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The 2nd Schizophrenia International Research Society Conference, 10–14 April 2010, Florence, Italy: Summaries of oral sessions

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ABSTRACT

The 2nd Schizophrenia International Research Society Conference, was held in Florence, Italy, April 10–15, 2010. Student travel awardees served as rapporteurs of each oral session and focused their summaries on the most significant findings that emerged from each session and the discussions that followed. The following report is a composite of these reviews. It is hoped that it will provide an overview for those who were present, but could not participate in all sessions, and those who did not have the opportunity to attend, but who would be interested in an update on current investigations ongoing in the field of schizophrenia research.

1. Introduction

This was the 2nd international conference on schizophrenia research sponsored by the *Schizophrenia International Research Society*. The theme of this meeting was bridging the laboratory to the clinic. Four full days were devoted to 3 plenary sessions covering diagnostic and basic science issues, genetics and brain imaging. The new proposed DSM-V criteria for diagnoses on the schizophrenia-spectrum were highlighted and debated. There were several sessions discussing new advances in understanding the underlying brain characteristics of people who develop schizophrenia and an equal number of sessions on the new genetic technology that has rapidly emerged for finding causes of common disease. New treatments, both pharmacologic and non-pharmacological also have continued to be a focus so that ultimately the field is devoted to improving the quality of life for people with schizophrenia worldwide. Student travel awardees volunteered to serve as "rapporteurs" of oral sessions to summarize the major findings that were reported and the conclusions in

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discussions that followed. A similar report from the 1st international conference has previously been published (Abubaker et al., 2008).

2. Diagnosis and clinical characteristics

2.1. Plenary session—Anticipating DSM-V: new paradigms (reported by Hiroyuki Uchida)

DSM-V is scheduled for release in 2013 and thus a plenary session was held to discuss the major changes relevant to the diagnosis of schizophrenia and its related disorders. *Dr. William Carpenter*, chairperson of the psychosis working committee for the DSM-V emphasized the need for making changes in criteria and the classification of the following: a] subtypes of schizophrenia, b] catatonia, and c] schizoaffective disorder. Domains of pathology with dimensions representing critical aspects of psychopathology are being considered that address syndrome heterogeneity. Other factors, such as age of onset and whether bipolar disorders should be grouped with psychotic disorders or mood disorders will be considered as well. He added that the DSM-V would provide missing information, identify treatment targets, shift the research agenda, and provide new research targets. *Dr. Richard Keefe* discussed the role that cognitive function could play in diagnostic criteria for schizophrenia, but that there would a need for training for these assessments, and thus they may not be a practical DSM addition. Nevertheless, cognitive function is important for understanding functional status and outcome and to facilitate treatment planning. *Dr. Alex Hofner* reviewed the previous findings on social cognition in schizophrenia and concluded that it had a strong relationship to functional outcome and should be regarded as a core symptom of this illness. *Dr. Dieter Naber* emphasized that the quality of life and subjective well being are distinct and important outcome dimensions. *Dr. Kim Mueser* focused on the clinical relevance of work as an outcome measure, which can easily be measured. He also highlighted the advantage of performing regular prospective assessments of working status, compared to retrospective reports over time. *Dr. Eric Chen* emphasized the necessity of systematic assessment of the time course of illness (schizophrenia), not sufficiently addressed in DSM-IV.

2.2. DSM 5 debate (reported by Anna-Karin Neubeck)

This debate focused on the proposal from the DSM working group to include a Psychosis Risk Syndrome (PRS) in the DSM 5 (Carpenter, 2009; Woods et al., 2009; www.dsm5.org/Proposed Revision, 2010-04-08). The panelists of the DSM 5 debate were; *Drs. Scott Woods*, *William Carpenter*, *Barbara Cornblatt*, *Alison Yung*, *Frauke Schultze-Lutter*, and *Stephan Ruhrmann*; *Dr. John Kane* was moderator. They represented three different points of view. Drs. Woods and Carpenter were in favor of including a Psychosis Risk Syndrome; Drs. Cornblatt and Yung were both against; while Drs. Ruhrmann and Schultze-Lutter suggested a new diagnostic concept, a psychosis spectrum disorder.

Arguments in favor of the proposal were that young people at risk for later manifestation of a psychotic disorder can be identified (www.dsm5.org/Proposed Revision, 2010-04-08) and that establishing this category will facilitate early intervention that may have long lasting benefit not achievable with later therapeutic interventions. However, some critical issues were raised that include the question of sensitivity and specificity of this separate category and issues related to stigma and potential harm of possible unnecessary treatment. Dr. Carpenter, stressed that it is necessary to include an at-risk syndrome in order to identify persons who do suffer and are in need of help. He argued that behaviors in an 'at-risk state' are stigmatizing in themselves, and even more stigmatizing than a label. Carpenter argued that it would be better to treat the individual and eliminate the odd behaviors. Dr. Woods further emphasized that the research criteria for these patients are reliable and valid (Woods et al., 2009) and those persons who meet proposed DSM-V clinical criteria are symptomatic, functionally impaired, treatment-seeking, and cognitively impaired. This current clinical state should be sufficient for inclusion of the disorder in DSM-V5, since no DSM-IV disorder accurately describes these individuals. Both Drs. Cornblatt and Yung argued against the proposal. Dr. Cornblatt expressed concern that potential negative consequences will outweigh the benefits given uncertainties that still characterize the current prodromal concept. Three main difficulties were highlighted: the high number of false positives, the lack of proven effective treatments and the stigma associated with the at-risk label. False positive identifications are shown to exceed 50% in the large majority of previous prodromal studies. False positive identifications are likely to increase when introduced into community practice and therefore must be considered before a final decision is made for inclusion. Currently, even in experienced research centers, accurate case identification requires training and consensus, procedures difficult to implement in a community setting. There is also a lack of clarity of the boundaries between the prodromal state of illness and the "normal" range of behaviors. Dr. Yung countered Carpenters' argument stating that such young people she sees in the clinic do not have stigmatizing behaviors. Instead, they are coming to the clinic before odd behaviors begin. She rather emphasized that being at risk for psychosis is potentially stigmatizing, especially if "risk" is treated as a "disorder". According to Dr. Yung one could envisage the scenario whereby schools screen students for unusual experiences and thus more and more people will be "caught in the net" even though a majority will not be at risk. She added that there is also an actual risk that people identified as in a prodromal state would be treated with antipsychotics, with further risk of side effects and stigma. Dr. Yung noted that young people with the at-risk syndrome do need help for current problems, but emphasized that this does not justify including a heterogeneous group with unproven validity and reliability in the DSM-V. A further issue discussed by Dr. Yung is that of what she called "diagnostic creep". By this she refers to the situation in which the threshold for a diagnosis gradually changes in response to clinical practice, political lobbying and other social forces. "It is a particular problem when the boundaries of the syndrome or disorder are ill defined or open to interpretation. For example, people on the border between the risk syndrome and "normality" (that is, just below the threshold) may be labeled as having the syndrome in order to access treatment

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and gain insurance coverage". Alternatively, someone previously diagnosed with schizophreniform or delusional disorder may be given a diagnosis of risk syndrome to reduce stigma while still enabling the prescription of antipsychotics. Thus what began as a rather small group, for which there was some evidence base for suspecting a high risk of a psychotic disorder, could potentially become a large group, the vast majority of whom would not be at risk. Drs. Stephan Ruhrmann and Frauke Schultze-Lutter presented a third view providing a new concept, a psychosis spectrum disorder, using the ICD 10 diagnosis of schizotypal disorder as a model (Ruhrmann et al., 2010). They suggested that spectrum disorder is a broader approach that uses cognitive basic symptoms not covered by the current risk class criteria proposed by others and these are important for prediction and diagnosis.

2.3. The many faces of psychosis (reported by Hsiao Piau Ng)

Understanding the varied presentation of the many types of psychotic disorders is still a major challenge. The approaches utilized to clarify their complex nature were presented by leading researchers in the field at this symposium.

Dr. Inez Myin-Germeys, from Maastricht University, presented findings from a study investigating the expression of positive and negative symptoms. Key issues raised were whether these symptoms were expressed daily and whether there are differences in the patterns of expression based on PANSS scores. Participants were asked to stop at certain times and take notes about their experience and feelings. This method put participants in "real-life" scenarios and helped to understand the relationship of mood to symptoms within the context of daily life. For positive symptom expression, paranoia was examined and noted to differ in intensity at various times of day. They observed that the onset of paranoia was associated with both an increase in anxiety and a decrease in self-esteem. With regard to negative symptoms, associations were with emotional disturbance, negative life experience and lack of hedonic capacity. It was also shown that the low negative symptom group, in contrast to the high negative symptom group, showed deviances in emotional processing patterns and had increased reactivity to the surrounding environment.

Dr. Peter Buckley, from Medical College of Georgia, focused on brain-derived neurotrophic factors (BDNF) as a neurobiological marker for vulnerability to psychosis. A number of previous BDNF studies have reported decreased BDNF levels in post-mortem hippocampus and decreased BDNF mRNA expression in the prefrontal cortex. He noted that clinical studies showing reduced peripheral BDNF were conducted on chronic and first-episode patients, but no studies reported to date involved prodromal subjects. The brain receptor for BDNF, TrkB has also been studied in post-mortem dorsolateral prefrontal cortex. All these data taken together suggest that BDNF is of pathological relevance as a biomarker for schizophrenia.

Dr. Charles Schulz, University of Minnesota, presented data from multi-modality brain imaging studies, including diffusion tensor imaging (DTI), spectroscopy and functional imaging (fMRI) to investigate the connectivity, chemistry and functioning of the human brain respectively. A multi-modality imaging pipeline was set up to investigate their relationship. Patients with first-episode psychosis, chronic schizophrenia and matched controls were recruited and underwent MRI, which included a structural scan, proton echo planar spectroscopic imaging (PEPSI), DTI and resting fMRI. Theberge et al. (2003) suggested that since previous studies have found higher than normal levels of glutamine in the left anterior cingulate of patients who were never-medicated, decreased levels of these metabolites in chronic patients could be related to neurodegeneration or the effects of chronic medication. On the other hand, Tibbo et al. (2004) found glutamate/glutamine abnormalities in a group of subjects at high genetic risk for schizophrenia, supporting both glutamate dysfunction prior to illness development and a neurodevelopmental hypothesis for schizophrenia. Segall et al. (2009) demonstrated in a multi-site study a consistent pattern of reduced relative gray matter concentration in patients with schizophrenia-spectrum disorders observed in the temporal lobes, anterior cingulate and frontal regions. In a structural MRI (sMRI) and fMRI study, Michael et al. (2010) introduced three methods to identify correlations between sMRI and fMRI voxels within the whole brain, and observed that the linkage between gray matter and functional activation is stronger in healthy controls than in schizophrenia. In a combined sMRI and DTI study by Kendi et al. (2008), it was noted that the early stages of schizophrenia are associated with a decrease in fornix volume without microstructural white matter changes and it was suggested that the volume differences may reflect an early insult to neighboring brain regions that could decrease the number of efferent fibers without necessarily disrupting fiber integrity. It is hoped that these multi-modality studies will lead to an understanding of significance of progressive brain changes over the course of illness.

