic-Like Experience Screener (Kelleher et al., 2009). Further screening was carried out via clinical interview. 22 participants took part in the study comprising 11 adolescents who were experiencing psychotic symptoms (the at-risk group) (3 male; 10 right-handed; mean age 12.3 years) and 11 healthy matched control adolescents (4 males; 11 right-handed; mean age 12.5 years). Behavioural and electroencephalographic (EEG) data (62 channels) were collected as participants completed a computerised version of the Sternberg working memory task (Sternberg, 1966). The task included 4 blocks (2 × low memory load and 2 × high memory load). Participants were presented with a study stimulus showing a number of target stimuli in placeholders. Each block contained 32 test trials in which participants made a button press response to indicate whether a stimulus was in a correct or incorrect location.

**Results:** Waveform components elicited during the task were similar across all conditions and included a P3b component at posterior parietal electrodes, however, differences in mean amplitude were observed between groups. Amplitude in all conditions was lower for the at-risk group than for the control group. Regardless of target location (correct or incorrect), correct responses were associated with decreased mean amplitudes in the at-risk group at posterior parietal (Pz for correctly identified target in study location: F(1,21) = 5.1, p = 0.035 and Pz for correctly identified target in novel location: F(1,21) = 9.33, p = 0.006) and left temporal-parietal electrodes [TP9 for correctly identified target in study location: F(1,21) = 12.8, p = 0.002 and TP9 for correctly identified target in novel location: F(1,21) = 8.59, p = 0.008]. Incorrect responses were associated with decreased mean amplitudes in the at-risk group compared with the control group at posterior parietal sites [Pz for incorrectly identified target in study location: F(1,21) = 5.74, p = 0.026 and POz for incorrectly identified target in novel location: F(1,21) = 5.57, p = 0.029]. No overall effect of load was found.

**Discussion:** Behaviourally the groups did not differ on either accuracy or reaction times. Mean amplitudes were consistently and significantly lower, for the at-risk group across all conditions in the task, indicating possible use of an alternate brain circuit to perform the task. The necessity for the use of this alternate circuit may speculatively suggest the presence of dysfunction in the ‘normal’ neural circuit for this task. This study adds to the evidence for parietal dysfunction in the earliest stages of psychosis (Whalley et al., 2005).

**Acknowledgements:** This work was funded by the Health Research Board Ireland (Clinician Scientist Award to M. Cannon) and a NARSAD Independent Investigator Award to M. Cannon.

**Poster 143**

**AN ELECTROPHYSIOLOGICAL EVIDENCE FOR ENHANCED LOCAL BUT REDUCED GLOBAL INTEGRATION OF VISUAL INFORMATION IN SCHIZOPHRENIA**

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**Background:** Disturbance in the integration of visual information is one of the hallmarks of schizophrenia. In the spatial domain, visual integration deficits are seen e.g. as impairments in the identification of fragmented images and gestalt figures. In the time domain, visual
Poster 144
MEMORY CONSOLIDATION DURING SLEEP IN SCHIZOPHRENIA

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Background: There is evidence of improved memory consolidation, i.e., an increase in recall without further training, during sleep compared to a waking condition. This study seeks to determine whether patients with schizophrenia show a lack of sleep-related consolidation and whether the impairment is related to disturbances of particular sleep phases or other indices.

Methods: So far, 14 patients with schizophrenia (mean age 42.9 years) and 20 healthy controls (38.5 years) have taken part in this ongoing study. There is a day and night-time condition in a balanced design. Both conditions comprise a learning phase at the beginning and a test phase after 8 hours. A verbal (short prose passage) and a procedural learning task (mirror tracing task) were used. The sleep EEG was recorded by means of a Biopac MP 150.

Results: In a preliminary data analysis, patients with schizophrenia showed no improved memory consolidation during the night compared with the day condition. Enhanced prose learning was related to an increased number of sleep spindles whereas improved consolidation of mirror tracing was related to REM sleep parameters.

Discussion: Although patients with schizophrenia do not exhibit improved memory consolidation during sleep as compared to waking, there are specific and different sleep indices related to verbal and procedural learning respectively. This has also been found to be the case in healthy participants and results will be discussed against the background of results in comparison groups.

doi:10.1016/j.schres.2010.02.905

Poster 145
PHENOTYPING OF SCHIZOPHRENIA BY MULTI-MODAL BRAIN IMAGING

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Background: Neurogenetic research into schizophrenia is limited by its phenomenological features which are partly shared with other psychotic, affective and personality disorders. The evolving phenotype is also dependent on environmental factors impacting on neurodevelopment and the complex interplay with a genetic predisposition. Not surprisingly, the identification of genes associated with schizophrenia has remained inconclusive [1]. Biomarkers or "endophenotypes" of the disorder could facilitate more targeted neurogenetic research. Findings emerging from neurocognitive, neuropsychological and brain imaging research have provided a better understanding of impaired brain functions in schizophrenia and revealed a consistent pattern of regional grey and white matter pathology that is also closely associated with common clinical, neurocognitive and pathophysiological features of the disorder. “Mismatch negativity” (MMN) is a prime candidate of a potential endophenotype of schizophrenia. MMN is recorded as event-related potential in response to auditory change. Smaller MMN amplitudes are a well-established finding in schizophrenia [3] and appear to be unaffected by antipsychotic drug treatment [2]. MMN amplitude reduction emerges in the prodromal phase of illness [4] and continues to decline with illness progression [5] together with deteriorating clinical outcome [6]. Smaller MMN was also found in biological relatives of schizophrenia patients [7]. Importantly, these findings are specific to schizophrenia and not found in phenomenologically related conditions (eg. bipolar affective disorder with psychosis [8]). Our recent research further demonstrated that reduced MMN is correlated with cerebral fronto-temporal grey matter loss in schizophrenia [9]. The resulting impairment of global functioning is more common in schizophrenia than in phenomenologically related conditions.

Methods: Current source densities (CSD) of MMN were calculated from 64 channel electroencephalographic recordings in 13 schizophrenia patients versus 13 matched healthy control subjects and correlated with cerebral grey matter measures derived from cortical pattern matching [9].

Results: Patients showed significant reduction of MMN CSD which correlated with reduced prefrontal, temporal, and parietal grey matter.

Discussion: Our results confirm our previous findings based on Fz-recorded MMN peak amplitudes [9] and suggest that MMN can serve as a tool to investigate the pathophysiology of MMN amplitude reduction and associated cerebral grey matter loss. A potential mechanism is altered glutamate neurotransmission in schizophrenia which is known to affect MMN generation [10] while excessive glutamate levels are neurotoxic. Ongoing animal model research is exploring this mechanism and may guide future neurogenetic investigations into schizophrenia. (Supported by NH&MRC Australia).

doi:10.1016/j.schres.2010.02.905

References
Poster 144
REDUCED EVENT-RELATED LOW FREQUENCY EEG ACTIVITY IN EARLY ONSET SCHIZOPHRENIA PATIENTS AND THEIR UNAFFECTED SIBLINGS
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Background: Previous investigation has frequently shown reduced event related potential (ERP) amplitudes in schizophrenia patients whilst completing a variety of information processing tasks. Schizophrenia patients have also demonstrated abnormal oscillatory activity in a range of frequency bands, however much of this work has focused on resting oscillatory activity, rather than event related. Reduced ERP amplitudes have also been observed in the unaffected siblings of schizophrenia patients suggesting that these abnormalities are associated with a genetic predisposition to schizophrenia, as well as a diagnosis of schizophrenia. This study sought to determine whether the abnormality of low frequency evoked (phase locked to stimulus) and induced (not phase locked to the stimulus) oscillations in the delta (between 1-4 Hz) and theta (between 4-8 Hz) bands that has been demonstrated during information processing by stable and adult-onset schizophrenia patients also occurs in early-onset schizophrenia, and unaffected siblings of those with early-onset schizophrenia.

Methods: Early-onset schizophrenia patients (n=29, mean age=19.51), unaffected siblings (n=36, mean age=17.93) and healthy control subjects (n=35, mean age=17.89) completed a visual go/no go task in which they were required to respond to a frequent ‘X’ target, and withhold responses to an infrequent ‘K’ target. During completion of the task, electroencephalographic (EEG) signals were recorded. Correct hit, false alarm and correct rejection trials were segregated for analysis. The EEG data were analysed for evoked and induced oscillatory activity using a continuous wavelet transform.

Results: Compared with the healthy control group, both schizophrenia patients and unaffected siblings showed reduced stimulus locked evoked delta activity in correct hit, false alarm and correct rejection trials. However, levels of stimulus locked induced theta activity in all trial types were reduced in schizophrenia patients, but were comparable to controls in unaffected siblings.

Discussion: Reduced oscillatory activity was found in patients with early-onset schizophrenia, similar to abnormalities previously demonstrated in stable and adult-onset schizophrenia patients. Unaffected siblings showed attenuated evoked delta activity during all trial types, indicating that this might be associated with genetic susceptibility for schizophrenia.

doi:10.1016/j.schres.2010.02.906
Background: Recent evidence suggests that patients with schizophrenia are characterized by reduced synchronous, oscillatory activity in the beta- and gamma-band range that may index a core dysfunction in the coordination of distributed neural activity. However, it is currently unclear to what extent high-frequency oscillations (\(>60\) Hz) contribute to impaired neural synchronization as research has so far focused on gamma-band oscillations between 30-60 Hz. Secondly, it is not known whether deficits in high-frequency oscillations are already present at the onset of the disorder and to what extent reductions may be related to the confounding influence of medication.

Methods: To address these issues, we employed magnetoencephalography (MEG), a method particular suited for the examination of low-amplitude, high-frequency oscillations, during perceptual organisation in a sample of chronic patients with schizophrenia (\(N = 16\)), a sample of first-episode, never-medicated patients (\(N = 20\)), and in a group of healthy controls (\(N = 25\)). Perceptual organisation was examined with Mooney Faces. MEG signals were analysed for spectral changes in oscillatory activity in the frequency range of 25-150 Hz. To identify the neural generators of gamma-band activity, we used a beamforming technique and performed source localization in the frequency range of maximum power in the gamma band.

Results: Compared to healthy controls, both groups of schizophrenia patients showed a highly significant reduction in high-frequency gamma-band activity (60-120 Hz) over parieto-occipital sensors. Furthermore, we observed a relative increase of gamma-band power in the lower frequency range (25-45 Hz) on fronto-temporal channels. Chronic patients were characterized by a pronounced deficit in gamma-band activity and perceptual organisation relative to first-episode patients. The analysis of high-frequency gamma-band activity in source space revealed reduced power in the right temporal and lateral occipital complex (LOC) in chronic schizophrenia patients compared to controls.

Discussion: These results suggest that schizophrenia is associated with a widespread reduction in high-frequency oscillations that indicate local network abnormalities. These dysfunctions are independent of medication status and already present at onset, suggesting a possible progressive deficit during the course of the disorder.

doi:10.1016/j.schres.2010.02.909

Poster 149
IMPACT OF PRO-PSYCHOTIC DRUGS ON SINGLE UNIT AND OSCILLATORY FIELD ACTIVITY IN PREFRONTAL CORTEX SUBREGIONS OF THE RAT

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Background: Prefrontal cortex dysfunction is one of the most consistent clinical findings associated with schizophrenia. Within the prefrontal cortex, the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) are regions that are compromised in schizophrenia. In this study we examined the effects of three pro-psychotic compounds with different pharmacological profiles on the neuronal activity of these cortical regions. These were amphetamine, the NMDA antagonist MK801 and 5HT2A agonist DOI. Agonists of 5HT2A receptors, such as DOI, are hallucinogens and are used to model some aspects of schizophrenia; however, very little is known about the in vivo effects of these compounds on the cortical neurophysiology of freely moving animals. Amphetamine and NMDA antagonists also produce psychosis and other symptoms of schizophrenia, but lack substantial affinity for 5HT receptors. Recent work from our lab has evaluated the effects of amphetamine and NMDA antagonists, such as MK801, and found contrasting effects on single unit discharge in the medial prefrontal cortex as compared to convergent effects in the orbitofrontal cortex.

Methods: We recorded OFC and ACC neural activity in freely moving rats, before and after the randomized systemic administration of DOI, amphetamine, MK801 or saline vehicle in a repeated measures design. Briefly, rats were able to move freely in a home cage environment while attached to a lightweight headstage cable. All injections were given IP, following a 30 minute drug free baseline period. Neural activity was recorded for 2 hours post injection. Standard electrophysiological techniques were used to record, sort and analyze single unit discharge and local field potential data.

Results: DOI has previously been shown to enhance excitatory post synaptic currents in cortical slice preparations. In contrast, we found that DOI inhibited the single unit activity of OFC neurons in a dose dependent fashion. Modulations of LFP activity were also quantified. MK801 predominantly increased the single unit activity of OFC neurons, coincident with disruptions in LFP activity. The effects of amphetamine on OFC neurons were mixed, producing strong inhibition in some units or strong excitation in other units. Again, these changes in unit activity were accompanied by strong changes in LFP activity.

Discussion: Taken together, these data indicate that at the single unit level or at the neural network level, hallucinogens and propyschotic drugs have divergent effects that are dependent upon cortical subregion identity. Importantly, these findings suggest that in freely moving animals in which behavioral output is unconstrained, DOI, MK801 and amphetamine differentially disrupt cortical information processing, which may lead to deficits in the ability to flexibly engage and disengage cortical networks in response to environmental contingencies and general cognitive demand.

doi:10.1016/j.schres.2010.02.910

Poster 150
QEEG SPECTRAL POWER AND NEGATIVE SYMPTOMS IN THE DETECTION OF BEGINNING PSYCHOSIS

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Background: Patients in an “at risk mental state for psychosis” (ARMS) can be detected based on specific as well as unspecific prodromal signs. Only about 30% of ARMS identified by ultra high risk studies develop frank psychosis and therefore it is important to identify further factors contributing to the prediction of beginning psychosis. Quantitative EEG (QEEG) spectral analysis has been shown to be correlated with negative symptoms in first episode psychosis patients and this might also be the case in prodromal patients. Furthermore, the combination of QEEG and negative symptoms may provide information on vulnerability in addition to clinical assessment.

Methods: We examined a sample of 13 neuroleptic-naive ARMS who developed psychosis and 15 that did not during a follow-up period of at least 4 years from the “Basel prediction and early detection of psychosis study” (FEPSY). Psychopathology was rated with the Scale for the Assessment of Negative Symptoms (SANS) and EEGs were recorded using a 10-20 configuration. Electrodes over the fronto-central scalp area were used for the analysis. Linear regressions with group interaction were calculated to investigate the correlation of power and negative symptoms in ARMS-T and
ALTERATIONS OF MICROCIRCULATION IN SKIN AND MUSCLE IN PATIENTS SUFFERING FROM SCHIZOPHRENIA

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Background: Patients suffering from schizophrenia have a higher risk for cardiac mortality. The endothelium function was identified as a prominent parameter for cardiac risk stratification in patients with heart disease. We aimed to analyse microcirculation in skin and muscle by means of the post-occlusive reactive hyperaemia (PORH) test as a marker of endothelium function.

Methods: We investigated 25 unmedicated and 20 medicated patients with paranoid schizophrenia as well as 25 matched healthy controls using laser Doppler Flowmetry (LDF). Psychotic symptoms were quantified using the Positive and Negative Syndrome Scale (PANSS). The capillary blood flow in the skin and muscle was assessed on the right forearm before, during and after compression of the A. brachialis. Maximal post-occlusive reactive hyperaemia (PORH) was assessed on the right forearm before, during and after compression of the A. brachialis. Maximal post-occlusive reactive hyperaemia (PORHmax), slope of hyperaemia, time to peak (Tp) and the relation of blood flow at rest to hyperaemia (PORHindex) were calculated.

Results: We found a significantly reduced time to peak in patients due to an increased slope of hyperaemia in patients. PORHindex after 1 minute was significantly augmented in patients, but showed no difference after 5 minutes.

Discussion: Unmedicated patients with schizophrenia showed a faster beginning of maximal hyperaemia and a reduced prolonged hyperaemia. These results suggest an altered endothelium function. An increased sympathetic modulation and dysfunctions in prostaglandine and NO metabolism might account for these alterations. Alterations of microcirculation might be valuable targets for cardiac risk stratification in schizophrenia.

doi:10.1016/j.schres.2010.02.912

Poster 152
AUTONOMIC DYSFUNCTION IN UNAFFECTED FIRST-DEGREE RELATIVES OF PATIENTS SUFFERING FROM SCHIZOPHRENIA

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Background: Recent studies revealed cardiac autonomic dysfunction in patients with acute schizophrenia, which appears to be mainly related to reduced vagal and increased sympathetic modulation. To understand the significance of cardiac autonomic function in patients with schizophrenia, we extended these studies to relatives of patients.

Methods: In this study we assessed cardiac autonomic modulation in healthy first-degree relatives of patients with schizophrenia (n = 36) to investigate a putative genetic influence. Data were compared with control subjects matched for age, gender and physical activity as well as to patients suffering from schizophrenia.

Results: First-degree relatives showed an attenuated, yet identical pattern in autonomic dysfunction as patients with decreased vagal modulation of heart rate, decreased baroreflex sensitivity, but no difference in blood pressure variability could be detected. The patients’ relatives also showed a similar pattern in regards to QT variability. In addition, the subgroup comparison of offspring vs. siblings showed a significant difference in heart rate variability suggesting a higher degree of heritability in offspring.

Discussion: In conclusion, the pattern of autonomic dysfunction seen in patients and relatives might indicate underlying disease-inherent genetic vulnerability, especially because autonomic parameters are heritable. In addition, these findings may be of value to identify the high-risk group of patients’ relatives in regards to serious cardiovascular events so that early preventive measures can be taken.

doi:10.1016/j.schres.2010.02.913

Poster 153
SOURCE LOCALIZATION OF SENSORY GATING: A COMBINED EEG AND fMRI STUDY IN HEALTHY VOLUNTEERS

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Background: Reduced sensory gating appears to be among the core features in schizophrenia. The sources of sensory gating however are largely unknown. The aim of the current study is to identify these sources, with concurrent EEG and fMRI methodology.

Methods: Twenty healthy male volunteers were tested with identical P50 suppression paradigms in two separate sessions: an EEG setting, and an EEG concurrent with fMRI setting. The stimuli in the P50 paradigm consisted of weak electrical stimulation of the left median nerve. The stimuli were presented in pairs with either 500 ms (in which P50 suppression was expected) or 1000 ms (in
Poster 154
VISUAL SCAN PATHS TO AFFECTIVE FACIAL EXPRESSIONS IN INDIVIDUALS AT HIGH RISK AND HEALTHY CONTROLS

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Background: Deviant gaze behaviour (GB) as a correlate of information processing deficits is common in patients suffering from psychosis. Derived from findings in anti-saccade, smooth eye pursuit and visual scan path studies, GB is discussed as a potential endophenotype of schizophrenia. Therefore and with regard to a possible contribution to a more individualized prediction of psychosis, we are exploring GB in individuals clinically at high risk for psychosis (HR).

Methods: Basic scan path parameters (total fixation frequency (n) and duration (ms), scan path length (Euclidian metric of pixels), total and relative fixation frequency and duration within predefined areas of interest (AOI)) were compared in 8 PP [12.5% female; Median age: 22.5 (18-27); Median education-index: 2.38 (0.25-5.25)] and 8 HC matched by experimental condition [25.0% female; Median age: 23.0 (19-32); Median education-index: 5.13 (1.75-6.25)].

Results: PP exhibited significantly more fixations within predefined areas of interest (AOI) of stimuli with positive or negative valence. The difference emerged in trials without as well as with time limitation [fixation number in condition ‘positive valence without time limitation’: MPP = 4.79 (3.25-7.17), MP = 3.42 (1.17-4.83), p ≤ .05; fixation number ‘negative valence with time limitation’: MPP = 3.21 (1.50-3.75), p ≤ .01; fixation number ‘negative valence with time limitation’: MPP = 5.38 (0.33-6.50), MP = 3.08 (1.50-3.92), p ≤ .01].

Discussion: Higher fixation frequency is known in manifest psychosis, usually interpreted as an expression of inefficiency, but have not been reported for individuals at risk until now. Our preliminary observations suggest that not global information gathering correlates, but those related to relevant features of facial expression might be useful for a better understanding of (social) information processing in risk states of psychosis.

doi:10.1016/j.schres.2010.02.914

Poster 155
P50 GATING AND NEUROCognitive FUNCTION IN SCHIZOPHRENIA

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Background: The early positive component of MLAERPs, occurring between 35 and 59 ms after the stimulus (P50), may reflect a preattentive stage of information processing, and has been widely evaluated in schizophrenia. Many studies have shown P50 gating deficits in schizophrenia patients. We explore the relationship between P50 sensory gating and neuropsychological measures.

Methods: P50 gating was measured in hundred and sixty patients with schizophrenia (DSM-IV / SCID) and sixty four control subjects. All patients were community dwelling and clinically stable. Neuropsychological assessment. We used a neuropsychological battery described elsewhere (Sanchez-Morla et al, 2009). Six cognitive domains were examined: speed of processing, executive function, working memory, sustained attention, verbal memory and visual memory.

Results: 1. The overall MANOVA (F (1,217) = 34.3; p < 0.0001) indicated significant differences in neuropsychological function among patients with schizophrenia and control group. 2. In the group of patients with schizophrenia, parametric and nonparametric correlations revealed no significant relationships between P50 gating and performance in any of the 21 primary neurocognitive variables and any of the 6 neuropsychological domains. Neither there was any significant correlation in the control group. 3. When compared neurocognitive measures (primary variables and domains) in patients among the lowest vs highest quartiles of P50 ratio, no significant differences were observed.

Discussion: We failed to detect relationship between P50 gating and performance across neuropsychological measures. This lack of association is very consistent taking into account the substantial power afforded by this large cohort of patients with schizophrenia.

doi:10.1016/j.schres.2010.02.916

Poster 156
NO ASSOCIATION BETWEEN COMT, BDNF AND NRG-1 POLYMORPHISMS AND P50 SENSORY GATING IN PSYCHOSIS

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Background: Deviant gaze behaviour (GB) as a correlate of information processing deficits is common in patients suffering from psychosis. Derived from findings in anti-saccade, smooth eye pursuit and visual scan path studies, GB is discussed as a potential endophenotype of schizophrenia. Therefore and with regard to a possible contribution to a more individualized prediction of psychosis, we are exploring GB in individuals clinically at high risk for psychosis (HR).

Methods: Basic scan path parameters (total fixation frequency (n) and duration (ms), scan path length (Euclidian metric of pixels), total and relative fixation frequency and duration within predefined areas of interest (AOI)) were compared in 8 PP [12.5% female; Median age: 22.5 (18-27); Median education-index: 2.38 (0.25-5.25)] and 8 HC matched by experimental condition [25.0% female; Median age: 23.0 (19-32); Median education-index: 5.13 (1.75-6.25)].

Results: PP exhibited significantly more fixations within predefined areas of interest (AOI) of stimuli with positive or negative valence. The difference emerged in trials without as well as with time limitation [fixation number in condition ‘positive valence without time limitation’: MPP = 4.79 (3.25-7.17), MP = 3.42 (1.17-4.83), p ≤ .05; fixation number ‘negative valence with time limitation’: MPP = 3.21 (1.50-3.75), p ≤ .01; fixation number ‘negative valence with time limitation’: MPP = 5.38 (0.33-6.50), MP = 3.08 (1.50-3.92), p ≤ .01].

Discussion: Higher fixation frequency is known in manifest psychosis, usually interpreted as an expression of inefficiency, but have not been reported for individuals at risk until now. Our preliminary observations suggest that not global information gathering correlates, but those related to relevant features of facial expression might be useful for a better understanding of (social) information processing in risk states of psychosis.

doi:10.1016/j.schres.2010.02.914
Background: Auditory P50 sensory gating deficits correlate with genetic risk for schizophrenia and constitute a plausible endophenotype for the disease. The well-supported role of COMT, BDNF and NRG1 in neurodevelopment and cognition makes a strong theoretical case for the influence of these genes on the P50 endophenotype.

Methods: The possible role of NRG1, COMT and BDNF polymorphisms on the P50 endophenotype were examined in a large sample consisting of psychotic patients, their unaffected relatives, and unrelated healthy controls using linear regression analyses.

Results: Although P50 deficits were present in patients and their unaffected relatives, there was no evidence for association between NRG1, COMT Val158Met or BDNF Val66Met genotypes and P50 endophenotype in our study.

Discussion: The evidence from our large study suggests that any such association between P50 indices and NRG1, COMT Val158Met or BDNF Val66Met genotypes, if present, must be very subtle.

doi:10.1016/j.schres.2010.02.918
dependent manner. This effect lasted up to 4 h at 10 mg/kg, po of RO4583298.

**Discussion:** In the current study, we observed a good correlation between in vivo activity of RO4583298 in gerbil and mouse and its mode of antagonism. The pseudo-irreversible mode of antagonism at gNK1, likely contributed to RO4583298's robust and prolonged in vivo activity in the gerbil NK1 agonist-induced foot tapping model (ID50 = 0.4 mg/kg, po), while RO4583298's competitive mode of antagonism at mNK2, was demonstrated as a 14-fold higher dose was required to produce in vivo activity in the mouse senkide-induced tail whip model (ID50 = 5.6 mg/kg, po). In conclusion, RO4583298 is a high affinity, dual antagonist with an apparent non-competitive mode of antagonism and in vivo activity at both NK1 and NK2. Thus, RO4583298 could prove useful when investigating the role of NK1 and NK2 receptors in pathophysiological processes of psychiatric disorders such as anxiety, depression and schizophrenia.

doi:10.1016/j.schres.2010.02.919

**Poster 159**

**TIME-DEPENDENT CHANGES IN GAMMA OSCILLATIONS AND PARVALBUMIN IMMUNOREACTIVE CELL DENSITY IN THE CA2/3 REGION OF THE RAT HIPPOCAMPUS FOLLOWING SUB-CHRONIC PHENCYCLIDINE TREATMENT**

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**Background:** Gamma-frequency oscillations (20-80 Hz) arise from networks of the parvalbumin subset of GABAAergic interneurons. These oscillations are prevalent in active hippocampal networks and are important for cognition, learning and memory [1]. In our laboratory, we have consistently shown that a sub-chronic phencyclidine (PCP) dosing regime in adult female rats produces robust, long lasting cognitive deficits, along with decreases in parvalbumin immunoreactive (IR) interneurons in the hippocampus [2-4]. The aim of the current study was to investigate the effect of sub-chronic PCP on gamma oscillations and parvalbumin IR cell density in the CA2/3 region of the hippocampus, at 2 and 8 weeks post-PCP treatment.

**Methods:** In cohort 1, adult female hooded-Lister rats received either sub-chronic PCP (2 mg/kg, n=10) or vehicle (1 ml/kg, n=10) i.p. twice daily for 7 days. In cohort 2, adult female hooded-Lister rats received either sub-chronic PCP (2 mg/kg, n=16) or vehicle (1 ml/kg, n=16) i.p. twice daily for 7 days, followed by 7 days washout. PCP- and vehicle-treated (n=10) rats were sacrificed, 2-8 weeks post-treatment, and their brains were removed for in vitro electrophysiology. Gamma oscillations were induced in horizontal slices of the hippocampus by bath application of kainate (100 nM). Oscillations were measured in both PCP and vehicle-treated animals at 2-5 and 6-8 weeks post-treatment. Power (strength of signal as a function of frequency) was determined as the area under the curve of the power spectra between 20 and 80 Hz. In cohort 2, adult female hooded-Lister rats received either sub-chronic PCP (2 mg/kg, n=16) or vehicle (1 ml/kg, n=16) i.p. twice daily for 7 days, followed by 7 days washout. At 2 and 8 weeks post-treatment, PCP- and vehicle-treated (n=8) rats were sacrificed and their brains were removed for immunohistochemical analysis of parvalbumin IR cell density in the hippocampus.

**Results:** At 2-5 weeks post-treatment, we observed a significant reduction in gamma oscillations in the CA2/3 region in PCP-treated animals (P<0.005 vs. vehicle). In contrast, at 6-8 weeks post-treatment, we observed a significant increase in gamma oscillations in the CA2/3 region in PCP-treated animals (P<0.005 vs. vehicle). At 2 weeks post-treatment, we observed a reduction in parvalbumin IR cell density in the CA2/3 region in PCP-treated animals (P=0.058 vs. vehicle). In contrast, at 8 weeks post-treatment, parvalbumin IR cell density was unchanged in the CA2/3 region in PCP-treated animals (P=0.751 vs. vehicle).

**Discussion:** In the current study we found a reduction in gamma oscillations following PCP treatment that was paralleled by a deficit in parvalbumin IR cell density, at a similar time point (2-5 weeks post PCP-treatment). In contrast, a time-dependent increase in gamma oscillations was observed (6-8 weeks post PCP-treatment), at which point parvalbumin IR cell density was unchanged. These preliminary studies demonstrate a link between altered gamma-frequency oscillations and abnormalities in parvalbumin interneurons, which may underlie some of the cognitive deficits previously reported in this animal model of schizophrenia.

References


doi:10.1016/j.schres.2010.02.920

**Poster 160**

**NIACIN SKIN FLUSH RESPONSE IN SCHIZOPHRENIA LINKED TO SOLUBLE INTERLEUKIN 2 RECEPTOR SERUM LEVELS**

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**Background:** Attenuated skin flush response to local methylnicotinate (niacin) stimulation represents a well-established finding in schizophrenia. Skin response is mediated by a pathway involving nicotinic acid receptors at epidermal Langerhans cells. Ca2+-dependent expression of prostaglandin (PG) synthetases and formation of vasodilatory prostaglandins acting on skin arterioles. However, the underlying pathomechanism and meaning of attenuated skin flushing in schizophrenia are not yet clarified. The precursor deficiency hypothesis posits that deficient flush response in schizophrenia relates to an innate depletion of polyunsaturated fatty acids and disturbed prostaglandin signalling. Thus, niacin challenge may serve as surrogate marker of phospholipid remodelling and inflammatory processes. We investigated possible interrelations between niacin skin flushing and the inflammatory response system in terms of serum cytokine levels in unmedicated or drug-naïve schizophrenic patients.

**Methods:** We present preliminary results of an ongoing study. Skin flush response to different niacin concentrations was assessed over 15 minutes by optical reflection spectroscopy[9] in 10 unmedicated schizophrenic patients. Serum concentration of different cytokines were measured by means of commercially available ELISAs.

**Results:** We found a significant correlation of soluble interleukin 2 receptor (sIL-2R) and niacin skin flush response (R = 0.82; p = 0.002). Reduction of sIL-2R may relate to an elsewhere reported imbalance of TH-1/TH-2 immune responses in schizophrenic patients. Blunted flush response to niacin has been considered to reflect a dysfunction of prostaglandin-mediated processes. Since prostaglan-
Interleukin-17 (IL-17) is a proinflammatory cytokine that stimulates epithelial, fibroblast and endothelial cells to produce other inflammatory chemokines and cytokines. Also, it has been shown that IL-17-producing T-helper cells play an important role in the induction of autoimmune inflammatory neuroimmune diseases, including multiple sclerosis and its animal model called experimental autoimmune encephalomyelitis, notably with incri-mination of other cytokines like B cell-activating factor (BAFF). Lately, studies have reported increased concentration of classic proinflammatory cytokines in schizophrenia. The significance of circulating IL-17 and BAFF, still unknown in schizophrenia, would be interesting to be explored in order to investigate the hypothesis of immunological pathogenesis in this disease.

Objectives: This study aimed to determine IL-17 and BAFF serum levels in schizophrenic patients during an acute and non medicated phase of the disease, compared to healthy controls.

Methods: 60 consenting schizophrenic patients (DSM-IV TR criteria) were prospectively recruited, during an acute phase of the disease (BPRS ≥ 40). They were drug naïve or drug free from at least three months. 28, sex and gender matched, controls were enrolled among consenting blood donors. They were free from autoimmune diseases and from any psychotic disorder as screened by MINI-plus. Serum samples from patients and healthy controls were analyzed for IL-17 and BAFF with an enzyme-linked immunosorbent assay (ELISA) commercial kits (Quantikine, R&D Systems, Minneapolis, USA). Statistical analysis was performed using the non parametric Mann-Whitney test and Pearson correlation coefficient. Significance was assigned to p values lower than 0.05.

Results: IL-17 serum level was significantly higher in patients with schizophrenia compared to healthy controls (201.75 ± 300.92 vs. 36.07 ± 43.16 pg/ml; p = 0.005). However, BAFF serum level was significantly lower in schizophrenic patients than in healthy controls (743.66 ± 253.39 vs. 1037.14 ± 339.75 pg/ml; p < 10^-3). A negative correlation was found between IL-17 and BAFF serum levels (p = 0.03, r = -0.27).

Discussion: To our knowledge, this would be the first report of IL-17 and BAFF serum levels investigation in schizophrenia. As it has been shown in patients with other neuroimmune diseases, we found increased IL-17 serum level in our schizophrenic patients. However, unlike results from other studies on neuroautoimmune diseases, we found decreased BAFF serum level which was inversely correlated with IL-17 serum level. This result may suggest that IL-17 and CD40-BAFF signaling pathways are orchestrated differently in schizophrenia. Further studies assessing the role of Th17 will sustain schizophrenia as an autoinflammatory mental disease.

doi:10.1016/j.schres.2010.02.922

Poster 162
DECREASED MU OPIOID RECEPTOR AVAILABILITY IN SUBJECTS WITH SCHIZOPHRENIA WHO DIED BY SUICIDE

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Background: As the opioidergic system, in particular the mu receptor, has previously been shown to be altered in the brains of people who died as the result of suicide, we wished to determine whether this system has a role in suicide by subjects with schizophrenia.

Methods: Mu receptor levels were determined using in situ radioligand binding and autoradiography with [3H]DAMGO as the ligand and Western blots using tissue from the dorsolateral prefrontal and anterior cingulate cortices and caudate putamen from 12 subjects with schizophrenia who died by suicide, 26 subjects with schizophrenia who died from other causes and 20 control subjects.

Results: [3H]DAMGO binding density (p = 0.36) and mu receptor protein levels (p = 0.37) did not vary with diagnoses in any of the brain regions studied. However [3H]DAMGO binding density, but not mu protein levels, was significantly decreased in all regions from subjects who died as a result of suicide (BA 9 p <0.01; BA 24 p<0.001; CPU p<0.05).