2.4. Einheitspsychose? Comparing schizophrenia and bipolar disorder: genes, brain and behavior (reported by Cali Bartholomeusz)

This symposium, chaired by *Drs. Melissa Green* (University of New South Wales, Australia) and *James van Os* (Maastricht University, Netherlands), challenged both the DSM-IV and ICD-10 diagnostic distinctions between schizophrenia and bipolar disorder. Speakers re-visited the Kraepelin hypothesis of a 'unitary psychosis' (or einheitspsychose), by focusing on commonalities and differences in developmental trajectories, symptomatology, brain abnormalities and genetic risk between these two disorders.

Dr. van Os reviewed the hypothesis put forth by Murray et al. (2004), proposing that the difference between the two disorders was that schizophrenia patients tended to have more obvious brain structural and neuropsychological abnormalities than individuals with bipolar disorder. Both share similar age of onset/gender interaction, prevalence: incidence ratios and symptomatology (albeit schizophrenia has more severe negative symptoms and cognitive impairments and less severe affective symptoms). Given there is substantial symptom overlap, 'points of rarity', such as copy number variants (CNVs; where the burden of CNVs have recently been shown to differ significantly between schizophrenia and

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bipolar patients; Grozeva et al., 2010), may prove more useful for distinguishing the two disorders. Using cognitive impairment in relatives as a measure of genetic risk, stronger genetic risk exists for schizophrenia than for bipolar disorder (Snitz et al., 2006; Arts et al., 2008). With respect to environmental factors, data suggests that cannabis use increases the risk of co-morbid mania and psychosis, as does growing up in an urban, rather than rural environment. However, urbanicity appears to be a risk factor specific to schizophrenia and does not independently increase the risk of mania, unlike migration. Further research is needed to determine whether cannabis use also increases the risk for mania.

The 'symptom domains' model, posed by Krabbendam et al. (2004) suggests that psychometric risk states for schizophrenia (i.e. paranoia, hallucinations, and first-rank delusions) and bipolar disorder (i.e. depression, somatic symptoms, and mania) exist within the healthy population. Dr. van Os highlighted that these domains are intercorrelated and reminded the audience of 'Berkson's Bias' (Maric et al., 2004), stating that the morbidity concentration of overlapping symptoms within the clinic will be higher than in the general population. He then presented new data suggesting that individuals who experience multiple symptom dimensions (specifically positive, negative and mania symptoms) will have a higher incidence of care. In summary, bipolar disorder and schizophrenia do co-occur, but this does not imply that they are the same disorder.

Dr. Alex Fornito (University of Cambridge, UK/University of Melbourne, Australia) presented data demonstrating common and distinct neuroanatomical changes across the course of illness for schizophrenia and affective psychoses. Ultra-high risk for psychosis patients (who later convert to full-blown psychosis), demonstrate enlarged pituitary volumes at baseline and the enlargement tended to be more pronounced for patients diagnosed with affective psychoses (Garner et al., 2005; Pariante et al., 2005). Data further suggests that this abnormality persists throughout the course of the illness in bipolar disorder(Takahashi et al., 2009c) but that volumes return to normal in chronic psychosis (Pariante et al., 2004). Amygdala enlargement was observed in first-episode affective psychoses, but not first-episode schizophrenia (Velakoulis et al., 2006). The paralimbic region of the anterior cingulate cortex (ACC) was found to be reduced bilaterally in first-episode schizophrenia (ACC; Fornito et al., 2008b). In contrast, male (but not female) bipolar patients showed right-sided increases in the subcallosal limbic ACC (Fornito et al., 2009b). A longitudinal study by Koo et al. (2008) also found differences in cingulate morphology, where only the subgenual cingulate was excessively reduced over time in bipolar patients, while all sub-regions were reduced in schizophrenia. To summarize, structural brain changes are significantly more extensive in schizophrenia than bipolar disorder. In schizophrenia, medial and lateral prefrontal cortex (PFC) reductions typically appear early during adolescence (at-risk state) and often progress to the point of widespread frontal, temporal, parietal and subcortical (especially hippocampal) reductions throughout early adulthood and into the chronic stage of illness. Conversely, in bipolar patients gray matter enlargements have been observed in the medial prefrontal cortex in young patients during the 'at-risk' phase, while this and other frontal regions are reduced during the later chronic phase of illness. Dr. Fornito concluded by highlighting the need for improvement in phenotypic and longitudinal characterization, and stated that differences between the two disorders may even manifest perinatally.

Dr. Andrew McIntosh (University of Edinburgh, UK), presented data from three functional magnetic resonance imaging studies that directly compared activation patterns between the two disorders as well as healthy controls. The Hayling Sentence Completion Task revealed significant activation differences between remitted schizophrenia and bipolar groups and controls. Specifically, contrasts of sentence completion versus rest showed schizophrenia patients to display decreased and increased mean activation in the left dorsolateral prefrontal cortex (DLPFC) and right insular respectively. This pattern was the opposite for the bipolar group. The face-name pairs task conversely showed decreased mean activation in the left DLPFC (i.e. early encoding and early retrieval phase) for bipolar compared with schizophrenia patients. The left dorsomedial prefrontal cortex (DMPFC) displayed greater activation for the schizophrenia group compared to bipolar, while right hippocampal activation was lower in schizophrenia compared to bipolar. The third task was an emotional memory task with images from the International Affective Picture System (36 neutral scenes and 36 emotionally positive scenes). Contrasts of emotional versus neutral scenes resulted in significant differences in mean hippocampal cluster activation between patient groups; control group activation was between the two clinical samples. Discriminant function analysis showed that the Hayling Task correctly identified patients 80% of the time while the face-name pairs/emotional memory tasks accurately identified patients 80–96% of the time. Thus these data do not support the concept that the two disorders are at opposite ends of a continuum. The findings suggest that differing neural bases underlie the two disorders, whereas a continuum would imply that involvement of the same networks existed.

Dr. Katherine Burdick (The Zucker Hillside Hospital, NY), presented neurocognitive genetic data linking the two disorders. Both disorders have a similar predisposition profile, where approximately the same percentage of variance explains unique and shared genetic effects as well as unique and shared environmental effects (Lichtenstein et al., 2009). The finding that susceptibility genes overlap between disorders (e.g. risk allele at CACNA1C, DTNBP1), which have also been linked to cognitive processes such as verbal fluency, supports the exploration of cognitive functioning as having possible endophenotypes common to both disorders. Dr. Burdick presented a model of cognitive impairment where the gradient of neuropathology is high at one end of the continuum and declines while at the same time the gradient of affective pathology is small and increases along the continuum. The clinical syndromes placed along this continuum (in order of most severe cognitive impairment) were mental retardation, autism, schizophrenia, schizoaffective disorder and BD/unipolar depression. Dr. Burdick proposed a small subgroup of bipolar patients with severe genetic-driven cognitive deficits falling between schizophrenia and affective disorder within this model.

The discussion was led by *Dr. Ulrich Schall* (The University of Newcastle, Australia). Dr. Burdick noted that her main goal

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was to highlight the importance of using intermediate phenotypes related to brain function, to better understand the inherent risk for and etiology of these two disorders. A comment that genes are purportedly coding for symptoms rather than one disorder or the other, brought focus back to Dr. van Os's presentation highlighting a 6-dimensional approach and supporting the abandonment of DSM-IV categorisation. Dr. Green commented that future research should "…..consider pooled samples of patients with psychotic and mood disorders, paying careful attention to subphenotypes defined by clinical, cognitive, and/or neurophysiological data, in order to delineate the homogenous targets for genetic association that may ultimately span or differentiate the traditional Kraepelinian divide". In conclusion, while there are correlated genetic liabilities and similar symptom profiles for both disorders, the differences in brain structural and neuropsychological abnormalities, which often manifest early on, are significant and do not support a continuum.

2.5. Psychotic symptoms in the community: where are we today? (Reported by Yousri El Kissi)

Population-based studies indicate that psychotic-like experiences (PLE) are present in up to 30% of apparently healthy individuals. Understanding the relationship (or lack of it) between these experiences and mental illness is crucial.

Dr. Mari Dominguez reported evidence from clinical patient populations indicating that affective dysregulation is strongly associated with reality distortion which characterizes psychotic symptoms. Attenuated forms of psychotic symptoms are found in up to 10% of the general population, with difficulty finding a cutting off from normality. Many authors assumed that these attenuated symptoms are predicting later development of psychosis (Poulton et al., 2000; Weiser et al., 2009) depending on demographic factors, environment risk factors, cognitive and motor deficits, family co-clustering and gene risk (Van Os et al., 2000; Henquet et al., 2005; Krabbendam et al., 2005). The relationship between psychotic experiences and affective symptoms was examined in a German prospective cohort community study (Van Rossum et al., 2009). A cohort of 2524 adolescents and young adults aged 14–24 years at baseline drawn from the early development stage of psychopathology study (Lieb et al., 2000) was assessed for psychotic experiences and hypomanic and depressive symptoms at two time points: 3.5 and 10 years from baseline. Most psychotic experiences occurred in a context of affective dysregulation and persistence of psychotic experiences over time was more likely to occur with a greater level of affective symptoms. In conclusion, affective and non-affective psychotic symptoms are correlated dimensions at the community level. In addition, affective dysregulation has a direct impact on the persistence and clinical relevance of psychotic experiences.

Dr. Mary Cannon reported on a study assessing the prevalence of psychotic and prodromal symptoms among adolescents in the community. As psychotic symptoms in the general population and the prodromal syndrome or "at-risk metal state" are both known to index an increased risk for later psychotic illness, the relationship between them was examined in 334 school children aged 11–13, using a 7-item psychosis screen. For all adolescents who scored 2 or more and for a random sample of those who scores less than 2 ($n = 129$), K-SADS interview was performed. Twenty-nine percent reported strong psychotic type experiences, 25% reported weak psychotic type experiences and 46.5% reported non-psychotic type experiences. Adolescents with strong psychotic type experiences were later assessed using the Schedule for Interview for Psychotic Symptoms (SIPS) and the scale of prodromal symptoms (SOPS). Nine of them (53%) fulfilled criteria for the prodromal risk syndrome. In conclusion, the prodromal risk syndrome can be diagnosed in adolescents from community or school settings. Up to half of adolescents reporting strong psychotic type experiences fulfilled criteria for the prodromal risk syndrome.

Dr. Marc Weiser provided evidence that psychotic experiences in non-ill people signal risk for mental illness. He reported on a longitudinal cohort study with outcome assessment, drawn from an Israeli national hospitalization case registry. A random stratified sample of 4914 community dwellers aged 25–34 screened in the 1980s were examined after a mean follow-up of 24 years. Twenty-five percent of them reported at least one psychotic experience. None of them had psychotic disorder as diagnosed by a psychiatrist's interview, but they had higher risk for later psychiatric hospitalizations and non-psychotic disorders, such as depression and anxiety.

Dr. John McGrath examined the prevalence of psychotic-like experiences in relationship to depression and anxiety in adolescents. He reported results from a community sample ($n = 8841$) drawn from the University of Queensland study of pregnancy (Varghese et al., 2009). Delusional-like experiences were assessed with the Peters Delusional Inventory (PDI). All subjects were asked about the presence of mental disorders in first-degree relatives and screened for lifetime individual diagnoses of major depression, anxiety disorder, substance use/abuse and psychotic disorders. Having a lifetime diagnosis of major depression or anxiety disorder was associated with higher PDI total scores and with any hallucination or delusion. Psychotic symptoms were also associated with family history of depression and anxiety. Psychotic-like experiences are thus not continuous with psychotic disorders, but are associated with a range of common mental disorders.

Dr. Shatij Kapur summarized the session by asking why there is so considerable research focus on psychotic symptoms in the community. The first explanation he gave is to better understand schizophrenia (epidemiology, demography, and biology), without medication interference. The second explanation is for prevention if the predictive value and specificity of psychotic-like experiences can be determined. Thirdly, people with psychotic symptoms in the community may be ill and may not be well functioning, although not in treatment.

2.6. Movement disorders should be a criterion for schizophrenia in DSM-V (reported by Renan P. Souza)

Dr. Diederik Tenback (Maastricht University Medical Center) presented evidence to support the inclusion of movement disorders as a criterion for schizophrenia. Movement disorders (e.g. dyskinesia and Parkinsonism) are often

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present in siblings of schizophrenia subjects (Koning et al., 2010). Further, antipsychotic-naïve schizophrenia subjects can exhibit movement disorders, although the prevalence is much higher in subjects who have received antipsychotics, particularly first-generation antipsychotics. Dr. Tenback hypothesized that movement disorders in schizophrenia subjects could be associated with a model of gradual supersensitivity and the severity of the movements and illness course could then be associated with a pandopaminergic sensitivity.

Dr. Bakker (Maastricht University Medical Center) outlined criteria to classify a trait as part of the illness spectrum: heritability, co-segregation within families and biological and clinical plausibility. Previous findings have shown a familial occurrence of tardive dyskinesia (Koning et al., 2010) and there is a biological basis for these movement disorders (i.e. Pappa and Dazzan, 2009). He reported results from a genetic study indicating significant associations of the brain-derived neurotrophic factor and dopamine DRD2 genes with dyskinesia; the PPP1R1B and DRD2 genes with Parkinsonism; and the serotonin HTR2A receptor gene with akathisia.

Dr. Jeroen Koning (Maastricht University Medical Center) presented an innovative method to assess movement disorders. Most of the research in movement disorders in schizophrenia used clinical rating scales to assess these symptoms. The most used scales are the Abnormal Involuntary Movement Scale (AIMS) and the Unified Parkinson's Disease Rating Scale (UPRDS). These scales are not sensitive to the measurement of subtle movements and their reliability and sensitivity depend heavily on the experience and subjectivity of the rater. To evaluate this problem, Dr. Koning assessed movement disorder symptoms in non-psychotic siblings of schizophrenia subjects and controls subjects using both scales (AIMS and UPDRS) and mechanical measurements. His results clearly showed that while no subject presented Parkinsonism assessed using UPDRS, 30% of the siblings and 2% of the control subjects showed movement disorder symptoms assessed by mechanical measurements. This indicates that the assessment of movement disorders may be more sensitive when performed using mechanical instruments instead of clinical rating scales.

Dr. Peter van Harten showed that movement disorders are common in schizophrenia, having been described over 100 years ago and agreed that they should be a DSM-V criterion. Moreover, he suggested that movement disorders should be considered in prodromal symptom scales. However, it is necessary to differentiate these from drug-induced dyskinesias.

2.7. Schizophrenia and homelessness (reported by Gul A. Jabbar)

Homelessness remains one of the least understood and most challenging of the service delivery problems in mental health today (Gonzalez and Rosenheck, 2002; McGray, 2004). This session included four speakers who discussed different aspects of homelessness.

Dr. Robert Rosenheck (Yale Medical School, Connecticut, USA) spoke on correlates of past homelessness nationally in the U.S, focusing on mental illness and substance abuse. He explored how personal risk factors such as socio-demographic, economic, and health characteristics, are likely to explain why some individuals are at greater risk for homelessness than others. Data from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) was utilized to investigate the association of mental illness and substance abuse with past homelessness. Diagnostic categories were created from the self reported data from the Alcohol Use Disorder and Associated Disabilities Interview Schedule DSM-IV (AUDADIS-IV). For schizophrenia, subjects indicated whether or not a health professional had ever given them a diagnosis of schizophrenia, or told them that they had a psychotic illness, or a psychotic episode. Multivariate analyses indicated that being male, cohabitating or having been born outside the US approximately doubled the odds that an individual had experienced past homelessness. Additionally, the most prominent independent risk factors for past homelessness were the diagnoses: schizophrenia (odds 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). This study emphasized the importance for homeless individuals to have access to mental illness and substance abuse treatment facilities.

Dr. Francesco Amaddeo (University of Verona, Verona, Italy) spoke on socio-economic status (SES) and use of psychiatric services by people suffering from schizophrenia. SES is a complex concept relating to social position, occupational status, educational attainment, income, wealth and standard of living with several ways of measuring it. The study used service data from the South-Verona psychiatric case register and the 1991 Italian Census to create an ecological SES index. The Italian Census was measured in the Census Block (CB) which is the smallest spatial unit of analysis. A validated composite index of SES was calculated and grouped into 4 categories for each CB ranging from SES-I-affluent to SES-IV-deprived. Amaddeo found that people living in the more deprived areas were making greater use of local mental health services compared to those individuals living in more affluent areas. His second study aimed to see if previous psychiatric history and SES predicted the cost of patients' care. The sample, consisting of 4420 patients, was divided into four groups: first-ever, ongoing episode, new episode after 90–1095 days and new episode after 1096 days. Cost of care was calculated by merging individual patients' service utilization data with unit cost estimates. Patients' postal addresses were geo coded and each patient was linked to a specific SES score through their own CB. Patients diagnosed with schizophrenia (841; 19%) were the highest service users, and the effect of SES on service use was significant for patients at a new episode after a period of no care >3 months. It was concluded that this SES score may be used as a factor for creating specific polices for homeless people with psychotic disorders.

Founder and CEO of Pathway Housing *Dr. Sam Tsemberis* (Columbia University, New York, USA) spoke on Pathways' Housing and Homelessness. Pathways' Housing serves people who are mentally ill, it challenges their assumptions and beliefs of what they are capable and incapable of doing. The four essential ingredients of Pathways discussed were the consumer choice philosophy, separation of housing and services, recovery oriented services and community-based work. Two models of permanent supportive housing, including a range of types, such as clustered site housing, mixed income developments and

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independent scattered apartments, were discussed. Separation housing and services (housing not in "special" housing complexes) avoids stigma and integrates individuals into the community. Based on Assertive Community Treatment (ACT), Pathway provides individuals with an offsite clinical team and even if individuals need to relocate into another housing site, they don't lose the relationship with their clinical team. This is unlike standard care programs that emphasize treatment first, where as Pathways does not require treatment compliance or abstinence from drugs and/or alcohol. To support this, Padgett et al. (2006) found that dual diagnosed adults can remain stably housed without decreasing their substance use. Additionally, this program has been found effective in ending homelessness for those labeled "treatment resistant" by providers. Tsemberis emphasized the relationship between choice and psychiatric symptoms in that if one follows the program assignments it will lead to personal mastery and in turn leads to reduction of their psychiatric symptoms. Identified in numerous research studies, Pathways is successfully growing throughout the United States, Canada and Europe.

Dr. Jonathan Burns (Nelson Mandela School of Medicine, South Africa) focused on the relationship between poverty, inequality, homelessness and psychosis in South Africa (SA). There is very little data on homelessness and no data on mental illness in the homeless population in SA. Burns suspected this is because of a significant increase in homelessness. Out of the 45 million population of SA, approximately 500,000 people (>80% male adults and children) are homeless with no shelter and live on the streets (Kok et al., 2010) possibly due to political and social factors such as urban migration and landlessness (Cross et al., 2010). The similarities between the risk factors for homelessness and psychosis, such as poverty and inequality, unemployment, HIV-AIDS, migration, violence, and substance abuse were also discussed. Approximately 40% South Africans live below the poverty line (+/−$75 a month) and 37% of adults are unemployed. Regarding violence and trauma, the homicide rate is 64.8/100,000 in SA and the injury death rate is twice the global average. There is also an increase of rape and sexual trauma, it is estimated that one third of women are victims of sexual trauma and the annual reported rapes are 117/100,000. HIV-AIDS is another factor, as 0.7% of the global population and 17% of the global burden of HIV infection are in SA. Eighty percent of the world's 14 million children orphaned due to AIDS live in SA. The consequences for these orphans are poverty and malnutrition along with foster-care or even homelessness. Thus, Burns lists as the multiple risk factors for homelessness as HIV/AIDS, violence/trauma, migration, poverty and being orphaned. However, there is very little data on homelessness and psychosis. Burns suggested that political, economic and social intervention strategies need to be implemented in SA in order to address these multiple inter-linked factors.

3. Cognition

3.1. Improving neurocognition in schizophrenia: reports from NIMH TURNS and MATRICS-CT (reported by Lisa Buchy)

The focus of this symposium was drug development of cognition-enhancing drugs for schizophrenia. Cognitive abnormalities are a core feature of schizophrenia. Cognitive dysfunction can be observed in early childhood and in non-affected family members of people with schizophrenia. They are a major determinant of functional outcome. First-generation antipsychotics have a small, limited effect for cognitive function. Second-generation antipsychotics, while having less D2-related neurotoxic effects, may have other pharmacologic properties that adversely affect cognitive function and offer little advantage over first-generation agents. Despite adequate antipsychotic treatment, people with schizophrenia continue to exhibit marked cognitive impairments. Adjunctive medications may offer an alternative approach to enhancing cognition in schizophrenia.