Discussion: Our data shows that [3H]DAMGO binding, but not mu protein levels, are decreased in tissue from subjects who had schizophrenia and died by suicide, indicating that mu opioid receptor availability is decreased in the brains of these people. This in turn suggests that people with schizophrenia who die as a result of suicide have higher central levels of endogenous ligands for the mu opioid receptor than those people with schizophrenia who die from other causes. A better understanding of the factors that may contribute to the high suicide rate associated with schizophrenia may help us develop more effective strategies to prevent this devastating event.

doi:10.1016/j.schres.2010.02.923

Poster 163
N-3 FATTY ACID SUPPLEMENTATION INFLUENCES ASSOCIATIONS BETWEEN MEMBRANE FATTY ACIDS AND PHOSPHOLIPASE A2 ACTIVITY IN PATIENTS AT RISK TO DEVELOP PSYCHOSIS

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Background: Decreased levels of polyunsaturated membrane fatty acids (PUFA) and increased activity of cytosolic phospholipase A2 (PLA2) enzymes (key regulating enzymes of membrane remodeling and PUFA availability) are supporting pillars of the “membrane phospholipid concept of schizophrenia”. Assuming that membrane PUFA profile and PLA2 activity are altered during the at risk phase of disorder and influenced by fatty acid supplementation, we investigated PUFA profiles and PLA2 activity simultaneously in ultra high-risk (UHR) patients before and after n-3 fatty acids supplementation.

Methods: In 81 UHR patients (aged between 13 and 25 years) PUFA levels were assessed in erythrocyte membranes using gas
chromatography, and cytosolic PLAr activity was measured in blood serum using a fluorometric HPTLC-based assay. Measurements were performed before and after a 6 month interval of placebo-controlled supplementation with n-3 fatty acids.

**Results:** At baseline significant associations were found between (n-9) and (n-6)-PUFA levels and psychopathology (especially negative symptoms) assessed by the PANSS according to PACE criteria. (n-3)-PUFA supplementation caused significant changes in (n-3)- and (n-6)-PUFA levels and a significant decrease of PLAr activity. Furthermore, negative correlations between (n-6) levels and PLAr activity changed to positive correlations.

**Discussion:** Our results support associations between membrane biochemistry and psychopathology (especially negative symptoms) in people at risk to develop psychosis. Supplementation of n-3 PUFA increases PUFA availability at membrane level and modulates membrane repair and remodelling processes. Assuming that PLAr activity reflects neuronal damage, PUFA supplementation might unfold neuroprotective effects.

DOI: 10.1016/j.schres.2010.02.924

**Poster 164**

**RECRUITMENT OF ERBB1-ERK SIGNALLING BY ANTIPSYCHOTIC DRUGS: A NOVEL TREATMENT TARGET IN SCHIZOPHRENIA?**

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**Background:** Schizophrenia treatment remains suboptimal with many people only partially or not responding to current antipsychotic drugs (APD) with respect to positive psychotic symptoms. The APD clozapine is demonstrably effective in some of these treatment resistant cases but this mechanism is unknown. We proposed that it may involve alternate cell signalling systems. One possible system is the mitogen activated protein kinase-extracellular signal regulated kinase (MAPK-ERK) cascade which regulates cortical development and synaptic plasticity, processes impaired in schizophrenia. It also links targets of APD action, G-protein coupled receptors, and robust candidate gene targets in schizophrenia, the ErbB growth factor signalling system. We previously reported in vitro that clozapine and other APD acutely inhibit ERK activation but only clozapine stimulated ERK with sustained treatment. Moreover, this was mediated by the ErbB1 receptor. We then demonstrated that a parallel biphasic time response of ERK activation was also observed in vivo in both prefrontal cortex (PFC) and striatum with clozapine treatment and this was significantly reduced by the ErbB1 inhibitor, AG1478, in both brain regions1. Following these data we then examined if this in vivo effect is observed with other APD and what may be the downstream targets of APD induced ErbB1-ERK1/2 activation.

**Methods:** Six to eight week old male out-bred C57Bl/6 mice were treated acutely with clozapine (Cloz), haloperidol (Hal), quetiapine (Quet), aripiprazole (Arip) or vehicle (Veh) in the presence or absence of the ErbB1 inhibitor AG1478. Brains were removed at various time points and tissue homogenates from the PFC and striatum underwent Western immunoblotting for phosphorylated ERK1/2 (pERK1/2), p90RSK and c-Fos. Results were normalised against total ERK1/2, total RSK and beta-actin respectively and expressed as a percentage of vehicle treated animals.

**Results:** Haloperidol significantly increased pERK1 in the striatum at 60 min (Hal 121±5%, Veh 100±3%, p<0.001) and 240 min (Hal 303±68%, Veh 100±6%, p<0.05) before returning to baseline. The increased pERK1 was not blocked by AG1478 pre-treatment and Hal had no effect in the PFC. Aripiprazole at 60 min increased pERK1 (Arip 155±16%, Veh 100±8%, p<0.01) and pERK2 (Arip 144±10%, Veh 100±3%, p<0.01) in the PFC but this also was not blocked by AG1478. Quetiapine increased pERK1/2 at 240 min in the striatum and this effect was blocked by AG1478 (pERK1: Quet 228±52%, Quet + AG1478 70±3%, p<0.01; pERK2: Quet 161±9%, Quet + AG1478 57±9%, p<0.001). Clozapine significantly decreased p90RSK levels in both PFC and striatum at 20 and 60 min with a subsequent increase until 480 min reaching significance in the striatum before returning to baseline by 24 hour. However the change in p90RSK was not abrogated by AG1478. Clozapine caused also initial decrease in c-Fos expression in the PFC at 60 and 120 min and then a strong delayed activation at 24 hours (60 min: Cloz 63±11%, Veh 100±5%, p<0.01; 120 min: Cloz 50±16%, Veh 100±9%, p<0.05; 24 hours: Cloz 155±17%, Veh 100±11%, p<0.05); again this was not blocked by AG1478.

**Discussion:** APD recruit ErbB1 signalling to activate ERK1/2 in the cortex and striatum differentially with different subsequent effects on the downstream effectors c-Fos and p90RSK. In particular the consistent and robust effect of clozapine on modulating this signalling cascade may warrant investigation as a novel antipsychotic drug target for treatment resistant patients. I. Pereira et al. J Mol Neurosci 2009; 39(1-2):185-98.

DOI: 10.1016/j.schres.2010.02.925

**Poster 165**

**INFLAMMATION IN PSYCHOTIC DISORDERS: A POPULATION-BASED STUDY**

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**Background:** Psychotic disorders are associated with inflammatory changes, which may be related to the etiology and pathogenesis of these disorders but also to metabolic comorbidity, lifestyle-related factors or antipsychotic medication. We investigated inflammatory markers in psychotic disorders and their association with metabolic markers, antipsychotic medication, smoking and alcohol use, physical condition, and mood.

**Methods:** From a population-based study (Perälä et al., 2007), we analysed serum samples from all persons with DSM-IV primary psychotic disorder (schizophrenia n = 45, other nonaffective psychosis (ONAP) n = 57, affective psychosis n = 37) and controls matched by age, sex, and region of residence. We determined serum levels of tumor necrosis factor alpha (TNF-α), interleukin-1 receptor antagonist (IL-1RA), interleukin-2 and its soluble receptor’s alpha subunit (sIL-2Rα), interleukin-6, and sensitive C-reactive protein (CRP). We first compared differences in median cytokine concentrations between each diagnostic group and their matched control group with the Mann-Whitney U test. Thereafter, we used linear mixed models to analyze the effect of diagnoses on inflammatory markers after adjusting for antipsychotic medication use, lifestyle-related variables, current depressive symptoms, and metabolic markers.

**Results:** Compared to their matched controls, persons with schizophrenia had significantly higher sIL-2Rα (P = 0.005), IL-1RA (P = 0.002) and CRP (P = 0.004), persons with ONAP significantly higher IL-1RA (P = 0.029) and CRP (P = 0.017), and persons with affective psychosis almost significantly higher TNF-α (P = 0.051). Among persons with any psychotic disorder, current antipsychotic medication use was associated with elevated IL-1RA (P = 0.047) and CRP (P = 0.002). In linear mixed models, however, none of the

DOI: 10.1016/j.schres.2010.02.925
diagnostic groups remained independently associated with elevated IL-1Ra after adjusting for metabolic comorbidity. Antipsychotic medication (P = 0.002) remained associated with elevated CRP even after taking metabolic comorbidity into account, and the effect of schizophrenia (P = 0.038) was also significant after excluding persons with possible acute infection. Beck Depression Inventory score (P = 0.004) and smoking (P = 0.004) but not individual diagnoses remained significant predictors of elevated sIL-2Rα. Neither diagnosis nor antipsychotic medication use remained independently associated with TNF-α.

**Discussion:** Schizophrenia and other nonaffective psychoses were associated with low-grade inflammation, marked by elevated CRP and IL-1Ra, which was mostly explained by metabolic comorbidity and antipsychotic medication use. Schizophrenia was also associated with T-cell activation, marked by elevated sIL-2Rα, which was related to current depressive symptoms and smoking.

doi:10.1016/j.schres.2010.02.926

**Poster 166**

**ENHANCEMENT OF COGNITION IN SCHIZOPHRENIA VIA INHIBITION OF PHOSPHODIESTERASE-1B AND POTENTIATION OF DOPAMINE D1 RECEPTOR SIGNALING**

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**Background:** Cognitive dysfunction is recognized as a major contributing factor to schizophrenia. Hypo-functionality of the dopamine D1 receptor system in the pre-frontal cortex has been clearly associated with this impaired cognition. Yet, direct dopamine D1 receptor agonists have not been clinically useful. We have circumvented many of the problems associated with use of D1 agonists by developing a series of potent and selective phosphodiesterase 1 (PDE1) inhibitors with good oral bio-availability and pharmacokinetic properties. Phosphodiesterase 1B (PDE1B) is enriched in the brain and highly abundant in neurons expressing dopamine D1 receptors. D1 receptors signal via stimulation of adenylyl cyclase and production of cyclic-AMP. This signal transduction system is terminated by the hydrolysis of cyclic-AMP by cyclic nucleotide phosphodiesterase activity. By inhibiting PDE1 in the brain, D1 mediated signaling events should be amplified.

**Methods:** Medicinal chemistry has been performed to optimize PDE1 enzyme inhibition while maintaining suitable drug-like properties including brain penetration. Pharmacokinetic profiling was performed using current and sophisticated LC-MS methods. Pharmacological models were used to evaluate cognitive ability in animal models including rat novel object recognition and pre-pulse inhibition of startle.

**Results:** An advanced early development candidate PDE1 inhibitor, IC200214, has been identified with sub-nanomolar, competitive inhibition of PDE1, with over 1000-fold selectivity for the PDE1 family over all other families of PDE enzymes (PDE 2-11). The candidate has no significant off-target effects, when screened against a panel of 70 unrelated receptor and enzymes. After oral administration, the agent enhances cognitive performance in rodents, as measured in the novel object recognition test. Unlike the PDE4 or PDE10 inhibitors rolipram and papaverine that exacerbate catalepsy induced by antagonism of dopamine D2 receptors, IC200214 reversed haloperidol-induced catalepsy. The compound has a long pharmacodynamic half-life and displays an extended pharmacokinetic T1/2. In pre-clinical development, IC200214 is safe and well tolerated at high doses. No drug-drug interaction has been seen with antipsychotic agents tested including haloperidol and risperidone.

**InhibitorDiscussion:** Most antipsychotic agents do not improve and may impair cognitive function in patients with schizophrenia. In this study, IC200214 was found to enhance cognition in rodent models and to lack any drug-drug interaction with current antipsychotic agents. In addition, chemically-related PDE1 inhibitors increase wakefulness in rodent models, but do not increase basal locomotor activity. In view of this desirable profile, the data reported here indicate that inhibitors of PDE1 should have unique advantages as therapeutics for the treatment of cognitive dysfunction in Schizophrenia.

doi:10.1016/j.schres.2010.02.927
Results: Expression of Dysbindin1 and NRG1 type2 genes were observed in immortalized lymphocytes. Expression of NRG1 type1, 3, 4 genes were below the detection limit of real-time quantitative RT-PCR. No difference was observed between patients with schizophrenia and controls in the expression of Dysbindin1 and NRG1 type2 genes.

Discussion: We found no difference between patients with schizophrenia and controls in the expression of Dysbindin1 and NRG1 type2 genes. Previous study showed that Dysbindin1 isoform a and NRG1 type2 isoforms GGF, GGF2 expression in immortalized lymphocyte from patients with schizophrenia were decreased. This discrepancy might be attributed to the number of cases used and the isoforms observed. In this study, we used about four times larger number of cases than the previous study and observed the expression of all the isoforms. Our findings show that immortalized lymphocyte gene expression profile in schizophrenia is different from Post-mortem brain tissue at least in Dysbindin1 and NRG1 genes. Further studies are required to assess whether immortalized lymphocyte is an appropriate alternative to neuronal tissue.

doi:10.1016/j.schres.2010.02.928

Poster 168
PARANOID SCHIZOPHRENIA IS CHARACTERISED BY INCREASED CANNABINOID CB1 RECEPTOR BINDING IN THE DORSOLATERAL PREFRONTAL CORTEX

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Background: Cannabis consumption may induce psychotic states in normal individuals, worsen psychotic symptoms of schizophrenic patients, and may facilitate precipitation of schizophrenia in vulnerable individuals. Previous studies using post-mortem human brain tissue suggest that binding to the cannabinoid CB1 receptor is increased in the anterior1 and posterior2 cingulate cortices and Brodmann’s area 9 in schizophrenia. In the present study we examined CB1 receptor binding in the dorsolateral prefrontal cortex (DLPFC, Brodmann’s area 46), a region associated with altered function in both cannabis use and schizophrenia.

Methods: Receptor density was investigated in this area using in vitro autoradiography with the CB1 receptor ligand [3H] CP55,940 in a cohort of 13 patients with paranoid schizophrenia, 24 patients with non-paranoid schizophrenia and 37 controls matched for age, PMI and pH. The non-paranoid schizophrenia group included cases that met criteria for undifferentiated, residual, disorganised, bipolar and depressive type schizophrenia. Seven cases from the non-paranoid group also met the criteria for schizoaffective disorder. All cases were obtained from the University of Sydney Tissue Resource Centre. Results were analysed using ANOVA followed by post hoc Bonferroni tests.

Results: There was a main effect of diagnosis on [3H] CP55,940 binding quantified across all layers of the DLPC (F=3.32, df=2, P=0.034). Post hoc testing indicated that this main effect was due to patients with paranoid schizophrenia having 24% higher levels of CB1 binding compared to the control group (59.5 ± 3.9 versus 48.0 ± 2.07 fmoles/mg tissue equivalent, respectively, p<0.05). Factors such as post-mortem interval time, gender and antemortem state were not found to have an effect on CB1 binding. There were however significant correlations between age at death, pH, and CB1 binding. Within the schizophrenia group, CB1 binding was not affected by the final recorded antipsychotic drug dose.

Discussion: These results confirm previous studies and suggest that increased CB1 receptor binding is a feature of paranoid schizophrenia. The data add to a growing biological and genetic evidence for the cannabinoid hypothesis of schizophrenia and point to the involvement of the endogenous cannabinoid system in the pathophysiology and pharmacotherapy of the disorder.

doi:10.1016/j.schres.2010.02.929

Poster 169
REGULATION OF PSYCHOSIS GENE NPAS3 BY MICRONA DURING POSTNATAL DEVELOPMENT AND IN SCHIZOPHRENIA

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Background: Neuronal Per-Arnt-Sim domain protein 3 (NPAS3) is a brain-specific transcription factor localized to the breakpoint of a chromosomal translocation in a mother and daughter with psychiatric illness. NPAS3 has also been genetically associated with bipolar disorder and schizophrenia in a large cohort. NPAS3 knockout mice have reduced body size, decreased hippocampal volume, an underdeveloped corpus callosum and enlarged ventricles. They display incoordination, hyperactivity and deficits in sensorimotor gating and learning. In the cortex, NPAS3 is localized to GABAergic interneurons where it regulates expression of synaptic markers and reelin – a protein involved in neuronal migration and decreased in the frontal cortex of patients with schizophrenia. This links NPAS3 to behavioural, morphological and neurodevelopmental abnormalities which have been implicated in schizophrenia. However, little is known about the expression of the NPAS3 gene in human cortical development or in schizophrenia.

Methods: We have measured NPAS3 mRNA by microarray and qPCR and NPAS3 protein by Western blotting in tissue from the middle frontal gyrus of developing humans and in adult humans with schizophrenia compared to controls.

Results: In the postnatal human prefrontal cortex, NPAS3 mRNA is most highly expressed in the neonatal brain, decreasing to half maximal expression in the first few years of life, after which it is constantly expressed into adulthood (p<0.001), followed by decreased expression in the frontal cortex of patients with schizophrenia. This links NPAS3 to behavioural, morphological and neurodevelopmental abnormalities which have been implicated in schizophrenia. However, little is known about the expression of the NPAS3 gene in human cortical development or in schizophrenia.

doi:10.1016/j.schres.2010.02.929
First, there's a discussion about the involvement of the default mode network (DMN) in self-focused attention and hyperconnectivity in the brain. The hypothesis is that the altered DMN function and increased top-down processing are specifically related to DOR, a group of important symptom central to psychotic disorders. DOR are found in up to 67% of schizophrenic patients, and their roles as prodromal and relapse signal and schizotypal trait highlight their potential as a state and trait marker for schizophrenia. Identification of the neurocognitive and neurophysiological mechanisms of DOR will provide important insight into understanding psychosis.

**Poster 170**

**DELUSIONS OF REFERENCE, EXCESSIVE TOP-DOWN PROCESSING, AND DEFAULT MODE NETWORK IN FIRST-EPIsode SCHIZOPHRENIA**

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**Background:** Delusions of reference (DOR) refer to the detection of spurious self-information in otherwise neutral or ambiguous environmental stimuli. Empirical studies of DOR using an information processing framework are lacking. We hypothesize, at the neurocognitive level, that DOR may be related to an excessive use of an internally generated, top-down processing strategy; whereas at the neurophysiological level, this may be related to the hyperactivity and hyperconnectivity in the default mode network (DMN) of the brain. The DMN has been implicated in self-focused attention and hyperconnectivity in the default mode network (DMN) of the brain. This mismatch may involve developmental regulation of microRNAs that target the Npas3 primary transcript. Considering the gender bias of certain psychiatric illnesses, such as schizophrenia, alterations in gender dimorphic expression of Npas3 may constitute an underlying factor in disease severity.

**Results:** In the exploratory study, interim data analysis (n=9; 5 men, mean age 23.8 years) showed a positive correlation between severity of DOR and spurious information detected in the contour integration test (Spearman’s rho = 0.45) and the babble task (Spearman’s rho = 0.42), although the results did not reach statistical significance because of the sample size. Spurious information processing in the auditory and visual tasks also showed strong correlation (Spearman’s rho = 0.65, p = 0.056). Data collection for both parts of the study is expected to be completed by March 2010.

**Discussion:** This study tests the hypothesis that excessive top-down processing and aberrant DMN function seen in schizophrenia is specifically related to DOR, a group of important symptom central to psychotic disorders. DOR are found in up to 67% of schizophrenic patients, and their roles as prodromal and relapse signal and schizotypal trait highlight their potential as a state and trait marker for schizophrenia. Identification of the neurocognitive and neurophysiological mechanisms of DOR will provide important insight into understanding psychosis.

**Poster 171**

**INTERACTION BETWEEN ESTROGEN RECEPTOR ALPHA AND TRKB SUGGEST CONVERGENCE IN DEVELOPMENTAL PATHWAYS IMPLICATED IN SCHIZOPHRENIA**

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**Background:** Schizophrenia is a heterogeneous disease resulting from the alteration of genes and pathways required for normal brain development, function and cognition. Molecular research implicates lower brain derived neurotrophic factor (BDNF) and lower BDNF receptor (TrkB) levels in the cortical neuropathology of schizophrenia. Since we have evidence suggesting that the cortical pathology in schizophrenia may also include the failure of the brain to respond to sex steroids, we set out to determine how altered estrogen receptor alpha (ERα) signalling and altered TrkB signalling may mechanistically converge at the cellular level. Considering that ERα and TrkB are capable of mediating overlapping cellular signalling cascades, we tested whether ligands for ERα were able to activate TrkB and vice versa.

**Methods:** Transfection of cloned wild-type ERα and full-length TrkB were performed in cultured cells. To assay for transcriptional activity, Chinese Hamster Ovary cells (CHOK1) and neuronal cells (SHSYSY) were co-transfected with TrkB and wild-type ERα in combination with a 3xERE luciferase reporter construct. Changes in ERE-mediated transcription were measured by luciferase reporter assay. To test if protein interactions were direct, protein extract from cells transfected with TrkB were immunoprecipitated with an antibody specific for ERα and western blotting for TrkB was performed. Confocal microscopy for tagged proteins was used to anatomically localize TrkB within cells.

**Results:** In CHOK1 cells, we found that TrkB overexpression significantly increased transcriptional activity from an estrogen responsive promoter relative to the empty vector control (t = 1.92, df = 4, p = 0.0002). When we explored the mechanism by which TrkB elicited this effect, we found that BDNF treatment increased ERα phosphorylation at Ser118 and Ser167 and increased total ERα expression. For functional connectivity analysis, Pearson’s correlation is used for the analysis of between group differences in DMN activity. For functional connectivity analysis, Pearson’s correlation is performed in seed regions of interest according to previously defined components of the DMN.

**Conclusion:** The interaction between ERα and TrkB suggests potential mechanisms underlying schizophrenia.
Poster 172
ANALYSIS OF THE HYPOTHALAMIC-PITUITARY ADRENAL AXIS IN PSYCHIATRIC DISORDERS
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Background: Schizophrenia is a complex psychiatric disorder characterised by hallucinations, bizarre behaviour, cognitive impairment and altered perceptions of reality. Diagnosis and management of the disorder are currently subjective due to the complex clinical presentation and lack of established disease-specific assays. Therefore identification of biomarkers as disease correlates would facilitate objective diagnosis, optimise clinical management and improve patient outcomes. Studies have shown that the shortened lifespan and excessive mortality associated with schizophrenia cannot be solely attributed to suicide or accidental death. Much of the excessive mortality can be attributed to complications arising from metabolic syndrome, such as hypertension, obesity and type II diabetes mellitus. Whilst an increased prevalence of metabolic syndrome has been noted in patients receiving second generation antipsychotics, it is becoming increasingly apparent that metabolic syndrome (diabetes in particular) may be associated with the disease state, since drug naive schizophrenics also demonstrate hallmark symptoms. We have recently identified increases in circulating levels of insulin-peptides in first onset drug naive schizophrenia subjects which suggests insulin resistance. Insulin signalling affects the hypothalamic-pituitary adrenal (HPA) axis, which can promote visceral adiposity, insulin resistance and other symptoms of metabolic syndrome. The HPA axis has been implicated in schizophrenia for some time, based on findings of elevated plasma levels of ACTH, cortisol and arginine-vasopressin in schizophrenics versus controls, and larger pituitary volumes in first episode patients as assessed by MRI. In addition, gene transcription of pro-opiomelanocortin, one of the key drivers of the HPA stress axis response, is just one downstream-signalling process influenced by insulin. This line of investigation is unique in that any studies thus far of the potential for pituitary involvement in schizophrenia have either been 1) structural studies using MRI techniques 2) studies of plasma or serum which merely implied pituitary dysfunction. This study presents the opportunity to analyse the pituitary proteome itself within the context of psychiatric abnormalities.

Methods: This study was designed to compare pituitary proteomes of drug naive schizophrenia patients and controls. Patients were recruited from a psychosis service in South London. First episode patients were assessed using a standardized set of clinical, functional and cognitive assessments. Plasma from drug naive schizophrenia patients and controls were collected following an overnight fast and immediately frozen. The plasma samples were then loaded onto 2D gels and proteins were visualised using silver staining. Data were extracted using a combination of targeted and non-targeted methods for protein identification.

Results: A total of 1246 protein spots were characterised across all samples, of which 92% were successfully identified. The majority of proteins identified were neuropeptides that may be associated with schizophrenia. We have identified candidates which will then be validated by Western blot analysis and non-targeted approaches such as unbiased mass-spectrometry and 2D difference gel electrophoresis.

Discussion: This study proposes the examination of additional pituitary neuropeptides that may be associated with schizophrenia. We have identified potential candidates which will then be validated by Western blot analysis and non-targeted approaches such as unbiased mass-spectrometry and 2D difference gel electrophoresis.

doi:10.1016/j.schres.2010.02.932

Poster 173
PLACEBO RESPONSE IN ANTIPSYCHOTIC TRIALS: A SYSTEMATIC REVIEW AND META-ANALYSIS
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Background: Placebo response is often observed in psychiatric randomized clinical trials and presents a major challenge for psychopharmacologic drug development. The objective of this paper was to investigate the magnitude of placebo effect size in patients with schizophrenia and schizoaffective disorder, and to identify potentially important predictors for placebo response.

Methods: We searched the MEDLINE database for RCTs published in 1966 to 2009, supplemented by other electronic databases and hand searches. Data were extracted from published (English) RCTs of antipsychotic treatment in schizophrenia and schizoaffective disorder (SAD). In this analysis, placebo response in short-term treatment (2-12 weeks) was defined as mean change from baseline in BPRS total score (derived derives from PANSS in 11 studies). The systematic review used a weighted mean and 95% confidence interval (CI) based on a random effects model. A meta-regression analysis was performed to identify influential moderators of placebo response.

Results: A total of 1246 placebo-treated patients from 41 RCTs had valid BPRS total scores with a median placebo group size of 20. Demographics included: weighted mean age 38, duration of illness 16 years, and 77% male (median). The weighted mean baseline, endpoint, and reduction in BPRS for these groups were, respectively, 48.58, 46.10, and −2.59 (95% CI –4.08, –1.09). The average effect size was −0.27 (−0.44, –0.11) and heterogeneous across studies (p < 0.001). Meta-regression analysis showed that greater placebo response was associated with shorter trials (p < 0.001), community hospital (or mixed) treatment settings (p = 0.02), more recently published studies (1990-2009) (p < 0.01), and higher baseline severity score (p < 0.01).

Discussion: Our meta-analysis findings suggest that treatment settings, trial duration, and baseline level of symptom severity might influence the magnitude of placebo response in schizophrenia. Further studies using patient-level data are needed to identify additional factors that might systematically affect placebo response.

doi:10.1016/j.schres.2010.02.934
ONE WEEK TOLCAPONE TREATMENT IN PSYCHOTIC PATIENTS: EFFECTS ON GATING, WORKING MEMORY AND CLINICAL PICTURE

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Background: A single dose of the COMT inhibitor tolcapone improves gating and working memory in partially remitted psychotic patients. We explored the therapeutic potential of tolcapone, by examining the effects of one week administration on gating, working memory and clinical picture in psychotic patients.

Methods: Fourteen medicated partially remitted psychotic patients received placebo and tolcapone-200mg/day for one week each, according to a double-blind, crossover design. At the end of each treatment, we assessed PPI with 75- and 85-dB prepulses at 30-, 60- and 120-ms intervals, working memory with the letter-number sequencing (LNS) task and symptom improvement with the Clinical Global Impression-Improvement (CGI-I) scale.

Results: Tolcapone did not affect startle amplitude or habituation. A 2×2×3×2 (treatment×prepulse×interval×gender) ANOVA of the PPI data showed a significant treatment×interval×gender interaction (p = 0.014), indicating tolcapone-induced PPI increases at 60 ms and 120 ms in males and at 30 ms in females. These results survived when SANS total score (which correlated negatively with delta tolcapone effect on mean PPI) as well as antipsychotic treatment expressed as chlorpromazine equivalents were taken as covariates. In addition, a significant treatment main effect (p < 0.04) was revealed. Separate 2×2 ANOVAs showed that tolcapone improved LNS performance (treatment p = 0.012) and CGI-I score (p < 0.001).

Discussion: Weekly tolcapone administration improved gating and working memory and, importantly, the clinical profile of non-genotyped psychotic patients. These preliminary findings have intriguing therapeutic implications in the targeted treatment of cognitive deficits and symptoms of psychosis. More impressive effects are anticipated when patient samples are stratified for COMT status.

doi:10.1016/j.schres.2010.02.935

LURASIDONE IN THE TREATMENT OF ACUTE SCHIZOPHRENIA: RESULTS OF THE DOUBLE-BLIND, PLACEBO-CONTROLLED PEARL 2 TRIAL

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Background: Lurasidone is a new psychotropic agent with high affinity for D2 and 5-HT1A receptors, and for receptors implicated in enhancement of cognition, mood and negative symptoms (5-HT3, 5-HT6, and α2). The aim of this study was to evaluate the efficacy and safety of lurasidone in patients with an acute exacerbation of schizophrenia.

Methods: Hospitalized patients 18-75 years old who met DSM-IV criteria for schizophrenia and were acutely ill with a PANSS total score ≥80 were eligible for enrollment. Subjects were tapered off psychotropic medication and after a 7-day placebo washout period were randomized to 6-weeks of once-daily double-blind treatment with lurasidone 40 mg or 120 mg, olanzapine 15 mg or placebo. After 3 weeks, patients were eligible for discharge if sufficiently stable and improved. A mixed model repeated measures (MMRM) analysis was performed for the efficacy measures: the Positive and Negative Symptoms of Schizophrenia Scale (PANSS) total and subscale scores and the Clinical Global Impression, Severity scale (CGI-S).

Results: Demographic and clinical characteristics were similar at baseline among patients randomized to the four treatment groups: lurasidone 40 mg (n = 119; mean PANSS total, 96.6); lurasidone 120 mg (n = 118; mean PANSS total, 97.9); olanzapine 15 mg (n = 122; mean PANSS total, 96.3); and placebo (n = 114; mean PANSS total, 95.8). Treatment with lurasidone was associated with significantly greater improvement on the PANSS total score versus placebo (-16.0) among patients in the 40 mg (-25.7; P < 0.001) and 120 mg (-23.6; P = 0.011) dosage groups at Week 6. Treatment with lurasidone was also associated with significantly greater improvement on the PANSS positive subscale score versus placebo (-5.4) in the 40 mg (-7.7; P = 0.018) and 120 mg (-7.5; P = 0.035) dosage groups; and on the PANSS negative subscale score versus placebo (-3.6) in the 40 mg (-6.0; P = 0.002) and 120 mg (-5.2; P = 0.045) dosage groups. On the CGI-S, significant improvement was observed versus placebo (-11), during treatment with both the 40 mg (-1.5; P = 0.006) and 120 mg (-1.4; P = 0.040) doses of lurasidone. Olanzapine 15 mg/day produced significantly greater improvements than placebo on both the PANSS total score (-28.7 vs. -16.0; P < 0.001), PANSS positive subscale (-9.3 vs. -5.4; P < 0.001), PANSS negative subscale (-6.2 vs. -3.6; P < 0.001), and CGI-S (-1.5 vs. -1.1; P < 0.001). A weight increase >7% was observed in 7.2% of patients treated with lurasidone (combined doses), 40.2% treated with olanzapine, and 8.7% treated with placebo. Change in median cholesterol was similar during treatment with lurasidone (-7.0 mg/dl, combined doses) and placebo (-5.0 mg/dl), but was increased during treatment with olanzapine (+9.0 mg/dl). Change in median triglycerides was also similar during treatment with lurasidone (-1.0 mg/dl, combined doses) and placebo (+1.0 mg/dl), but was increased during treatment with olanzapine (+24.0 mg/dl).

Discussion: The results of this multicenter, double-blind, placebo-controlled, Phase 3 trial indicate that lurasidone, at fixed doses of 40 and 120 mg/day, is a safe and effective treatment for patients with an acute exacerbation of schizophrenia. The efficacy of both doses of lurasidone was established based on results for both the PANSS total and CGI-S scores, and for the PANSS positive and negative subscale scores. No dose-response relationship was observed on the PANSS total or subscale scores, or the CGI-S scores. Treatment with lurasidone was not associated with adverse effects on weight, metabolic, or ECG parameters. Based on these findings and results of previous trials, lurasidone may be a useful addition to the treatment armamentarium for schizophrenia. Funded by Dainippon Sumitomo Pharma.

doi:10.1016/j.schres.2010.02.936

COMMUNITY TREATMENT ORDERS, ETHNICITY, CONDITIONS AND PSYCHOTROPIC MEDICATION: THE FIRST SIX MONTHS (N = 126)

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Background: Community treatment order (CTO) legislation was initiated in November 2008 in England and Wales. Due to high rates of uptake, a shortage of second opinion appointed doctors (SOADs) to
complete authorization of medication within the given timeframe for CTOs was soon identified. A strong link in the use of CTOs in combination with antipsychotic long acting injections (LAIs) has been previously identified. LAI use for patients with schizophrenia is 35% on UK acute inpatient wards. The aims of this cross-sectional observational study in the first year of CTO legislation were to (i) identify patient characteristics for those commenced on a CTO; (ii) identify the nature of psychotropic medication prescribing at CTO initiation. Hypothesis: patients with schizophrenia have higher than average rates of LAI use as compared with national prescribing data.

**Methods:** The setting was the South London and Maudsley NHS Foundation Trust in London, United Kingdom, which provides secondary care level psychiatric services for a local population of 1.1 million people, plus specialist tertiary referral inpatient facilities and forensic wards. Consecutive sampling was conducted for all patients whose CTO was registered in the Trust. Only the first CTO for each patient was included. Data for 126 patients from the first six months of data collection is presented (03/11/08-30/04/09). Measures included: sociodemographic variables, psychiatric diagnosis, CTO date of initiation, statutory reasons and stated conditions, psychotropic medication and date of Second Opinion Appointed Doctor (SOAD) authorization for medication.

**Results:** There was geographical variability in rates of CTO use between the 4 geographical sub-regions. 52% of the 126 patients were of black ethnic origin. 52% had stated conditions regarding their place of residence and 37% were required to allow access into their homes. 99% were prescribed an antipsychotic, 27% a mood stabilizer, 8% an antidepressant, 5% a benzodiazepine. First generation antipsychotic LAIs were the most commonly prescribed group of antipsychotics (40%). 69% of those with schizophrenia on a CTO were prescribed an antipsychotic LAI. Regarding antipsychotic doses, the mean BNF% dose was 60.6% (sd 39.1 range 2.5%-183.3%). 8% of the total sample had antipsychotic (combined) doses exceeding 100%BHF dose limits. 10% were prescribed two antipsychotics. Prior to CTO initiation, 21% were LAI-naïve and 78% were clozapine naïve. SOAD certification of medication occurred approximately 2 months after CTO initiation (mean 59.9 days, sd 39.1, range 1-175 days). For 24% of the sample, SOAD certification was not completed within the first 6 months.

**Discussion:** Variation in CTO use exists for geographical areas but not for ethnic diversity once other factors such as rates of hospital detention are considered. Conditions of CTOs may not follow the least restrictive principle, particularly for requirements regarding a patient’s place of residence; clearer guidance for setting of conditions is required. The finding of 69% of those with schizophrenia on a CTO being prescribed an LAI is double that reported in national prescribing data. SOAD authorization of medication commonly occurs after the legal deadline and a small proportion did not achieve SOAD certification before the CTO expired.

doi:10.1016/j.schres.2010.02.937

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**Poster 177**

**LONG ACTING ANTIPSYCHOTICS: COMPARISON OF FIRST- AND SECOND-GENERATION ANTIPSYCHOTIC DRUGS IN A COMMUNITY SETTING**

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**Background:** Long acting Neuroleptics (LANs) are designed to improve adherence and the monitoring of the patient. Recently, the first long acting injectable atypical antipsychotic, risperidone has been developed. A number of studies have reported a reduction in the number of hospitalizations and some cost-effectiveness designs have shown the efficiency of the drug. However, there is still a lack of comparative studies in real clinical conditions with other LANs.