Dr. Donald Goff (Boston, MA) discussed TURNS (Treatment Units for Research on Neurocognition in Schizophrenia), a program that was established to identify compounds with the potential to enhance cognition in schizophrenia. He started by introducing MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia), the "tool" developed for use in TURNS. Several obstacles hamper the development of cognitive enhancing agents in schizophrenia. These included the lack of consensus regarding cognitive targets, ambiguity in trial design and a lack of path to FDA approval. This program successfully developed the MATRICS Consensus Cognitive Battery for assessment of cognition in schizophrenia, provided guidelines for trial design for cognitive enhancing agents and identified potential psychopharmacologic targets. Dr. Goff then discussed the evolution of MATRICS into TURNS, an NIMH funded study with a mission to identify compounds with potential efficacy for cognitive enhancement in schizophrenia as assessed through multi-site clinical trials. He outlined the organizational structure of TURNS, the investigators, and the seven participating USA sites each with pharmacologists and neuropsychologists as Co-PIs. The group selected compounds based on drug efficacy, pharmacology, safety/tolerability, innovation and pharmacokinetics. Of the initial 57 that were nominated, 17 were accepted and a final 6 were pursued formally. These 6 are: (1) Org 24448, a positive allosteric modulator of the AMPA glutamatergic receptor. Org 24448 provided some positive effects on cognition in animal studies and was shown to preferentially increase mRNA levels in the rat cortex in a dose-dependent manner. However, prior to the clinical trial a toxicology concern arose, and the compound was withdrawn from further study. (2) Ispronicline TC 1734, a partial agonist of the α4 and β2 nicotinic receptors. This compound showed efficacy in animal models on several variables. Importantly, TC 1734 was shown to ameliorate age associated cognitive impairment and mild cognitive impairment in human trials. This compound was eventually licensed to Astra Zeneca and had most recently demonstrated high efficacy in a phase II trial in ADHD. (3) The D1 agonist, DAR 0100 (dihydrexadine): DAR 0100 demonstrated high tolerability and was associated with enhanced prefrontal cortical perfusion; however, no effects on cognition were observed. (4) AV965, an agonist for 5HT1, was initially pursued but ultimately aborted due to insufficient funds. (5) MK-0777, a $GABA_A$ α2/α3 partial agonist, and (6) the neuroprotective protein AL108 NAP.

Dr. Daniel Javitt (Orangeburg, NY) presented a TURNS study of the effects of intranasal AL-108 (Davunetide) on neurocognition and functional outcome in schizophrenia.

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Davunetide is an intranasal drug product containing NAP, an 8 amino acid peptide fragment of Activity-Dependent Neuroprotective Protein (ADNP). This study was motivated by work in people with amnestic mild cognitive impairment, in which Davunetide was shown to enhance visual delayed match-to-sample task performance. The schizophrenia study was a 12-week double-blind randomized controlled clinical trial with parallel group assignment in three arms, each with 20 patients: Placebo, 5 mg and 30 mg AL-108. Patients were chronic and stable with controlled positive symptoms. The primary outcome measure was neurocognition as measured by MATRICS and the secondary outcome measure was functional outcome assessed with the UCSD Performance-based Skills Assessment (UPSA) test, and these were administered at baseline, 6 weeks and 12 weeks. A significant test–retest effect was observed in total scores for the placebo group between the 6 and 12 week assessments. Improvement in the 5 mg and 30 mg groups was observed at week 12, but this was a small effect size ($d = 0.21$). Considering the cognitive domains separately, the 30 mg group improved visual learning, but had worse verbal learning relative to the other groups. A significant treatment effect emerged in UPSA scores in the 30 mg group, though this may be due to poorer baseline performance. The drug demonstrated no safety concerns and was well tolerated.

Dr. Javitt also discussed a separate study that examined the effect of Davunetide on neuronal integrity in the dorsolateral prefrontal cortex of 11 patients with schizophrenia using magnetic resonance spectroscopy. The dependent measure was the NAA/Cr ratio; NAA is a marker of neuronal integrity and Cr is related to energy metabolism. The findings suggested a beneficial effect of Davunetide and he thus concluded that compounds developed for treatment of Alzheimer's disease, like Davunetide, may be relevant to schizophrenia.

Dr. Robert Buchanan (Baltimore, MD) discussed another TURNS study which examined MK-0777. He began by discussing GABA as the primary central nervous system inhibitory neurotransmitter, commenting about its importance for the regulation of prefrontal cortical function, including working memory via the dorsolateral prefrontal cortex. GABAergic chandelier interneurons synchronize pyramidal cell activity and inhibit their output through $GABA_A$ $\alpha 2$ receptor activation. MK-0777 is a $GABA_A$ $\alpha 2/\alpha 3$ partial agonist, with no activity at $\alpha 1$ or $\alpha 5$ subunits and no known activity at other receptors. This compound has been shown to enhance delayed memory in schizophrenia when compared to placebo, and improve performance on n-back reaction time, and continuous performance test scores (Lewis et al., 2008). The TURNS study of MK-0777 was a double-blind, randomized controlled clinical trial with three treatment arms: Placebo, MK-0777 3 mg BID and MK-0777 8 mg BID. Participants in the study were schizophrenia patients on stable doses of second generation antipsychotics. The dependent measures of interest were scores on the MATRICS battery, UPSA and Schizophrenia Cognition Rating Scale (SCoRS). One hundred nine patients participated. No significant beneficial effects of MK-0777 were observed on total MATRICS scores or other measures used. The drug was well tolerated, but was associated with an ocular safety concern. In summary, neither low nor high doses of MK-0777 improve cognition in people with schizophrenia. MK-0777 is a relatively weak partial agonist, and a more selective agent with greater intrinsic activity at the $GABA_A$ $\alpha 2$ site may be more promising.

Dr. Michael Green (Los Angeles, CA) spoke about the validation of intermediate (co-primary) measures for clinical trials of cognition-enhancing drugs for schizophrenia. In order to receive FDA approval, a neurocognitive drug for schizophrenia must improve cognition and functioning on a co-primary measure. The present Validation of Intermediate Measures (VIM) study conducted by MATRICS-CT was designed to assess potential intermediate measures. A RAND panel was responsible for the selection of the intermediate measures. Three performance-based measures were selected: full and short versions of the Test of Adaptive Behavior in Schizophrenia (TABS), and the UPSA and the Independent Living Scale (ILS). In addition, Cognitive Assessment Interview (CAI) and Clinical Global Impression (CGI) interview measures were included. In the study, stabilized patients with schizophrenia across 4 sites were assessed at baseline and after 4 weeks on co-primary measures selected by the RAND panel. The conclusions drawn from this study were that the UPSA is the best measure with good test–retest reliability, excellent shared variance with cognitive performance, good utility as a repeated measure (no ceiling or floor effects) and reasonable tolerability and practicality. For the short forms, TABS and UPSA were the leading measures because each had moderate shared variance with cognitive performance and acceptable utility as a repeated measure.

Discussant, *Dr. Wolfgang Fleischhacker* commented that one challenge for cognitive enhancing agents is to match targets to compounds that in fact affect the target. He suggested two future approaches for finding such appropriate phenotypes: (1) development of better rating instruments for studying cognitive-enhancing agents; and (2) pursuing compounds that stimulate neurogenesis to optimize the effects on cognition.

3.2. Autistic and cognitive traits in the genetic understanding of the continuum in neurodevelopmental disorders and functional psychosis (reported by Hanan D. Trotman)

Despite the similar genetic and neurobiological mechanisms that likely underlie schizophrenia-spectrum and autism spectrum disorders the clinical overlap is rarely examined. *Dr. Krebs* described a study of 276 schizophrenia and schizoaffective patients. Delayed developmental milestones (walking, standing, talking, and bladder/bowel control) were associated with an earlier age of onset of psychiatric symptoms in these adult-onset patients. These patients were more likely to be treatment resistant, have a higher rate of neurological soft signs, higher rates of psychiatric disorder in childhood, and greater severity of disorganized symptoms. Krebs and colleagues constructed a screening questionnaire designed to examine childhood autistic spectrum features in adult-onset patients, and showed that adult-onset patients do demonstrate autistic-like features in childhood but to a lesser degree than childhood onset schizophrenia cases. Krebs concludes that a continuum model of schizophrenia and autistic spectrum disorders may be useful in genetic studies of schizophrenia.

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Dr. Fatjó-Vilas provided a report of the importance of examining CNVs in early onset psychosis, as well as cases with overlapping autistic features (social difficulties), low IQ, poor premorbid adjustment, and developmental milestones (language and motor delays). Early-onset patients differed from adult-onset patients in the KIAA1267 Gene MLL1 on chromosome 17q21.31. KIAA1267 has a role in transcription regulation through modification of histones. This chromosomal region could be an important region containing CNVs that influence age at onset and illness severity.

Dr. Guy Rouleau described the identification of rare, highly penetrant de novo mutations in genes coding for synaptic proteins in schizophrenia and related neurodevelopmental disorders. He suggested that a high rate of de novo mutations could explain the similar continued illness prevalence across cultures, despite reduced reproductive fitness. Twenty-two de novo variants were identified in 16 different genes. Animal models were used to test the potential functional effects on protein function. Some identified genes from the current presentation had deleterious effects in patients from the three different disease groups (schizophrenia, autism spectrum disorders, and mental retardation) suggesting overlapping genetic mechanisms.

Dr. David Collier presented data from a genome-wide search for schizophrenia-associated rare CNVs examining 9878 transmissions from parent to offspring. Sixty-six de novo CNVs were identified and tested for association in a sample of 1433 cases with schizophrenia and 33,250 controls. Three deletions at 1q21.1, 15q11.2, and 15q13.3 demonstrated a significant association with schizophrenia and other psychotic disorders. He concluded that one CNV (15q13.33) can give rise to multiple clinical disorders.

3.3. International perspectives on group based approaches to treating cognition in schizophrenia (reported by Renate Thienel)

Dr. Alice Medalia chaired this session and noted that several meta-analytic studies showed moderate effect sizes for behavioral treatments. Since some clinical settings only allow for group treatment, this session focused on group samples from an international perspective.

Dr. Elizabeth Twamley spoke about the use of compensatory cognitive training in order to treat cognitive impairments, as they are not targeted sufficiently by current antipsychotic medication. Cognitive deficits tend to be generalized, with processing speed, attention, learning abilities, and executive functioning impaired. Those cognitive symptoms have a very strong effect on social, functional and vocational, outcome. The effect sizes for cognitive training (Twamley et al., 2003: including 17 studies) vary between 0.3 on cognition, 0.26 on symptoms, and 0.5 on functioning. Compensatory cognitive training uses different strategies that take advantage of each individual's strengths, and to activate different brain regions. Strategies in general can be classified into internal and external strategies. An example of an internal strategy is 'visual imagery' and for an external strategy 'note-taking'. Patients need to recognize that they have deficits in internal strategies in order to accept the need to use external ones. With external strategies they need not generalize, and cues are the same all the time.