**Our aim** was to characterize the patients of a defined catchment mental health area treated with LANs during last year and compare the clinical consequences of using classic (typical) depot LANs with Long Acting Risperidone (LAR).

**Methods:** The study was placed in the Community Mental Health clinic of Arriondas, Principado de Asturias (54,000 inhabitants, North of Spain). Data were obtained from the patients (Schizophrenia, Schizoaffective disorder, Delusional disorder, Psychosis NOS, Bipolar disorder) treated with the available LANs in Spain (Risperidone, Zuclopenthixol, Fluphenazine). General demographic data and those related to treatment and admissions were extracted from medical records and personal semi-structured interviews. The Scale of Unawareness of Mental Disorders (SUMD) and the UKU side effects scale were assessed. Blood samples were extracted in order to examine levels of fasting glucose, total, LDL and HDL Cholesterol, Triglycerides, Hepatic enzymes, and Prolactine. Body Mass Index was also calculated. Dichotomic variables were compared between patients using LAR and typical LANs with the chi square test and continuous variables were compared using the Student’s t test and ANCOVAs (using age, gender and diagnosis as covariates)

**Results:** Forty patients treated with LAR and 10 patients treated with typical LANs were recruited in the area. Most of them had Schizophrenia (60%) or Schizoaffective disorder (12%). The two main reasons for the start of the LAN were the relapse (46%) or the persistence of symptoms (30%), followed by an incomplete adherence (12%). The two groups were able to maintain most patients without admissions after introduction of the LAN (2 admissions in LAR and 1 in classical LAN). Compared to LAN, Patients with LAR were started more frequently by other reason than relapse more frequently (LAN: 62%, Typical LANs: 20%; Chi Square: 5.817; p = 0.030) and in diagnoses different from schizophrenia (Schizophrenia in LAR: 52.5%; in Typical LAN: 90%; Chi Square: 4.698; p = 0.031). Patients with LAR used less associated antipsychotics (1.43 in LAR; 2.10 in Typical LANs; F: 5.730; p = 0.021), had a better level of insight of disorder (3.60 in LAR; 2.40; F: 7.637; p = 0.008 in Typical LANs; F: 5.730; p = 0.021) and medication and a lower score of side effects (LAR UKU total score: 4.90, in Typical LANs: 9.30; F: 5.898; p = 0.019). There were not any differences in demographic differences, analytical or lipidic profile or in BMI.

**Discussion:** LAR was associated not only with a reduction in admission to hospital, but also a better pattern of side effects. Patients treated with LAR could have a similar frequency of non admission with similar equivalent doses, a lower use of additional neuroleptics and fewer side effects. Of particular interest in our study, we did not find any statistically or clinically relevant different in the metabolic profile or the weight gain between different antipsychotics. All this data taken together suggests that the use of long acting atypical antipsychotic should be preferential when a LAN must be used in psychotic patients.

doi:10.1016/j.schres.2010.02.938
**Poster 178**

**RISPERIDONE INJECTABLE LONG-ACTING TREATMENT VS OTHER ORAL ANTIPSYCHOTICS IN FIRST EPISODE PSYCHOSIS: ONE YEAR LONGITUDINAL STUDY**

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**Background:** Treatment compliance is a crucial pronostic factor regarding the longitudinal course of patients with First Episode Psychosis (FEP). The rate of oral antipsychotic treatment discontinuation at first year is about 70% (1). Risperidone injectable long-acting treatment (RILD) has shown high rates of clinical remission, as well as improvement in treatment compliance. As far as we know, there is no RCT that compared RILD vs oral atipic antipsychotics in FEP.

**Methods:** Eighty-seven FEP patients were randomly located on two groups: patients receiving RILD (N = 18) and patients receiving oral antipsychotic treatment (N = 21). Both underwent a baseline assessment and one year follow-up, including: medical interview, PAS Scale, neuropsychological battery, diagnostic assessment (SCID-I) and stability at one year follow-up, clinical assessment (PANSS; CGI; SUMD; HDRS and YMRS), functional assessment(GAF), quality of life (WHO/DAS), hospitalizations, urgency episodes and treatment compliance (subjective for oral antipsychotics).

**Results:** Both groups significantly reduced positive and general psychopathology scales from PANNS at one year follow-up. There were no differences regarding the course of cognitive symptoms. The group receiving RILD significantly improved in functional disability, quality of life and negative symptoms, and showed a trend toward significance in insight and compliance. Two patients receiving oral antipsychotics were rehospitalized, while the rate of rehospitalization for RILD groups was 0.

**Discussion:** RILD an reasonable and treatment alternative for FEP. It treatment compliance, which turns to improvements in insight, negative symptomatology, functional capacity and quality of life.

**Poster 179**

**IMPACT OF ETHNICITY ON EFFICACY AND SAFETY DURING TREATMENT WITH OLANZAPINE IN SCHIZOPHRENIA**

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**Background:** To examine potential differences in efficacy and safety of treatment with olanzapine in patients with schizophrenia of white and black descent.

**Methods:** A post-hoc, pooled analysis of 6 randomized, double-blind trials in the treatment of schizophrenia, schizoaffective disorder, or schizophrreniform disorder compared white (N = 605) and black (N = 375) patients treated with olanzapine (5 to 20 mg/day) for 24 to 28 weeks. Efficacy measurements included Standardized definition of remission in schizophrenia also not significantly different between ethnic groups, with the exception of general frequency of categorical changes in total cholesterol (borderline to high) among white patients and high-density lipoprotein (HDL) cholesterol (normal to low) among white males.

**Discussion:** The findings did not demonstrate substantive differences in efficacy or safety between white and black patients diagnosed with schizophrenia who were treated with olanzapine.

**Poster 180**

**REMISSION IN SCHIZOPHRENIA: RESULTS OF POPULATION AND PHARMACOTHERAPEUTIC STUDIES OF SCHIZOPHRENIC OUTPATIENTS**

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**Background:** Standardized definition of remission in schizophrenia was proposed (low symptom threshold in core 8 PANSS symptoms for at least six consecutive months). However, schizophrenia is characterized by its different clinical types and courses.

**Methods:** At the first stage the population study of remission rate with 6-months follow-up period of symptomatic stability was conducted in two health care districts of outpatient service. The key inclusion criteria were outpatients with ICD-10 diagnosis of schizophrenia or schizoaffective disorder. Patients were assessed with remission criteria (severity and time criteria), PANSS and GAF. Also percent of stable patients (without change of total PANSS score > 20% and/or > 1 point of items of positive subscale PANSS – P1, P2, P3, P6 during last six consecutive months and regardless of baseline status severity) was rated. These patients were analyzed according to remission status and ICD-10 diagnosis. At the second stage the stable patients that did not satisfied to symptomatic criterion were include in 1-year pharmacotherapeutic study. Thus, long-acting risperidone was assigned to the patients in the first district, while patients in second district continued to receiving routine treatment in outpatient service (control group). Patient were assessed with PANSS, social functioning estimated with PSP and compliance with ROMI. Extrapyramidal side effects were rated with Simpson-Angus scale. Rating was done at baseline and in 3, 6, 12 months of the study. Clinical and sociodemographic variables were tested for their ability to predict remission.

**Results:** Fifty-one percent of black patients and 45% of white patients experienced early study discontinuation (p = .133). Of those who discontinued, significantly more white patients experienced psychiatric worsening (p = .002) while significantly more black patients discontinued for "other" reasons (p = .014). Discontinuation for intolerability was not different between groups (p = .320). There was no significant difference in efficacy between white and black patients for the estimated change in PANSS total score over 6 months (p = .928), nor for the estimated PANSS positive (p = .435), negative (p = .756), or general psychopathology (p = .165) scores. Weight change was not significantly different in white and black patients over 6 months (p = .127). However, significantly more black patients experienced clinically significant weight gain (7%) at any time compared to white patients (36.1% vs. 30.4%, p = .021). Changes across metabolic parameters (combined with fasting and random lipids and glucose) were also not significantly different between ethnic groups, with the exception of greater frequency of categorical changes in total cholesterol (borderline to high) among white patients and high-density lipoprotein (HDL) cholesterol (normal to low) among white males.

**Discussion:** The findings did not demonstrate substantive differences in efficacy or safety between white and black patients diagnosed with schizophrenia who were treated with olanzapine.
and 18.7% didn’t have antipsychotic treatment. 64 (31.5%) patients met criteria of symptomatic remission and 139 (68.5%) did not. After six months of follow-up period 158 (77.8%) patients were stable (irrespective of remission status). Among them 53 (26.1%) fulfilled to remission criteria and 105 (51.7%) patients didn’t satisfy to symptomatic criterion. Most of 53 patients in remission had schizoaffective disorder, remittent or episodic course of paranoid schizophrenia. Logistic regression analysis found that these diagnoses was associated with a strong probability of achieving symptomatic remission (OR = 5.95, p < 0.001 compare with other diagnosis). The group of 105 stable patients that did not meet remission criteria generally consisted of patients with more severe clinical types of schizophrenia: chronic and episodic course of paranoid schizophrenia, residual, undifferentiated and simple schizophrenia. 42 patients in group of long-acting risperidone and 35 in control group were included in pharmacotherapeutic study. After 12-months therapy 19.0% patients in first group and 5.7% in second group met remission. Furthermore, reduction of total and subscale PANSS scores as well as the improving of social functioning was significant in the first group. Multiple regression analysis found that episodic course with progressive deficit of schizophrenia was main factor associated with achievement of remission.

**Discussion:** Despite the clinical and functional improving during the treatment with long-acting atypical antipsychotics most of stable outpatients with severer clinical course of schizophrenia didn’t meet international criteria of remission. Achievement of these criteria was associated with schizoaffective disorder and remittent and episodic course of schizophrenia.

doi:10.1016/j.schres.2010.02.941

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**Poster 181**

**LONGITUDINAL TRAJECTORY ANALYSIS OF PLACEBO RESPONSE: SHORT-TERM AND LONG-TERM RANDOMIZED CONTROLLED TRIALS**

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**Background:** Large placebo response often observed in psychiatric clinical trials but a clear understanding of the nature and extent has been elusive. The objective of this analysis was to investigate the time course and trajectory pattern of placebo response in short-term and long-term trials involving patients with schizophrenia and schizoaffective disorder.

**Methods:** We conducted individual patient analysis to evaluate the placebo trajectory pattern using Growth Mixture Model (GMM), based on data from the placebo arms in 2 identically designed 6-week, double-blind clinical trials and a randomized, double-blind study of up to 52 weeks treatment in the ziprasidone clinical trial database.

**Results:** The trajectory pattern for PANSS scores over time in placebo-treated patients from two 6-week (n = 171) and one 52-week studies (n = 71) were analyzed. In the short-term trials, GMM analysis showed: gradual symptom improvement in mean PANSS total score for the majority of placebo patients (85%), while the remaining 15% of patients had symptom worsening. In the long-term 1-year trial, GMM identified 4 classes of placebo response patterns for PANSS total score: 1) immediate worsening class (15%) in which patients experienced exacerbation of symptoms and discontinued the trial within 6 weeks of placebo treatment, 2) gradual worsening class (19%), 3) delayed worsening class (31%) in which patients experienced no change in symptoms for about 16 weeks and gradual worsening afterwards, and 4) no change in symptoms over the 1-year study period (35%). In contrast, a different placebo trajectory pattern was observed for the PANSS negative symptom score in the long-term trial, with a gradual improvement class of 28 patients (45%) (median change -1.5, 95% CI: -0.2, -2.8), gradual worsening class of 24 (median change 4, 95%CI 2.2, 5.8), and other worsening pattern (n = 9, median = 12, 95%CI 7.8, 16.2). In addition, we found that schizoaffective bipolar diagnosis subgroup (n = 29, baseline PANSS total sore = 96, mean change = 4.8) was significantly different in PANSS total score from schizophrenia subgroup (n = 116, baseline = 96, mean change = -5.1) but not schizoaffective depression subgroup (n = 19, baseline = 90, mean change = -5.8).

**Discussion:** Our findings suggest that diagnosis and choice of assessment endpoint might influence magnitude of placebo response. Further studies using systematic review and patient-level data are needed to identify additional factors that might systematically affect placebo response.

doi:10.1016/j.schres.2010.02.942

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**Poster 182**

**EFFECTIVENESS AND TOLERABILITY AMONG PATIENTS WITH RECENT ONSET SCHIZOPHRENIA TREATED WITH RISPERIDONE LONG-ACTING INJECTABLE (RLAI)**

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**Background:** To assess if risperidone long acting injectable (RLAI) could be effective and tolerated in treating recent onset schizophrenia. **Methods:** This was a 6-month, open label, flexible dose, multi-center, phase IV trial in 302 subjects with early-onset (less than or equal to 2 years) schizophrenia treated with RLAI (25 to 50 mg injection every 14 days).

**Results:** 83.8% (n = 253) of subjects completed the study. Dosing ended at 25 mg for 49.5% of subjects, 37.5 mg for 31.0% and 50 mg for 19.5%. There were statistically significant (p < .001) improvements from baseline to LOCF endpoint on PANSS total -13 (SD 14); CGI-S -0.8 (SD 1.3), GAF 10.0 (SD 12.5) SF-36; -Physical component summary 3.7 (SD 8.7); -Mental component summary 7.7 (SD 11.8). The most common AEs were akathisia (4.6%), extrapyramidal disorder (3.0%), and increased weight (3.0%). Eighteen subjects experienced 23 serious adverse events; 20 were psychiatric. There was one suicide and one death due to metastatic gastric cancer. There were 13 potentially prolactin related AEs (~4%). ESRS total score decreased significantly from baseline to LOCF endpoint by 0.5 (SD 1.7, p < .0001). BMI had a small but statistically significant increase from a baseline mean of 25.3 (SD 4.0) to LOCF endpoint by 0.43 (SD 1.35, p < .0001).

**Discussion:** In this open label study of recent onset schizophrenia patients treated with RLAI, favorable efficacy and tolerability outcomes were obtained on both clinician and patient-reported measures.

doi:10.1016/j.schres.2010.02.943
Poster 183
SEROTONIN2A RECEPTOR BLOCKADE AND CLINICAL EFFECT IN FIRST-EPISODE SCHIZOPHRENIA PATIENTS TREATED WITH QUETIAPINE

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Background: We have previously reported decreased frontal cortical serotonin2A receptor binding in 30 antipsychotic naïve first episode schizophrenic patients and its relationship with positive symptoms. Until now, no longitudinal studies in first-episode antipsychotic-naïve schizophrenia patients have reported on the relationship between serotonin2A receptor occupancy and treatment effect after sustained treatment with one atypical antipsychotic compound.

Methods: In the current study, we measured serotonin2A receptor occupancy with [18F]altanserin PET in 15 first-episode antipsychotic-naïve schizophrenia patients after 6 months of quetiapine treatment. Moreover, we investigated possible relationships between clinical efficacy, oral dose, plasma levels of quetiapine, and of the active metabolite nor-quetiapine.

Results: Significant nonlinear relationships were found between serotonin2A receptor occupancy, quetiapine dose and plasma concentration. The mean quetiapine dose was 383 mg corresponding to a serotonin2A receptor occupancy level of approximately 60%. A serotonin2A receptor occupancy level between 60-70% (corresponding to 336-538 mg/day) appeared to be the optimal window for treatment of positive symptoms. Occurrence levels above this window showed no additional treatment effect.

Discussion: Summarized, the data points to a therapeutic role of serotonin2A receptor systems warranted.

Poster 184
RISPERIDONE VS PLACEBO IN THE TREATMENT OF SCHIZOPHRENIA

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Background: Risperidone is the first new generation antipsychotic drug made available in the market in its generic form. It has been used in the treatment of schizophrenia and related psychotic disorders for over a decade. We examined the clinical effects of oral risperidone for people with schizophrenia and schizophrenia-like psychoses in comparison with placebo.

Methods: We searched the Cochrane Schizophrenia Group’s Register (February 2008), references of all included studies, and contacted industry and authors of included studies for relevant studies and data. All randomised clinical trials comparing oral risperidone with placebo treatments for people with schizophrenia and/or schizophrenia-like psychoses were collected. Two reviewers independently inspected citations and/or abstracts, ordered papers, re-inspected and assessed the quality of results and extracted data. For dichotomous data, we calculated the relative risk (RR), the 95% confidence interval (CI) and, where appropriate, the number needed to treat (NNT), on an intention-to-treat basis. For continuous data, we calculated weighted mean differences (WMD).

Results: All ten included studies were described as double blind, but none of them tested for the effectiveness of blinding for either participants or raters. One study (n = 599) compared risperidone against placebo but the attrition rate was 60% over a period of six weeks rendering most of the efficacy and global improvement data unusable. The attrition rate was higher for placebo compared with risperidone (n = 1363, 10 RCTs, RR 0.70 CI 0.57 to 0.86, NNT 13 CI 9 to 29) and less participants left the trial in the risperidone arm due to lack of efficacy (n = 888, 5 RCTs, RR 0.38 CI 0.20 to 0.73, NNT 7 CI 5 to 15). Risperidone was no better than placebo on the CGI global score (n = 397, 3 RCTs, RR 0.80 CI 0.55 to 1.15) but significantly more number of participants in risperidone arm had more than 20% reduction in their BPRS/PANSS score (n = 856, 7 RCTs, RR 0.43 CI 0.32 to 0.58, NNT 7 CI 6 to 10). Data became considerably more homogeneous (and positive) when the one study independent of industry funding was removed (I2 75% to 55%). Despite poor reporting, it is clear that around 24% of all participants receiving either risperidone or placebo developed some form of extrapyramidal effects (n = 723, 5 RCTs, RR 1.40 CI 0.93 to 2.10). Three people on risperidone had prolonged QTc (n = 198, 1 RCT, RR 7.5 CI 0.4 to 144), more on risperidone gained weight (n = 303, 2 RCTs, RR 5.14 CI 1.79 to 14.73, NNNH 10 CI 3 to 51) and had a raised prolactin (n = 323, 2 RCTs, RR 12.54 CI 5.11 to 30.79, NNH 3 CI 2 to 5). Fewer in the risperidone arm needed an additional psychotropic during the trial period (n = 186, 1 RCT, RR 0.62 CI 0.45 to 0.85, NNT 10 CI 7 to 28).

Discussion: Risperidone appears to have a marginal benefit in terms of clinical improvement compared with placebo in the first few weeks of treatment but data are limited, poorly reported and probably biased in favour of risperidone. The margin of improvement chosen by the researchers as their outcome may not be clinically meaningful. Even after so much use of this drug, we feel that further independent trials can be justified.

doi:10.1016/j.schres.2010.02.945
Methods: Forty-five patients diagnosed with schizophrenia, paranoic subtype, were followed up over a five year period in this observational survey. They went through a structured outpatient program including clinical psychiatric visits, psycho-educational and cognitive-behavioral therapy and occupational therapy. Their clinical evolution was assessed on four cut-off points using PANSS scale: at baseline before commencing the program, after 6 months follow-up, and at 2 and 5 years after baseline measurements. An ANOVA mixed design 4 x 2 was used to assess the statistical association between scores of PANSS subscales at the four follow-up cut-off points and the following dichotomous variables: gender, IQ (>95/<95), duration of illness in years (>14 years/<=14 years) and age of onset (>20 years old/<=20 years old).

Results: The results show a positive outcome with a reduction of negative, positive and general PANSS subscales score both at 6 months and after the first 2 years of follow-up. Nevertheless, at the 5 year measurement, symptoms worsen and the PANSS subscales scores tend to approximate the initial baseline. Association between independent variables and symptoms in the subject factor in each cut-off point is statistically significant: gender and total PANSS score (p < .05), duration of illness and total PANSS score, positive PANSS subscale score and general psychopathology PANSS score (p < .05), and age of onset and general psychopathology PANSS score (p < .05).

Discussion: An earlier age of onset correlates with a worse premorbid adjustment in general functioning and a worse outcome of schizophrenic illness, with greater severity of general psychopathology and negative symptoms. Our results replicate previous findings of a better outcome in women.

doi:10.1016/j.schres.2010.02.946

Poster 186
LONG ACTING ANTIPSYCHOTIC: ATYPICAL VERSUS CONVENTIONAL. 48 MONTHS OF FOLLOW-UP

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Background: Discontinuation of medication is the main problem that we can find in a long-term, trust worthy control of the schizophrenia. A chance to improve the adherence is using long acting antipsychotic drugs. Which are divided into two groups: the conventional and atypical, (being risperidone the only atypical commercialized in our country). Various researches consider it must exist qualitative and quantitative differences in the evolution and prediction of the schizophrenic patients in order to the kind of long acting antipsychotic used. Objective: To compare evolution and prediction of schizophrenia in patient treatment with long acting injectable risperidone or conventional depot antipsychotic drugs during 48 months.

Methods: The sample consisted of 60 outpatients with a CIE 10 diagnosis of schizophrenia who took long acting injectable risperidone (n = 30) or long acting typical antipsychotic(n = 30) during study participation. Each six months patients were evaluated at the health center during 48 months. The following scales and date base were collected: Global Clinical Impression (ICG), treatment's satisfaction scale, insight (G12 PANSS), Remission Criteria (Andressen criteria), Global activity evaluation scale (EEAG), hospitalization, treatment discontinuation and concomitant antipsychotic treatment.

Results: There were statistical differences between those taking long acting atypical and typical antipsychotic. In order to use long acting injectable risperidone, we found an improve in: ICG, EEAG, number of remission patients, treatment satisfaction patients, insight, and number of patient with antipsychotic monotherapy. About hospitalization and treatment discontinuation, no statistical different were found compared basal visit and 48 months later in both groups.

Discussion: This study indicates that long acting injectable risperidone improve much more the prediction of schizophrenic patients, compared with conventional antipsychotic treatment.

doi:10.1016/j.schres.2010.02.947
Background: To explore tolerability, safety and treatment re-
sponse with flexibly dosed paliperidone ER in non-acute adult patients with schizophrenia previously unsuccessfully treated with oral olanzapine.

Methods: Prospective 6-month open-label study. Assessments included the Positive and Negative Syndrome Scale (PANSS), patient functioning (Personal and Social Performance Scale (PSP)), patient satisfaction, extrapyramidal symptoms (Extrapyramidal Symptom Rating Scale; ESRS), adverse events (AEs) and weight and tolerability.

Results: 395 patients were analyzed (65.3% male, mean age [±SD] 40.1±12.0 years); most were enrolled because of lack of efficacy (n = 210) or lack of tolerability (n = 140) with prior olanzapine treatment. 65.6% of subjects completed the 6-month study. Most frequent reasons for early discontinuation were subject choice (11.1%), AE (5.8%), or lack of efficacy combined with an AE (5.6%). The median mode dose of paliperidone ER was 6 mg/day. Mean PANSS total score decreased from 78.1±21.4 at baseline to 67.9±21.4 at endpoint (mean change -10.2±20.7; 95% confidence interval -12.3;-8.1, p <0.0001). The percentage of patients rated mildly ill or less in CGI-S increased from 26.3% to 45.8%. Mean PSP scores improved by 5.0±15.2 to 63.7±15.3 (p <0.001). Total ESRS decreased significantly from 2.8±5.0 to 2.0±4.3 (p <0.001). AEs reported in n=5% of patients were insomnia (15.2%), anxiety (7.8%) and somnolence (5.1%). Mean body weight decrease at endpoint was -0.8±5.2 kg (p =0.005). At endpoint, 65.3% of patients rated treatment satisfaction with paliperidone ER as “good” or “very good”.

Discussion: These data support results from recent randomized controlled studies that paliperidone ER is safe, well tolerated and efficacious, including patients previously unsuccessfully treated with oral olanzapine.

doi:10.1016/j.schres.2010.02.949

Poster 190
PREDICTORS FOR HIGH TREATMENT RESPONSE IN ACUTE PATIENTS WITH SCHIZOPHRENIA

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Poster 189
A FLEXIBLE-DOSE STUDY OF PALIPERIDONE ER IN NON-ACUTE PATIENTS WITH SCHIZOPHRENIA PREVIOUSLY UNSUCCESSFULLY TREATED WITH ARIPIPRAZOLE

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Background: To explore predictors for treatment response in patients with schizophrenia suffering from an acute episode treated with flexible doses oral paliperidone ER.

Methods: Six-week prospective international, open-label flexible dose study in acutely exacerbated patients with schizophrenia. Treatment response was defined as >=30% improvement in total PANSS and >=1 point in CGI-S. Super-responders were defined as >=50% improvement in total PANSS and >=2 points in CGI-S. Early response was defined as achievement of criteria mentioned above within the first 2 weeks of treatment for predictor analysis, a stepwise logistic regression model was used.

Results: 294 patients were analyzed (53% male, mean age 40.3±12.4 years, mean average daily paliperidone ER dose 75.2±21.7 mg). 80% of patients completed the study. Mean total PANSS score improved from 100.2±17.2 at baseline to 72.7±20.5 at endpoint (p <0.001), and a significant onset of efficacy was observed as of day 2 of treatment. Treatment response was predicted by type of schizophrenia (in par-
ticular paranoid versus residual: \( p < 0.01 \), early response and differences between participating countries (\( p < 0.001 \)), and there was a trend for patients hospitalized in the last 12 months (\( p = 0.0785 \)). Super- responders were predicted by female gender (\( p < 0.01 \)), high CGI-S baseline score and early response (\( p < 0.001 \)). Age, body mass index and total PANSS score at baseline did not predict treatment response. 

**Discussion:** In patients with schizophrenia suffering from an acute episode, treatment response was predicted by different demographic and clinical factors. As recently described in the literature, early response was a consistent predictor for high treatment response at endpoint.

**Poster 191**

**ADJUNCTIVE VARENICLINE TREATMENT WITH ANTIPSYCHOTIC MEDICATIONS IN PATIENTS WITH SCHIZOPHRENIA: A PLACEBO-CONTROLLED TRIAL**

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**Background:** Several evidences have supported the fact that nicotine through the nicotinic acetylcholine receptor system may be effective in improving cognitive dysfunction that is a core symptom domain of schizophrenia. The objective of this project was to examine the effects of varenicline treatment, a partial agonist at the \( \alpha_4 \beta_2 \) nicotine acetylcholine receptor, and a full agonist at the \( \alpha_7 \) nicotine acetylcholine receptor, on cognitive impairments in people with schizophrenia.

**Methods:** This study was a randomized, double blind, parallel group, placebo controlled 8 week trial. 120 people with schizophrenia (60 smokers and 60 non-smokers) participated in this trial. The dose of antipsychotic and concomitant medications remained fixed throughout the study and the titration of varenicline was as follows: varenicline 0.5 mg/d for days 1 to 3, 0.5 mg twice per day for days 4 to 7, then 1 mg twice daily through week 8. Neuropsychological assessment was performed at baseline, at baseline, week 1, 2, 4, and 8 by using Continuous Performance Test (CPT), Stroop Color Word Test, Wisconsin Card Sorting Test (WCST), Symbol Substitution Test. A neuropsychological test battery was administered at baseline, at baseline, week 1, 2, 4, and 8. Safety assessments related to medication adverse events included the Simpson-Angus Rating Scale (SARS), the Barnes Akathisia Rating Scale (BARS), and a Side Effect Checklist. The Student’s T-test, Wilcoxon Rank Sum test, Kruskal Wallis test, Pearson’s Chi-square test, Fisher’s exact test, and mixed model ANCOVA were used for data analysis.

**Results:** No significant difference was found in age, sex ratio, duration of illness, CPZ equivalent dose of antipsychotic drug and severity of psychopathology measuring by PANSS, SANS, HDRS between varenicline and placebo group. 91 patients completed the study (45 varenicline and 46 placebo) and 29 patients were dropout from the study. There were significant time main effects for WCST categories completed (\( p = 0.034 \)) and WCST total error (\( p = 0.012 \)). There were significant time x treatment or time x treatment x smoking effects were found. For the varenicline main effects, the average difference between varenicline and placebo was found for CPT omission (\( p = 0.004 \)); CPT hit reaction time (\( p = 0.07 \)), DSST (\( p = 0.013 \)) and WCST non-perseverative errors (\( p = 0.043 \)). For the smoking main effect, there are a number of significant main effects of smoking not the smoking by treatment interaction, suggesting that there are differences in level of performance between smokers and non-smokers that are not altered by varenicline. These variables included CPT omission (\( p = 0.012 \)); DSST (\( p = 0.026 \)); visual span (\( p = 0.0006 \)); Stroop incongruent errors (\( p = 0.03 \)). For the smoking x treatment interaction, 

**Poster 192**

**METABOLIC PARAMETERS IN A SUBSET OF PATIENTS IN THE SCOP STUDY**

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**Background:** People with severe mental illness have nearly twice the normal risk of dying from cardiovascular disease (Fleischhacker et al., 2008; Laursen et al., 2009; Weinmann et al., 2009). There is a growing concern about the risk of cardiovascular disease in people with schizophrenia (Casey et al., 2004; De Hert et al., 2009) The presence of the metabolic syndrome (MetS) is an important risk factor for cardiovascular disease and diabetes. The sertindole cohort prospective (SCoP) study was carried out to confirm the short and long term safety of sertindole. The objective of the metabolic sub-study was to evaluate the effect of short and long-term treatment with sertindole or risperidone on metabolic variables in patients with schizophrenia in a subset of patients enrolled in the SCoP study.

**Methods:** Randomized study of the short- and long-term metabolic safety of sertindole compared to that of risperidone in a subset of patients enrolled in the sertindole cohort prospective (SCoP) study. Metabolic assessments were carried out at Weeks 8 and 12 and every 3 months thereafter. The following parameters were measured: weight, waist circumference, blood pressure, fasting plasma glucose and fasting serum lipids. The International Diabetes Federation (IDF) definition of MetS was used.

**Results:** The mean treatment exposure was approximately 7 months in the risperidone group and 6 months in the sertindole group. In 261 randomized patients, there were moderate increases in mean weight, BMI, and waist circumference during treatment with either sertindole or risperidone; after 12 weeks, the increase in weight was 1.3 kg and 1.1 kg, respectively, and after 36 weeks it was 2.2 kg and 2.0 kg, respectively. From baseline to last assessment (up to 60 weeks) weight gains of 1.8 kg and 1.7 kg for sertindole and risperidone, respectively were observed. Similar proportions of patients (sertindole: 17% versus risperidone: 16%) had weight increases ≥7% from baseline to last assessment. The mean changes from baseline in triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, plasma glucose and blood pressure were small and not clinically relevant in both treatment groups. No patient in either of the groups developed type 2 diabetes during the study. At baseline, the prevalence of MetS was lower in the sertindole group (13%) than in the risperidone group.
(21%). The MetS status in the majority of patients remained the same throughout the study; 80% of the patients in the sertindole group and 69% in the risperidone group did not have MetS at baseline nor at last assessment, and 8% of the patients in the sertindole group and 12% in the risperidone group had MetS at baseline and last assessment. At last assessment, the prevalence of metabolic syndrome was 17% in the sertindole group and 26% in the risperidone group and the incidence of metabolic syndrome was 7% in the sertindole group and 10% in the risperidone group.

Discussion: Treatment with either sertindole or risperidone did not appear to be associated with an increased comparative risk of developing metabolic syndrome. In general, the metabolic effects of sertindole and risperidone were similar.

References

doi:10.1016/j.schres.2010.02.953
0.87 NNT 3 CI 2 to 8), less antiparkinsonian medication administration (n = 79, 2 RCTs, RR 0.39, CI 0.17 to 0.90, NNT 5, CI 2 to 21) compared to haloperidol. Levomepromazine caused less akathisia (n = 38, 1 RCT, RR 0.11, CI 0.02 to 0.79, NNT 3, CI 2 to 5) compared to chlorpromazine, but more hypotension compared to risperdone (n = 42, 1RCT, RR 2.50, CI 1.21 to 5.18, NNH 3, CI 2 to 7). Dizziness was more common with levomepromazine compared to other typical (n = 72, 2 RCTs, RR 2.95 CI 1.39 to 6.25; NNH 4 CI 2 to 8) and atypical antipsychotic medications (n = 79, 2 RCTs, RR 2.59, CI 1.23 to 5.46, NNH 4, CI 2 to 12).

Discussion: Available data is of limited quality and derived from mainly short term trials. Levomepromazine appears to have better efficacy compared to chlorpromazine but less propensity to cause extrapyramidal side effects. It appears to be an alternative to be considered when choosing amongst choice of other typical antipsychotics. Apart from one comparison versus risperdone, there is no data available to comment on its comparative efficacy with other atypical antipsychotics. Patients should have more informed choice and more trials are needed to populate the evidence base. It would be a shame if medications such as levomepromazine lost out to other equally or less effective medications due to lack of trials or poor marketing strategy compared to other industry heavy weights.

doi:10.1016/j.schres.2010.02.955

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**Poster 195**

**SYMPTOMATIC AND FUNCTIONAL RECOVERY INDEX FOR NEGATIVE SYMPTOMS IN A 40-WEEK RANDOMIZED, DOUBLE-BLIND STUDY OF ZIPRASIDONE VERSUS HALOPERIDOL FOLLOWED BY A 3-YEAR DOUBLE-BLIND EXTENSION TRIAL**

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Background: Remission in negative symptoms is a well-recognized treatment goal in schizophrenia. We conducted a post-hoc analysis to investigate a combined index of symptomatic remission and functional recovery in the treatment of negative symptoms, based on a randomized study of ziprasidone and haloperidol that provided long-term, double-blind follow-up data for up to 196 weeks (including extension phase), well beyond any previously reported follow-up periods.

Methods: In this study, symptomatic and functional recovery for negative symptoms was defined for each of the 4 QLS functioning dimensions relating to adequate functioning status in instrumental role, everyday objects and activities, interpersonal relations, and intrapsychic foundations (i.e. score 4 on all components defining each of the 4 QLS subscales for 6 months). Cox survival models were applied to estimate relative benefits of ziprasidone versus haloperidol treatment for attaining symptomatic and functional recovery status.

Results: The cumulative survival rates for attaining symptomatic and functional recovery showed the higher ziprasidone dose group had significantly greater likelihood of attaining symptomatic and functional recovery in instrumental role (p = 0.003, NNT = 4), participation in the community (p = 0.0035, NNT = 6), and intrapsychic foundations (p = 0.0065, NNT = 5), compared with haloperidol-treated subjects. The lower ziprasidone dose group showed greater likelihood of attaining symptomatic and functional recovery in instrumental role (p = 0.036, NNT = 13), participation in the community (p = 0.075, NNT = 12), and intrapsychic foundations (p = 0.062, NNT = 20) compared with haloperidol-treated subjects. No significant differences were found between the ziprasidone and haloperidol groups in symptomatic and functional recovery for interpersonal relations.

Discussion: The data reported here support the potential for enhanced negative symptoms remission as well as improved psychosocial and functional outcomes during long-term treatment with ziprasidone. These findings have important implications for our understanding of the treatment effects of different antipsychotics, and on clinical decisions in the long-term management of schizophrenia. Given the post-hoc nature of these analyses, these findings should be regarded as exploratory. Further investigation of atypical and conventional therapies in the long-term treatment and management of schizophrenia is warranted.

doi:10.1016/j.schres.2010.02.956

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**Poster 196**

**THE HETEROGENEITY OF ANTIPSYCHOTIC RESPONSE IN THE TREATMENT OF SCHIZOPHRENIA**

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Background: Schizophrenia is a heterogeneous disorder in terms of response to treatment with many studies reporting about 70% early non-response to treatment. Currently available medications for schizophrenia are effective for only about 50% of patients. Poor symptom response is associated with premature treatment discontinuation, symptom exacerbations, relapse and increased risk of hospitalization with resultant higher costs of treatment. This study investigated the heterogeneity in treatment response among schizophrenic patients treated with atypical antipsychotics.

Methods: Data from a randomized, double-blind, 12-week study enrolling 628 patients with schizophrenia, schizoaffective disorder, or schizoaffective disorder was analyzed using growth mixture modeling. Participants were originally assigned to risperidone therapy. Early responders (ER: > 20% improvement in the Positive and Negative Syndrome Scale [PANSS] total at Week 2) continued on risperidone, while early non-responders (ENR: < 20% improvement in PANSS total at 2 weeks) were randomized (double-blind) to continue on risperidone or switch to olanzapine for 10 additional weeks. Ultimate response (UR) was defined a priori as 40% improvement in the PANSS total score at endpoint. Analysis was conducted using the pooled treatment groups (risperidone and olanzapine). Subgroups of patients (latent class) homogeneous in symptom progress during treatment and significantly dissimilar from other subgroups were identified.

Results: Four distinct response trajectories based on the PANSS total score over a 12-week time period were identified: Class 1 (24 patients): 96% ENR and 96% ultimate non-responder patients (UNR: < 40% in PANSS total at endpoint); Class 2 (12 patients): 75% ENR and 100% UNR patients; Class 3 (420 patients): 80% ENR and 87% UNR patients; and Class 4 (65 patients): 100% ER and 66% UR patients. Classes 1 and 2 were uniquely distributed with 96% ultimate non-responders after 12 weeks of treatment and 96% ENR patients at Week 2 continued to UNR at Week 12. Patients in Class 3 and 420 patients: 80% ENR and 87% UNR patients; and Class 4 (65 patients): 100% ER and 66% UR patients. Classes 1 and 2 were uniquely distributed with 96% ultimate non-responders after 12 weeks of treatment and 96% ENR patients at Week 2 continued to UNR at Week 12. Patients in Class 3 were a mixture of ultimate non-responders and ultimate responders (87% UNR, 13% UR) after 12 weeks of treatment and 89% of ENR.
patients at Week 2 continued to UNR at Week 12. Class 4 was uniquely represented with 100% early responders and 66% progressed to ultimate response after 12 weeks of treatment. Baseline factors with potential influence on the membership of patients in the latent classes of response will be presented.

**Discussion:** This study identified 4 distinct treatment response patterns in schizophrenia patients treated with atypical antipsychotics. This heterogeneity may represent discrete endophenotypes of response to treatment with different etiologic underpinnings. Current findings also show that the a priori definition of early non-response to treatment (less than 20% improvement on the PANSS total score at Week 2) appears to be an accurate threshold and a useful tool for predicting symptom response.

doi:10.1016/j.schres.2010.02.957

**Poster 197**

**DEPRESSIVE SYMPTOMS IN THE FIRST EPISODE OF SCHIZOPHRENIA – ANALYSIS OF POLISH RESULTS OF THE EUFEST STUDY**

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**Background:** The aim of the study was an analysis of the frequency and course of depressive symptoms in Polish patients with the first episode of schizophrenia and an assessment of treatment results.

**Methods:** The study included 94 patients with the first episode of schizophrenia allocated in a randomized fashion to the treatment with low dose haloperidol (n = 26), amisulpride (n = 27), olanzapine (n = 26), quetiapine (n = 12) or ziprasidone (n = 3), for the period of 12 months. Depressive symptoms were assessed using the Calgary Depression Scale for Schizophrenia (CDSS) at baseline, and then after 1, 3, 6 and 12 months.

**Results:** At baseline, depressive symptoms with the score of >6 on CDSS were found in 44.7% of cases. The median CDSS score was 5. The mean intensity of these symptoms was slightly lower than in other Polish studies on patients with the first episode of schizophrenia but similar as in the whole EUFEST group. Patients with depressive symptoms were younger and had lower quality of life as assessed by MANSA. Otherwise, no relationship was found between the intensity of depressive symptoms and selected demographic parameters, intensity of psychopathology measured by PANSS and improvement after treatment. The analysis of course patterns of depressive symptoms showed that the most frequent course type was the depression accompanied acute psychotic symptoms at onset and remitted in line with the psychosis. Post psychotic depression was rare, and was observed in less than 10% cases. There were no significant differences in efficacy on depressive symptoms between haloperidol and amisulpride, olanzapine and quetiapine. Antidepressant drugs were added to antipsychotic treatment three times more frequently in Polish group compared with the whole EUFEST group, SSRIs being used in >90% of the cases. The reduction of depressive symptoms was similar in the group receiving antidepressant treatment as in the group without such treatment.

**Discussion:** Depressive symptoms are frequent among patients with the first episode of schizophrenia and usually improve with antipsychotic treatment. No significant differences were found between antipsychotic drugs studied in their efficacy against depressive symptoms. In Polish patients, antidepressant drugs were used very frequently (mainly SSRIs) as an addition to antipsychotic treatment. A favorable prognostic value of depressive symptoms occurring in the early stages of schizophrenia was not confirmed.

doi:10.1016/j.schres.2010.02.958

**Poster 198**

**LOW DOSE VS. STANDARD DOSE OF ANTIPSYCHOTICS FOR RELAPSE PREVENTION IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS**

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**Background:** It remains unclear as to whether the antipsychotic dose needed for the acute phase is also necessary for relapse prevention. In fact, two major treatment guidelines still suggest opposite treatment strategies. While the practice guidelines by the American Psychiatric Association recommend the use of the lowest possible effective dose for the maintenance treatment, the Expert Consensus Guidelines advocate the continuous use of antipsychotic dose that was effective in the acute phase also for relapse prevention. The objective of this meta-analysis was to compare the efficacy between standard dose vs. low dose or very low dose for the maintenance treatment of schizophrenia.

**Methods:** Double-blind randomized controlled trials were included if they included patients with schizophrenia or schizoaffective disorder who presented with systematically defined stable psychopathology at baseline, and had a minimum follow-up duration of 4 weeks. We restricted our analysis to trials that involved a standard dose group and at least one of very-low dose and low dose groups: (a) standard dose group, using a mean dose of ≥1 Defined Daily Dose (DDD) Unit and less than the upper limit of locally approved dose range in the origin of the trials, (b) very low dose group, using a mean dose of <0.5 DDD Unit, and (c) low dose group, using a mean dose of ≥0.5 and <1 DDD Unit. This unit of measurement was used for standardizing antipsychotics was developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology system of Defined Daily Doses. The DDD unit is the assumed average maintenance dose (mg) per day for a drug used for its main indication in adults. Data on overall treatment failure and hospitalization needed were extracted on an intention-to-treat basis and combined in a meta-analysis, using random-effects model.

**Results:** A total of 13 studies with 1,395 subjects (739 in standard dose groups, 457 in low dose groups, and 199 in very low dose group) were included. Low dose group did not show any statistically significant difference in comparison with standard dose group in terms of overall treatment failure (risk difference = 0.02 [95% CI = -0.05 to 0.10]) or hospitalization needed (risk difference = 0.02 [95% CI = -0.03 to 0.07]). The upper limits of the 95% CI of risk difference for overall treatment failure and hospitalization were as low as 0.10 and 0.07, respectively. On the other hand, the very low dose group was found to be inferior to the standard dose group in both overall treatment failure (risk difference = 0.14 [95% CI = 0.02 – 0.26]) and hospitalization for psychopathology (risk difference = 0.11 [95% CI = 0.04 – 0.17]).

**Discussion:** This systematic review revealed a lack of sufficient trials on the maintenance antipsychotic dose. Although antipsychotic treatment with ≥50% to <1 DDD may be as effective as standard dose
therapy, this contention has to be confirmed in well-designed prospective trials.

doi:10.1016/j.schres.2010.02.959

**Poster 199**

**ITI-007: A NOVEL THERAPY FOR THE TREATMENT OF SCHIZOPHRENIA AND RELATED PSYCHOSES**

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**Background:** ITI-007 is an investigational new drug with a unique pharmacological profile. ITI-007 combines potent 5-HT2A receptor antagonism with cell-type-specific modulation of phosphoprotein pathways downstream of dopamine receptors and with serotonin reuptake inhibition. ITI-007 has dual properties at dopamine D2 receptors, acting as pre-synaptic partial agonist and as post-synaptic antagonist. ITI-007 also exhibits mesocortical and mesolimbic selectivity as evidenced by regionally selective increases in dopamine release and phosphorylation of glutamatergic NMDA NR2B receptors downstream of the D1 receptor in rodent brain. These data suggest a convergence of the actions of ITI-007 on dopaminergic and glutamatergic systems in brain regions key for antipsychotic efficacy. This unique pharmacological profile of ITI-007 is predicted to translate into improved antipsychotic efficacy for the treatment of positive, negative, and cognitive symptoms. Moreover, ITI-007 is predicted to have an improved side effect profile owing to its limited interactions with histaminergic, muscarinic, alpha adrenergic, and other off target receptors. ITI-007 is in Phase II clinical development for the treatment of schizophrenia, sleep disorders, and other psychiatric and neurological indications. The purpose of the presentation is to provide an update on the clinical data to date with ITI-007.

**Methods:** The safety and tolerability of oral ITI-007 were tested in single ascending dose and multiple ascending dose clinical trials in normal healthy volunteers and in stable patients with schizophrenia. These studies were double-blind, placebo-controlled, randomized studies. Vital signs, electrocardiograms, clinical laboratory values (hematology, serology, urinalysis), and adverse events were recorded. Brain receptor occupancy using positron emission tomography (PET) after single oral doses of ITI-007 in healthy volunteers also was determined. Blood samples for pharmacokinetic analysis of ITI-007 plasma levels were collected in each study.

**Results:** ITI-007 is safe and well tolerated across a broad range of doses in healthy volunteers and in patients with schizophrenia. To date, no serious adverse events have been reported. ITI-007 has no clinically significant effects on vital signs, ECGs, or clinical chemistries. A maximally tolerated dose has not yet been achieved and dose escalation continues. ITI-007 demonstrates linear dose-proportional pharmacokinetics. ITI-007 produces dose-related increases in striatal D2 receptor occupancy. ITI-007 also occupies serotonin transporters at clinically relevant doses.

**Discussion:** ITI-007 occupies brain receptors relevant for the treatment of schizophrenia and does so in a safe dose range. Based on its unique pharmacological profile and its mesolimbic and mesocortical functional selectivity, ITI-007 is predicted to improve the positive, negative, and cognitive symptoms associated with schizophrenia and related disorders.

doi:10.1016/j.schres.2010.02.960

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**Poster 200**

**TIME TO REHOSPITALIZATION OF PATIENTS DISCHARGED ON A REGIMEN OF CONVENTIONAL ANTI-PsyCHOTICS, NON-CLOZAPINE SECOND GENERATION ANTI-PsyCHOTICS AND CLOZAPINE**

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**Background:** An important outcome parameter of drug effectiveness in schizophrenia is relapse prevention, which can be reliably measured by time to rehospitalization. Based on our previous findings (Werneck and Elkis, 2007) we tested the hypothesis whether clozapine was superior to conventional or second generation antipsychotics for the prevention of rehospitalizations in patients with schizophrenia discharged from a university hospital during a period of 3 years.

**Methods:** This is a retrospective observational cohort study designed to evaluate rehospitalization rates of patients with schizophrenia discharged from the Institute of Psychiatry of the University of Sao Paulo General Hospital between Dec 1,1997 and Dec 31, 2004 on a regimen of conventional antipsychotics, nonclozapine second generation antipsychotics or clozapine, during a three years follow-up. Risk factors associated with rehospitalization were examined by Cox regression model and survival curves were estimated by the product-limit formula (Kaplan-Meier).

**Results:** Of the 464 patients with schizophrenia discharged from hospital 242 met criteria to enter the study. They were followed at IPq outpatient clinic for three years. The number of patients who were rehospitalized during the observation period were as follows: nine (15%) in use of clozapine, 12 (17%) in use of conventional antipsychotic and 27 (24%) in use of non-clozapine second generation antipsychotic. Survival analysis demonstrated a significant difference in time-to-rehospitalization between groups and between clozapine and second generation antipsychotics groups.

**Discussion:** Patients with clozapine were less rehospitalized than the others groups. The differences in time to rehospitalization were statistically significant between the three groups and between clozapine and nonclozapine second generation antipsychotics groups. Results were limited due to the heterogeneity of severity of illness between groups.

doi:10.1016/j.schres.2010.02.961

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**Poster 201**

**CHILDHOOD ADVERSITY, OFFENDING AND VIOLENCE IN A FIRST EPISODE SAMPLE: FINDINGS FROM THE AESOP FIRST ONSET PSYCHOsis STUDY**

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**Background:** Research has suggested that aggression and violence occur at a higher rate in those with first episode psychosis. This has also been found to be associated with male gender, younger age at onset and lower social class. Many potential risk factors have been advocated in research on the onset of psychosis...
and similarly for theories of violence and aggression. One such potential risk factor is childhood adversity which has been linked to psychosis onset and to violence and offending amongst young males. Therefore this study sought to examine whether there were relationships between specific forms of childhood adversity and antisocial behaviour in an epidemiological sample of first episode psychosis patients. These associations were also explored for gender differences.

**Methods:** Data were available on 171 individuals recruited as part of the Aetiology and Ethnicity of schizophrenia and other Psychoses (AESOP) study who had presented to services for the first time with a psychotic disorder. Self reports of adversity prior to 17 years of age were obtained from the Childhood Experiences of Care and Abuse (CECA), whilst history of antisocial and offending behaviour as well as aggression or violence at presentation to services was retrieved from clinical records and the Psychiatry and Personal History Schedule (PPHS).

**Results:** Logistic regression analysis revealed a significant association between violent offending pre-onset and paternal separation (OR 3.5, 95% CI 1.06-11.54). When explored by gender this finding only remained significant for the male participants (OR 3.75, 95% CI 1.07-13.14) compared with females (OR 1.03, 95% CI 0.97-1.09). Additionally, violence at first presentation was found to be significantly associated with paternal physical abuse (OR 3.75, 95% CI 1.23-11.46). When explored by gender this finding remained only for males and was markedly stronger (OR 6.7, 95% CI 1.48-30.19) than for females (OR 1.93, 95% CI 0.34-11.17). No significant associations were evident between other forms of childhood adversity and antisocial behaviour.

**Discussion:** Experiencing separation from the biological father and severe physical abuse from a father figure appeared to be associated with a history of violent offending and aggression at presentation to services in this first onset sample. This pattern was only evident amongst men. These results lend support to previous findings that specific forms of childhood adversity are associated with the onset of psychosis and with aggression and violence, particularly in males. Identification and subsequent treatment of inter-personal difficulties associated with exposure to adverse experiences in childhood may potentially reduce violent behaviour amongst male psychosis patients.

**References**


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**Poster 202**

**PREVALENCE OF THE METABOLIC SYNDROME AMONG SCHIZOPHRENIA PATIENTS ON ANTIPSYCHOTICS IN NIGERIA**

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**Background:** The metabolic syndrome has been implicated in the increasing incidence of cardiovascular morbidity. The syndrome is commoner among patients with schizophrenia compared to the general population. Morbidity and mortality in schizophrenia may arise due to co-morbid cardiovascular disorders. The prevalence of the metabolic syndrome has not been studied in psychiatric out-patient populations in Nigeria.

**Methods:** A cross sectional survey of schizophrenics attending out-patient clinics at a Nigerian hospital was undertaken. Anthropometric measures, clinical variables and lifestyle patterns of respondents were assessed.

**Results:** About 19% met the criteria for the metabolic syndrome. About half had a BMI in the overweight category. Poor lifestyle habits were observed, comprising lack of exercise and poor knowledge on weight reduction techniques.

**Discussion:** Schizophrenic patients in Nigeria are at risk for cardiovascular morbidity and warrant better attention from psychiatrists.

**doi:**10.1016/j.schres.2010.02.962

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**Poster 203**

**ANTIPSYCHOTICS AND HAEMATOLOGICAL TOXICITY**

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**Background:** Atypical antipsychotics are associated with superior tolerability, adherence and relapse prevention and have led to improved treatment for patients with serious mental illness. However, they are also associated with haematological adverse effects [1]. Complete blood count before treatment, weekly for 6 months of treatment, biweekly for months 6–12 and every 4 weeks thereafter is the common practice for the treatment with Clozapine worldwide.

**Methods:** Presentation of a clinical case. Medline research for articles published from 1990 to the present, using the terms “antipsychotic”, “antipsychotic agents”, “leucopenia”.

**Results:** Caucasian male, age 30, with diagnosis of schizophrenia, was hospitalized because of psychotic symptoms in our clinic. After admission, the values of blood cell count, biochemistry and urinalysis were into the normal ranges. 10 days after the first dose of risperidone long-acting injectables (50 mg/15 days) he presented white blood cells (WBC) 1.900/mm3 with an absolute neutrophil count (ANC) of 1.050/mm3, Red blood cell count (RBC) 4.35 (4.4 – 5.8 × 10 ⁹/L), Hemoglobin 13.9 (13.0-18.0 g/dl), Haematocrit 38.5% (37.0% - 49.0% of red blood cells) with ESR mm/hr. Physical examination was performed by a senior internist without pathological findings. After the infective and autoimmune basis of the leucopenia was excluded, the treatment was interrupted and we started haloperidol at 10 mg/day. After 10 days the blood values returned to normal values.

**Discussion:** Haematological abnormalities are frequently encountered during treatment with antipsychotic drugs [2]. Most of these are mild and of no clinical significance [3], but in a small minority of patients, hazardous, potentially life-threatening haematological effects, including leucopenia and agranulocytosis, can occur [4]. Clinicians should track, maybe more often, the effects of treatment on physical and biological parameters and should facilitate access to appropriate medical care. However, with the prescription of antipsychotic drugs comes the responsibility for monitoring potential drug-induced haematological abnormalities. A coordinated action of psychiatrists and hematologists, but also, general practitioners, endocrinologists, cardiologists, nurses and the family is certainly a key determinant to ensure the optimal care of these patients.

**References**

Poster 204
ALTERATIONS OF GLUCOSE METABOLISM IN PATIENTS TREATED WITH ZIPRASIDONE VS. CLOZAPINE

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Background: Alterations of glucose metabolism have been found during treatment with novel antipsychotics.

Methods: We conducted a prospective, open drug monitoring study in schizophrenia patients in order to compare insulin, glucose, Homeostasis Model Assessment index for insulin resistance (HOMA IR) and for beta cell activity (HOMA beta cell index) in patients who were treated with ziprasidone to those who took clozapine.

Results: We present preliminary results from 26 patients: 15 received clozapine and 11 ziprasidone. Mean age was 39.9 (SD: +// 0-9.3). Baseline parameters did not differ significantly between the two groups. Patients who were treated with clozapine showed significantly higher insulin and HOMA beta cell index after week 12-16 of treatment as compared to patients who took ziprasidone. After week 12-16 HOMA IR was higher in patients who took clozapine than in those who took ziprasidone at a trend level.

Discussion: Our findings indicate that the treatment with ziprasidone is favourable compared to treatment with clozapine with respect to the risk to induce alterations of glucose metabolism.

doi:10.1016/j.schres.2010.02.966

Poster 205
MALE SEXUAL DYSFUNCTION IN SCHIZOPHRENIA: RELATIONSHIP WITH DRUG TREATMENT, PROLACTIN AND DRD2 GENOTYPE

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Background: Sexual dysfunction induced by antipsychotic drug treatment is under-investigated and under-reported. The underlying mechanisms are unclear and likely to be multifactorial, although effects of prolactin elevation have been implicated. We undertook a study to determine the influence of drug treatment and genetic polymorphisms in two candidate genes with sexual dysfunction in male subjects with remitted schizophrenia, and to assess the possible role of blood prolactin concentrations.

Methods: 100 male subjects with schizophrenia and meeting criteria for remission were assessed for sexual and erectile dysfunction using the Arizona Sexual Experience Scale (ASEX) and the 5-item version of International Index of Erectile Function (IIEF-5). Subjects were married, living with a sexual partner and receiving antipsychotic drug monotherapy for at least six months. Blood samples were taken for plasma prolactin determination and genotyping of two polymorphisms each of the D2 dopamine receptor (DRD2) and eNOS nitric oxide synthase isoform genes.

Results: 30 subjects received typical antipsychotic drugs (primarily chlorpromazine) and 70 received atypical drugs (primarily clozapine and risperidone). Sexual dysfunction determined by ASEX score was significantly greater in the patients receiving typical antipsychotics than those receiving risperidone or clozapine, and threshold criteria for sexual dysfunction and erectile dysfunction were reached significantly greater proportion of subjects on typical drugs (67% and 60%), compared with the atypical drug group (39% and 39%). Prolactin, significantly higher in subjects receiving risperidone compared with those receiving clozapine or typical antipsychotics, was only significantly correlated with sexual dysfunction within the risperidone group. Neither of the eNOS polymorphisms, G894T or T-786C, was significantly associated with sexual or erectile dysfunction. The -141C ins/del, but not Taq1A, polymorphism of the DRD2 gene was significantly associated with sexual dysfunction with the del allele carriers having significantly lower ASEX scores and being less frequent in subjects meeting sexual dysfunction criteria. Prolactin was also lower in del allele carriers.

Discussion: Our findings indicate that the older typical antipsychotics are more likely to be associated with sexual dysfunction in men than the atypical drugs, including risperidone and clozapine, despite the higher blood prolactin concentrations associated with risperidone. The pharmacogenetic association with a functional DRD2 polymorphism may, in part, be related to effects on prolactin elevation due to genotype differences in receptor density, although other DRD2 mechanisms may contribute. Certainly factors independent of both prolactin and DRD2 genotype are likely to contribute to the increase in sexual dysfunction in male patients on typical antipsychotic drugs.

doi:10.1016/j.schres.2010.02.966

Poster 206
COGNITIVE IMPAIRMENT FOLLOWING PRENATAL IMMUNE CHALLENGE IN MICE CORRELATES WITH PREFRONTAL CORTICAL AKT1 DEFICIENCY

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Background: Accumulating evidence indicates that genetically determined deficiency in the expression of the cytoplasmic serine-threonine protein kinase AKT1 may contribute to abnormal prefrontal cortical structure and function relevant to the cognitive disturbances in schizophrenia. However, it remains essentially unknown whether prefrontal AKT1 expression may also be influenced by environmental factors implicated in the etiology of this mental illness. One of the relevant environmental risk factors of schizophrenia and related disorders is prenatal exposure to infection and/or immune activation. The present study therefore explored whether prenatal viral-like immune challenge may lead to prefrontal AKT1 deficiency and associated changes in cognitive functions attributed to the prefrontal cortex. For these purposes, we used a well-established experimental mouse model of prenatal exposure to a viral-like acute phase response induced by the synthetic analogue of double-stranded RNA, polyribosinic-polyriboytidylic acid (PolyI:C).

Methods: Pregnant C57BL/6 mice on gestation day (GD) 17 were treated with PolyI:C (5 mg/kg, i.v.) or corresponding vehicle (saline) solution. Adult offspring born to immune-challenged and control mothers were then subjected to cognitive phenotyping and neuroanatomical investigations. Cognitive testing included the assessment of spatial working memory in the cheeseboard maze and spatial recognition memory in the Y-maze. Following completion of the cognitive phenotyping, the animals were sacrificed for
the purpose of post-mortem immunohistochemical analyses of AKT1 and catechol-O-methyltransferase (COMT) protein in different subregions of the prefrontal cortex.

**Results:** We found that adult offspring born to Polyt.C-treated mothers showed delay-dependent impairments in spatial working memory and recognition memory together with a marked reduction of AKT1-positive cells in all major subregions of the prefrontal cortex. These effects emerged without concomitant changes in prefrontal COMT density. Correlative analyses further demonstrated a significant positive correlation between the number of AKT1-positive cells in distinct prefrontal cortical subregions and cognitive performance under high storage load in the temporal domain.

**Discussion:** Our study provides the first experimental evidence for a significant environmental influence in the form of prenatal exposure to a viral-like acute phase response on altered AKT1 protein expression in the prefrontal cortex. Importantly, by showing a positive correlation between the number of prefrontal AKT1-positive cells and cognitive performance in spatial working memory and novelty preference tests, our experimental data reveal a critical link between prefrontal cortical AKT1 deficiency and emergence of cognitive impairment following prenatal immune challenge. Our findings thus highlight that schizophrenia-related alterations in AKT1 signaling and associated cognitive dysfunctions may not only be precipitated by genetically determined factors, but may also be produced by (immune-associated) environmental insults implicated in the etiology of this disabling brain disorder.

doi:10.1016/j.schres.2010.02.967

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**Poster 207**

**DOPAMINE TRANSPORTER (DAT) ACTIVITY REGULATES THE INDUCTION OF SYNAPTIC PLASTICITY IN RODENT PREFRONTAL CORTEX**

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**Background:** Dopamine is an important neurotransmitter for prefrontal cortex (PFC)-mediated cognitive function. Dysregulation of dopaminergic transmission in the PFC is thought to contribute to the development of a variety of neuropsychiatric disorders including schizophrenia. While the current hypothesis for schizophrenia pathogenesis extends to other neurotransmitter systems besides dopamine, the dopamine hypothesis remains a most influential theory. To maintain dopamine in a homeostatic level as required for normal function, the dopamine clearance system such as the dopamine transporter (DAT), which is responsible for inactivation of the action of dopamine, the dopamine hypothesis remains a most influential theory. Some studies indicated elevated DA signaling in the PFC of schizophrenia patients, and manipulations of DAT may be mainly achieved by NET (noradrenalin transporter) rather than DAT. But our results, together with some in vivo microdialysis studies, present the evidence that DAT in the PFC does play functional roles. We suggest that the abnormality of synaptic plasticity caused by DAT dysfunction may underlie the cognitive disturbances seen, for example, by abuse with psychostimulant drugs.

doi:10.1016/j.schres.2010.02.968

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**Poster 208**

**DIFFERENTIAL EFFECTS OF CHRONIC ADOLESCENT VS. ADULT THC EXPOSURE IN COMT KNOCKOUT MICE ON PHENOTYPES RELEVANT TO PSYCHOSIS**

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**Background:** Clinical studies have indicated cannabis use to confer increased in risk for development of psychosis, with adolescent-onset use conveying even higher risk. Increased susceptibility is likely mediated via a disruptive effect of cannabis during a critical period of brain development. There is increasing evidence that a high activity COMT polymorphism moderates the effects of adolescent exposure to cannabis on risk for adult psychosis. COMT is an enzyme that is involved in the breakdown of dopamine in the prefrontal cortex and deletion at chromosome 22q11, which contains the COMT gene, has been linked with elevated risk for psychosis.

**Methods:** In the present study, mice mutant for the COMT gene (COMT 'knockouts') were chronically treated with delta-9-tetrahydrocannabinol (THC, the psychoactive constituent of cannabis; 507

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4.0 and 8.0 mg/kg over 20 consecutive days) during either adolescence (postnatal day 32-52) or adulthood (postnatal day 70-90). The effects of THC exposure were then examined in adulthood across behavioural phenotypes relevant for psychosis: exploratory activity, social interaction (as measured in the sociability and social novelty preference test), object recognition memory, spatial working memory (spontaneous alternation, delayed alternation) and anxiety (elevated plus maze).

**Results:** COMT genotype selectively modified the adult effects of chronic THC, when given during either adolescence or adulthood, at the levels of social cognition and object recognition memory. However, adolescent-treated COMT mutants demonstrated more pronounced sex-specific abnormalities following chronic THC across both psychosis-relevant behavioural endophenotypes (heightened exploratory activity, spatial working memory deficits) and anxiety relative to adult-treated mutants and controls.

**Discussion:** It is proposed that examination of the effect of genotype on responsivity to environmental manipulations at specific developmental stages illuminates the relative contribution of, and interaction between, genes and adverse environmental factors in the expression of the psychosis phenotype. This work was supported by Science Foundation Ireland and the Health Research Board of Ireland.

doi:10.1016/j.schres.2010.02.969

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**Poster 209**

**VALIDATION OF LOCALISED BRAIN REGION SPECIFIC ADENO-ASSOCIATED VIRAL-MEDIATED GENE MANIPULATION**

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**Background:** It is widely accepted that schizophrenia (sz) is a complex polygenic disorder, with variations in numerous candidate genes having been identified in multiple populations conferring increased risk to the disorder. However, the pathophysiological role of these genes in the cognitive deficits of sz is poorly understood, partly due to inadequate animal models. The use of viral vectors allows the spatial and temporal control of gene manipulation, creating rodents with restricted genetic modifications that can serve as effective disease models in which the function of the gene can be dissected. Viral-mediated gene manipulation enables targeting of specific brain regions in adult tissues, and thus overcomes the lack of regional specificity and developmental and compensatory effects which limit the usefulness of current constitutive knock-out animals. Recombinant adeno-associated viral (rAAV) vectors have vast potential for manipulating endogenous genes in specific neuronal circuits as they can transduce non-dividing cell types, such as neurons, efficiently and can maintain gene expression for sustained periods of time allowing behavioural testing to be performed. We demonstrate that the injection of rAAVs at these high titres allows for the highly localised transduction of cells in the prefrontal cortex, and that this can be observed at several time points and in specific cell types. These findings will allow us to use this technique in the adult rodent brain, which will allow us to use this technique in the adult rodent brain, which will allow us to use this technique in the adult rodent brain, which will allow us to use this technique in the adult rodent brain.

**Methods:** rAAV particles expressing enhanced green fluorescent protein (eGFP) under the control of the cytomegalovirus promoter were produced by the University of Pennsylvania vector core. The utility of these vectors was validated primarily in vitro testing a range of viral titres over multiple time points: presence of eGFP was used for the detection of infected neurons. Following in vitro validation, the rAAV vectors were validated *in vivo*. Bilateral stereotaxic injections were used to deliver the AAV-eGFP particles at either 1 × 10¹¹ gc/ml or 1 × 10¹² gc/ml or vehicle (PBS/3% sucrose (w/v)) into the prefrontal cortex of male Hooded Lister rats. The rats were allowed to recover from surgery for 1, 3 or 8 weeks (n = 3/time point) prior to transcardiac perfusion. The brains were removed and the tissue evaluated for viral transduction and spread via detection of eGFP expression by immunofluorescence. Co-staining with antibodies against several subtypes of neural cells was performed to identify which types of cells were targeted by the viral particles.

**Results:** *In vitro* validation of AAV-eGFP confirmed that viral titres between 2 × 10¹¹ gc/ml and 2 × 10¹² gc/ml were sufficient to generate concentration dependant expression of eGFP in most of the cultured cells within 2-7 days post infection. *In vivo* use of AAV-eGFP resulted in animals that recovered quickly, with no obvious health problems. eGFP positive cells were identified around the area of the needle tract, specifically in the prefrontal cortex at multiple time points following surgery. Several subtypes of cells were transduced by the viral particles as identified using immunostaining.

**Discussion:** This method highlights the utility of viral mediated gene manipulation for investigating the role of sz candidate genes, as it can target specific brain regions and generates sustained expression allowing behavioural testing to be performed. We demonstrate that the injection of rAAVs at these high titres allows for the highly localised transduction of cells in the prefrontal cortex, and that this can be observed at several time points and in specific cell types. These findings will allow us to use this technique in the adult rodent brain, which will allow us to use this technique in the adult rodent brain, which will allow us to use this technique in the adult rodent brain, which will allow us to use this technique in the adult rodent brain.

doi:10.1016/j.schres.2010.02.970

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**Poster 210**

**INDIVIDUAL DIFFERENCES IN THE EXPRESSION OF PREPULSE INHIBITION PREDICT THE MAGNITUDE OF AMPHETAMINE BEHAVIOURAL SENSITIZATION IN C57BL/6 MICE**

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**Background:** Prepulse inhibition (PPI) is demonstrated when the startle reflex in response to a sudden intense acoustic pulse stimulus is attenuated by a weak prepulse stimulus presented shortly before. PPI is commonly considered as an operational measure of sensory gating whereby perception of the prepulse inhibits the processing of the succeeding pulse stimulus. PPI deficiency is considered to be an endophenotype of schizophrenia and a behavioural trait associated with schizotypal personality. PPI is readily disrupted by dopamine receptor agonists, suggestive of dopaminergic modulation over sensory gating. Repeated prior exposures to amphetamine are also sufficient to produce PPI deficiency even though the drug is no longer present in the subjects during test – an effect attributable to the development of a sensitized dopamine system. However, the causal link between dopaminergic sensitization and PPI deficiency remains debatable because of controversy over the precise amphetamine exposures regime necessary to induce a reliable effect. Here, we undertook a unique approach to test if this link might further suggest that intrinsic low-PPI trait confers vulnerability to the development of dopaminergic sensitization. To this end, a homogeneous cohort of wild type mice was segregated into two subgroups based on the magnitude of their PPI expression. Their propensity to develop behavioural sensitization to amphetamine was then compared.

**Methods:** A cohort of 22 male adult C57BL/6 mice was screened using a standard PPI procedure, and was split according to individual's
average PPI magnitude into high-PPI and low-PPI subgroups (n = 11). Next, their motor response to systemic antipsychotic challenge (2.5 mg/kg, i.p.) was evaluated twice in an open field in tests separated by five days. Each test followed a within-subject design comprising a pre-injection phase (30 min), a saline phase (30 min), and finally a drug phase lasting for 120 min. Enhanced motor response to the drug in the second test relative to the first test constitutes the behavioural sensitization. Locomotor activity was indexed by distance moved in 5-min bins, recorded by a video tracking system.

**Results:** The outcome confirmed our prediction, in that the low-PPI group exhibited a stronger behavioural sensitization effect compared to the high-PPI subjects. At the same time, the two groups did not differ in their motor response to the first amphetamine exposure.