The cognitive training called 'class' was run with 4–6 clients plus 2 instructors, 1/week for 12 weeks. Sessions lasted 2 h with ample time for practicing. Homework was given. The following cognitive domains were targeted: prospective memory (rationale: this is aiming to improve attendance, treatment adherence, task compensation with compensatory strategies like using calendars, reminders, and linking tasks), conversational task vigilance (rationale: association with functional outcome and compensatory strategy: conversational skills and 'self-talk'), verbal memory (rationale: association with functional outcome and compensatory strategy: reducing information, meaning, remembering people's names, and writing things down), and executive functioning (rationale: linked to functional outcome and compensatory strategy: problem solving methods, brainstorming, and hypothesis testing). Baseline assessments were performed and then 38 patients were randomized into cognitive training and 31 into standard pharmacological treatment only. Follow-up assessments were done after 3 and 6 months. A hierarchical linear modeling was used for analysis, effect sizes, for time, time × treatment interaction, attention, learning and memory, executive functioning and prospective memory are targeted cognitive domains, and clinical ratings. A functional capacity measure 'shopping task' and a quality of life interview were completed. The patients' diagnoses were half schizophrenia and half schizoaffective with a mean age of 47, 13 years of education, 24 years of illness and a CPZ equivalent medication dose of 335 mg. The attendance at classes was 82%. There were no significant effects on positive and depressive symptoms, and the non-targeted cognitive symptoms. However, there was an effect on the targeted cognitive symptoms ($P = 0.046$). Whereas the control group was better at the initial assessment, after 3, and 6 months the group receiving cognitive training was better. Functional capacity in the cognitive training group improved most extensively ($P = 0.007$). Negative symptoms also improved ($P = 0.019$), but after training they went back to baseline. Quality of life also increased in the cognitive training group ($P = 0.039$) while the control group showed a decline. Moderate effect sizes were achieved for visual memory (0.6 effect size). The sample size was small, the follow-up period was brief, and drop-out rates limit generalisability of results. Instruction manuals are available from Dr. Twambey (etwamley@ucsd.edu.au).

Dr. Muhammed N.M. Alwi from Malaysia reported on a multisite study of a cognitive remediation program (CREP), in the developing country of Malaysia. CREP based on NEAR (a computerised program developed by Alice Medalia), was officially launched in December 2005. Challenges were that computer programs had to be developed in Malaysian and that there are no neuropsychologists in Malaysia. Also the team had to overcome a certain resistance for change among clinicians. Eighty-five patients diagnosed with schizophrenia attended 20 training sessions. Occupational therapists, nurses and assistant medical officers ran the computerised program. Training workshops around the country were run including training on assessment tools. Guidance for the therapists was provided by email and phone. $N = 20$ per group, 1 h/twice a week, in group meetings plus 1 weekly additional group meeting. The computer based program targeted processing speed, attention, memory and problem solving. Training was

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conducted at 5 centers with a cognitive training group versus a waiting list group. Furthermore additional so-called booster sessions (4 sessions) after a 2-week gap were included, assessing whether this would have any enhancing effects on cognition? Clinical measures were BPRS, CGI, and psychological functioning. The cognitive training group significantly improved on cognitive outcome measures of attention, speed of processing, visual learning and memory with moderate effect sizes. They also improved on secondary clinical measures, like the BPRS-Score, and psychosocial functioning. Booster sessions had no significant effect. The cognitive training was effective and this effect remained stable after 5 weeks.

Dr. Medalia talked about the necessity to improve awareness of cognitive impairments in patients as in general the magnitude of cognitive impairment is vast and the majority of the patients do have impairments. But subjective awareness is often poor (Medalia and Thysen, 2008). When assessed with the BACS (Brief Assessment into Cognition in Schizophrenia) and the MIC-CR (Measure of Insight into Cognition-Clinician Rated) over 80% of patients had impairments but only 40% were aware of them. More precisely 52% had no awareness, a quarter had some awareness, and the other quarter had full awareness. When asking for patients' attribution to illness, 26% attributed them to the illness and 35% partially attributed their deficits to the illness. This data clearly stresses the need for psychoeducation of patients about cognition. Dr. Medalia also referred to a handbook, available at www.omh.state.ny.us and to the work of Carol Dweck 'brain-check', which integrates cognitive screening into 1–2 group or individual sessions. The sessions are interactive, and include a self-screening of cognitive skills, to get people aware and engaged. The task used is a brief digit symbol exercise followed by an interpretation of the score and a discussion about cognition and illness and options of treatment. In a randomized control trial, whether a discussion session ('brain-check') can improve awareness was assessed. Thus far data from 63 patients were analyzed (controls and brain-check subjects). The control group sat in the waiting room, watching television. Measures: Measure of Insight into Cognition-Clinician Rated (MIC-CR), TOCA (Test of Cognitive Ability), and RECT (Receptiveness to Treatment). One to two brain-check sessions, and discussions were run. Subjects were excluded when their working memory index indicated that they were unimpaired. No results were significant; however, awareness correlated with receptiveness to treatment. Thus, it would be helpful to include cognition into psychoeducational programs, as there is some evidence that awareness improves receptiveness to treatment. Nonetheless, awareness of cognitive disability differs from incite into the illness.

Dr. Volker Roder reported that 75–85% of patients show long lasting cognitive deficits (Gray and Roth, 2007). Cognitive deficits predict lack of compliance and explain 20–60% of the variance in functional outcome. Whereas cognition interacts with functional outcome, social cognition could be an intermediate step between neurocognition and functional outcome. The Integrated Psychological Therapy (IPT) combines neurocognitive remediation with training in social cognition, social skills, and problem solving. IPT has recently been evaluated in a meta-analysis including 34 studies (Roder et al., 2006). The effect sizes of cognitive remediation were small, but adding a second part to the program, increased the effect sizes up to 0.74–0.84 in neurocognition, and social cognition. These results lead to further development of IPT towards an integrated neurocognitive training (INT). The INT includes 4 modules: highly structured exercises with Cogpack (a computer based cognitive training), a social part with interactive groups, increase of complexity, decrease of structural groups, and increase of emotional relevance and personal reality reference. The cognitive domains targeted are: speed of processing, attention, vigilance, verbal and visual memory, reasoning and problem solving. The modules are structured into: 1. Introductory sessions, self-perception sessions, and further sessions including homework. The best effect is achieved with training twice a week. A multi-site study of INT-training was conducted in 3 countries including 9 centers. Stronger effects occurred at follow-up compared to immediate periods. Patients needed time to establish change in social cognition and neurocognition modules. PANSS and GAF scores also improved. The effect sizes in the active INT-group were 0.36 for the immediate effect with an increase up to 0.52 at follow-up. However, the longer the duration, the less the effect size.

Discussant, Dr. Til Wykes asked what effects groups have? Groups have the non-specific beneficial effect of shared experience, and they have the potential to normalize by sharing with others. Also they help identify common factors, and help sharing natural coping strategies. In general they provide social support. These are important processes to use as part of therapy. Within group settings more people can receive therapy, and groups can increase engagement. On the negative side, groups are less tailored to the individual. In general there is a need of group therapy expertise. Targets of the different studies reported on were cognition, and metacognition. With respect to functional outcomes, it's questionable whether these are primary, secondary, or how they are related to cognition. One suggestion might be that therapy affects the ability to transfer cognition into functional outcome. Dr. Wykes stressed the importance of good trial designs with blind ratings. She also suggested using the term "limitations" rather than "impairments", as this can affect self-esteem. In the general discussion: the importance of group training was emphasized and that integration with psychosocial treatment is better than stand-alone cognitive training.

4. Animal models

4.1. New directions for animal modeling in schizophrenia (reported by Gabriela Novak)

Based on the current state of our knowledge, schizophrenia is not caused by any one single gene, but rather by a complex interaction of etiopathological factors, with accordingly varied behavioral manifestations. The resulting phenotype reflects the interaction of genes, development and the environment. Therefore, schizophrenia is the result of a dynamic process and as such is difficult to model. In order to better understand the complex etiology of the disease, we need reliable approaches to quantify the behavioral output,

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ones that are translatable from animals to humans. Such approaches were discussed in this session.

Dr. Bita Moghaddam highlighted the necessity for a conceptual shift from the analysis of a static system of "risk" genes to "risk networks". Because of the complex nature of behavior, the same input can result in an array of outputs. Thus, we need to focus on understanding neural networks. An ideal analytical approach would (1) identify behaviorally relevant dynamic abnormalities at the level of neural networks, (2) identify micro and macro circuits that influence function of these networks, and (3) through analysis of mutations or other interventions in these circuits, confirm whether these are relevant to schizophrenia using measures common to both animals and humans. She then discussed the role regulation of the cortical pyramidal network plays in the "dynamic synapse hypothesis" of schizophrenia. The excitatory afferent hippocampal input to the cortex regulates both the pyramidal neurons of the cortex, as well as their inhibitory GABAergic neurons. At the same time, this excitatory input stimulates pyramidal neurons, as well as activates their inhibition by GABAergic neurons. There is evidence that GABAergic neurons are more sensitive to this stimulation because of a lower action potential threshold, leading to an overall inhibition of the pyramidal neurons. This sensitivity of GABAergic neurons to excitatory input also explains the pro-psychotic action of NMDA antagonists.

Dr. Akira Sawa set criteria for schizophrenia animal models. Since schizophrenia is likely to be the result of multiple genes, individual genetic mutations should be expected to model aspects of schizophrenia endophenotypes, rather than the full disease. These are essential tools used in dissection of the etiology of this disease. Thus, a good model should (1) reflect the etiology and pathogenesis of schizophrenia, including the combination of genetic and environmental factors and involve the pathways identified to play a role in the disease. (2) It should be able to reproduce a key pathophysiology observed in schizophrenia, with measures translatable between humans and rodents, such as neuroleptic response or imaging data. (3) It should reflect the time course of the disease, involving early postnatal brain maturation and onset in early adulthood.

Dr. Sawa then presented his research involving the BACE1–NRG1–ErbB–Akt–DISC1 pathway (Niwa et al., 2010). He used an in-utero gene transfer to simultaneously modulate various factors and their effect on disease pathways in question. In particular, this approach was used to induce a transient knockdown of DISC1 during prenatal development, showing that such prenatal reduction in DISC1, without further postnatal insult results in dopaminergic signaling pathway deficits with early pubertal onset. Therefore, such animal models may be particularly useful in identifying a strategy for early intervention, because they can provide models of early development and of time of onset of the disease (Jaaro-Peled et al., 2009).

Dr. Peter J. Uhlhaas emphasized the paradigm shift in schizophrenia research from gene or lesions to a "disconnectivity syndrome". Such shift reflects the current observations of a disturbed dynamic coordination of neuronal responses, analysis of which will require modeling of large-scale mechanisms that coordinate neural activity (Singer, 1999; Varela et al., 2001). Synchronization of neural processes, especially oscillations, is one mechanism for coordination of distributed neural activity (Singer, 1999; Uhlhaas et al., 2009a). This mechanism is crucial not only for higher cognitive processes, but also for basic phenomena such as synaptic plasticity. Evidence shows that this process is disturbed in schizophrenia (Kwon et al., 1999; Spencer et al., 2003; Uhlhaas et al., 2006) and that the deficits of neural synchrony are at least in part due to alteration in GABAergic and glutamatergic neurotransmission (Lewis et al., 2005; Moghaddam, 2003), which is likely a result of aberrant neurodevelopment (Wright et al., 1999; Phillips and Silverstein, 2003; Uhlhaas et al., 2009b, 2010a).