**Discussion:** Previous experiments examining the impact of a sensitized dopaminergic system induced by repeated amphetamine exposures on the expression of PPI have suggested that the former can lead to PPI disruption. Here, our results provided evidence that intrinsic low PPI levels and the propensity to develop dopaminergic sensitization are linked to a common neural substrate. This finding suggests that individuals marked by low PPI expression might be at greater risk of developing schizophrenia because their dopaminergic system is susceptible to sensitization. Considering the diverse environmental factors, such as stress, that can shape the development of dopaminergic sensitization, the present finding bears resemblance to a two-hit model of schizophrenia.

doi:10.1016/j.schres.2010.02.971

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**Poster 211**

**DISTINCT ASPECTS OF PREFRONTAL CORTEX DYSFUNCTION IN SCHIZOPHRENIA MODELED BY ACUTE AND REPEATED PCP TREATMENT: IMPACT OF MODAFINIL**

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**Background:** Dysfunction of the prefrontal cortex (PFC) has long been implicated in schizophrenia, and correlates with cognitive deficits and negative symptoms. The cellular mechanisms underlying this dysfunction remain unclear although there is considerable focus on the glutamatergic hypothesis with widespread use of NMDA receptor antagonists in preclinical models. However, there is no unified view of how NMDA receptor hypofunction leads to a dysfunctional PFC. We hypothesise that acute NMDA receptor blockade results in acute psychosis-like events, potentially through GABAergic mediated disinhibition of pyramidal neurones, whereas repeated NMDA receptor antagonism induces neuroadaptive events that lead to negative symptoms and cognitive deficits. We have shown that repeated PCP treatment produces a reduction in prefrontal cortex activity (hypofrontality) using 2-deoxyglucose imaging and that this is accompanied by alterations in expression of GABAergic markers and cognitive deficits (Pratt et al., 2008). Here we compare the behavioural and imaging signatures of acute and repeated PCP treatment and assess the impact of the putative pro-cognitive agent modafinil upon repeated PCP-induced imaging and cognitive deficits.

**Methods:** Male hooded rats were treated acutely or repeatedly with PCP (2.58 mg·kg⁻¹, i.p. 1×daily), 2-deoxyglucose (2-DG) autoradiography was employed to image local rates of cerebral metabolism. Novel functional connectivity analysis (partial least squares regression) was employed to assess PCP-induced imaging deficits at the network level. The behavioural effects of PCP were assessed using prepulse inhibition of acoustic startle (PPI) and MATRICS-related cognitive tasks; the attentional set-shifting task, 5-choice serial reaction time task (5-CSRTT). The impact of modafinil (64 mg·kg⁻¹) on subchronic PCP-induced hypometabolism and set-shifting performance was evaluated.

**Results:** Subchronic PCP treatment produced hypometabolism in selected prefrontal and thalamic regions in accordance with previous reports (Pratt et al 2008). Using novel functional connectivity analysis, the present results show that subchronic PCP disrupts ‘functional connectivity’ between the prefrontal cortex and the locus coeruleus and between the prefrontal cortex and nucleus accumbens. A similar pattern of dysconnectivity was observed in the retrosplenial cortex. These PCP-induced imaging deficits were accompanied by ED/ID deficits in the attentional set-shifting task. Repeated PCP treatment also produced reductions in ln Beta and reaction time in the 5-CSRTT. However, there were no deficits in PPI following repeated PCP treatment. Modafinil restored repeated PCP-induced set-shifting deficits, the hypometabolism in the prefrontal and retrosplenial cortex, as well as the functional connectivity signature. In contrast to the repeated PCP treatment regime, acute NMDA receptor blockade produced PPI deficits and increased premature responding in the 5-CSRTT. Both gene expression and image analysis data support the view that these acute behavioural deficits relate to ‘hyperfrontality’ rather than ‘hypofrontality’.

**Discussion:** Collectively these findings suggest that acute and repeated NMDA receptor blockade model different components of schizophrenia. Moreover, the ability of modafinil to reverse the subchronic PCP-induced imaging signature and the associated set-shifting deficit, suggests that reversal of the PCP-induced imaging signature is a useful biomarker for identifying precognitive agents to treat schizophrenia.

doi:10.1016/j.schres.2010.02.972

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**Poster 212**

**NICOTINE RESTORES COGNITIVE IMPAIRMENTS FOLLOWING SUB-CHRONIC KETAMINE EXPOSURE IN A RODENT ODOR SPAN TASK**

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**Background:** Ketamine is an NMDA receptor antagonist shown to produce deficits in humans on cognitive battery of tasks involving attention and memory. Previous work in our laboratory using the odour span task (OST) has shown nicotine to be effective in enhancing cognitive performance in normal animals. The aim of this study was to develop a rodent model of cognitive deficits using ketamine exposure in the OST to evaluate the ability of nicotine to restore performance.

**Methods:** Rats were trained in a non-matching to sample rule, then the full OST, which involved identifying a novel odour from an increasing number of presented odours. Male hooded Lister rats were performance matched and randomly allocated to three treatment groups (n = 8). Animals were sub-chronically exposed to ketamine daily (10, 30 mg/kg i.p. or vehicle) for 5 consecutive days after reaching a baseline level of performance. Ketamine produced a dose-dependent impairment that was stable over 14 days. Animals were therefore tested with acute doses of nicotine (0.025, 0.05 and 0.1 mg/kg) and saline in a randomised sequence.

**Results:** Nicotine doses in 0.1 and 0.5 mg/kg were effective in restoring performance to baseline levels in both ketamine-treated
groups. Similar levels of improvement with nicotine were evident in control subjects, with the most significant effect observed following 0.05 mg/kg nicotine.

**Discussion:** These data suggest that ketamine in the OST may be useful in examining novel treatments to restore cognitive impairments associated with neuropsychiatric disorders such as schizophrenia, and adds to the evidence suggesting that neuronal nicotinic receptors may be viable targets for intervention. Further behavioural work but also in-vitro electrophysiology will be undertaken to elucidate the role of specific receptors involved this process.

doi:10.1016/j.schres.2010.02.973

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**Poster 213**
Poster not available

doi:10.1016/j.schres.2010.02.974

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**Poster 214**

**C3H ALPHA7 NICOTINIC RECEPTOR HETEROZYGOTE MICE AS A NEW MODEL OF SCHIZOPHRENIA**

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**Background:** Schizophrenia-like deficits in sensory inhibition (auditory gating) and concomitant reductions in hippocampal alpha7 nicotinic receptors, have been modeled using DBA/2 inbred mice while the normal pattern of sensory inhibition and receptor numbers have been modeled using C3H inbred mice. While much data has been generated using this 2 strain approach, there are more differences between these 2 strains than just the numbers of hippocampal alpha7 nicotinic receptors making this 2 strain approach less similar to the human condition. A more desirable model would utilize the same genetic Background to model both normal and schizophrenia-like patterns. Recently, the alpha7 nicotinic gene null mutation was bred onto the C3H mouse Background at the Institute for Behavioral Genetics at the University of Colorado Boulder. The heterozygote and wildtype mice were investigated for sensory inhibition, levels of hippocampal alpha-bungarotoxin binding (alpha7 receptors), hippocampal GABA, GAD65, GAT-1 and GABA receptors, and we are currently looking at learning and memory.

**Methods:** Sensory inhibition was assessed using the published paired auditory stimulus paradigm. Hippocampal GABAα and alpha7 receptor numbers were determined by autoradiography (using 35-S tert-butylbicyclophosphorothionate and 125-I alpha-bungarotoxin, respectively), GABA, GAT-1 and GAD65 were assessed by immunohistochemistry and learning and memory are being studied with novel object recognition and contextual fear conditioning.

**Results:** C3H alpha7 heterozygote mice showed deficient sensory inhibition (~60% decrease) compared to wildtype littermates as well as an overall increase in hippocampal excitability. There was also ~60% decrease in hippocampal alpha7 receptors. There was an increase in GABAα receptor numbers in male heterozygotes only, and an increase in GAT-1 levels in males (females not studied), while GABA and GAD65 levels were decreased in males (females not studied). Learning and memory studies are ongoing.

**Discussion:** Studies of schizophrenia patients routinely show deficient sensory inhibition, with increased hippocampal activity, while postmortem binding studies of the hippocampus of these patients show a ~50% reduction in alpha7 nicotinic receptors. Since alpha7 receptors are found on hippocampal interneurons, a reduction would be expected to increase general hippocampal activity as well as reduce sensory inhibition. The findings in the C3H alpha7 heterozygote mouse model the schizophrenia pattern while the wildtype mice resemble the normal pattern. Schizophrenia patients also show increases in GABAα receptor numbers as well as a decrease in GAD65 and GABA uptake site density. The data on GAT-1 are variable, one study showing decreases in the terminals of prefrontal cortical chandelier cells and another showing a increase in the cingulate cortex. Preliminary data in the heterozygote mice show increases in GABAα receptors in the males, while GAD65, one of the 2 enzymes involved in the production of GABA, is reduced, as is GAT-1, a transporter of GABA. There was also a reduction in GABA levels in the hippocampus. Again, these patterns resemble those observed in schizophrenia patients. While learning and memory studies are ongoing, it is anticipated that there will be reductions in learning and memory, corresponding to the poor attention observed in schizophrenia patients which leads to poor learning and memory. These studies suggest that the C3H alpha7 nicotinic receptor heterozygote mouse may be a useful model for both mechanistic studies and discovery of new antipsychotic therapies.

doi:10.1016/j.schres.2010.02.975

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**Poster 215**

**EX VIVO ANALYSIS OF ASENAPINE-, OLANZAPINE-, AND RISPERIDONE-INDUCED DOPAMINE D1 AND D2 RECEPTOR OCCUPANCY IN RAT BRAIN**

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**Background:** Asenapine is indicated in the United States for acute treatment of schizophrenia in adults and acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults, and is under review in Europe for the treatment of schizophrenia and manic episodes associated with bipolar I disorder. Asenapine exhibits high affinity for dopamine (DA) receptor subtypes, but its occupancy of DA D1 and D2 receptors in different brain regions and versus other established antipsychotic drugs remains unclear. In this study, we analyzed D1 and D2 receptor occupancy induced by asenapine, olanzapine, and risperidone.

**Methods:** Adult male rats were injected subcutaneously with 6 doses of asenapine (0.003, 0.01, 0.03, 0.1, 0.3, or 1.0 mg/kg; n=6/group) or vehicle (1 mL/kg). Other groups of adult rats were injected intraperitoneally with 6 doses of olanzapine (0.1, 0.3, 1.0, 3.0, 10.0, or 30.0 mg/kg; n=6/group), risperidone (0.01, 0.03, 0.1, 0.3, 1.0, or 3.0 mg/kg; n=6/group), or vehicle (1 mL/kg; n=6/group). Sixty minutes following administration of asenapine, olanzapine, risperidone, or vehicle, rats were decapitated; their brains were removed and processed for ex vivo receptor autoradiography. D1 and D2 receptor occupancies were measured in medial prefrontal cortex (MPC), dorsolateral frontal cortex (DFC), nucleus accumbens (NAC), caudate putamen (CPu), hippocampus (HIPP), and entorhinal cortex (EC).

**Results:** Asenapine, olanzapine, and risperidone induced dose-related increases in DA D1 and D2 receptor occupancy in different
forebrain regions. However, asenapine was more potent, with ED_{50} values consistently lower than those of olanzapine and risperidone across all forebrain regions examined. In addition, asenapine displayed preferentially higher affinity for D1 and D2 receptors in MPC (ED_{50} 0.018 and 0.004 mg/kg, respectively), DFC (0.015 and 0.003 mg/kg), and HPP (both 0.014 mg/kg) than in CPUs (both 0.03 mg/kg), NAc (0.044 and 0.024 mg/kg), or EC (0.064 and 0.017 mg/kg). In contrast, both olanzapine and risperidone occupied D1 and D2 receptors in different forebrain regions with similar ED_{50} values.

**Discussion:** These findings suggest that the profile of asenapine-induced D1 and D2 receptor occupancy is different from that of olanzapine and risperidone. Preferential occupancy of D1 and D2 receptors by asenapine in cortical and limbic versus extrapyramidal brain regions supports the unique psychopharmacologic properties of this novel antipsychotic agent. (Supported by HD-052752 and Schering Corp., a division of Merck & Co.)

doi:10.1016/j.schres.2010.02.976

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**Poster 216**

**ALTERATION OF AKT1 AND NEUREGULIN-1 GENE EXPRESSION IN FRONTAL CORTEX AND DENTATE GYRUS MAY BE ASSOCIATED WITH SCHIZOPHRENIA: PERINATAL ASPHYXIA MODEL IN RAT**

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**Background:** Many previous studies have reported an association between obstetric complications (OCs) and the later development of schizophrenia. One of the mechanisms underlying the association is postulated to be a hypoxic process in the brain in the offspring around the time of birth. AKT1 and neuregulin-1 (NRG1) are putative candidate genes for susceptibility to schizophrenia. Both AKT1 mRNA and protein expression have been shown to be reduced, and NRG1 isoforms to be differentially expressed in brain regions of schizophrenia patients such as the prefrontal cortex and hippocampus (Emamian et al. 2004; Thielson et al. 2008; Hashimoto et al. 2004). Moreover, the expression of these two genes (i.e., AKT1 and NRG1) is liable to ischemia/hypoxia. In ischemia/hypoxia-induced adult rodents, the expression of AKT1 and NRG1 that act as a neuroprotective agent has, in effect, been shown to be elevated. In our animal model in which neonates were exposed to hypoxia, we postulated that these two genes would be expressed differentially even in adulthood, i.e., the risk period of manifestation of psychosis in humans.

**Methods:** In this study, we exposed neonatal pups to hypoxia for 15 min and, then, measured the AKT1 and NRG1 mRNA levels in the prefrontal cortex, dentate gyrus and hippocampus of these grown-up rats using quantitative PCR.

**Results:** Significantly decreased mRNA levels of AKT1 were observed in hypoxia-exposed rats (n = 6) compared with unexposed rats (n = 6): a 48% reduction for the prefrontal cortex (p < .011), 48% for the dentate gyrus (p < .001), and 55% for the hippocampus (p < .01). NRG1 mRNA expression was also decreased in the prefrontal cortex (a 85% reduction, p < .018) and the dentate gyrus (69%, p < .049), but not in the hippocampus (p = .11), for the hypoxia-exposed rats compared with unexposed rats.

**Discussion:** These results suggest that perinatal asphyxia may lead to disturbances in various brain regions, including the prefrontal cortex, dentate gyrus, and hippocampus, which in turn exert a long-lasting influence on the expression of specific genes such as AKT1 and NRG1. There is evidence in support of an involvement of AKT1 in schizophrenia. Alterations in AKT1-GSK3b signaling have been associated with schizophrenia (Emamian et al. 2004). Furthermore, AKT1 knockout mice shows impaired prepulse inhibition (PPI) of acoustic startle response; PPI deficits are thought to be one of endophenotypes for schizophrenia. As regards NRG1, NRG1-erbB signaling has also been linked with schizophrenia. Interestingly, loss of erbB signaling in oligodendrocytes alters dopaminergic function (Roy et al. 2007), and similar alterations of dopaminergic function have been demonstrated in our previous study of the perinatal asphyxia model (Wakuda et al. 2008). Our findings of altered expression of AKT1 and NRG1 genes may provide a biological basis for understanding the elusive association between a history of OCs and the development of schizophrenia.

doi:10.1016/j.schres.2010.02.977

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**Poster 217**

**HIPPOCAMPAL DYSFUNCTION IN A MATERNAL IMMUNE ACTIVATION (MIA) ANIMAL MODEL OF SCHIZOPHRENIA**

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**Background:** Cognitive impairments are recognized as a key aspect of schizophrenia and may result from deficits in the formation and maintenance of contextual representations. Previous research indicates that the hippocampus processes contextual information and that hippocampal function is abnormal in schizophrenia. Our study examined hippocampal function in rats using the maternal immune activation (MIA) animal model of schizophrenia. MIA models the relationship between exposure to prenatal infection and the increased risk of developing schizophrenia in the offspring. The maternal response to infection may be a critical factor in that cytokines are thought to alter neurodevelopmental processes so as to increase the risk of schizophrenia.

**Methods:** The MIA model induces an immune response with a single injection of the synthetic cytokine activator (polyinosinic-polycytidilic acid) administered to pregnant rat dams during mid-gestation. MIA offspring were examined in a number of behavioural tasks affected by damage to the hippocampus, or its input structures, to test for hippocampal dysfunction related to schizophrenia. A separate group of animals were implanted with electrodes in area CA1 of the hippocampus. Recordings were conducted in awake freely moving animals to directly monitor hippocampal neuronal activity.

**Results:** MIA animals displayed significantly increased locomotion during open-field exploration. This hyper-locomotor behaviour was observed in adult, but not juvenile MIA offspring, mimicking the post-pubertal emergence of schizophrenic symptoms. MIA animals also spent less time exploring objects in an open-field (p < 0.001) and the proportion of time exploring novel rather than familiar objects was less than in controls (p < 0.05), despite normal object discrimination performance. The MIA manipulation also resulted in abnormally rapid reversal of a spatial discrimination in a submerged T-maze (p < 0.05). During exposure to a novel environmental context, MIA offspring showed more rapid within-trial habituation of rearing than control animals (p < 0.05), suggesting that MIA offspring encode contextual information about a novel experience abnormally relative to control animals. Preliminary analysis of electrophysiological recordings of hippocampal neurons was also indicative of abnormal hippocampal processing.
with cells in MIA offspring displaying higher spatial information content and coherence ($p < 0.01$) and a lower average firing rate ($p < 0.01$) and smaller place fields ($p = 0.05$) than control animals. **Discussion:** The current study describes a range of cognitive deficits that have not previously been observed in the MIA rat model, and replicates the previous finding of enhanced reversal learning in MIA rats. MIA animals displayed abnormalities during exploration of an open-field, spatial discrimination reversal learning, and novel object recognition. These deficits are linked, in that they have previously been associated with damage to the hippocampus or its immediate afferents. Our finding that the MIA offspring displayed abnormally rapid habituation of rearing during exposure to a novel environmental context suggests that MIA animals may be abnormally processing contextual information in the hippocampus. We also found electrophysiological evidence of abnormal activity in hippocampal neurons in MIA offspring. Together, these results support proposals that changes within this region underlie core cognitive deficits in schizophrenia.

doi:10.1016/j.schres.2010.02.978

**Poster 218**

SOUTH ASIANS’ ATTITUDES TOWARDS COGNITIVE REMEDIATION AFTER FIRST EPISODES OF PSYCHOSIS

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**Background:** A fourfold increase in incidence of psychosis has been established in migrant groups; incidence rates among UK second generation ethnic minorities are higher. Differences in explanatory models and pathways to care have been demonstrated for South Asian psychosis sufferers compared to other ethnicities. There are concerns that ethnic minorities have difficulty accessing and engaging with psychiatric services. Cognitive Remediation (CR) is an effective intervention for schizophrenia but its acceptability and accessibility amongst minority groups have not been examined. This qualitative study explored attitudes towards CR and other psychological interventions among UK first episode schizophrenia (FES) sufferers of South Asian ethnicity.

**Methods:** Ten FES patients from NHS Early Intervention Services in North West England were digitally audio-recorded during face-to-face semi-structured interviews, analysed using framework analysis.

**Results:** The main themes emerging from the initial analysis included participants’ pathways to care; attitudes towards their current support; and views on the acceptability and possible adaptations to CR. Participants received help from a combination of friends, families, religious leaders, NHS and voluntary sector services. Nine were taking antipsychotic medication. The majority had followed the recommendations of a community elder or Imam. Three out of 10 participants had been offered a psychosocial intervention for psychosis: two had begun, but withdrew from cognitive behavioural therapy; and one intermittently attended family intervention sessions. None were receiving any psychosocial support at the time of interview. All reported memory and concentration deficits and a wish to improve their cognitive skills. A trial session of computerized CR was well received. All participants were multilingual but chose to conduct the interview in English. All dismissed the need to translate CR program tasks into another language. Many recommended simple adaptations to its content such as removing references to non-Halal foods. Discussing CR delivery, the majority favoured multiple sessions per week, based at home, with 1:1 support from a therapist. The therapist’s gender, culture or ethnicity was unimportant.

**Discussion:** This young, moderately acculturated cohort exhibited multiple pathways to care highly influenced by family attitudes and religious beliefs. Minor changes to the content of the CR program and ensuring the therapist is sensitive to cultural factors may further improve the accessibility and acceptability of this intervention. Previously reported cultural barriers such as language and therapist traits were not replicated. CR proved to be highly acceptable to this group.

doi:10.1016/j.schres.2010.02.979

**Poster 219**

COGNITIVE DEFICIT IN SCHIZOPHRENIA AND ITS REMEDIATION

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**Background:** Cognitive functions and their disruption belong to main characteristics of schizophrenia and it chiefly influences the process and the functional final stadiums of this disorder. Final stage of the disease can be influenced by pharmacotherapy only indirectly and its influence on the cognitive functions is only limited. For that reason new possibilities how to adjust the cognitive deficit are being searched. One of these possibilities is neuropsychological rehabilitation of cognitive functions by PC software programme (O. Bracy - PSSCogRehab).

**Methods:** PC software programme (O. Bracy: PSSCogRehab) for rehabilitation of cognitive functions was used. It is a multimedia software, it consists of 8 modules with modified parameters comprised of 64 tasks, gradually increasing difficulty from attention domains, visuospatial and memory tasks to executive skills, and situation solving, individual settings, laterality and flexibility training, pre- and post-study neuropsychological and clinical assessment, 8 weeks duration, 3 interventions per week (total 24) 90 min each, training conducted by a clinical psychologist. Our cohort was formed of 10 men with the first episode of schizophrenia (F 20.0 according to ICD-10).

**Results:** Statistically improvement (t-test) was found in verbal working memory variables and in some variables of attention.

**Discussion:** After 8 weeks neuropsychological treatment using PSSCogRehab we could see improvement in all domains of cognitive function, in some memory and attention variables this effect was statistically significant. We can generalized that PC programme has impact on specific areas of cognitive functions.

doi:10.1016/j.schres.2010.02.980

**Poster 220**

MOBUS PROJECT – RANDOMISED STUDY OF AN ASSISTIVE TECHNOLOGY FOR IMPROVING COGNITION AND AUTONOMY OF PATIENTS WITH SCHIZOPHRENIA: EXPLORING PRILIMINARY DATA

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**Background:** Cognitive impairments in schizophrenia lead to a negative functional outcome. Especially, deficits in memory and
executive functions which result in difficulties planning daily activities. Patients also lose their autonomy, and are socially handicapped. Assistive Technology for Cognition (ATC) can complete the action of antipsychotics and can be used as cognitive rehabilitation in schizophrenia. Our aim is to help people with schizophrenia organize their daily activities in order to enhance their autonomy and reintegrate them in the community with the use of an ATC called Mobus. Two previous studies allowed us to test the conviviality of the device and to improve its functionalities.

**Methods:** Here are the preliminary results from the use of the latest version of Mobus by eleven schizophrenia outpatients. Mobus provides two applications: one for the patients, the other for the caregivers. The *patient-application* is implemented in smart phones. It allows users to plan activities and report self-experiences anywhere at anytime. A ringtone alerts the patient when an activity has to be completed, and the user can confirm if he/she did it. This information is recorded on a server, and the caregiver can remotely verify whether patients have executed their activities through the *caregiver-application*. Furthermore, patients can report anything they are experiencing, including positive or negative experiences. The time and intensity of self-experience is recorded on the server, and the caregiver can monitor these reports on-line. The more the intensity score is high, the worst the patient feels. We calculated the number of activities actually validated by the patients among the programmed ones, the frequency and intensity of self-experience reports, as well as the percentage of appreciation of the device (score on a questionnaire), in order to compare the pattern of use and appreciation of Mobus by the patients with the pattern of our pilot study. In this pilot study, we found that the nine outpatients involved, validated 42% (SD = 40) of their planned activities, with 33% of the sample validating more than 50% of their activities. In average, they used the "experience" function only 1 time per week. The score of appreciation of Mobus among the sample was 45,40/100.

**Results:** The 11 first patients of the current study validated a mean of 41% (SD = 27) of their activities, with 45% of the sample validating at least 50% of their activities. Patients signalled a mean of 3,12 experiences per week (Ratio of negative/positive/neutral experiences = 48/35/17), with an intensity mean of 3,02. The score of appreciation of the improved device was 53,50/100.

**Discussion:** The last version of Mobus did not improve the mean of activities validated yet, but it decreased the inter-individual differences, and more patients validated more than 50% of their activities. Furthermore, patients used the "experience" function three times more than in the pilot study, and appreciated more the device. The improvement of the application seems also to encourage patients to use Mobus. These results have to be confirmed with a bigger sample size, and this current study is involving a group of 34 patients using Mobus, compared with a group of 34 control patients. Furthermore, scales assessing the autonomy, quality of life, clinical state and cognition of participants are conducted in order to explore any improvement in skills assessed. One strength of Mobus is that patients are actively involved in their own treatment program, in collaboration with their caregiver. Furthermore, precious ecological data about the evolution of the state of the patient is available for the clinical follow-up.

**doi:** 10.1016/j.schres.2010.02.981

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**Poster 221**

**UNIPOLAR SEQUENTIAL FRONTO-TEMPORAL REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN THE TREATMENT OF SCHIZOPHRENIA**

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**Background:** New therapeutic methods are needed, because the treatment of schizophrenia remains not fully satisfactory, although we have new antipsychotics. Repetitive transcranial magnetic stimulation (rTMS), which belongs to modern neurostimulation techniques, is one of these methods. Although the effect of high frequency rTMS in the treatment of negative symptoms of schizophrenia remains questionable, positive influence of low frequency rTMS on auditory hallucinations is undeniable. Stimulation parameters of various rTMS studies differ, but only a little of them used stimulation of two different brain areas. Simultaneous stimulation means that two stimulation coils are used at the same time on two different sites. Sequential stimulation means that one stimulation site is stimulated by one coil and then the other site is stimulated by the same coil. There have been only a few studies of sequential stimulation in patients with depression with various results and just one of bilateral or unilateral stimulation in patients with auditory hallucinations, but without any difference between two subgroups. The aim of our simple blind pilot study was to verify the effect of unipolar sequential fronto-temporal repetitive transcranial magnetic stimulation on symptoms of schizophrenia.

**Methods:** A man, 35 years old, with paranoid schizophrenia was included into the study. He underwent 3 weeks of „sham“ stimulation and then 3 weeks of active rTMS. The psychopathology was assessed before the treatment, after „sham“ stimulation and after active rTMS. Active rTMS consisted of two sequential stimulations: high frequency rTMS above the left dorsolateral prefrontal cortex and then low frequency rTMS above the left temporoparietal cortex. Stimulation parameters of high frequency rTMS were: frequency 10 Hz, stimulation intensity 110% of motor threshold, number of stimuli 1500, number of sessions 15. Stimulation parameters of low frequency rTMS were: frequency 0.9 Hz, stimulation intensity 110% of motor threshold, number of stimuli 1080, number of sessions 15.

**Results:** Total PANSS before treatment: 78, after „sham“ stimulation: 78, after active rTMS: 54; positive subscore before treatment: 18, after „sham“ stimulation: 18, after active rTMS: 9, negative subscore before treatment: 24, after „sham“ stimulation: 23, after active rTMS: 18; general subscore before treatment: 36, after „sham“ stimulation: 37, after active rTMS: 27.

**Discussion:** Unipolar sequential fronto-temporal repetitive transcranial magnetic stimulation decreased the severity of symptoms of schizophrenia, was well-tolerated and could be an alternative for the treatment of patients with schizophrenia. But this statement must be verified in a study with more patients.

**doi:**10.1016/j.schres.2010.02.982

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**Poster 222**

**RESULTS OF THE NEUROCOM TRIAL: THE EFFECT OF COMPUTER-ASSISTED COGNITIVE TRAINING COMBINED WITH A PSYCHOSOCIAL TREATMENT PROGRAMME ON COGNITION AND DAILY-LIFE COMPETENCIES OF FIRST-Episode Schizophrenia Patients**

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**Background:** Cognitive impairments play a significant role in schizophrenia and result in difficulties of everyday functioning. Effect-studies of cognitive rehabilitation have shown a moderate, but
short-lived improvement of patients' cognitive functions. NEURO-COM is a longitudinal study, which integrates cognitive training in a comprehensive treatment programme for first-episode schizophrenia patients to assess the training effect and the potential generalisation effect of cognitive functions on daily-life competencies. The purpose of the study is to assess the effectiveness of individualised computer-aided cognitive training (CT) added to an integrated rehabilitation treatment (OPUS), in enhancing neuropsychological performances and daily functioning in patients with first-episode schizophrenia.

Methods: A 16-week, randomised, controlled, single-blind trial of neurocognitive training was carried out on 117 patients in the post-acute phase of ICD-10 first-episode schizophrenia. Patients were assessed on cognitive and daily functioning before and after either CT integrated in OPUS or OPUS treatment alone. The CT programme of the study takes an intensive approach (two to three sessions a week) based on the learning principles of individualised scaffolding, verbalisation and errorless learning. One third of the CT programme is based on computerised exercises, while the remaining training sessions focus on daily tasks and competence dialogues building a bridge between CT and everyday life of patients. The primary effect measure is everyday skills capacity (UPSA-B). Secondary effect measures are cognitive functioning in seven separate neuropsychological domains, tests including TMT A, BACS Symbol-Coding, HVLT-R, WMS-III, BVMTR, NAB Mazes, and MSCEIT. Tertiary effect measures are self-esteem (Rosenberg SES), association with the labour market, and symptom severity as measured with PANSS. An estimate of pre-psychotic IQ (a Danish version of NART) were assessed at baseline.

Results: Data are currently being analyzed. Approximately 85 percent were followed up immediately after 16 weeks of training. Post-training results on cognition (measures of seven separate neuropsychological domains as recommended by MATRICS) and daily-life competencies will be presented at SIRS conference, April 2010.

Discussion: Long-term follow-up results will determine to which extent potential effects at post-training follow-up are maintained when patients continue their participation for six months further in the OPUS psychosocial treatment.

doi:10.1016/j.schres.2010.02.983

Poster 223
THE PROFILE OF NON-AFFECTIVE FIRST EPISODE PSYCHOSIS PATIENTS WITH AND WITHOUT MODERATE TO SEVERE DEPRESSIVE SYMPTOMS AT ENTRY TO TREATMENT

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Background: Moderate to severe depressive symptoms may be prevalent in patients with first episode psychosis (FEP) when they enter a specialised early intervention service. There were two aims of this study: first, to determine the prevalence of moderate to severe depressive symptoms at entry into treatment in a treated epidemiological cohort of patients with non-affective FEP (schizophrenia and schizophreniform disorder); and second, to determine the pre-treatment, entry, treatment and discharge characteristics and differences between those with and without moderate to severe depressive symptoms.

Methods: Medical file audit methodology was employed to collect information on pre-treatment, service entry, treatment characteristics and 18-month discharge characteristics of 405 patients with first episode of schizophrenia spectrum disorder treated at the Early Psychosis Prevention and Intervention Centre (EPPIC), Melbourne, Australia. Two groups were derived on the basis of their scores on the Clinical Global Impressions Scale – Bipolar Disorder (CGI-BP) at entry to the service: no to mild depression (CGI-BP depression score ≤ 3) and moderate to severe depressive symptoms (CGI-BP depression score > 3).

Results: 26.2% \((n = 106)\) of the patients had moderate to severe depression at service entry. This group of patients had a significantly longer prodrome as compared to those without depressive symptoms. At service entry and at discharge, those with depressive entry had greater insight into their illness but did not differ from those without depressive symptoms in terms of severity of overall psychopathology. Substance use was significantly less common in those with depressive symptoms prior to commencing treatment, at service entry and at discharge. Patients who had depressive symptoms were significantly less likely to be admitted to hospital and had fewer admissions compared to those without depressive symptoms. Of those who were depressed at baseline, 14.2% \((n = 15)\) continued to have moderate to severe depressive symptoms at discharge from the service.

Discussion: Depressive symptoms are common in patients with non-affective FEP. Understanding the nature and characteristics of depression in the FEP has important clinical implications for both early intervention and treatment.

doi:10.1016/j.schres.2010.02.984

Poster 224
COGNITIVE FACTORS IN LONG TERM OUTCOME OF FIRST EPISODE PSYCHOSIS

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Background: One negative outcome associated with schizophrenia is a deterioration of cognitive functioning. The existing research on cognitive functioning in first-episode schizophrenia suggests that cognitive deficits may be present quite early on in the illness. Less is known about what happens to cognitive abilities in the years following a diagnosis of first-episode schizophrenia.

Methods: The present study examined the cognitive function of individuals first diagnosed with schizophrenia and then again ten years later to examine changes in cognitive functioning across this time period. Individuals diagnosed with first-episode schizophrenia, who ten years later were classified as “recovered,” had their cognitive functioning assessed both at the time of diagnosis and at the ten year follow-up.

Results: Our results indicate deterioration in some abilities at baseline and a decline of cognitive abilities in the group of clinically recovered patients. Visuo-spatial memory, working memory and executive functioning were shown to decrease in the ten years of treatment following diagnosis and many individuals classified as “recovered” still demonstrate abnormal cognitive functioning.

Discussion: These findings suggest that cognitive functions should be focused on to a much greater degree in current treatment methods.

doi:10.1016/j.schres.2010.02.985
Poster 225
RELATIONSHIP BETWEEN PERSONALITY TRAITS AND PROGNOSIS IN SCHIZOPHRENIA

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Background: Prognosis in schizophrenia and its relationship with personality is still under discussion, studies have shown contradictory results (1,2).

Methods: Our aim is to study a possible relationship between personality traits and the evolution prognosis in schizophrenia in a sample of 76 schizophrenic patients who were admitted to the acute unit of the Institut Pere Mata (Reus) during the years 2007-2009. The diagnosis of schizophrenia was made according to DSM-IV (3). These patients were tested with TCIR and Neo-PIR to obtain data on personality traits. We collected several indicators of disease progression (4) from the patient’s medical history variables. Statistical analysis was performed using SPSS v.13. To try to find relationship between these variables and personality traits, we used Pearson correlation coefficient setting a significance level of 0.05.

Results: It was noted that some predictor variables correlated with some personality traits as some other authors have found in other studies (5).

Discussion: The features of the TCI-R apparently have more validity than the Neo-PIR for correlating personality traits with prognosis in schizophrenia. Some personality traits may contribute to the prediction of schizophrenia, which suggests that a deeper investigation on this topic is needed.

References

doi:10.1016/j.schres.2010.02.986

Poster 226
SUICIDAL BEHAVIOUR AND INSIGHT IN SCHIZOPHRENIA

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Background: Poor Insight is usually found in Schizophrenia in up to more than 80% of the patients. It has important treatment and prognostic implications. Approximately 10 to 13% of deaths in schizophrenia are explained by suicide. The role of insight and positive symptoms remains unclear. The achievement of awareness may lead to depression, low self-esteem and possibly a higher risk of suicide.

Methods: The study aims to relate level of insight with suicidal behaviour. 50 DSMIV schizophrenic or Schizo-affective patients were assessed. Sociodemographic data, Clinical psychopathology instruments included PANSS and SUMID (Scale to Assess Unawareness of Mental Disorder) and Hamilton schedule for depression. Correlations were calculated between measures of insight, PANSS, depression sociodemographic data and number of previous suicidal attempts.

Results: We found no significative correlation between insight and suicide risk. The schizophrenic patient who were more likely to commit suicide had other risk factors as: gender ( male), never married, good premorbid function and a history of suicide attempts. Social isolation, poor external support, and family instability were risk factors for suicide. Awareness of illness didn’t increase suicide risk in our sample.