Synchrony depends on a balance of excitation and inhibition. Importantly, because indices of this synchrony can be obtained both in animals and in humans, this approach is ideally suited for translational research. Currently there are a number of available measures that satisfy these criteria. These include steady-state potential (Kwon et al., 1999), long-range synchrony (Uhlhaas et al., 2006), and source localization. Kwon and colleagues used auditory steady-state paradigm, consisting of auditory click trains that are presented in a certain frequency and produce evoked oscillatory response. The cortex is entrained to this oscillation, which reflects passive intrinsic reflex phenomena. In schizophrenia this oscillatory response is reduced, specifically in the auditory cortex and particularly to stimulation of 40 Hz (Kwon et al., 1999).

Another approach was reported by *Dr. Uhlhaas* (Uhlhaas and Singer, 2010). Subjects were presented with a visual stimulus and precise phase synchronization of oscillatory response and EEG recordings were examined, allowing an analysis of temporal coordination in milliseconds. In schizophrenia, between 200 and 300 ms, the synchronization between the two electrode sites is dramatically reduced, suggesting a strong impairment of large-scale coordination (Uhlhaas and Singer, 2010). These studies suggest possible mechanisms involved in the deficits observed in schizophrenia that involve inhibitory interneurons important in generating these rhythms and in maintaining balance of the high-frequency activity neocortical networks. In direct anatomical correlates, the layout of excitatory cortical–cortical connections is a functional parameter for the generation of synchronization between and within brain regions.

Dr. Inna Gaisler-Salomon discussed the relevance of glutaminase as a novel therapeutic target for schizophrenia. Presynaptic glutaminase is a mitochondrial enzyme that converts glutamine to glutamate and is involved in the recycling of glutamate to glutamine. Glutamate is then released into the synapse, taken up by the glial cell, converted to glutamine and again taken up by the neuron and converted to glutamate. This cycle is responsible for 70% of neurotransmitter glutamate in the brain. The Rayport laboratory has created a mouse with high expression of glutaminase in the hippocampus and frontal cortex. While the homozygous mice die at P1, the heterozygous mice (GLS1 het) show a significant reduction of glutamate in hippocampus and frontal cortex. Interestingly, these mice do not show schizophrenia-like deficits. However, they may be useful for the study of a specific pharmacological aspect of schizophrenia (Gaisler-Salomon et al., 2009a).

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Using an fMRI cerebral blood volume measurement (Small, 2003), *Dr. Schobel* has shown that there is an increased activity in the CA1 and in the subiculum both in patients with schizophrenia and in high risk individuals (Schobel et al., 2009). However, GLS1 heterozygous mice show a decrease in activity in the same sub-regions of the hippocampus, compared to wild-type littermates (Gaisler-Salomon et al., 2009b). These mice also show other phenotypes, which can be considered as protective, such as attenuated behavioral response to amphetamine and ketamine and reduced amphetamine-induced dopamine release in the striatum. They also show an antipsychotic drug-like profile in the latent inhibition assay that is frequently used as a screening tool to assess the actions of antipsychotic drugs (Gaisler-Salomon et al., 2009a).

In conclusion, over-expression of glutaminase is not a model for schizophrenia. However, it appears to play a role in other neurotransmitter systems, in particular other aspects of the glutamate and the dopamine systems, to confer protection against some of the pathological mechanisms that underlie psychosis. The glutaminase molecule may, therefore, be a novel therapeutic target for schizophrenia.

Dr. Patricio O'Donnell concluded the session with a discussion of the future of developmental animal models. Assessments at various end-points, including behavioral, electrophysiological, and anatomical methods reveal remarkable convergence of evidence for defects in dopamine, glutamate and GABA interactions in most of these models and highlight a disbalance in inhibition/excitation in these networks. He mentioned his own studies in animals treated prenatally with the antimitotic methylazoxymethanol acetate (MAM), showing a loss of parvalbumin staining in the mPFC and ventral subiculum of the hippocampus at adulthood without a loss in neuronal numbers. This indicates hypoactivity of the GABA system (Lodge et al., 2009). In addition, using the neonatal ventral hippocampal lesion (NVHL) model (Tseng et al., 2008; 2009), it was shown that the D2 agonist (quinpirole) enhances the excitability of interneurons from normal adult rats, but not from adult animals with NVHL. This suggests deficient interactions between dopamine and GABA in NVHL animals, and also that this interneuron deficiency is dynamic, since the anomaly is only revealed when challenged by dopamine.

Combining two models, an immune challenge and a NVHL, by injecting the bacterial endotoxin lipopolysaccharide (LPS) into the ventral hippocampus, the O'Donnell team was able to show that a neonatal hippocampal immune challenge is able to produce the same phenotype as NVHL (Feleder et al., 2010). In summary, the excitation/inhibition balance, for which interneurons are critical, matures during adolescence. The ability of dopamine to engage interneurons emerges and becomes more effective during adolescence and subsequent adulthood. This does not seem to occur in many schizophrenia models.

We now have a number of schizophrenia-relevant pathophysiology models that integrate dopamine, GABA and glutamate signaling. These can address questions such as why blocking NMDA can make interneurons malfunction, why a schizophrenia phenotype is obtained with DISC1 manipulation, or with lesions in areas that project to PFC. These models can more closely address the etiology of the disease and other factors involved, such as BDNF. Genetic models can also provide information to test these circuit-based models. The timing of the disease can also be addressed. The equivalent of a prodromal stage can be modeled in juvenile animals and experiments designed to model mild cognitive dysfunction and even environmental interactions, such as social isolation or cannabis use.

4.2. Gene expression in schizophrenia—animal models and post-mortem studies (reported by Moogeh Baharnoori)

Genetic studies have significantly contributed to our understanding of the etiopathology and neurobiology of schizophrenia. More recently, extensive research effort has been dedicated to unravelling important changes in the epigenetic regulation of gene expression by the use of post-mortem brains. The main focus of this session, chaired by *Dr. Amanda Law* (NIMH, Bethesda, USA) was to review recent advances in gene expression profiling in schizophrenia combining the findings from animal models with post-mortem studies. The first speaker was *Dr. Karoli Mirnics* (Vanderbilt University, USA), reporting on a novel transgenic model based on the cellular findings in post-mortem brains of schizophrenic patients. He began with an introduction about the critical role of the neocortical GABA inhibitory system in the pathophysiology of schizophrenia. He talked about the interneuron subpopulation, their differential laminar distribution and distinct electrophysiological properties. One of the most consistent findings in post-mortem studies is reduction in the expression of the enzyme glutamate acid decarboxylase1 (GAD1; Lewis et al., 2005). In addition, the expression of neuropeptide Y (NPY), a marker for a subpopulation of GAD1-containing interneurons, is also decreased in the prefrontal cortex of schizophrenic subjects. Applying an endogenous mechanism for gene silencing, a transgenic mouse was developed with down-regulation in the GAD1 gene and simultaneous expression of GFP in NPY neurons. To do so, they combined a bacterial artificial chromosome (BAC) containing the NPY promoter-enhancer elements, the reporter molecule (eGFP) and a modified intron containing a synthetic micro RNA (miRNA) targeted for GAD1. The validity of the construct was tested both *in vivo* on CHO and HEK293 cell lines and *in vivo* in transgenic mouse brain. The cell lines were primarily incorporated with GAD1 and then co-transfected with the miRNA silencing construct. As a result, GAD1 protein was significantly decreased (>90%) in both cell lines. Furthermore, the transfected cell lines maintained a high level of eGFP expression indicating that the addition of miRNA did not interfere with the eGFP coding potential of the construct. *In vivo* experiments showed that the morphology and anatomical distribution of eGFP expressing cells in the transgenic mouse brain were strongly correlated with the normal distribution of NPY containing cells in wild-type animals (e.g. high levels in neocortex, hippocampus and the arcuate nucleus of hippocampus) suggesting that the transgene was selectively expressed in the NPY subpopulation of interneurons. The efficient reduction in GAD1 protein expression was also studied in NPY expressing interneurons in the transgenic brains. Almost none of the eGFP positive cells (NPY+) showed detectable level of GAD1 expression in the neocortex or hippocampus further indicating the cellular

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specificity of this knockdown approach. He concluded with a summary of the several advantages of a novel gene silencing technique. For example, there is cell-type specific down-regulation which can be visualized by the eGFP reporter gene; and the transgenic mice are cost benefit, reproduce rapidly and can be easily cross bred. Importantly, this novel strategy can be used to generate various splice-variant-specific transgenic animals (due to the small size of silencing miRNAs). He ended encouraging further development of other similar animal models, such as NPY-GAD67 knockdown or NPY-PV-CCK driven GAD1 miRNA transgene mice, in order to gain a better understanding of the critical role of different interneuronal systems in cortical neurotransmission, behavior and cognitive function.

Dr. Schahram Akbarian (University of Massachusetts Medical School, USA) presented data on epigenome mapping in developing and diseased prefrontal cortex. Knowledge of epigenetic regulation of gene expression has significantly progressed in recent years. The study of chromatin modification allows focus on one aspect of transcriptional regulation within the human brain. Histone proteins are subject to epigenetic modification by methylation and this may induce various effects on gene transcription depending on the specific positioning of the histone tail residue. Trimethyl-H3-lysine 4 (H3K4me3) is a histone marker highly enriched in the gene promoter region associated with transcriptional activation (Akbarian and Huang, 2009). Notably, the progressive up-regulation of GABAergic mRNAs during maturation of cerebral cortex in both human and rodents is accompanied by a significant increase in H3K4 methylation. Applying a chromatin precipitation assay (ChIP), significant deficits in GAD1 mRNA and H3K4me3 levels were found in the prefrontal cortex of female schizophrenic subjects. However, due to the limitation of the ChIP assay (lack of single cell resolution) it was not possible to identify the specific neuronal population responsible for those epigenetic changes. In addition to active regulation during early brain development, histone methylation may also be important in the molecular mechanism operating during different stages of psychotic illness. In a separate experiment, they looked at the epigenetic architecture of human prefrontal cortex aiming to map the genome-wide distribution of H3K4me3 enriched sites during postnatal brain development using ChIP-Seq in conjunction with an Illumina Solexa sequencing platform. They found that H3K4me3 peaks at several high risk loci such as a transcription site for DARPP32 (a target gene in dopaminergic system) and also Neuregulin-1 (NRG1), a promising susceptibility gene for schizophrenia. Based on gene ontology (GO) categories, the neuron enriched H3K4me3 peaks common among the 11 neuronal samples are mostly related to neuronal development, axonal guidance and synaptic transmission. Their results also indicate a significant age correlated epigenome change in the prefrontal cortex. Six hundred H3K4me3 peaks are lost in the first postnatal year (mainly through demethylation).

Dr. Amanda Law (NIMH, USA) presented recent findings on an intracellular signaling pathway containing Neuregulin1 (NRG1). The NRG1 receptor, ERbB4 and NRG1 are candidate genes for schizophrenia suggesting that the NRG1 signaling cascade might be involved in its pathophysiology. The expression of an ErbB4 splice isoform containing exon 26 (CYT-1) and exon 16 (JM-a) is significantly elevated in the dorsolateral prefrontal cortex of schizophrenic patients. The increased expression of ErbB4 variants, which activate the PI3K pathway, may explain the PI3K overactivation observed in schizophrenia (Law et al., 2007). PI3K gene expression (PI3KCD), its intracellular signaling and cell migration were measured in lymphoblast cell lines (LCL) derived from schizophrenia patients and healthy controls in relation to genetic variation in ErbB4 (rs7598440, rs707284, and rs839523). ErbB4 risk variation predicted Nrg1 mediated intracellular signaling and Nrg1 mediated cell migration. Impaired transmission of SNP alleles in PI3KCD was also present in two independent family samples. However, unlike in LCLs, PI3KCD was not increased in the brains of medicated schizophrenic patients. In conclusion, these findings provide direct evidence that variation in the ErbB4 gene is able to induce significant functional differences in the PI3K pathway at the molecular and cellular level and further confirm that an aberrant Nrg1/ErbB4 signaling is an upstream effecter of impaired PI3K function in schizophrenia.

Dr. David Porteous (University of Edinburgh, UK) spoke on DISC1, a susceptibility gene for schizophrenia, originally identified at a breakpoint of a chromosome translocation t (1;11) in a large Scottish family with major mental disorders, including schizophrenia and mood disorders (Millar et al., 2001). He described the behavioral phenotype and predictive validity of two DISC1 missense mutant models. Q3IL mice exhibited depressive like behaviors (forced swim test) that were reversed by antidepressant treatment, while the other mutant, L100P displayed schizophrenia-like behaviors (prepulse inhibition and latent inhibition) that were reversed by antipsychotic treatment. These findings further support the critical role for DISC1 mutations in major mental disorders. In addition, both mutations decrease the association between DISC1 and its binding partner PDE4B. In turn, altered DISC1–PDE4B interaction can dysregulate cAMP signaling that is likely to contribute to the molecular mechanisms underlying abnormal phenotypes in these mutants. They also conducted a global analysis of the common SNP variants of DISC1 and its common binding partners (PDE4 and NDE1) in gene expression in human LCLs. The data revealed that these genetic variants specifically regulate synaptogenesis, neurodevelopment and sensory perception proteins. Seven psychoactive drug targets within the DISC1 pathway were identified that can be used as reliable predictors of individual response to therapeutic agents.

4.3. Mutant models and psychosis at the crossroads: a critical re-evaluation of techniques and translation (reported by Aurelie Boucher)

The four speakers of this symposium reviewed new developments in the generation and evaluation of mutant animal models of schizophrenia.

Dr. Mikhail Pletnikov (Johns Hopkins University, Baltimore, Maryland, USA) studied the neurodevelopmental and schizophrenia-like phenotype of mice mutants of DISC1. The expression of the mutant gene is inducible at different time points of neurodevelopment of forebrain regions such as in the cortex, hippocampus, striatum but not the cerebellum. While there was no gross effect/abnormalities in those mice,

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enlargement of lateral ventricles was observed. At a molecular level, decreased DISC1 was observed in mutants. Behaviorally, an increase in spontaneous locomotor activity of male DISC1 mice, impaired spatial memory using the Morris water maze only in females and increased aggressiveness in males was found. The evaluation of the effect of different timings of expression was also studied. Four different groups were analyzed that expressed the mutation: from conception to sacrifice ("pre + post"), only from conception to birth ("pre"), only from birth to sacrifice ("post") or never ("No"). Results showed that schizophrenia-like behavioral alterations have a prenatal origin in male DISC1 mutants. Depression-like behaviors have a postnatal origin in females, and structural brain abnormalities have a postnatal origin.

Dr. John Waddington (Royal College of Surgeons, Dublin, Ireland) described the characteristics of NRG1 mutant mice, including increased locomotor activity, orofacial dyskinesia (increased chattering), and behavioral differences that included disrupted social novelty, but not deficits in working memory. On the other hand, COMT mutants showed intact social behavior, but selective disruption in working memory. An acute PCP challenge decreased hyperactivity in NRG1 mutants. In animals subchronically pretreated with PCP, an increased activity sensitization was observed in NRG1 mutants compared to controls. In conclusion, he suggested a "bottom–up" approach to genetic modeling, i.e. trying to find novel gene models instead of using the current ones implicated in clinical studies of schizophrenia. For example, mutant mice for semaGA, a gene involved in thalamocortical connectivity, show hyperactivity that is reversed by clozapine.

Dr. Maria Karayiorgou (Columbia University, New York, USA) presented a new mouse model of copy number variants on 22q11.2. Knockout mice were generated that were Dgcr8 deficient (a segment syntenic to the human 22q11.2 locus). Prepulse inhibition and water maze performance were affected in these mice, but they had no changes in locomotor activity and fear conditioning. Dgcr8 deficiency affected dendritic spine development but not size. Thus Dgcr8 haploinsufficiency led to cognitive impairment with underlying neuronal abnormalities and dysregulation of synaptic genes.

Dr. Bart Ellenbroek (Evotec Neurosciences, Hamburg, Germany) presented a D1 knockout rat model created by replacing an isoleucine with a serine that then disrupts the interaction between the third and fourth transmembrane domains. Decreased D1 labeling in homozygous mutants was confirmed by autoradiography. The advantage of using mutant rats is that there is a huge evolution gap between mice and rats and ethological differences exist between mice and rat. For example, mice dislike water more than rats, which can be an important consideration when studying water maze performance. There are also neurochemical differences in the function of dopamine receptors in mice versus rats. Results obtained from these mutant rats showed that amphetamine and cocaine-induced hyperactivity was reduced in the mutants. Social behavior was decreased in mutants especially playing behavior in young rats. In the Morris water maze, spatial learning was affected as seen by an increased latency in mutants, but they did learn over time. In the egocentric task of the water maze (specific to dopaminergic frontostriatal function) where the platform changes all the time, mutant rats did not learn the task. Finally, decreased prepulse inhibition was observed in the mutants. In conclusion, this is an interesting model for studying the negative and cognitive symptoms of schizophrenia.

5. Treatment

5.1. An update on psychosocial treatment of schizophrenia (reported by Juan Gallego)

Dr. Lisa Dixon (Maryland, US) spoke on first-episode psychosis and assertive community treatment. She initially outlined some of the 2009 schizophrenia Patient Outcomes Research Team (PORT) recommendations (Dixon et al., 2010). According to those recommendations, assertive community treatment (ACT) should be offered to those patients at risk for repeated hospitalizations or recent homelessness. ACT is composed of a multidisciplinary team including a medication prescriber. They have a shared caseload between team members and provide direct service with a high frequency of patient contact. ACT has a low patient-to-staff ratio and they perform outreach to patients in the community. ACT has been shown to decrease hospitalization and homelessness and also has some effect on reduction of symptoms, increased medication adherence and treatment satisfaction. ACT has also been associated with increased likelihood of employment and paid employment (Furlong et al., 2002), competitive employment (McFarlane et al., 2000), and performing more effectively in a work role (Jerrell, 1995). Dr. Dixon mentioned that the addition of a vocational specialist to the ACT team has led to positive employment outcomes. Furlong et al. (2002) have found superior outcomes when an ACT program is combined with a vocational specialist compared with a traditional ACT program or conventional vocational rehabilitation. With substance use, there were no clear advantages of ACT combined with substance use expertise compared to traditional ACT or clinical case management (Essock et al., 2006). Mixed results have been found about ACT and subsequent arrests with jail time (Lamberti et al., 2004).

Dr. Dixon's talk then focused on the NIMH Recovery After Initial Schizophrenia Episode (RAISE) project. This project aims to test whether early, aggressive, and pre-emptive intervention can slow or halt clinical and functional deteriorations in schizophrenia. Contracts were awarded to two independent research teams: 1) The Connection Program at the Research Foundation for Mental Hygiene at Columbia University in New York and 2) The Early Treatment Program at the Feinstein Institute for Medical Research in Manhasset, New York. Dr. Dixon, as a co-primary investigator of the former team, went on to explain the details of the Connection program. They expect to enroll 330 to 370 participants. The subjects will be aged 15–35 with a diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, psychosis NOS or delusional disorder and who present with at least one psychotic symptom at any time during the current episode or a recent episode with a duration of illness of less than 2 years. Participants will be randomized 1:1 to Connection Team or Connection Partnership. The Connection Team is a comprehensive multi-element approach with a clinician team leader, a psychiatrist, a supported employment/

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education specialist and a skills training specialist. The Connection Partnership is a clinical case management approach coordinating access to community-based services. Participants will receive treatment for two years and assessments will be conducted every three months. There will be quarterly assessments of functional status, symptoms, relapse, remission, quality of life, treatment satisfaction, side effects and substance abuse. There will be annual or biannual assessment of diagnosis, cognition and family experience. Dr. Dixon explained that they will be partnering with state mental health authorities for implementation, training and financing. For those insured, they plan to pursue reimbursement of all eligible items including medications, labs and specific services or pursue appropriate insurance coverage. State mental health will cover residual costs. In summary, Dr. Dixon stressed that the ACT team remains a stable evidence-based practice within the USA and that the relevance of a team-based treatment for persons experiencing first episode of psychosis is being tested.

Dr. David Kingdon (Southampton, UK) discussed cognitive therapy in schizophrenia. He explained that the techniques of cognitive-behavioral therapy for psychosis (CBTp) are based on the general principles of CBT that were initially developed for depression. They were developed for schizophrenia against a backdrop of intense skepticism because of past failures of other individual psychotherapies. Dr. Kingdon stressed that CBTp plus medication is now a first line treatment for schizophrenia. The benefits of CBTp are multiple but the most important is that it has a powerful normalizing effect on patients; it does not require acceptance of a schizophrenia diagnosis; it expresses an interest in personal understanding of symptoms and it has a strong focus on individualized engagement, with emphasis placed on understanding the first psychotic episode in detail. In CBTp, agendas are less specific and homework is used sparingly. Information on current beliefs and how they were arrived are assembled into a formulation which helps patients make sense of their beliefs and experiences. The overall aim is to reduce distress and disability, to improve medication adherence and to enhance recovery. Two recent meta-analyses have examined the effects of CBTp (Lynch et al., 2010; Wykes et al., 2008). Wykes et al. (2008) showed average effect sizes for target symptoms: 0.40, average effect size for rigorous RCTs: 0.22 and significant effect sizes (ranging from 0.35 to 0.44) for positive symptoms, negative symptoms, functioning, mood and social anxiety. Turkington et al. (2006, 2008) showed benefit on negative symptoms, delayed time to rehospitalization and a decrease in the time spent in the hospital for those who relapsed. Benefits have also been shown on patients with dual diagnosis by Barrowclough et al. (2001) and Haddock et al. (2003). Trower et al. (2004) found benefits on command hallucinations, Haddock et al. (2009) on patients with history of violence, and Fowler et al. (2009) on social recovery. Garety et al. (2008) did not show any benefit on relapse prevention and symptom reduction. Dr. Kingdon added that various studies are now being conducted in different parts of the world, such as Beijing, Texas, and New York and he pointed out that the NIMH RAISE by the Feinstein Institute for Medical Research team will have CBTp components as part of the treatment provided to first-episode schizophrenia patients. Furthermore, CBTp is now part of treatment guidelines in Europe, North America, Australia and NZ. Some examples of specific guidelines are PORT, APA, NICE and the guidelines for the World Federation of Societies of Biological Psychiatry (WFSBP). However, CBTp is not available in many countries because of the difficulties in implementation.