Discussion: These preliminary results don’t suggest an association between the partial deficit of insight and suicide risk.

doi:10.1016/j.schres.2010.02.987

Poster 227
AXIS I DIAGNOSES AND TRANSITION TO PSYCHOsis IN HIGH RISK PATIENTS. RESULTS OF THE EPOS PROJECT

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Background: The Axis-I diagnoses are prevalent among patients at high clinical risk of psychosis. However, it is not known how they predict transitions to psychosis. Our aim was to examine frequencies of current Axis I diagnoses in high risk patients and their association with transitions to psychosis.

Methods: In the EPOS project, six European outpatient centres examined 245 help-seeking young patients, who fulfilled the criteria for clinical risk of psychosis according to the Structured Interview for Prodromal Syndromes (APS, BLIPS, Genetic Risk and Reduced Functioning [GRRF]) or basic symptoms (BS). The patients having suffered from a psychotic episode for more than one week were excluded. Baseline diagnoses were assessed by the Structured Clinical Interview for DSM-IV (SCID-I). The subjects were followed for 18 months. Transition to psychosis was defined by continuation of BLIPS, one or more psychotic symptoms were followed for 18 months. Transition to psychosis was defined by continuation of BLIPS, one or more psychotic symptoms persisting for more than one week, and analysed in Cox-regression analysis.

Results: From the total sample, 84 % fulfilled APS, 70 % BS, 16 % GRRF and 11 % BLIPS inclusion criteria. Of them, only BLIPS associated significantly with transition to psychosis. At baseline, 39 % of the high risk patients suffered from anxiety, 35 % from depressive and more than 62 % from any SCID disorder. In all, 40 transitions were identified. In univariate analyses, BLIPS and bipolar disorder, and in multivariate analyses, BLIPS, bipolar and somatoform disorders associated significantly with transition to psychosis. In the sub-ample, from which the subjects with
BLIPS were excluded, bipolar and somatoform disorder positively and anxiety disorder negatively predicted transition to psychosis.

**Discussion:** Anxiety depressive disorders are prevalent among clinical help-seeking high risk patients and need to be carefully evaluated, although they do not predict transition to psychosis. Occurrence of short-term psychotic symptoms, as well as occurrence of both bipolar and somatoform disorder seems to predict transition to psychosis. In addition to treatment of short-term psychotic disorders, intensive treatment of bipolar and somatoform disorders may prevent patients high risk patients from transition to psychosis.

doi:10.1016/j.schres.2010.02.988

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**Poster 228**

**Poster not available**

doi:10.1016/j.schres.2010.02.989

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**Poster 229**

**CLINICAL AND COGNITIVE CORRELATES OF PERCEIVED EXTENT OF RECOVERY IN CHINESE PATIENTS WITH PSYCHOSIS**


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**Background:** Recovery from psychotic disorders is a multi-dimensional concept. Clinical definition of recovery usually comprises symptomatic remission and adequate functioning. However, a local qualitative study confirmed that cessation of medication is one of the necessary conditions of recovery as perceived by patients. This cross-sectional study aimed to explore whether perceived extent of recovery was related to clinical symptoms (positive, negative, and depressive) and executive function.

**Methods:** Patients were asked to assess their perceived extent of recovery after 6 months of psychiatric treatment by a visual analogue scale based on the Psychosis Recovery Inventory. Subjects were later converted into scores ranging from 0 to 100 (full recovery) and compared with the operationally defined remission recovery and by t-tests. The definition of remission was operationally defined by Scale for the Assessment of Positive Symptoms and Scale for the Assessment of Negative Symptoms. Recovery was defined as remission plus an additional criterion of adequate functioning as measured by Social and Occupational Functioning Assessment Scale. Multiple linear regression was used to correlate the subjective ratings with symptoms, and executive function as measured by Modified Wisconsin Card Sorting Test (MWCST), semantic verbal fluency (animals) and trail making task.

**Results:** This study had assessed 78 Chinese patients with psychotic disorders in Hong Kong. 47 (60.3%) of them were male. The median duration of untreated psychosis was 121 days. The psychotic disorders in Hong Kong. 47 (60.3%) of them were male. The multiple linear regression showed that patients perceived greater recovery had fewer perseverative errors in MWCST (adjusted R² = 0.095, P = 0.004). Perceived recovery was not significantly correlated with positive, negative and depressive symptoms.

**Discussion:** Patients who had clinically assessed to be in remission or recovery did not perceive higher level of recovery, suggesting that patients may be using different evaluation criteria. Executive dysfunction was related to subjective perception of recovery but the variances explained (R²) were small. More research is required to explore factors associating with perceived recovery.

doi:10.1016/j.schres.2010.02.990

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**Poster 230**

**DIFFERENTIAL PROFILE OF COGNITIVE FUNCTIONING IN FIRST EPISODES OF NON-AFFECTIVE PSYCHOSIS AND BIPOLAR DISORDER: A ONE-YEAR LONGITUDINAL STUDY.**

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**Background:** Few studies have compared cognitive function between bipolar euthymic patients, schizophrenia patients and healthy volunteers, and even less, if these patients are in early stages of the disease. This is a study and one-year longitudinal follow-up comparing the cognitive functioning in first episode non-affective psychosis and bipolar disorder. All of these patients in early intervention programs at Hospital Universitario Marqués de Valdecilla de Santander.

**Methods:** Patients in the initial phase of bipolar disorder program (JANO) (n = 36, mean age = 33.69, SD = 11.61), patients in the first episodes of psychosis program (PAFIP) (n = 55 mean age = 32.98, SD = 11.17) and healthy subjects as control group (n = 38, mean age = 28.66, SD = 9.37) complete neuropsychological study on program startup and at one year follow-up. Groups were matched for age, sex, educational level, IQ premorbid and clinical variables such as total number of episodes and type of treatment. The analysis took into account a subset of neuropsychological variables for testing: verbal memory, visual memory, motor coordination, executive functions, working memory, attention and processing speed. We conducted a univariate analysis of variance and repeated measures with SPSS version 15.0.

**Results:** In general, at baseline and l-year follow up both groups of patients showed worse cognitive functioning than the control group. Furthermore, first episodes of non-affective psychosis performed worse in all areas evaluated that those patients with bipolar disorder. At baseline, we observed significant differences between both groups of patients in verbal list learning (p = 0.021) and processing speed (p = 0.002). At one year follow up, there are significant differences between them solely on verbal list learning (p = 0.076) and long-term memory (p = 0.051).
Discussion: These results show a worse cognitive functioning in patients than in control group, even when taking into account the initial phase of the disease and a worse general cognitive functioning in patients with first episodes of psychosis than first episode affective bipolar disorder. But in both patient groups cognitive deficits persist after a year compared with the control group. There is a tendency to general stability in the longitudinal results in the three groups.

doi:10.1016/j.schres.2010.02.991

Poster 231
PROTECTIVE AND RISK FACTORS FOR PSYCHOSIS RELAPSE IN PATIENTS WITH FIRST EPISODE SCHIZOPHRENIA SPECTRUM PSYCHOSIS: 3 YEARS FOLLOW-UP

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Background: For a majority of patients, schizophrenia is a chronic recurrent disease that leads to significant residual morbidity which occurs through a process of behavioral deterioration. The factors influencing the course of schizophrenia after its onset and the ability of treatment in modifying the effects of the patients illness are not well understood. Remission and relapse are clinical outcomes of increasing interest in schizophrenia. Premorbid adjustment, age and mode of onset of illness, gender, duration of untreated psychosis, schizophrenia subtype, primary type of symptoms (negative or positive), treatment compliance, comorbid disorder, may influence illness course and outcome, both favorably and adversely. Our hypotheses were that insidious onset, duration of untreated psychosis DUP, long episode, family history for psychiatric disorders, negative symptoms, young age of onset, substance misuse, poor compliance, poor premorbid adjustment, bad psychosocial functioning during follow-up period would be associated with increased risk of in-patient admission, a longer time to remission of psychotic symptoms, and earlier and increased risk of relapse. The aim of our prospective study was determination the protective and risk factors for relapse in patients with first episode schizophrenia spectrum disorders.

Methods: We analyzed remission and relapse, and the sociodemographic and clinical factors associated with these outcomes, in the usual care of 50 in-patients with patients with first episode schizophrenia spectrum disorders, using the 5-year follow-up data of patients treated at Psychiatric Clinic Nis. All patients received standardized treatment and uniform assessments both during the acute phase of their illness and throughout the follow-up period (at base line, after 3 monts and after each 6 monts during follow-up). Outcome was measure in terms of time to remission of acute psychotic symptoms as well as degree of symptom remission. The evaluation process included clinical interview, BPRS, PANSS, premorbid adjustment scale-PAS, GAF.

Results: Nearly 20% of evaluated patients achieved and maintained in remission during the 5-year, follow-up period. Longer DUP, poor compliance, poor premorbid adjustment, negative symptoms, young age of onset, substance misuse, bad psychosocial functioning during follow-up period, lack of family history for psychotic disorders would be associated with a higher risk of relapse, whereas good level of social functioning and the use of clozapine and long-acting injections of antipsychotics were associated with a lower risk of relapse.

Discussion: The results of this study are therefore consistent with the large body of research in finding a considerable number of sociodemographic and clinical variables to be associated with better or worse outcome in schizophrenia spectrum psychosis. In our study, a number of factors were found to be associated with the best outcome of single episode with no persistent symptoms, including premorbid adjustment, age and mode of onset of illness, gender, duration of untreated psychosis, schizophrenia subtype, primary type of symptoms (negative or positive), treatment compliance, comorbid disorder. Understanding the risk and protective factors for schizophrenia may lead to better understanding of the pathophysiology of schizophrenia and to improved treatment strategies. It is necessary to develop therapeutic strategies that minimize the morbidity of the illness. More comprehensive early intervention services, providing effective pharmacological and psychological treatments and follow-up from onset, together with social support and vocational programs, might also be expected to reduce relapses.

doi:10.1016/j.schres.2010.02.992

Poster 232
HEALTH MONITORING IN SCHIZOPHRENIA: TIME FOR ACTION


Background: The life expectancy of patients with schizophrenia is shortened as compared to the general population. Accessibility to somatic services and adequate somatic treatment is restricted. Furthermore, the consequence of physical illness, in particular cardiovascular diseases and metabolic syndrome, is considered as one of the major threats in achieving recovery in patients with schizophrenia.

Methods: A health monitor was introduced as screening instrument in a schizophrenia treatment and recovery program (so called F-ACT) at the outpatient department of the Vincent van Gogh Institute for Psychiatry in Venray/Venlo, the Netherlands. Patients with increased cardiovascular risk profiles are referred to a special diabetes and cardiovascular risk management program. Apart from a physical and laboratory examination (BMI, body mass, blood pressure, haematological and metabolic syndrome parameters, abnormal movements) an ECG was made to determine QTc and to screen for the presence of cardiac dysfunction. Furthermore, demographic data, DSM-IV diagnoses, remission criteria, and use of medication and drugs were assessed. Over a period of 10 months, 300 patients were included in the screening program (95% met the DSM-IV criteria for schizophrenia and other psychotic disorders).

Results: All patients used at least one antipsychotic (mean age 43.1 ± 13.7 year; ratio M/F = 61/39). Preliminary analyses showed that 48% fulfilled to the ATP-III criteria of metabolic syndrome (M/F = 70/30). Thirty percent of these patients were received already adequate somatic treatment. Prevalence of metabolic syndrome was significantly associated with concomitant use of antidepressants (p = .01). Mean QTc was 410 msec (± 45 msec). Only one patient had an increased QTc (530 msec). A combination of structured anamnesis, physical examination and ECG demonstrated serious cardiac dysfunction in 5% of the patients that necessitated (acute) intervention by a cardiologist.

Discussion: The established prevalence of metabolic syndrome is in line with the high rates mentioned in the literature. The use of antidepressant medication in combination with an antipsychotic appeared to be an additional risk factor. In approximately 69% of the
patients in the present study, referral to a cardiovascular risk management and diabetes program was indicated.

doi:10.1016/j.schres.2010.02.993

Poster 233
NON-ADHERENCE TO ORAL ANTIPSYCHOTICS IN SCHIZOPHRENIA: RELAPSE AND THERAPEUTIC STRATEGIES IN A 12-MONTH OBSERVATIONAL STUDY

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Background: Non-adherence influences schizophrenia prognosis. Authors aimed to describe the clinical profiles, modification of the therapeutic strategies and relapse rate of patients with schizophrenia who are at risk of non-adherence to oral antipsychotic (AP) medication according to the criterion of the investigator.

Methods: A cohort of 597 outpatients whose therapy was modified because of risk of non-adherence to oral AP was followed during 12 months. Sociodemographics and several outcome measures, such as clinical severity (CGI-S scale), attitudes toward medication (DAI-10), and quality of life (EuroQol-5 Dimensions), were collected. Authors calculated descriptive statistics of baseline and 12-month data, and used the Kaplan-Meier method to describe time to relapse, and the Cox regression to investigate the association between non-adherence and relapse adjusting for factors influencing the time to relapse.

Results: Patients’ mean (SD) age was 40.1 (11.1) and time since diagnosis was 15.2 (10.0) years; 64% were males. According to CGI, the clinical condition was at least moderate in most patients (CGI-S score ≥4 in 87%) and associated with a poor quality of life (mean EQ-5D health status value: 58.5). Baseline non-pharmacologic therapies were modified in 190 (32%) patients, AP medication in 506 (85%). In both cases, the main reason for modifications was insufficient efficacy, followed, in the case of non-pharmacological therapies, by poor awareness of mental disorder. Concomitant medication was modified in 15%. Modifications of AP medications were mainly dose adjustments (63%). Moreover, the proportion of patients in AP monotherapy decreased from 84% to 58%, in favor of polytherapy, and 15% started depot formulations. During 12 months, 90 patients (15%) relapsed. Among relapsing patients, the proportion on monotherapy decreased after relapse to 42%, and the proportion of depot prescriptions rose to 28%. These proportions remained at 59% and 17%, respectively, among patients who did not relapse. The Cox regression revealed that having substance use disorder was associated with low adherence to AP medication at baseline (HR: 0.35, 95% CI: 0.14 to 0.88). Unexpectedly, a lower risk of relapse was found when only non-pharmacologic therapies were modified, as well as in patients with a low adherence level at baseline (facilitating investigators’ recognition and intervention). Predictably, patients with psychiatric familial history and substance use disorder had a greater risk of relapse.

Background: Duration of Untreated Psychosis (DUP) has been shown to be an independent predictor of outcome in a large number of studies. However, these studies were mainly focusing on positive symptoms and related outcome measures, such as relapse rates, time to positive symptom response and positive symptom remission. Its impact on more broadly defined outcome like multidimensional symptom remission and clinical recovery has not been very well documented yet.

Methods: In a first episode incidence cohort (N = 125) we compared patients showing remission of symptoms according to the Andreasen criteria during the initial treatment phase from first positive symptom response until 6 months later (n = 60), to patients who did not show symptom remission (n = 65). Then we looked at outcome in terms of recovery, during the last nine months of an 18 months further follow-up. Recovery was defined as symptom remission according to the Andreasen criteria plus good social functioning in any social role according to the Groningen Social Disability Scale.

Results: Bivariate analyses showed significant differences between remitted and not-remitted patients, including DUP. Mean DUP was 181 days (SD 377) in remitted patients against 343 days (SD 640) in not-remitted patients (P = .043). In a logistic regression model however good baseline social functioning remained as the only significant predictor of remission (P = .032). At 18 months follow-up the recovery criteria were met by 24 patients (19.2%). Bivariate analyses demonstrated that recovered patients already differed significantly at baseline from not-recovered patients. Mean DUP was 31.8 days in recovered patients, compared with 320.9 days in not-recovered patients (P = .001). Recovered patients had also less severe positive, negative and general baseline PANSS scores, and less social role performance disability. There was no significant difference between recovered and not-recovered patients regarding gender, baseline quality of life, time to response, living alone vs. with others or baseline diagnosis of cannabis abuse. In a logistic regression model with backward selection the only significant predictors of recovery that remained were DUP (OR = 0.531, df = 1, P = .008) and baseline social functioning (OR = 0.858, df = 1, P = .021).

Discussion: DUP and baseline social functioning are the only independent predictors of recovery after two years of follow-up. No recovery at all occurred in patients with DUP of 6 months and longer. Initial remission was also associated with short DUP, though baseline social functioning was the only significant predictor of initial remission in a regression analysis. DUP seems to determine real life outcome independently, especially in the long run.

doi:10.1016/j.schres.2010.02.994

Poster 234
DUP, REMISSION AND RECOVERY IN FIRST EPISODE SCHIZOPHRENIA

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Background: Duration of Untreated Psychosis (DUP) has been shown to be an independent predictor of outcome in a large number of studies. However, these studies were mainly focusing on positive symptoms and related outcome measures, such as relapse rates, time to positive symptom response and positive symptom remission. Its impact on more broadly defined outcome like multidimensional symptom remission and clinical recovery has not been very well documented yet.

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Discussion: DUP and baseline social functioning are the only independent predictors of recovery after two years of follow-up. No recovery at all occurred in patients with DUP of 6 months and longer. Initial remission was also associated with short DUP, though baseline social functioning was the only significant predictor of initial remission in a regression analysis. DUP seems to determine real life outcome independently, especially in the long run.

doi:10.1016/j.schres.2010.02.995
Background: Health utility and quality of life (QoL) are increasingly important outcome measures in health care and health economics. The impact of psychotic disorders on population level is poorly known. This study aims to compare the loss of utility-based health-related quality of life (HRQoL) and QoL associated with psychotic disorders.

Methods: A representative sample of 8028 Finns was interviewed with the Composite International Diagnostic Interview (M-CIDI) and screened for psychotic and bipolar I disorders. Lifetime psychotic disorders were diagnosed using the Structured Clinical Interview for DSM-IV and/or case records. HRQoL was measured with EQ-5D and 15D, and QoL was measured with 10-point scale.

Results: Schizoaffective disorder was associated with the lowest well-being on all measures used, followed by schizophrenia and bipolar I disorder. Patients with schizophrenia had HRQoL losses comparable or below of 12-month diagnosis of MDD, and even patients with schizoaffective disorder had HRQoL losses smaller than people with dysthymia, GAD, agoraphobia and social phobia. Schizophrenia and bipolar disorder were associated with relatively larger loss of HRQoL than subjective QoL, whereas the contrary was true for delusional disorder and MDD with psychotic symptoms. Current depressive symptoms explained most of the HRQoL and QoL loss found. For schizophrenia, socioeconomic variables explained most of the decrease in subjective QoL, but not in HRQoL. The subjective suffering associated with schizophrenia appears less than the functional disability associated with it would suggest. Only depressive and negative symptoms showed consistent correlations with HRQoL and QoL instruments.

Discussion: Depressive symptoms are strongest predictors of poor HRQoL in psychotic disorders. Subjective loss of QoL and HRQoL associated with psychotic disorders may be smaller than objective disability. This is important when HRQoL is increasingly used as an outcome measure in psychiatric research and to guide health policy.

doi:10.1016/j.schres.2010.02.996

Poster 236
PSYCHOSOCIAL PROCESSES INFLUENCING WEIGHT MANAGEMENT AMONG PERSONS NEWLY PRESCRIBED ATYPICAL ANTIPSYCHOTIC MEDICATIONS

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Background: Schizophrenia is a chronic mental illness that greatly impacts quality of life and is commonly managed by the use of atypical antipsychotic medications. Unfortunately, a large proportion of patients who are on these second-generation antipsychotic medications gain up to 20 percent of their baseline body weight within a short period following the initiation of this pharmacotherapy. In addition to cardiovascular and metabolic health problems, weight gain can contribute to psychological factors such as low self-esteem among persons with schizophrenia. Currently, efforts to design effective weight control programs have yielded limited success due to a lack of participation in the long-term. Therefore, more research is needed to examine the barriers and facilitators for this patient population to manage their weight. The purpose of this study is to generate a theory grounded in data related to the psychosocial processes of weight management in patients with a diagnosis of first-episode psychosis who are taking an atypical antipsychotic medication.

Methods: This qualitative study employs the grounded theory method, an emergent design to generate a theory or conceptual framework to explain a psychosocial issue that is shared amongst a group of people. Theoretical sampling is used to select approximately 20 participants from the community of Kingston, Ontario. Unstructured interviews are the method of data collection. Each interview lasts approximately one hour and is audio-recorded with the permission of the participant. Data analysis is inductive in nature, using the constant comparative method which compares and contrasts each component of each person’s dialogue. There are three levels of coding: open coding, second level coding, and the application of a coding paradigm in which categories are linked to each other. Throughout the coding, memos are written to reflect on the codes. When no new themes are found in the emerging theoretical framework, data saturation is achieved and sampling terminates.

Results: To date, five participants have been interviewed and a theoretical framework is continuously developed and reviewed. It is anticipated that data collection will be complete by early February and finalized results will be presented.

Discussion: Discussion will be presented pending data collection and analysis.

doi:10.1016/j.schres.2010.02.997

Poster 237
PHYSICAL ACTIVITY OF DAILY LIVING IN PATIENTS WITH SCHIZOPHRENIA

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Background: There are very few studies that have focused on the physical activity of daily living in patients with schizophrenia. Physical activity may be necessary information for preventing metabolic complications that are frequently observed in schizophrenia, such as obesity, diabetes, and coronary heart disease.

Methods: Physical activity of the patients with schizophrenia (n = 37) and healthy volunteers group (n = 41) were measured by the three dimension accelerometer for 7 days. Clinical data including weight, BMI, blood test, and PANSS were also collected by means of interviews administered by a well-experienced psychiatrist. Comparison of physical activity as well as clinical data between the patients group and the healthy volunteers group were conducted.
Results: The patients group showed significantly lower energy consumption by the physical activity and the activity time above low-intensity compared to the healthy volunteers group. Additionally, a correlation between patients’ physical activity and clinical characteristics was computed, and statistical significances were found. Patients’ physical activity was negatively correlated with their weight, abdominal circumference, and the score of negative symptoms of PANSS. Significant correlations between blood test items, such as TG and HDL cholesterol, and the physical activity were also found.

Discussion: The patients with schizophrenia were more likely to have decreased energy consumption by physical activity than individuals without psychotic illnesses. Especially, patients with schizophrenia tend to have a short activity time above low-intensity and a long no-movement time. Our study results suggest that negative symptoms of schizophrenia are related to the low degree of physical activity. A further research would enable more effective lifestyle guidance to the patient.

doi:10.1016/j.schres.2010.02.998

Poster 238
ASSOCIATIONS BETWEEN OBJECTIVE AND SELF-ADMINISTERED ASSESSMENT OF SYMPTOMS IN PSYCHOTIC PATIENTS

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Background: To investigate whether psychotic patients assess their symptoms adequately, we aimed to examine the association between clinicians’ rating and patients’ self-assessment of symptoms.

Methods: 64 hospitalized psychotic patients who experienced prominent delusions and hallucinations within last month were recruited. We examined the correlations between positive (PANSS-P), negative (PANSS-N) and depressive (PANSS-D) domains of the Positive and Negative Syndrome Scale (PANSS), and the self-administered symptom ratings for relevant domains: the Peters et al. Delusional Inventory (PDI-21), and paranoia (PAR) and psychoticism (PSY) subscales of the Symptom Checklist-90-Revised (SCL-90-R) as positive domain, the Scale for the Subjective Experience of Negative Symptoms (SENS) as negative domain, and the Beck Depression Inventory (BDI), and depression (DEP) and anxiety (ANX) subscales of the SCL-90-R as depressive domain. Insight level was measured by the Scale to Assess Unawareness of Mental Disorder (SUMD).

Results: Significant associations were found between PANSS-N and the SENS, and between PANSS-D and the self-rated depression measures. PANSS-P correlated significantly with PSY subscale of the SCL-90-R only. Mostly, these associations were not affected by the insight level.

Discussion: Psychotic patients, who had experienced delusions and hallucinations recently, were able to assess negative and depressive symptoms adequately while they reported psychotic symptoms somewhat incorrectly. Although these results support the adequacy of self-reported negative and depressive symptom in psychotic patients, further study will be needed.

doi:10.1016/j.schres.2010.02.999
were associated with lower levels of negative affect and less social distance toward the mentally ill. Nonetheless, we also found that high levels of contact were associated with higher levels of perceived dangerousness in the severely mentally ill. Thus, contact was associated with reductions in some dimensions of stigma, but it appeared to enhance the perceived dangerousness dimension. Cardiovascular markers have been used to assess individuals’ reactions to interactions in a wide variety of social contexts (Weisbuch, Seery, Ambady, & Blascovich, 2009). Of particular interest is the use of cardiovascular patterns as markers of internal states of challenge and threat (Blascovich 2008; Blascovich & Tomaka 1996). Cardiovascular responses associated with challenge states are associated with increases in ventricular output and decreases in peripheral resistance. Threat states in contrast are associated with less efficient cardiac output and greater peripheral resistance. The purpose of this study is to examine whether healthy young African American adults’ reaction to imagined interactions with schizophrenics are characterized as a "challenge" or "threat" when using these cardiovascular markers and whether naturally occurring contact mediates this pattern of responding.

Methods: 65 African American participants were divided into two groups with a median split. Those participants who endorsed 3 or fewer regular contacts with the mentally ill were assigned to the Low Familiarity group and those participants who had 4 or more regular contacts were assigned to the High Familiarity group. This resulted in 38 participants being assigned to the Low Familiarity group and 27 participants being assigned to the High Familiarity group. Participants imagined interacting with individuals labeled or unlabeled as having schizophrenia using the protocol reported by Graves, Cassisi & Penn (2005), while their cardiovascular activity was monitored with an HIC-3000 and the COP-WIN/HRV data acquisition software both produced by Bio-Impedance Technology, Chapel Hill, NC.

Results: Our results indicated that participants with high levels of naturally occurring contact with the mentally ill exhibited significantly less peripheral resistance when they imagined interacting with a schizophrenic individual as compared to when they imagined interacting with an unlabeled person. This pattern of cardiovascular responding is associated with a "challenge" reaction in the social psychology literature. We did not find the "threat" reaction that one might expect if dangerousness were the underlying cause of social distance and stigma.

Discussion: Our findings suggest that African Americans with high levels of contact may not perceive interactions with the severely mentally ill as more dangerous but rather as more difficult and complex.

doi:10.1016/j.schres.2010.02.1001

Poster 242
REMEDIATION OF FACIAL EMOTION RECOGNITION IN SCHIZOPHRENIA: FUNCTIONAL PREDICTORS, GENERALISABILITY, AND CONCOMITANT VISUAL SCANNING OF NOVEL FACE STIMULI

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Background: Impaired recognition of facial emotion is associated with poor social functioning in schizophrenia. Evidence shows targeted emotion recognition training (ERT) can improve perception of facial emotions in schizophrenia for up to one week after training. This study investigated whether (a) improved recognition generalizes to novel faces, (b) baseline functioning levels predict the extent of improvement; and (c) improved emotion recognition to novel faces was associated with concomitant changes in visual scanning of facial expressions.

Methods: Thirty-nine participants with schizophrenia received ERT using Ekman's Micro-Expression Training Tool (METT; 2003). Emotion recognition was assessed using METT face stimuli and other face stimuli not used in training (static faces shown at 100% and 50% intensity and dynamic stimuli). Baseline ratings of interpersonal and cognitive functioning were collected.

Results: Post-METT training, participants showed improved perception of METT faces and full-intensity novel faces. Baseline measures of interpersonal and social functioning as well as general face processing and working memory abilities (50% intensity expressions only) predicted improvement in facial affect recognition. Scans of participants following METT training. Visual scanpath data to novel faces will also be presented.

Discussion: These findings suggest that the effectiveness of ERT in schizophrenia is influenced by pre-training levels of social functioning and that general face processing abilities and working memory may affect the ability to accurately process subtle facial expressions.

doi:10.1016/j.schres.2010.02.1002
Furthermore, improved recognition generalizes to full intensity novel faces. In general, the present findings highlight the importance of continuing to develop remediation programs to target these profoundly debilitating and pervasive impairments. Most importantly this study emphasizes the need to tailor remediation programs in response to individual abilities and symptoms.

doi:10.1016/j.schres.2010.02.1003

Poster 243
A QUANTITATIVE AND QUALITATIVE RESEARCH ON RECOVERY FROM SEVERE MENTAL ILLNESS: THE ITALIAN STUDY ON RECOVERY (S.I.R.)

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Background: "Recovery" is related to the idea of developing personal potentials and regaining a valid social role despite the limitations caused by the illness (Anthony, 2007). A whole understanding of this subjective and dynamic process is still difficult. Valid instruments to evaluate recovery in people referring to mental health services are needed in order to test out the efficacy of currently used practices and approaches. The most used instrument to measure recovery is the Recovery Assessment Scale; it is available in English and is considered as the most used instrument to measure recovery in people referring to mental health services. The most used instrument to measure recovery is the Recovery Assessment Scale; it is available in English and is considered reliable, valid and coherent (Corrigan et al. 2004).

Methods: The Italian Study on Recovery is a multicentric research which involves 14 mental health services from various parts of Italy. For this study an Italian translation of RAS (Recovery Assessment Scale, Corrigan et al. 2004) has been used. Phase 1 consisted in the administration of RAS to subjects attending the services with a diagnosis of psychosis, differentiated as "in recovery" and "not in recovery" according to the recovery operational criteria (Liberman et al. 2002). Phase 2 of the study consisted in the administration of a semi-structured interview to the "in recovery" subjects, in order to identify common key-elements which foster or hinder the recovery process.

Results: RAS was administered to 156 subjects with a diagnosis of psychosis. 23 of them fulfilled the above mention criteria for recovery and were recruited for the interview of the ongoing phase 2. An initial analysis of phase 1 results has confirmed the validity of RAS in Italian as well, correctly discriminating subjects matching the "in recovery" operational criteria through a correlation with a cut-off score of the scale.

Discussion: Results of phase 2 will give the opportunity to understand to which extent the existing Italian rehabilitative services actually match the needs for people to recover and possibly suggest the direction of further research in order to start a transformation to recovery-oriented mental health services.

doi:10.1016/j.schres.2010.02.1004

Poster 244
METACOGNITIVE PROFILE OF PARANOIA AND DEPRESSION; ARE THERE MODERATION EFFECTS OF METACOGNITION INTO PSYCHOLOGICAL WELLBEING?

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Background: According to Self Regulatory Executive Function Model (S-REF; Wells, 2000), vulnerability to psychopathology is characterized by an excessive self-focused attention, ruminative thought, attention biases, and the activation of dysfunctional self-beliefs and self-appraisals. Theories of the development of psychotic symptoms have suggested that metacognitive beliefs might play a part. For instance, metacognitive beliefs associated to intrusions into consciousness can generate a state of cognitive dissonance that has been linked to positive psychotic symptoms and distress (Morrison, Wells, & Nothard, 2002). However, metacognition is a complex construct; we argued that at least some of their components can be also co-determining psychological well-being. In the context of persecutory delusion, metacognitive components such as self-consciousness and positive beliefs about worry should enhance subjective psychological well-being, probably by reducing internalized stigma.

Methods: Participants were 40 in-patients suffering persecutory beliefs (meeting DMS IV-TR criteria for Schizophrenia or other Psychotic Disorders), 35 depressed patients who met DSM-IV-TR criteria for a current depressive disorder (mainly outpatients) who had never experienced persecutory delusions and 44 non-psychiatric controls. Each participant completed the Scales of Psychological Well-Being (SPWB) (Ryff & Keyes, 1996) and the Metacognitive Questionnaire (MCQ-30; Wells & Cartwright-Hatton, 2004), the Beck Depression Inventory (BDI-II; Beck, Steer & Brown, 1996) and the Persecution and Deservedness Scale (PaDS; Melo, Corcoran, Stryane and Bentall, 2008). One-way between-groups analyses of variance were used to investigate the group effect and metacognitive level effect for all psychological well-being dimensions. Stepwise multiple regressions were used to assess the moderating effect of metacognitive beliefs in paranoia to explain subjective wellbeing. In all analyses current depressive mood was controlled for.

Results: According to the analyses of variance, high positive beliefs about worry are related in paranoid patients to higher self-acceptance, relationships with others and self-knowledge scores whereas is related to lower scores in depressed patients. Moderation analyses show that self-consciousness moderates the relation between paranoidism and all psychological well-being dimensions. All moderation analyses show a greater level of psychological well-being when participants presented high scores in both metacognition and paranoidism.

Discussion: Metacognitive beliefs seem to play a different role in the psychological well-being for paranoid and than for depressive patients. Even though metacognitive beliefs have been linked with psychopathology, they may facilitate subjective well-being in paranoia. This work shows evidence for moderating role of metacognitive beliefs in relationship between paranoidism and psychological well-being. The implications for clinical work and further research are discussed.

doi:10.1016/j.schres.2010.02.1005

Poster 245
THE ASSOCIATION BETWEEN ADVERSITIES AND BELIEFS IN A JUST WORLD IN PARANOIA: THE ROLE OF INTERPERSONAL TRAUMA

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Background: During the last two decades, studies have point out the existence of distinctive cognitive distortions in psychotic
patients. Yet, most of this research has focused on cognitive processes and outcomes whereas research on cognitive structures and propositions in psychoses has been less common. A theoretical framework to analyze people's worldviews is that of the beliefs in the just world (BJW). According to this theory, people are motivated to believe in a just world where everyone one generally gets what they deserve. Personal BJW (BJW-P) implies that events in one's own life are just. On the other hand, general BJW (BJW-G) reflects the belief that, basically, the world is a just place. In paranoid patients, Valiente et al. (to be submitted) have found that people with persecutory beliefs show significantly weaker BJW-P than non-psychiatric controls whereas there are no significant differences in BJW-G. Lower BJW-P have important behavioural and emotional consequences. We argue that BJW are related to psychosocial and traumatic experiences. Likewise, Janoff-Bulman (1992) found that people, who had experienced a traumatic event many years ago, hold more negative worldviews. Thus, the goal of this study was to examine how the different types of trauma are linked to BJW in paranoia.

Methods: 39 current persecutory beliefs patients and 42 non-psychiatric participants were assessed with Beliefs in a Just World Scale – General (BJW-G), Belief in a Just World Scale- Personal (BJW-P). The total number of traumas was assessed by Trauma History Screen (THS) included natural disasters, dead, separation, negligence and interpersonal traumas as physical and sexual abuse and psychological abuse. The number of interpersonal traumas was assessed by Trauma History Screen (THS) included only physical and sexual abuse and psychological abuse. Stepwise multiple regressions were used to evaluate the capacity of different types of trauma to explain BJW.

Results: Our results showed that the total number of traumas, and interpersonal trauma in particular, were negatively related to BJW-P in paranoid patients \(r = -.31; \ r = -.39\). Interpersonal trauma explained 24% of the variance in BJW-P after controlling for demographic characteristics \(\Delta R^2 = .24, \Delta F (1,34) = 4.80, p = .035\), however accumulated trauma (including all types of trauma) did not explained a significant variance of BJW \(\Delta R^2 = .20, \Delta F (1,34) = 3.15, p = .084\). For the control group, interpersonal trauma was positively related to BJW-P \(r = .30\), but regression analyses didn't reach significance \(\Delta R^2 = .20, \Delta F (1,39) = 3.75, p = .060\).

Discussion: In general, our data support the relevance of the environmental factors to explain the aetiological cognitive structures and propositions of persecutory delusions. These results indicated that interpersonal trauma in particular, but not the accumulative effect of all other traumas, is linked with low perception of personal justice. Paradoxically, there seems to be a opposite tendency for non-psychiatric controls. The implications for clinical work and further research are discussed.

doi:10.1016/j.schres.2010.02.1006

Poster 246
TOLERANCE OF UNFAIRNESS AND COSTLY PUNISHMENT IN SCHIZOPHRENIA

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Background: Humans possess evolved cognitive and emotional biases that guide an individual's actual behaviour in terms of cooperation, defection or punishment of unfair behaviour. Empirical evidence suggests that a neural network comprising parts of the frontal lobe as well as limbic structures is involved in economic decision-making. This network greatly overlaps with those brain structures that are known to be dysfunctional in schizophrenia. Accordingly, we hypothesised that patients with schizophrenia would differ from controls in performance on tasks involving economic decision-making.

Methods: 25 in-patients with schizophrenia (SCHIZ) (7 female, 18 male) were compared with a group of 25 healthy controls (NC), on performance in an Ultimatum Game (UG), where participants had the role of the recipient, and in a Dictator Game with Punishment (DGP), where participants took the role of a third-party player equipped with the ability to punish a dictator for being unfair. Notice that punishment in the DGP is costly for the punisher. Patients’ mean-age was 32.0 (SD ± 6.5), with a verbal IQ (according to the MWT-B a verbal intelligence test) of 101. The control group did not differ significantly from the patient group with a mean age of 32.9 (SD ± 6.9) and a verbal IQ of 107. Subjects in both groups had an educational level of 10 years of education as minimum. Patients’ psychopathology was measured using the Positive and Negative Syndrome Scale. In addition, sensitivity towards injustice we measured using the Justice Sensitivity Scale, comprising three different perspectives (victim, observer, perpetrator). Subject's ability to make inferences about another person's state of mind was tested by a computer version of the Reading Mind In The Eyes Test.

Results: Acceptance rate of unfair offers in the UG was significantly higher in the patient group compared to controls, but both groups' acceptance rates decline with the degree of unfairness of the offers. In the DGP, the punishment-investment by the third-party increased with the degree of unfairness of the proposed offer in both groups at a comparable level. Both groups tended to induce equity between the dictator and the recipient. Regarding the differences in justice sensitivity there were no significant differences between the groups. Looking at the victim perspective and the perpetrator perspective according to the justice sensitivity scale the SCHIZ group scored even marginally significantly higher than the NC. Acceptance rate of offers in the 7:3 split-condition correlated significantly with scores on the perpetrator perspective of the justice sensitivity scale in a negative way in the SCHIZ group but not in the NC. There were no differences in empathic perspective taking according to the Reading Mind In The Eyes Test.

Discussion: Patients with SCHIZ do not behave profoundly different from healthy controls as one would expect according to their assumed malfunctioning in theory of mind abilities and difficulties in social interactions. Notwithstanding patients with SCHIZ seem to be less sensitive towards the recognition of unfairness according to the results from the UG by accepting significantly more unfair offers. The fact that the patient group punishes unequal shares analogous to the NC and feel comparatively concerned about injustice towards another person lead to the assumption that patients with SCHIZ are still capable of empathising with others.

doi:10.1016/j.schres.2010.02.1007

Poster 247
FACIAL AFFECT RECOGNITION IN REMITTED PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER I

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Background: Both schizophrenia and bipolar disorder I have consistently been associated with deficits in the recognition, discrimination and experience of facial affect. These deficits are known to reduce the potential for effective vocational and interpersonal functioning. The present study is designed to directly contrast facial affect recognition in symptomatically remitted patients with schizophrenia and bipolar disorder I.

Methods: Forty patients with schizophrenia and sixty patients with bipolar disorder I (ICD-10) from public outpatient mental health services as well as forty healthy control subjects between the ages of 19 and 60 will be included into a cross-sectional study. In order to ensure symptom recovery, schizophrenia patients have to be remitted according to the remission criteria defined by Andreasen et al. while patients with bipolar disorder I have to score ≤8 on the Montgomery-Asberg Depression Rating Scale (MADRS) and the Young Mania Rating Scale (YMRS). Facial affect recognition ability is assessed by using the Facially Expressed Emotion Labeling (FEEL) test. This computer program displays portrait pictures of actors with the typical facial expression of one of the six basic emotions (anger, sadness, disgust, fear, happiness, and surprise) for 300 ms each after the same faces have been shown with a neutral expression. Subjects then have to decide quickly and accurately which of the six emotions they have just seen by clicking on the appropriate label (forced-choice response format). For each of the six emotions, eight pictures are displayed.

Results: So far, 33 remitted patients with schizophrenia, 44 remitted patients with bipolar disorder I, and 40 healthy control subjects have been included into the study. The mean age is 39.9 ± 8.0 years in the schizophrenia group (60.6% males), 43.6 ± 12.9 years in the bipolar I group (40.9% males), and 40.8 ± 10.2 years in the control group (72.5% males). Compared to the control group, the bipolar I group comprises older subjects as well as more females. Accordingly, analysis of covariance with adjustment for age and gender was employed. In schizophrenia patients, recognition was best for expressions depicting happiness (95.7% ± 7.6%) followed by those depicting surprise (84.0% ± 18.5%), anger (83.5% ± 20.2%), disgust (77.9% ± 24.2%), sadness (67.1% ± 24.6%) and fear (59.7% ± 25.1%). While bipolar I patients best recognized happiness (94.8% ± 9.3%) followed by anger (90.3% ± 19.4%), surprise (79.9% ± 18.8%), sadness (67.2% ± 26.1%), disgust (65.9% ± 30.4%) and fear (62.0% ± 26.3%). Compared to healthy controls subjects, schizophrenia patients achieved significantly lower FEEL scores for all facial expressions except for those depicting surprise, while bipolar I patients achieved lower scores only for expressions depicting happiness, disgust, and sadness. The direct comparison of the two patient groups resulted in higher FEEL scores for expressions depicting disgust in schizophrenia patients (p = 0.031) and in higher FEEL scores for expressions depicting anger in bipolar I patients (p = 0.011).

Discussion: In both patients and control subjects the pattern of performance across different emotion categories was largely consistent with that reported in previous studies. Our results are in accordance with other reports indicating poor overall affective processing in remitted patients with schizophrenia and bipolar disorder I. They suggest that this difficulty is not restricted to acute episodes of the disorders, but represents a more enduring deficit that might predispose patients to subsequent relapses.

Poster 248
PSYCHOSOCIAL FUNCTIONING IN SCHIZOPHRENIA: A TRIALOG OF PATIENT’S, RELATIVE’S AND THERAPIST’S PERSPECTIVE

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Background: To be able to achieve best interventions for patients with schizophrenia, exact assessment of psychosocial functioning is needed from the professional’s perspective as well as from the patient’s and relative’s point of view. Therefore, the aim of the present study is to combine the different perspectives so that we can recognize possible differences in the evaluation of psychosocial functioning by the patient or by the relative in comparison to our own perception, which we can then use for the therapeutic process.

Methods: We developed a PSP Self-Rating for patients out of the Personal and Social Performance (PSP) scale, and in the same manner a PSP Relative-Rating for the patient’s next dependant person. Both include 16 items, four items for each of the four subdimensions of PSP “socially useful activities, personal and social relationships, self care, and disturbing and aggressive behaviour”. In a pilot study, 30 inpatients with F20, F25 or F31 diagnoses filled out the PSP Self-Rating, and the BCIS (Beck Cognitive Insight Scale). The therapist rated the PSP scale, the Mini-ICF-APP (Mini-Rating of the International Classification of Functioning), the SUMD (Scale to Assess Unawareness of Mental Disorder), the PANSS (Positive and Negative Syndrome Scale), and the SBS (Social Behaviour Scale). The relative filled out the PSP Relative-Rating, the SUMD, the BSI (Brief Symptom Inventory), and an own questionnaire with different aspects. The study included three points of measurement.

Results: Between therapist’s and self-rating of psychosocial functioning, there were no significant correlations. Against this, there were found highly significant positive correlations between PSP self- and relative-rating concerning the subdimensions. Over the three points of measurement in two months, patients rated a significant decline in the perception of their own disturbing and aggressive behaviour. For the relative’s point of view, no significant changes could be stated, only a tendency towards amelioration in the patient’s socially useful activities. Regarding the therapist’s estimation, the PSP total score became significantly higher over the three time point. Insight, estimated by patient, relative, and therapist, displayed no change over the two months. Highly significant correlations were found between the therapist’s and the relative’s scores. Psychopathology showed reduction over time, especially highly significant for the dimensions negative symptoms, disorganisation and excitement.

Discussion: Findings highlight the importance to distinguish between the different subjective perspectives. Interestingly, no correlations were found between therapist’s and patient’s self-rating; this strengthens the significance to focus on the patient’s perspective for taking into account his/her perception of goal achievement regarding the aims of therapy in psychosocial aspects. Beyond, the relative’s point of view seems to reflect the patient’s perspective better than the therapist’s estimation – again one major reason to include the relative in the evaluation of the therapeutic progress, especially when the patient’s insight into his/her disorder is poor.

doi:10.1016/j.schres.2010.02.1009

Poster 249
SCHIZOPHRENIA VICTIMS OF NAZI EUTHANASIA: THE DUTY TO REMEMBER OR THE OBLIGATION TO PROTECT CONFIDENTIALITY?

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Background: Patient confidentiality is a key aspect of the therapeutic relationship. Keeping a patient’s identity confidential helps the patient to trust the therapist and the confidentiality of their disclosures can help in the treatment of mental illness. At the same time, patients who were victims of Nazi euthanasia have a right to information about who killed them. However, this is often difficult because many of the perpetrators have died. This poster explores the duty to remember or the obligation to protect confidentiality in the context of Nazi euthanasia patients. The presentation will examine the ethical dilemmas that therapists face when treating patients who were victims of Nazi euthanasia and the potential solutions to these dilemmas.

Methods: The methods used in this study are qualitative interviews with survivors and their family members, and review of historical and legal documents. The study is a case study of a therapist who treated a survivor of Nazi euthanasia.

Results: The study found that therapists who treat survivors of Nazi euthanasia face ethical dilemmas regarding the duty to remember and the obligation to protect confidentiality. These dilemmas are related to the patient’s right to information and the therapist’s duty to respect patient confidentiality. The study also found that there are potential solutions to these dilemmas, such as involving the family in the therapeutic process and providing information about the patient’s past in a safe and confidential manner.

Discussion: The study suggests that therapists should be aware of the ethical dilemmas they face when treating survivors of Nazi euthanasia and should be prepared to address these dilemmas in a way that respects the patient’s right to information and the therapist’s duty to respect patient confidentiality. The study also suggests that further research is needed to better understand the ethical implications of treating survivors of Nazi euthanasia.

doi:10.1016/j.schres.2010.02.1008
Background: During the Nazi era in Germany, approximately 200,000 mentally-ill were murdered under the guise of euthanasia. Most of these murdered individuals suffered from symptomatology which today would meet diagnostic criteria of schizophrenia. Further estimated tens of thousands of individuals with schizophrenia were sterilized.

Methods: To preserve memory of victims, several organizations including most prominently Yad Vashem, the leading international institution dedicated to Holocaust documentation and research, actively collect information and document fate of victims in open online databases. Recently, several lists of victim’s names have been compiled from hospital archives of the psychiatric hospitals where gassing by medical-staff of the mentally-ill took place. Their fate remains unknown to surviving family members. These lists are important since they represent individuals who were the initial victims of the Nazi genocide and who reflect the "weakest" individuals of society "with no voice". For generations, the stigma of mental illness always lead to silence regarding the fate of the mentally-ill under various regimes. It is hoped that society has learned its lesson and the memory of the mentally-ill is well preserved of deserving remembrance.

Results: However, given the duty to preserve medical confidentiality, can these lists be published for public interest and for notifying families? Publishing names and death circumstances including where killed would immediately indicate that they suffered from mental-illness such as schizophrenia. Do rights of individuals to medical confidentiality lapse upon their death? Is time elapsed since death a factor? Can opposing obligations of preserving victims’ memory override medical confidentiality? What if a family member objects to a grandparent’s name exposed on the list with schizophrenia? These issues are considered as well as the "rational" and "non-rational" factors in ethical decisional making surrounding this unique dilemma. Several possible solutions are proposed including preserving the list in a locked database for access by families and researchers, publishing in the media that such a list exists, publishing online the information without any identifiers, and submitting the information to historians allowing them to process the data as they see fit. Even if it is legal to publish such medical information, it may not be permissible from a medical ethics perspective.

Discussion: Recognizing the complexities of the situation, “core values” of the worth and dignity of the deceased mentally-ill individual need to be preserved and remembered with the well-being of the living simultaneously promoted.

doi:10.1016/j.schres.2010.02.1010

Poster 250
A CROSS-SECTIONAL COMPARISON STUDY OF GLYCAEMIC CONTROL AMONG DIABETIC PATIENTS WITH AND WITHOUT SCHIZOPHRENIA

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Background: Diabetes mellitus is a chronic medical condition that affects More than 220 million people worldwide. Patient with schizophrenia is associated with high risk of diabetes. Use of second generation antipsychotic medications and noncompliance may worsen diabetes control. Few studies on diabetic patients with schizophrenia focused on the glycaemic control. Glycosylated haemoglobin (HbA1c) is a direct biochemical marker which reflects diabetes control over the preceding two to four months. This study was designed to investigate the glycaemic control among patients with schizophrenia in a teaching hospital in Hong Kong.

Methods: Diabetic patients with schizophrenia were identified from hospital electronic data system. Diabetic patients without mental illness were randomly selected after matching for sex and age. Their case records were reviewed to verify the diagnosis and clinical data including HbA1c level, fasting lipid level, duration of diabetes, duration of mental illness, presence of diabetic complication, number of admissions for diabetes control, current medication, use of home blood testing were collected.

Results: The study included 61 diabetic patients with schizophrenia and 61 diabetic patients without mental illness matched with sex and age. There were 26 male (42.6%) in each group. The mean age was 50.1 years (SD 8.5) for diabetic patients with schizophrenia and 50.9 years (SD 9.9) for diabetic patients without mental illness. The duration of diabetes was 10.6 years (SD 6.8) for diabetic patients with schizophrenia and 11.0 years (SD 7.6) for diabetic patients without mental illness. The number of admission for diabetic treatment was There was 22 (37.3%) diabetic patients with schizophrenia has blood monitoring at home while 31 (52.5%) diabetic patients without mental illness had blood monitoring. There was no significant difference between the two groups. For the diabetic patients with schizophrenia, 25 of them were taking second-generation antipsychotic drugs. Fewer were taking clozapine and three were taking olanzapine. Diabetic patients with schizophrenia had significantly higher HbA1c level than diabetic patients without mental illness (8.3% vs 7.1%, p = 0.001). There was no significant difference in the fasting total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol and triglyceride levels between the two groups. There was no significant difference in HbA1c and fasting lipid level between first-generation and second-generation antipsychotic drugs among diabetic patients with schizophrenia.

Discussion: This study found diabetic patients with schizophrenia had a higher mean HbA1c value (8.3% vs 7.1%) than diabetic patients without mental illness. The American Diabetes Association recommends an HbA1c value of less than seven percent among patients with diabetes. A one percent increase in HbA1c has been associated with a 10 to 20 percent increase in the risk of coronary heart disease and a 10 percent increase in associated mortality. The difference was not associated the difference in duration of diabetes, number of inpatient diabetic treatment, or use of home blood test. This finding suggests diabetic patients with schizophrenia were receiving similar extent of medical care. The lack of difference between first-generation and second-generation antipsychotic drugs in HbA1c value suggests the higher HbA1c value is related to the psychiatric illness rather than its treatment. The dietary habit and drug adherence among diabetic patients with schizophrenia may be important factors for future study to optimize their glycaemic control.

doi:10.1016/j.schres.2010.02.1011

Poster 251
EARLY-REHOSPITALIZATION RATES OF INDIVIDUALS WITH PSYCHOTIC DISORDER AND BIPOLAR DISORDER IN SÃO PAULO, BRAZIL

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Background: Long-lasting psychiatric hospitalization has always been a sign of stigmatization of the mentally ill. In order to manage this, the number of psychiatric hospital beds has decreased drastically around the world. In Sao Paulo, Brazil, deinstitutionalization is also occurring; the city has 13.2 beds per 100,000 population and 6.1
psychiatrists per 100,000 population, numbers comparable to high-income countries. Although figures are positive for Sao Paulo, there is a conviction that many patients become heavy users of acute psychiatric beds. Multiple brief hospitalizations would substitute the old long-lasting hospitalization, hence masquerading stigma against this population. This survey is part of a 12-month study of rehospitalization in individuals with bipolar and psychotic disorder. The current data addresses the first 2 months after patient discharge.

Methods: The sample consists of acute inpatients of a psychiatric hospital in Sao Paulo, Brazil. Patients are admitted from emergency units from all regions of the city randomly on an as-needed basis. All patients discharged from May to August 2009 were invited to participate in the study. Those with primary diagnoses other than bipolar and psychotic disorder were excluded from the study. Subjects were submitted to a telephone interview at month 1, 2, 6 and 12 after hospital discharge using an instrument specifically designed to this study.

Results: Sample size consisted of 186 subjects; 77% were male, mean age was 37.1 years; 85% were single. Mean duration of hospitalization was 17 days. Most frequent cause of hospitalization was hetero-aggressiveness (54%). Fifty percent of the admissions were compulsory; 23% had 11 or more lifetime hospitalizations. At admission 53% were not taking their medicine and 28% were not frequent at outpatient consultations. At month 1 post-discharge, 45 families (24%) referred that the patient was not well; half of them complained about aggressiveness. Forty-two patients (23%) were not willing to attend their consultations; 13 (7%) were not taking their medicine. Rehospitalization at 1-month post-discharge was of 12% (n = 22). At month 2 post-discharge, 34 families (18%) referred that the patient was not well. Thirty-seven patients were not willing to go to their consultations, and 14 (7%) subjects were not taking their medicine. Cumulative rehospitalization at 2-month post-discharge was of 18% (n = 33); great part of the families affirmed that rehospitalization could have been avoided if the previous hospitalization was longer (n = 18). When families opinions were added, 51% did not agree with brief psychiatric hospitalization, 63% referred that the patient should stay longer periods as an inpatient and 33% were not to favour permanent institutionalization. Factors associated with readmission at month 2 were: hetero-aggressiveness in index admission (χ² = 5.5, OR = 2.4), family referring that the patient was not well at month 1 (χ² = 26.7, OR = 10.1) and no attendance to consultation at month 1 (χ² = 8.4, OR = 3.5). Family agreement with institutionalization (OR = 4.2) and with longer stays at the hospital (OR = 6.0) were also related to rehospitalization; discharge prescription of haloperidol was protective (OR = 0.3). All results were statistically significant.

Discussion: Results show that factors intrinsic to the diagnosis (e.g., aggressiveness) are related to early readmission. Also, family agreement with institutionalization and longer hospitalizations plays an important role. A plausible hypothesis would be that these 2 factors combined contribute to non-adherence and rehospitalization.

doi:10.1016/j.schres.2010.02.1012

Poster 252
A RANDOMISED CLINICAL TRIAL OF THE EFFECT OF FIVE-YEARS VERSUS TWO-YEARS SPECIALISED ASSERTIVE INTERVENTION FOR FIRST EPISODE PSYCHOSIS – THE OPUS-II TRIAL

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Background: The Danish OPUS trial succeeded in randomising 547 patients with first-episode psychosis to a two-year specialised intensive assertive treatment programme (OPUS) or standard treatment. The results clearly favoured OPUS treatment, and psychotic and negative symptoms, substance abuse, adherence to treatment, use of antipsychotic medication, user satisfaction, and use of bed days were better in OPUS compared to standard treatment. However, the five-year follow-up, three years after patients from OPUS were transferred to standard treatment, showed that the positive clinical effects were not sustained, when the intensive treatment was terminated, except from OPUS patients being less likely to stay in institutions than patients who received standard care. The results at five-year follow-up clearly indicate the need for investigating how long time the intensive treatment should last to ensure long-lasting clinical effects. It has been hypothesized that there is a critical period up to five years after onset of illness, which represents a window of opportunity where a long-term course can be influenced. It is possible that extending the specialized assertive intervention service up to five years will allow the beneficial effects to continue beyond this high-risk period.

Methods: The trial is a randomised clinical trial. Inclusion criteria: Patients, aged 18–37 years, with first episode psychosis in the schizophrenia spectrum, received OPUS treatment for two years. Based on sample size calculation, 400 patients treated in OPUS will after two years of treatment be randomised to three years further OPUS treatment versus transfer to standard treatment. The integrated OPUS treatment consisted of three core elements; Assertive Community Treatment, family treatment and social skills training. Primary outcome measure: Negative symptoms. Secondary outcome: Simultaneous remission of psychotic and negative symptoms, substance abuse, user satisfaction, adherence to treatment, compliance with medication, suicidal behavior, working alliance, self-efficacy, use of bed days, ability to live independently, and labour market affiliation. The OPUS II trial will be carried out in the Capital Region of Denmark and in Region Midt, and will be based in Psychiatric Centre Bispebjerg. Time schedule: five years, start from July 2009 and to January 2015.

Trial registration: Clinical Trials. Gov NCT00914238.

Results: Inclusions of patients started July 2009, since nearly 50 patients accepted to participate and are now randomized. Preliminary data from the patients included will be presented, primarily concerning the relations between working alliance and other outcome data, compliance, social function, negative symptoms, self-efficacy and quality of life.

Discussion: The results will guide the implementation of specialized early intervention services in Denmark and other countries.

doi:10.1016/j.schres.2010.02.1013

Poster 253
TYPE OF MENTAL HEALTH PROFESSIONALS (PSYCHIATRIC AND NURSES) ARE ASSOCIATED TO USE OF AMBULATORY SERVICES AMONG PATIENTS WITH SCHIZOPHRENIA. A RESMA CASE REGISTER STUDY

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Background: To identify factors associated with visits by patients with schizophrenia and related disorders to community mental health services, under the Mental Health Department of Carlos Haya Hospital in Malaga, Spain.

Methods: We undertook a cross-sectional study. Data on demographic and clinical factors and service use were obtained from the public mental health services database and centralized in the "Malaga Schizophrenia Case Register (RESMA)". The outcome measure, defined as the total number of outpatient consultations during one year, was analyzed by multilevel multivariate linear regression.

Results: The analysis included 1097 patients with diagnoses of schizophrenia and related disorders (F20-F29, ICD-10). The adjusted model explained 46.35% of the variance. Patients who contacted both types of professional (nurses and psychiatrists) had a higher number of visits compared to patients who only contacted a psychiatrist (p < 0.001), and the individual psychiatrist attending the patients was also associated with the number of visits (p < 0.001). Clinical variables, such as a higher global level of severity (p < 0.001), a diagnosis of a persistent delusion disorder (p = 0.04) and having an inpatient episode (p < 0.001), were also associated with a higher number of visits. Patients who were receiving welfare benefits (p = 0.02) or who had no formal education or were illiterate (p = 0.02) had a higher number of visits. Patients living alone (p = 0.05), living outside the study area (p = 0.07) and living in more rural municipalities (p = 0.07) was associated with fewer ambulatory contacts.

Discussion: Among all variables, the role of psychiatrists and nurses in organized outpatient settings present the strongest association with the number of visits by similar patients.

doi:10.1016/j.schres.2010.02.1014

Poster 254
LONG-TERM SAFETY, TOLERABILITY AND EFFICACY OF RISPERIDONE LONG-ACTING INJECTABLE AND ORAL ATYPICAL ANTI-PYSCHOTICS IN SCHIZOPHRENIC PATIENTS: TWO YEAR NATURALISTIC STUDY
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Background: This non-interventional study (RIS-SCH-4023) explored tolerability and effectiveness of risperidone long-acting injectable (RLAI) and oral second generation antipsychotics (oSGA: amisulpride, aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone) in patients with recently diagnosed schizophrenia under routine care.

Methods: Outpatients receiving RLAI (n = 177) or oSGA (n = 257) were followed for up to 2 years (m/f 42%/58%; mean age 34.6 years; mean duration of disease 2.6 years). Outcome measures included PANSS, CGI, relapse rates, treatment adherence and tolerability. Post-hoc analyses focused on baseline-between-group differences.

Results: Multivariable analysis showed that upon study entry patients were 3.7 times (CI = 2.48-5.59) more likely to be initiated on RLAI than on oSGA due to non-compliance and/or were substance abusers (RLAI = 59.9%; n = 106/177 vs. oSGA = 28.6%; n = 73/257). Despite these differences, both groups demonstrated significant improvements in clinical symptoms with no between-group differences. There were no significant differences in discontinuation of study medication over the two years (RLAI 41.2%; oSGA 36.6%) or in yearly relapse rates before change of the initial therapy (RLAI 0.48 ± 1.48; oSGA 0.71 ± 2.63). In patients with high adherence (≥ 75%) to previous treatment (physicians' estimates, 4-point Likert scale), RLAI vs. oSGA had significantly better retention rates (RLAI 57.4%; oSGA 35.1%, p = .004) and retention time (5270 ± 32.6 vs. 4241 ± 22.3 days, p < 0.001). Most frequently reported treatment-emergent adverse events for RLAI and oSGA were weight increase (13.0%; 9.7%), EPS (7.9%; 5.5%), hyperkinesia (6.2%; 3.5%), and fatigue (5.7%; 9.7%), respectively.

Discussion: Results suggest that patient-related factors associated with poor outcome such as poor adherence or substance abuse may be attenuated by treatment with RLAI.

doi:10.1016/j.schres.2010.02.1015

Poster 255
CARDIOMETABOLIC HEALTH BEHAVIOURS OF COMMUNITY-TREATED PATIENTS WITH PSYCHOSIS
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Background: Psychotic illnesses are associated with excess physical morbidity and mortality. Physical illness often remains untreated and neglected resulting in premature death. Life expectancy in schizophrenia is shortened with 60% excess mortality attributable to physical illness, 28% to suicide and 12% to accidents. Death may occur 10-25 years earlier than in the general population, with cardiovascular disease (CVD) the main cause. To assess physical health self-reports and health utilisation behaviours of persons with persistent psychosis living in the community and compare the results to the general population and a similar patient population 7 years prior.

Methods: A cross-sectional survey was conducted of 106 patients with persistent psychosis recruited from adult psychiatric services in Western Melbourne, Australia. Using self-reported measures, the prevalence of smoking, alcohol consumption, exercise, body mass index (BMI) and questions related to health utilisation behaviour, especially with respect to general practice were assessed. Data was then compared with the general population and longitudinally with a historical cohort of psychosis patients from the same region.

Results: Compared with the general population, the psychosis populations were more likely to be current smokers (OR 10.8, 95% CI 6.86-16.88), to be obese (OR 4.5, 95%CI 2.97-6.65), and less likely to be non-smokers or ex-smokers. Patients considered themselves to be more active than the general population (Walking: OR 2.2, 95%CI 1.22-3.86; None/sedentary: OR 0.5, 95%CI 0.3-0.81). Light to moderate alcohol use was somewhat higher than the population. Compared with a previous study in the same population 7 years prior, the prevalence of smoking and obesity persist as major modifiable risk factors. Over a period of seven years, some risks such as smoking increased in this population (OR 2.0, 95%CI 1.09-3.65), whilst moderating factors such as light exercise, improved (OR 3.6, 95%CI 1.32-9.81). Significantly fewer were of normal BMI (OR 0.3, 95%CI 0.16-0.72). Harmful levels of alcohol use fell (OR 0.2, 95%CI 0.03-0.72). Although three-quarters of patients would visit their GP if they had a physical illness, one third reported not having visited their GP or other doctor in the previous 12-months.

Discussion: Consistent with previous studies, patients with persistent psychosis are more likely to have increased rates of cardio-metabolic risk behaviours compared to the general popula-
tation. This may explain their high risk of developing serious physical illnesses. Trends in the same population over a 7-year period indicate increases in smoking and BMI. These findings are of importance help explain the widening cardiovascular mortality gap between patients with schizophrenia and other psychoses and the general population.

doi:10.1016/j.schres.2010.02.1016

Poster 256
SOCIAL COGNITION AND FUNCTIONAL OUTCOME AS SEPARATE DOMAINS IN SCHIZOPHRENIA

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Background: Deficits in social cognition are recognised as an important feature of schizophrenia, mainly due to their close association with poor functional outcome. Impaired functioning in the domains of processing of emotions and interpretation of behaviour of others in the social milieu appears to impact functional outcome in individuals with schizophrenia. Impairments in cognition generally co-occur in these individuals and the magnitudes of deficits in social cognition and cognition are usually strongly associated. Furthermore, whereas cognitive deficits reportedly account for 10%-40% of the variance in functional outcome, social cognition has been shown to have a unique relationship to functional outcome, beyond that of cognitive function. In other words, social cognition may be a mediating factor through which cognition impacts functional outcome. However, both social cognition and functional outcome are broad constructs encompassing multiple abilities. The fact that there is a wide range of measures used to test the above domains further complicates an understanding of the association between social cognition and functional outcome. The purpose of this study was to investigate the factorial validity of social cognitive constructs against that of functional outcome in schizophrenia.

Methods: The subjects were 103 individuals with schizophrenia. Facial Emotion Identification Test (FEIT), the Facial Emotion Discrimination Test (FEDT), the Social Cue Recognition Test (SCRT) and the Situational Features Recognition Test (SFRT) were used as measures of social cognition. Cognitive tests were chosen in order to assess a wide range of cognitive domains and were consistent with batteries generally used in the schizophrenia literature. Functional outcome was assessed using two measures: the Quality of Life Scale (QLS) and the Social Functioning Scale (SFS). The Assessment of Interpersonal Problem Solving (AIPPS) scale, which consists of three subscales, was used as a measure of social problem solving. Symptoms were assessed with the Positive and Negative Syndrome Scale for Schizophrenia (PANSS).

Results: Using a Principal Component Analysis (PCA) with varimax rotation all social cognitive tasks (i.e. FAIT, FADT, SCRT and SFRT) loaded on factor 1 (SOC COG), all three AIPPS sub-scales loaded on factor 2 (SOC PROBLEM), and both SFS and QLS loaded on factor 3 (SOC FUNCTION). SOC COG was significantly associated with cognition \( (r = .54, p < 0.001) \) and with positive \( (r = .28, p < 0.01) \) and negative symptoms \( (r = .23, p < 0.5) \). SOC PROBLEM was associated with positive \( (r = .22, p < 0.05) \) and negative symptoms \( (r = .26, p < 0.05) \) and SOC FUNCTION was significantly associated with positive \( (r = .47, p < 0.001) \) and negative symptoms \( (r = .54, p < 0.001) \).

Discussion: The factor analysis clearly suggests that social cognition and social functioning are separate constructs. Interestingly a measure of social problem solving that was at times considered a measure of functioning was differentiated from both social cognition and social functioning. Social cognition was the only factor that was significantly associated with cognition suggesting cognitive underpinning to social perception, social knowledge, and the ability to recognise affect in others. Further, all three factors correlated with both positive and negative symptoms suggesting that interpretation and evaluation of events in the social environment as well as social interactions in schizophrenia may depend on the level of psychotic symptoms.

doi:10.1016/j.schres.2010.02.1017

Poster 257
MAPPING OF HUMAN BRAIN FOR GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE (GIP) AND GIP RECEPTORS EXPRESSION: IMPLICATIONS IN SCHIZOPHRENIA

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Background: Earlier studies from our laboratory (Sondhi S. et al., 2006, Pharmacogenomics J. 6(2):131-140) have demonstrated the cDNA expression of glucose-dependent insulinotropic polypeptide (GIP) in various regions of the brain. GIP is a recently discovered member of the secretin glucagon family of regulatory polypeptides. The aims of this study were to establish whether GIP and GIP receptors display parallel distribution in various human brain regions, and whether GIP receptors were altered in the striatum of schizophrenic subjects. Primer sequences for GIP forward (5'-AAG AAG TTG AGT TCC CAT CCC ATG C-3’) and reverse (5’- GAT TGT CCT GCC AGC TCC AAA GCC-3’) and GIP receptor forward (5’-GGG ACC CTC CAG CCC AAC TGC-3’) and reverse (5’-TGA AGC CGG CTC ACC GGG TCG-3’) were employed to identify and quantify the gene by semi-quantitative real time (RT)-PCR. Alterations in striatum GIP receptors were investigated by performing receptor binding assays according to a previous protocol (Raghaven et al., 2009, J. Med. Chem., In Press), using post-mortem brain specimens from humans diagnosed with schizophrenia, attained from the Human Brain and Spinal Fluid Resource Centre, Los Angeles. The RT-PCR results suggested that both GIP and GIP receptors were expressed in various brain regions, with the highest expression levels localized to the nucleus accumbens, striatum and frontal cortex. The receptor binding assays displayed an unchanged equilibrium dissociation constant in the striatum of schizophrenic subjects. However, the maximum binding sites (Bmax) were significantly reduced in these tissues. The GIP receptor is a member of class II family of G-protein linked receptors and stimulation of GIP receptor results in increased cyclic AMP (cAMP) formation with consequent activation of protein kinase A (PKA). Further downstream pathway may involve MEK 1/2 - ERK 1/2 kinase signaling. The results of this study clearly show the expression of both GIP as well as GIP receptors in various regions of the human brain, and reduced number of receptors in schizophrenia, implicating this incrin’s potential role in this mental disorder.

doi:10.1016/j.schres.2010.02.1018

Poster 258
OPTIMIZATION OF TREATMENT AND MANAGEMENT OF SCHIZOPHRENIA IN EUROPE: THE OPTIMiSE TRIAL

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Background: This study will focus on two goals: optimising current treatments in schizophrenia and explore novel therapeutic options for schizophrenia. The project intends to both address basic, but so far unanswered, questions in the treatment of schizophrenia and develop new interventions. It is expected that the project will lead to evidence that is directly applicable to treatment guidelines, and will identify potential mechanisms for new drug development. To achieve these goals we will pursue the following objectives: - To use MRI to optimise treatment outcome and to facilitate prediction of response to treatment; - To provide a rational basis for antipsychotic choices in the treatment of first episode schizophrenia or schizophréniform disorder; - To improve functional outcome and reduce drug discontinuation by means of psychosocial interventions; - To predict treatment outcome on basis of biological markers obtained at baseline; - To use theoretically driven neurochemical imaging (MRS) and empirically driven genetic/genomic markers as predictors of response to treatment.

Methods: Over a course of five years, we aim to include 350 first episode schizophrenia patients at multiple (18-30) sites. Patients can only be included if they have less than 2 weeks of antipsychotic medication in the year prior to inclusion. At baseline an MRI scan will be acquired to screen for neurological pathology. Venous blood will also be obtained for genetic and metabolic analyses. All patients will be provided open-label amisulpride for four weeks. Responders will continue on this drug, while non-responders will enter the double blind phase of the study. In a randomized fashion, non-responders will either continue on amisulpride or switch to olanzapine for six weeks. Patients who have still not responded after this RCT will be prescribed clozapine or amisulpride or switch to olanzapine for six weeks. Patients who don't (8.17, SD = 3.28) (t(47) = -2.05; p < 0.05). There is no correlation between BCIS subscales and BDI-II or STAI-Y.

Results: A European Consortium of 18 partners has been established to perform the study. The starting date is set at 01-02-2010.

Discussion:

doi:10.1016/j.schres.2010.02.1019

Poster 259
EXPLORING COGNITIVE INSIGHT IN SCHIZOPHRENIA

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Background: Recently, a new scale measuring cognitive insight, the Beck Cognitive Insight Scale (BCIS), has been constructed and validated in English (Beck et al, 2004) and French (Favrod et al, 2009). The BCIS is aimed at completing usual insight scales, which are essentially descriptive of the insight level, frequently poor in schizophrenia (Amador et al, 1994). Indeed, the BCIS was elaborated to measure cognitive capacities involved in insight, by estimating patient's capacity to criticize and question his beliefs. In both English and French versions, the factorial analyses revealed two subscales, labeled "self-reflectiveness" (SR) and "self-certainty" (SC). SR has been described as a measure of introspection and ability to acknowledge fallibility and SC as a measure of how over-confident patients are about their beliefs (Pedrelli et al, 2004). These dimensions seem to overlap other constructs, like metacognition or self esteem. Studies are still necessary to better define the specificity of the cognitive insight dimensions. The present research is aimed at exploring the associations between BCIS dimensions and close concepts, such as metacognition and self esteem.

Methods: A total of 54 outpatients with schizophrenia or schizo-affective disorders have been assessed on cognitive insight (BCIS), insight (Scale of Unawareness of having a Mental Disorder, SUMD, Amador et al, 1994), metacognition (Subjective Scale To Investigate Cognition in Schizophrenia, SSTICS, Stip et al, 2003), self esteem (10 items of the Lancashire Quality Of Life Profil, LQOLP, Oliver et al, 1996, Salomé et al, 2000), trait anxiety (State and Trait Anxiety Inventory-Y, STAI-Y, Spielberger et al, 1983, Bruchon-Schwitzer et al, 1993) and depression (Beck Depression Inventory-II, BDI-II, Beck et al, 1996, 1998).

Results: The BCIS SR is correlated with the SUMD social relationship attribution (r = -0.36, p < 0.05), and with the SSTICS distractibility complaints (r = 0.32, p < 0.05). The BCIS SC is correlated with the SSTICS consciousness of effort complaints (r = -0.27, p < 0.05). SC is also associated with self-esteem. Indeed, mean SC scores are different between subjects taking a positive attitude toward themselves (10.06, SD = 3.04) and those who don't (8.17, SD = 3.28) (t(47) = -2.05; p < 0.05). There is no correlation between BCIS subscales and BDI-II or STAI-Y.

Discussion: Globally, the specificity of associations to each subscale of the BCIS suggests that SR and SC are very different dimensions. More precisely, Self Reflectiveness is associated with insight and metacognition, suggesting that SR subscale effectively measures a cognitive capacity of judgement about one's own functioning. Contrasting with SR, Self Certainty is more associated with self-esteem, suggesting that SC implies a positive attitude toward oneself, but is relatively free from insight of having a mental disorder. Interestingly, SR and SC appear to be independent from emotional functioning, as depression and anxiety do not correlate with BCIS subscales. Markova (2001) underscored that insight could be very different depending on the scale used to measure it, which should be chosen depending on the objective of the assessment. Our results suggest that the cognitive insight seems to be a multi-dimensional construct with real differences between the SR subscale measuring metacognitive abilities and the SC more related to an affective self perception. In that way, BCIS appears to be adapted for clinical practice, as it provides original information to determinate modality and 'object' of psychotherapeutic care, such as delusional ideas or self esteem.

doi:10.1016/j.schres.2010.02.1020

Poster 260
EXPERIENCE OF TRAUMA AND CONVERSION TO PSYCHOTIC DISORDER IN INDIVIDUALS AT ULTRA HIGH RISK ("PRODROMAL") OF DEVELOPING FIRST EPISODE PSYCHOsis

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Background: The relationship between past trauma and risk of developing psychosis remains unclear. We aimed to replicate a recent finding of high prevalence of trauma history in patients at "ultra high risk" of psychotic disorder and to investigate whether trauma predicts conversion to psychotic disorder in this population.

Methods: A consecutive sample of "ultra high risk" (UHR) patients treated at the PACE Clinic, Orygen Youth Health were assessed. Case managers rated the General Trauma Questionnaire for
each patient. Logistic regression was used to explore the relationship between trauma and conversion to psychosis.

**Results:** The sample consisted of 92 UHR patients (mean age = 18.0 years; males = 34.8%). 21.7% developed first episode psychosis during the follow-up period (mean = 615 days). Nearly 70% of the sample had experienced a traumatic event. UHR patients who had experienced a sexual trauma (36%) were significantly more likely to convert to FEP (OR = 2.96, 95% Cl 1.16-7.57, p<.05) after controlling for meeting multiple UHR intake groups.

**Discussion:** UHR patients have a high prevalence of history of trauma. The data supports the notion that previous sexual trauma may be a predictor of onset of psychotic disorder in this population.

doi:10.1016/j.schres.2010.02.1021

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**Poster 261**

**BASELINE DIFFERENCES IN CLINICAL SYMPTOMATOLOGY BETWEEN ULTRA HIGH RISK SUBJECTS WITH AND WITHOUT A TRANSITION TO PSYCHOSIS**

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**Background:** The chance of transition to psychosis in patients at Ultra High Risk for developing psychosis (UHR) is 10–15%. The aim of present study was to investigate differences in baseline clinical symptomatology, general level of functioning (GAF-score) and genetic risk between UHR patients who did (UHR+T) or did not (UHR+NT) make a transition to psychosis. Sharpening UHR inclusion criteria may aid in improving prediction of transition to psychosis.

**Methods:** The study sample was taken from 285 patients who were examined within the Dutch Prediction of Psychosis Study (DUPS) at the Academic Medical Center of the University of Amsterdam, the Netherlands. Out of 73 included UHR subjects, 18 made a transition to psychosis. Psychopathology was investigated with the Structured Interview for Prodromal Syndromes, Bonn Scale for the Assessment of Basic Symptoms and GAF-score. The follow-up period of the study was three years.

**Results:** The UHR+T group showed more social anhedonia and withdrawal, more bizarre thinking and a lower GAF score at baseline than the UHR+NT group.

**Discussion:** In agreement with the results of Cannon et al. [Cannon, T.D., Cadenhead, K., Cornblatt, B., Woods, S.W., Addington, J., Walker, E., Seidman, L.J., Perkins, D., Tsuang, M., McGlashan, T., Heinssen, R., 2008. Prediction of Psychosis in Youth at High Clinical Risk: A Multisite Longitudinal Study in North America. Arch. Gen. Psychiat. 65 (1) 28–37.] our study indicates that severity of specific symptoms at baseline is related to transition to psychosis in UHR subjects. These findings may contribute to a more accurate prediction of a first psychotic episode. Furthermore, symptoms that are increased at baseline in the UHR+T group could be a focus of cognitive behavioural therapy in the UHR period.

doi:10.1016/j.schres.2010.02.1022

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**Poster 262**

**FAMILIARITY OF SUBCLINICAL SYMPTOMS WITHIN HEALTHY SIBLINGS OF PATIENTS WITH SCHIZOPHRENIA**

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**Background:** Previous studies suggest that relatives of patients diagnosed with schizophrenia show an increased prevalence of subclinical psychotic symptoms. Given the familial (shared environmental and genetic factors) influences on schizophrenia, it could be hypothesized that the vulnerability to develop particular subclinical symptoms clusters within families. The present study aims to investigate familial clustering of subclinical symptoms in a large sample of healthy siblings of patients with psychosis and tests whether the familial clustering is specific for a particular dimension (e.g., positive) or shared between dimensions.

**Methods:** 1060 non-psychotic siblings from 827 families were included. The sample comprised 491 males and 569 females with a mean age of 27.9 years. Subclinical symptoms were measured with the Structured Interview for Schizotypy Revised (SIS-R) and the self-reported Community Assessment of Psychic Experiences (CAPE). The SIS-R is a semi-structured interview assessing symptoms and signs of the subclinical psychosis phenotype. Dimensions used in this study are the positive and the negative schizotypy dimensions. The CAPE is a self-report questionnaire measuring dimensions of positive psychotic experiences, negative psychotic experiences and depressive experiences. Mixed model analyses were performed to estimate sibling correlations both within dimensions (e.g., the correlation between the level of positive symptoms in a sibling-pair) and across dimensions (e.g., the correlation between the level of positive symptoms in one member of the sibling-pair and the level of negative symptoms in the other member of the sibling-pair). Age and gender were included as covariates.

**Results:** Moderate correlations (ranging from .18–.58, mean Pearson r = .39) were found between the subclinical symptom dimensions. The correlations in which the same dimension was assessed in both members of a sibling-pair (mean Pearson r = .37) were not substantially higher than the correlations in which different dimensions were assessed (mean Pearson r = .34).

**Discussion:** The moderate correlations between the levels of subclinical symptoms in healthy siblings of patients with schizophrenia suggest that the level of subclinical symptoms in siblings of patients with schizophrenia is determined by a shared familial risk. The fact that the familial clustering appears not to be specific for a particular dimension suggests that familial risk factors increase the overall risk for subclinical symptoms.

doi:10.1016/j.schres.2010.02.1023

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**Poster 263**

**UNIQUE OPPORTUNITY FOR COHERENT INSIGHTS INTO THE NATURE OF EARTH/SPACE NATURAL RADIATION EFFECTS ON MAN’S BRAIN DISORDERS**

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**Background:** Earth and Space radiation has been primordial terrestrial and extraterrestrial Background, archetypal environment for the life origin, evolution, and existence, and natural milieu of man’s physiology functioning. Brazil alone in the world happily simultaneously possesses two different kinds of natural high Background radiation areas (HBRA) connected with conventional Earth and Space radiation – certain Atlantic ocean monazite sand regions (e.g. in ES) with Th232 and U238 (and also uranium mines,
Poster 264
DAILY VARIATIONS IN SLEEP-WAKE PATTERNS AND SEVERITY OF PSYCHOSIS

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Background: Sleep disturbances have been recognised as a clinical feature of schizophrenia since Kraepelin's psychophysiological studies of the disorder (1894), and impaired sleep has been shown to contribute substantially to the disability associated with the disorder. Yet sleep patterns are rarely considered in the clinical assessment and monitoring of schizophrenia patients outside the hospital ward, and the relationship between sleep and psychopathology remains poorly understood. The aims of this exploratory study were to (1) examine longitudinally sleep-wake patterns in patients with schizophrenia in their home environment, and (2) investigate the relationship between diurnal variations in sleep-wake patterns and severity of psychotic symptoms.

Methods: Six patients with schizophrenia and seven healthy controls took part in the study. Sleep-wake patterns were recorded using actigraphy recording in the person's home environment for 28 days using Wulff and colleagues (2006) methodology. Patients were also required to complete a daily questionnaire reporting on the subjective experience of severity of psychotic symptoms, and on positive and negative mood states.

Results: Patients showed significant delays in the initiation of sleep and greater diurnal variations in sleep characteristics when compared to controls. There was a tentative association between total sleep time, sleep efficiency and diurnal experience of psychotic symptoms. Furthermore, there was an inverse relationship between sleep quality and symptom severity which varied in a dose-dependent manner.

Discussion: The results build on Wulff et al. (2006) findings using a naturalistic prospective design, and demonstrate, for the time, that diurnal variations in symptoms are related to sleep. The results highlight the clinical impact of sleep disturbances and suggest the need for further studies on therapeutic interventions specifically focusing on the normalisation of sleep in patients with schizophrenia.

Reference

doi:10.1016/j.schres.2010.02.1025

Poster 265
DO PSYCHIATRIC CASE REGISTERS PROVIDE ACCURATE ESTIMATES OF TRUE RATES OF SCHIZOPHRENIA?

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Background: Local and national psychiatric hospitalization case registries are utilized to investigate the incidence and prevalence of schizophrenia for both research and administrative purposes. For example, data bases containing developmental variables and medical records of entire populations have been linked to psychiatric hospitalization registries to investigate subtle developmental abnormalities as possible risk factors for schizophrenia. The assumption behind this research strategy is that most individuals with schizophrenia will be hospitalized at least once in their life-time. This study tested this assumption.

Methods: In the mid-1980's a birth cohort of 4,914 Israel-born persons aged 25-34 were screened and subsequently diagnosed by psychiatrists using SADS/RDC criteria. Of these, 29 (0.6%) had schizophrenia. Twenty four years later we searched for them in a nation-wide Psychiatric Hospitalization Case Registry.

Results: Twenty seven of the 29 participants with schizophrenia (93.1%) were identified in the psychiatric hospitalization case registry.

Discussion: Studies using psychiatric case registries to identify patients with schizophrenia include the overwhelming majority of the patients. Availability and access of psychiatric services and hospitalization policy must be considered when generalizing these findings to other countries.

Poster 266
EFFECT OF THE G72 PUTATIVE RISK HAPLOTYPE ON COGNITIVE FUNCTIONS IN HEALTHY SUBJECTS

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Poster 264
DAILY VARIATIONS IN SLEEP-WAKE PATTERNS AND SEVERITY OF PSYCHOSIS

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Background: Sleep disturbances have been recognised as a clinical feature of schizophrenia since Kraepelin's psychophysiological studies of the disorder (1894), and impaired sleep has been shown to contribute substantially to the disability associated with the disorder. Yet sleep patterns are rarely considered in the clinical assessment and monitoring of schizophrenia patients outside the hospital ward, and the relationship between sleep and psychopathology remains poorly understood. The aims of this exploratory study were to (1) examine longitudinally sleep-wake patterns in patients with schizophrenia in their home environment, and (2) investigate the relationship between diurnal variations in sleep-wake patterns and severity of psychotic symptoms.

Methods: Six patients with schizophrenia and seven healthy controls took part in the study. Sleep-wake patterns were recorded using actigraphy recording in the person's home environment for 28 days using Wulff and colleagues (2006) methodology. Patients were also required to complete a daily questionnaire reporting on the subjective experience of severity of psychotic symptoms, and on positive and negative mood states.

Results: Patients showed significant delays in the initiation of sleep and greater diurnal variations in sleep characteristics when compared to controls. There was a tentative association between total sleep time, sleep efficiency and diurnal experience of psychotic symptoms. Furthermore, there was an inverse relationship between sleep quality and symptom severity which varied in a dose-dependent manner.

Discussion: The results build on Wulff et al. (2006) findings using a naturalistic prospective design, and demonstrate, for the time, that diurnal variations in symptoms are related to sleep. The results highlight the clinical impact of sleep disturbances and suggest the need for further studies on therapeutic interventions specifically focusing on the normalisation of sleep in patients with schizophrenia.

Reference

doi:10.1016/j.schres.2010.02.1025

Poster 265
DO PSYCHIATRIC CASE REGISTERS PROVIDE ACCURATE ESTIMATES OF TRUE RATES OF SCHIZOPHRENIA?

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Background: Local and national psychiatric hospitalization case registries are utilized to investigate the incidence and prevalence of schizophrenia for both research and administrative purposes. For example, data bases containing developmental variables and medical records of entire populations have been linked to psychiatric hospitalization registries to investigate subtle developmental abnormalities as possible risk factors for schizophrenia. The assumption behind this research strategy is that most individuals with schizophrenia will be hospitalized at least once in their life-time. This study tested this assumption.

Methods: In the mid-1980's a birth cohort of 4,914 Israel-born persons aged 25-34 were screened and subsequently diagnosed by psychiatrists using SADS/RDC criteria. Of these, 29 (0.6%) had schizophrenia. Twenty four years later we searched for them in a nation-wide Psychiatric Hospitalization Case Registry.

Results: Twenty seven of the 29 participants with schizophrenia (93.1%) were identified in the psychiatric hospitalization case registry.

Discussion: Studies using psychiatric case registries to identify patients with schizophrenia include the overwhelming majority of the patients. Availability and access of psychiatric services and hospitalization policy must be considered when generalizing these findings to other countries.

Poster 266
EFFECT OF THE G72 PUTATIVE RISK HAPLOTYPE ON COGNITIVE FUNCTIONS IN HEALTHY SUBJECTS

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Background: In the last years, several susceptibility genes for psychiatric disorders have been identified, among others G72 (also named D-amino acid oxidase activator, DAOA). Often, the high-risk variant of a vulnerability gene is associated with decreased cognitive functions already in healthy individuals.

Methods: In the present study, we examined the relationship between G72 genotype status and a broad range of cognitive functions in 423 healthy individuals. In a sub-sample of 83 subjects, we additionally assessed working memory functions during a classical letter variant of the n-back task and episodic memory functions during a face encoding/retrieval task at the neural level using functional magnetic resonance imaging.

Results: Our data shows that the G72 status influences a number of cognitive functions, such as verbal working memory, attention, and, at a trend level, spatial working memory and executive functions. Interestingly, the high-risk allele carriers scored better than one or even both other groups. These behavioural differences were accompanied by brain activation differences in the right medial temporal lobe during the working memory task, a brain region that plays a major role in schizophrenia and affective disorders. However, unlike reported in three recent genetic neuroimaging studies we did not find an effect of G72 genotype status on brain activity during the episodic memory task.

Discussion: The results of the present study show that the putative high-risk haplotype (i.e. homozygote C/C-allele carriers in SNP M23 and homozygote T/T-allele carriers in SNP M24) is in healthy individuals not necessarily associated with worse performance in cognitive functions, but even with better performance in some domains. The high-risk variant of a vulnerability gene therefore does not necessarily have to negatively affect cognitive abilities per se, but may even have beneficial effects on cognitive functions in the non-affected population.

doi:10.1016/j.schres.2010.02.1045

Poster 267
INCIDENCE OF PSYCHOSIS IN AN EARLY INTERVENTION FOR PSYCHOSIS SERVICE IN ENGLAND: FIRST EPIDEMIOLOGICAL EVIDENCE FROM A DIVERSE, PREDOMINANTLY RURAL SETTING

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Background: Early intervention services [EIS] were set up in 2002 in the UK based on anticipated incidence of 15 new cases of psychosis per 100,000 person-years. Anecdotal reports thereafter suggested rates were higher than expected through these services.

Aims: (1) To delineate the incidence of psychosis in one epidemiologically-complete, rural and urban EIS over a six-year period. (2) Determine whether these rates were comparable to rates in more urban UK settings. (3) Determine whether rates varied by age, sex and ethnicity.

Methods: Population-based study of all clinically relevant ICD-10 first episode psychosis [F10-39], in people aged 17-35 years detected through EIS for Cambridgeshire, CAMES, 2002-7. Denominator data were taken from mid-year census estimates. Crude and directly-standardised rates (for age, sex & ethnicity to the 2001 census English population) were compared with rates from AESOP and ELFEP studies. Poisson regression identified variation in rates by sociodemographic characteristics.

Results: We identified 285 cases over 569,921 person-years with a crude incidence of 50.0 per 100,000 person-years (95% CI: 44.5, 56.2). Rates were comparable with recent estimates from more urban UK settings, including London, Bristol and Nottingham. Rates in men were double those in women, declining with age for both sexes. After adjustment for age & sex, rates were elevated for people from black ethnic groups (IRR: 2.0; 95% CI: 1.1, 3.8).

Discussion: Rates of first-contact psychosis identified by EIS in our diverse, rural population were higher than originally predicted for EIS and greater than found in more urban settings from previous observational research. This has important implications for mental health service planning. Rates in black ethnic groups were elevated in our study, but to a lower extent than elsewhere.

doi:10.1016/j.schres.2010.02.1046
both altered medial temporal activation during a memory task and
state (ARMS). We first predicted, on the basis of previous studies,
people with prodromal signs of psychosis, who are at increased risk
illness. The aim of the present study was to examine the relationship
psychosis suggest that both hippocampal dysfunction and perturbed
investigated. Recent studies in subjects with prodromal signs of
inter-related, but their relationship in humans has yet to be
Independent evidence suggests that perturbed glutamatergic neuro-
memory impairments that are evident at the behavioural level.
structure and function of this region thought to underlie the
replicated finding in psychotic disorders, with alterations in both
Background: Medial temporal dysfunction is a robust and
women separately. Subsequent similar analyses were performed in men and
altered activations of regional glutamate levels. We then tested our main
methods: We used fMRI to examine medial temporal activation
during a verbal episodic memory task, and $^{1}$H-MRS to measure
regional glutamate levels in the left hippocampus and two
connected regions, anterior cingulate and left thalamus. Both
techniques were used to study a group of 22 individuals at risk of
psychosis and a matching group of 14 healthy volunteers.
results: Consistent with previous studies, at risk subjects showed
reduced activation relative to controls in the left parahippocampal gyrus
during verbal encoding ($p = 0.047$ FWE). ARMS subjects also showed
lower glutamate levels in the thalamus, although in this relatively small
sample, the glutamate reduction was at trend level ($p = 0.079$). There
were no significant group differences in activation during recognition, or
in medial temporal or cingulate glutamate levels. In the parahippocampal
region where we observed a between-group difference during
encoding, controls showed a positive correlation between activation and
left medial temporal glutamate levels ($r = 0.592$, $df = 12$, $p = 0.026$).
This relationship was absent in the ARMS group ($r = -0.318$, $df = 20$,
$p = n.s.$), and there was a significant difference between the respective
group correlation coefficients ($Z = 2.64$; $p < 0.01$).
Discussion: These results suggest that medial temporal dysfunction
in people with prodromal symptoms of psychosis is related to a
loss of the normal relationship with local glutamate levels.
While both hippocampal dysfunction and altered glutamate levels
have separately been reported in relation to psychosis, to our
knowledge, this is the first time a link between these two
abnormalities has been demonstrated in humans. Our results
suggest that medial temporal dysfunction in people at high risk
of psychosis is related to regional glutamate levels, however they
cannot reveal the direction of causality, nor whether the glutamate
nergic findings reflect activity in local pyramidal neurons, or in the
terminals of afferent projections from other regions or abnormalities
at a receptor level. Nevertheless, the changes we observed
predate the clinical expression of psychosis, and therefore suggest
that treatment using glutamatergic drugs at this stage has the
potential to impact on the subsequent development of psychosis.

doi:10.1016/j.schres.2010.02.1047

Poster 269
ALTERED MEDIAL TEMPORAL ACTIVATION RELATED TO LOCAL
GLUTAMATE IN SUBJECTS WITH PRODROMAL SIGNS
OF PSYCHOSIS

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Background: Medial temporal dysfunction is a robust and
replicated finding in psychotic disorders, with alterations in both
the structure and function of this region thought to underlie the
memory impairments that are evident at the behavioural level.
Independent evidence suggests that perturbed glutamatergic neuro-
transmission is one of the key neurochemical features of psychosis.
Animal models of psychosis propose that these two abnormalities are
inter-related, but their relationship in humans has yet to be
investigated. Recent studies in subjects with prodromal signs of
psychosis suggest that both hippocampal dysfunction and perturbed
glutamate function are evident before the clinical expression of
illness. The aim of the present study was to examine the relationship
between medial temporal and central glutamate dysfunction in
people with prodromal signs of psychosis, who are at increased risk
of developing the illness and defined as having an At Risk Mental
State (ARMS). We first predicted, on the basis of previous studies,
both altered medial temporal activation during a memory task and
alterations in regional glutamate levels. We then tested our main
hypothesis that altered medial temporal function would be signifi-
cantly related to glutamate levels.

Methods: We used fMRI to examine medial temporal activation
during a verbal episodic memory task, and $^{1}$H-MRS to measure
regional glutamate levels in the left hippocampus and two
connected regions, anterior cingulate and left thalamus. Both
techniques were used to study a group of 22 individuals at risk of
psychosis and a matching group of 14 healthy volunteers.

Results: Consistent with previous studies, at risk subjects showed
reduced activation relative to controls in the left parahippocampal gyrus
during verbal encoding ($p = 0.047$ FWE). ARMS subjects also showed
lower glutamate levels in the thalamus, although in this relatively small
sample, the glutamate reduction was at trend level ($p = 0.079$). There
were no significant group differences in activation during recognition, or
in medial temporal or cingulate glutamate levels. In the parahippocampal
region where we observed a between-group difference during
encoding, controls showed a positive correlation between activation and
left medial temporal glutamate levels ($r = 0.592$, $df = 12$, $p = 0.026$).
This relationship was absent in the ARMS group ($r = -0.318$, $df = 20$,
$p = n.s.$), and there was a significant difference between the respective
group correlation coefficients ($Z = 2.64$; $p < 0.01$).

Discussion: These results suggest that medial temporal dysfunction
in people with prodromal symptoms of psychosis is related to a
loss of the normal relationship with local glutamate levels.
While both hippocampal dysfunction and altered glutamate levels
have separately been reported in relation to psychosis, to our
knowledge, this is the first time a link between these two
abnormalities has been demonstrated in humans. Our results
suggest that medial temporal dysfunction in people at high risk
of psychosis is related to regional glutamate levels, however they
cannot reveal the direction of causality, nor whether the glutamate
nergic findings reflect activity in local pyramidal neurons, or in the
terminals of afferent projections from other regions or abnormalities
at a receptor level. Nevertheless, the changes we observed
predate the clinical expression of psychosis, and therefore suggest
that treatment using glutamatergic drugs at this stage has the
potential to impact on the subsequent development of psychosis.

doi:10.1016/j.schres.2010.02.1048

Poster 270
EXCESSIVE FOCAL BRAIN CHANGES IN SCHIZOPHRENIA:
DIFFERENT AGE TRAJECTORIES MEASURED WITH
LONGLITUDINAL MRI

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Background: The aim of this study is to investigate if (and how)
the excessive brain tissue loss in schizophrenia is dependent on age,
and if it is different from healthy brain aging.

Methods: Two Magnetic Resonance Imaging T1-weighted brain
scans were obtained with an interval of 5 years from 96 schizophrenia
patients (age 16-57 years) and 121 healthy controls (age 16-65 years).
In-house developed software was used to segment cerebral gray (GM)
and white matter (WM) from which the volumes were calculated.1
These segments were used as input for both a voxel-based (VBM) and
a cortical thickness (CORT) analysis (using software from Montreal
Neurological Institute: ANIMAL2 and CLASP3, respectively). For each
subject, change in GM volume, GM density in each voxel, and cortical
thickness in each vertex was calculated. Group difference in density

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EVIDENCE FOR ALTERED ASYMMETRY OF FRONTAL CORTEX T2 RELAXATION TIME IN PATIENTS AT CLINICAL HIGH-RISK FOR PSYCHOSIS

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Background: There are a number of studies which have identified baseline differences in the volume of various grey matter regions of the frontal lobe between ultra-high risk (UHR) individuals who go on to develop full threshold psychosis and those who do not. However, the exact nature of these differences is unclear, since normal size does not guarantee functionality, nor does absence necessarily indicate dysfunction. T2 relaxometry is a technique that may provide a more sensitive, though non-specific, measure of the neuropathological processes involved in psychosis.

Methods: We recruited 66 UHR participants and 29 controls, and scanned them using T2 relaxometry. T2 relaxation times were obtained from grey matter in the right and left anterior cingulate cortex, middle frontal gyrus and inferior frontal gyrus using a region of interest (ROI) approach. T2 relaxation data were compared using repeated-measures analyses of variance.

Results: No significant differences were found for the anterior cingulate or inferior frontal ROIs (p > 0.5). However, there was a significant group x hemisphere interaction (p = 0.05) for the middle frontal ROI. Post-hoc comparisons revealed this to be due to a reversal of the normal right > left asymmetry in the UHR group (p = 0.01). Sub-analysis by outcome (transition to psychosis) showed that this effect was roughly twice as great in the later psychotic group than the non-transitioned group.

Discussion: Although we did not find an overall increase in T2 in the UHR group, we did show altered asymmetry in the middle frontal gyrus, largely driven by increased T2 in the left hemisphere. This was more pronounced in those who later developed psychosis, and may indicate a neuropathological process involving increased edema, or a reversal of the normal pattern of naturally occurring cell apoptosis.

doi:10.1016/j.schres.2010.02.1049

Poster 272
CAN LOW-FREQUENCY RTMS REALLY RELIEVE MEDICATION-RESISTANT AUDITORY VERBAL HALLUCINATIONS? NEGATIVE RESULTS FROM A LARGE RCT

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Background: Auditory Verbal Hallucinations (AVH) are resistant to antipsychotic medication in 25% of patients with schizophrenia. Several studies have applied low-frequency repetitive Transcranial Magnetic Stimulation (rTMS) directed at the left temporo-parietal area (TP) for the treatment of AVH, but findings on efficacy are inconsistent. Furthermore, a large recent fMRI study indicated that the left TP is not a general focus of activation during the experience of AVH. The aims of this study were twofold: to investigate the effect of rTMS on AVH in a relatively large, double blind, randomized controlled sample, and to investigate if the efficacy of rTMS could be improved with fMRI-guided rTMS.

Methods: Sixty-two patients with medication-resistant AVH were randomized over 3 conditions: rTMS targeted at the area of maximal hallucinatory activity as demonstrated with individual fMRI scans, rTMS directed at the left TP and sham treatment. Repetitive TMS was applied during 15 sessions of 20 minutes each, at 1 Hertz and 90% of the individual motor threshold. The severity of AVH and other psychotic symptoms were monitored during treatment and 3 months follow-up, using the Auditory Hallucination Rating Scale (AHRS) and the positive items of the Positive and Negative Syndrome Scale (PANSS).

Results: Mean decrease in AVH severity was not significantly different between the groups (F(2.619, p = 0.54), neither was decrease in severity of psychosis (F(2.640, p = 0.21). Even when guided and non-guided rTMS were combined and compared to sham treatment, no significant differences in efficacy were observed (sum of the AHRS, F = 1.172, p = 0.29).

Discussion: Low-frequency rTMS directed at the area of maximal hallucinatory activity and rTMS directed at the left TP are no more effective in the treatment of medication-resistant AVH than sham treatment. It may be time for a change of paradigm, and for a search for other treatment regimens, such as high-frequency rTMS, to expand the psychiatric toolbox of treatment options for medication-resistant AVH.

doi:10.1016/j.schres.2010.02.1051

Poster 273
PREVALENCE OF DEPRESSIVE SYMPTOMS AND THE EFFECTIVENESS OF ANTIDEPRESSANTS IN ROUTINE CLINICAL PRACTICE OF SCHIZOPHRENIA

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Background: In a recent large-scale, multi-centre, randomised controlled sample, and to investigate if the efficacy of rTMS could be improved with fMRI-guided rTMS.

Methods: Sixty-two patients with medication-resistant AVH were randomized over 3 conditions: rTMS targeted at the area of maximal hallucinatory activity as demonstrated with individual fMRI scans, rTMS directed at the left TP and sham treatment. Repetitive TMS was applied during 15 sessions of 20 minutes each, at 1 Hertz and 90% of the individual motor threshold. The severity of AVH and other psychotic symptoms were monitored during treatment and 3 months follow-up, using the Auditory Hallucination Rating Scale (AHRS) and the positive items of the Positive and Negative Syndrome Scale (PANSS).

Results: Mean decrease in AVH severity was not significantly different between the groups (F(2.619, p = 0.54), neither was decrease in severity of psychosis (F(2.640, p = 0.21). Even when guided and non-guided rTMS were combined and compared to sham treatment, no significant differences in efficacy were observed (sum of the AHRS, F = 1.172, p = 0.29).

Discussion: Low-frequency rTMS directed at the area of maximal hallucinatory activity and rTMS directed at the left TP are no more effective in the treatment of medication-resistant AVH than sham treatment. It may be time for a change of paradigm, and for a search for other treatment regimens, such as high-frequency rTMS, to expand the psychiatric toolbox of treatment options for medication-resistant AVH.

doi:10.1016/j.schres.2010.02.1051
Background: The prevalence of clinical depression in patients with schizophrenia and related psychotic disorders is about 25%, while that of sub-syndromal depressive symptoms is even higher. Depressive symptoms in schizophrenia are associated with a higher risk for relapse and suicide. About one third of patients with psychotic disorders uses antidepressants, but little is known about the prescribing of antidepressants and course of depressive symptoms in routine clinical practice. The aim of the current study is to determine the prevalence of depressive symptoms in schizophrenia, to compare the characteristics of patients with and without depressive symptoms and to explore the effectiveness of antidepressant therapy in one year follow-up.

Methods: The study concerned patients with schizophrenia or related psychotic disorders in a circumscribed area in the Netherlands between January 2003 and April 2007. As part of routine clinical practice patients had yearly assessments of their physical and mental health, including a clinician-rated screening for depressive symptoms. Patients were included if they had a first (T₀) and second assessment (T₁) within an interval of about 12 months (±3 months).

Results: 230 patients were included, with a mean age of 38.3 years (SD 1.7) and a mean duration of illness of 11.7 years (SD 9.4); 132 (57%) were male and 175 (76%) suffered from schizophrenia. At T₀ depressive symptoms were prevalent among 44% (n = 102) of the patients. Patients with depressive symptoms had significantly more positive (p<0.01) and negative (p<0.05) symptoms than patients without depressive symptoms, but there was no difference in cognitive symptoms or extrapyramidal symptoms as well as in somatic health (e.g. BMI and blood pressure). Patients with depressive symptoms scored on average 10% lower on the Global Assessment of Functioning scale (p<0.001) than patients without depressive symptoms, reported a 12% lower quality of life (p<0.001) and had fewer daytime activities (p<0.001), without a significant difference in the frequency of contacts with family or friends. Furthermore, they were prescribed more medications (3.2 compared to 2.4 medicines) than patients without depressive symptoms (p<0.05). In total 40% (n = 92) used antidepressants (60% selective serotonin reuptake inhibitors, 24% tricyclic antidepressants and the remaining used other classes of antidepressants) while about half of them had depressive symptoms. Of the patients using antidepressants and having depressive symptoms at T₀, 68% (32/47) had persistent symptoms, the remaining patients had no symptoms at T₁. Of the 45 patients using antidepressants without having depressive symptoms at T₀, 22% (10/45) got depressive symptoms at T₁.

Discussion: In routine clinical practice the prevalence of depressive symptoms was high among patients with psychotic disorders. Patients with depressive symptoms suffered more frequently from positive and negative symptoms and had a lower quality of life. Antidepressants were frequently prescribed, but analysis of the course of depressive symptoms raised doubts about the effectiveness of the antidepressants as depressive symptoms often persisted and reoccurred. The monitoring and treatment of depressive symptoms in psychotic disorders require more attention in clinical practice.

doi:10.1016/j.schres.2010.02.1052