Dr. McGurk on her talk about cognitive remediation started by stating that cognitive impairments are common and associated with increased risk of developing schizophrenia. Cognitive impairments are also predictive of poor response to rehabilitation. Dr. McGurk described two recent meta-analyses of cognitive remediation trials. The first meta-analysis (McGurk et al., 2007) included 26 studies with 1151 clients. The results showed that cognitive remediation was associated with significant improvement, with a medium effect size for cognitive performance (0.41), a slightly lower effect size for psychosocial functioning (0.36), and a small effect size for symptoms (0.28). A new more recent meta-analysis by Wykes showed moderate effect sizes on overall cognitive improvement on functioning (functional outcomes). She concluded that 1) adjunctive psychiatric rehabilitation is a moderator of functional outcome; 2) the positive effects of cognitive remediation are seen in the presence of adjunctive rehabilitation; 3) cognitive remediation helps with cognitive functioning and functional outcome, but much less with symptoms and 4) combining cognitive remediation with adjunctive psychiatric rehabilitation may help those who did not previously benefit from psychosocial treatment alone.

Dr. Pitschel-Walz defined psychoeducation as the systematic, didactic psychotherapeutic interventions which are capable of informing patients and their relatives about the illness and the treatment options available and of fostering the understanding of and coping with the illness. Likewise, the goals of family interventions are to decrease family anxiety about the patient, to increase self confidence, to educate about the illness, and to increase the ability to react constructively to the patient. Several meta-analyses have been conducted (Lincoln et al., 2007; Pharoah et al., 2006; Pilling et al., 2002; Pitschel-Walz et al., 2001). Overall, these studies found that family interventions help decrease relapse and rehospitalization with some increase in medication compliance and a decrease in the burden of care. Tarrier et al. (1994) demonstrated that when psychoeducation and family intervention were combined with CBT the rates of rehospitalization were lower at 5 and 8 years later. Bauml et al. (2007) and Hornung et al. (1999) found lower rates of rehospitalization in patients who received psychoeducation compared to those who received standard care. Bauml et al. (2007) also demonstrated a decrease in the number of hospital days in patients who were provided psychoeducation and thus a reduction in cost. Dr. Pitchel-Walz noted that only up to 8% of patients in US and Spain receive any kind of family intervention (Glynn et al., 2006). Barriers such as increased workload, higher costs, insufficient knowledge and skepticism towards the intervention could be the reason for this low rate of implementation (Barrowclough et al., 1999; Dixon, 1999). New outcomes with family interventions, such as recovery, quality of life and family burden, are being investigated. Trials are now being conducted in different cultural settings (Magliano et al., 2006; Rummel-Kluge et al.,

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2007). Family-based peer programs are also being explored (Pickett-Schenk et al., 2006) and special target populations are being examined such as the substance abuse population (Mueser et al., 2009) and those with a first episode of psychosis (Gleeson et al., 2009; Lyse et al., 2007).

Dr. Kim Mueser began his presentation by describing the concept of supported employment (SE). He noted that the focus of SE is on "real" jobs in the community, paying competitive wages with minimal prevocational assessment, and no prevocational skills training. It also looks for rapid job searches, attention to client preferences and follow-along support, as long as needed. He pointed out that there have been about 16 different trials that support the notion that SE is better than vocational/rehabilitation programs. It has been suggested that cognitive impairment is associated with less response to SE and that cognitive remediation improves cognitive functioning. Thus, he questioned whether cognitive remediation could improve response to SE. He noted that preliminary data suggest that adding cognitive remediation to vocational remediation improves vocational outcome but the main question remained whether or not cognitive remediation can improve outcomes in non-responders to supported employment. He then described social skills training (SST) as a systematic approach to teach more effective interpersonal behavior by breaking complex skills into simpler ones. Those skills are practiced over time in group format with extensive practice in and out of sessions, with training individualized to each client based on personal goals. It has a broad range of applications, including schizophrenia. A meta-analysis by Kurtz and Mueser (2008), where 23 studies were examined with 1599 clients, showed that the effect size of SST was higher for proximal outcomes (mastery tests of SST curriculum ES: 1.2) than for distal outcomes (negative symptoms ES: 0.4). SST is now being used with older patients having schizophrenia (Bartels et al., 2004), those with co-morbid substance use disorders (Bellack et al., 2006) and in combination with CBTp (Granholm et al., 2009), cognitive remediation (Silverstein et al., 2009), and social cognition training (Penn et al., 2007). He then spoke about the NIMH RAISE project. Dr. Mueser is a co-investigator in The Feinstein Institute for Medical Research team. The trial will identify approximately 400 patients, ages 16–40, with less than 3 months of exposure to antipsychotic medications, presence of psychotic symptoms and a diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, psychosis NOS or brief psychotic disorder. Patients will be randomized to the "Navigate" intervention or to usual treatment. The goal of the Navigate intervention is recovery, which was defined in terms of role functioning (work/school), social functioning, independent living, and well being. The Navigate team has a director or team leader, a psychiatrist, and supported employment and education specialist, and two individual resiliency trainer clinicians (who also provide case management). The primary outcome measure is quality of life. Randomization will occur by site (35 sites) and subjects will be followed for two years. Patients will be assessed via high speed videoconferencing technology (MedAvante) and raters will be masked to treatment condition with expert diagnostician and assessor available for every site.

Dr. Wykes began the discussion by citing meta-analysis which evidenced that family interventions (Pharoah et al., 2006), cognitive therapy (Wykes et al., 2008) and cognitive remediation therapy work. She also noted that investigating the effects of trial methodology with Clinical Trial Assessment Measure CTAM can help provide a clearer picture of the impact of certain interventions in clinical trials. She pointed out that family interventions and CBTp are currently included in NICE and PORT guidelines, whereas Social skills is included only in PORT, Art therapy is included only in NICE and CRT is not included in either of those guidelines. She then argued that evidence of efficacy is not enough and that the applicability of those therapies to "real-life" needs still needs to be proven. She pointed out that there are several limitations. In first-episode psychosis patients, for example, we know that it is hard to implement therapies and that patient engagement is an issue. It is also suggested that only experts can make a difference (group CBT, FI, and CRT). She stated that expectations are high and she wondered what the field should do in case the RAISE studies fail to show any differences. She argued that outcomes should be chosen carefully and gave the example how sometimes "work" or sometimes "just activity" is important. She also pointed out how trade-off outcomes such as "supported work" or "supported housing" could also be important. She concluded that one of the biggest challenges is that health and social care services have limited budgets, but that patients have high expectations.

5.2. Early intervention services for five years? (Reported by Hanan D. Trotman, Ph.D)

Drs. Malla and *Nordentoft* chaired a discussion on the benefit of early intervention programs. This is a critical topic particularly given evidence that early intervention may impact long-term outcome (Malla et al., 2002a,b; Malla and Norman, 2002). Presentations ranged from the optimal length of specialized early intervention (SEI) services, risk factors for relapse, to community-based interventions and efforts to improve real-world functioning and reduce medication use. Malla highlighted the high rate (80%) of patient relapse after 5 years of regular care and the better outcome gained after one year with enriched care (specialized early intervention services). The study presented was an extension of the Prevention and Early Intervention Program for Psychoses (PEPP) study Ontario, Canada. PEPP, a community-based program aimed at treating individuals in their first episode of psychosis, uses an assertive case management model of care (www.pepp.ca). All patients in the current study received SEI services for two years, patients then either continued to receive SEI services or began receiving regular care. Treatment for patients in the current sample included booster sessions, multiple family interventions, and cognitive-behavioral therapy (where indicated). Results suggest that the intervention in the current study was relatively palatable as the drop-out rate (23%) was low, with most of the drop-outs coming from the control condition (regular care). The Social and Occupational Functioning Assessment Scale (SOFAS) was administered as an outcome measure, and it predicted outcome better than relapse alone. Malla concluded that longer intervention trials were needed to determine whether extended specialized care was better than regular care for long-term outcome of early psychosis.

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Dr. Nordentoft presented results from the Danish OPUS trial and 5 year follow-up. Assertive community treatment (ACT), psychoeducational multi-family treatment, and social skills training were provided to schizophrenia-spectrum individuals aged 18–45 years old. Problem solving was included in the family intervention. Results indicated reduced substance abuse (an effect lost after return back to standard treatment) and spending less time in supported housing than the standard group. However, the effect was not maintained at the 5 year follow-up. In OPUS-II, 400 patients were treated over a 2 year period. The initial OPUS trial yielded more promising results and had lower costs.

Dr. Vazquez-Barquero addressed the length of medication use for effective symptoms in a first-episode patient sample from Northern Spain. There is lack of clarity of criteria for discontinuation due to a limited number of investigations related to medication withdrawal. For the current study, patients had to be symptom free for 18 months to be eligible. All patients were seen monthly during the first 6 months, and then every 2 weeks for the next 12 months. The discontinuation protocol included 46 patients. Sixty percent relapsed at 156 days, with the most relapses occurring in the first 6 months (43%). By 12 months, there were much fewer relapses. Family support was an important protective factor preventing relapse. Vazquez-Barquero concluded that better predictors of successful discontinuation are needed.

Dr. Verhaegh discussed function assertive community treatment (FACT) and results from a trial of assertive community treatment (ACT) in two mental health groups. Essential features of the program included vocational training, and supported education, and involvement of care-givers in the recovery process. In this study, 1/3 received FACT, another 1/3 received ACT, and another 1/3 received Crisis Intervention Services. Outreach increased from 39 to 50%. Over the 2 years, there were improvements in care-giver burden, social networking, drug use, patient willingness to share their opinions about their problems, and cost-effectiveness. For future studies, a longer intervention period (i.e., 3 years) was suggested.

Dr. Birchwood, the discussant provided "three reflections": 1) Early intervention services, are not treatments per se, but instead mechanisms for engaging young people in treatment. He suggested that engagement in services should be the primary outcome measure. 2) A patient's long-term trajectory is formed within the first two years of illness. Long DUPs and disability are already present. 3) Early intervention services do not solely account for individual trajectories and follow a "one size fits all" paradigm. He suggested enhancing outcome by combining early intervention services and methods for decreasing DUP. The challenge is to sustain change and put in place the needed specialized long-term structures.

5.3. An update on the next wave of schizophrenia therapeutics (reported by Nashaat Mohamed Abdel-Fadeel)

This session examined the new wave of schizophrenia pharmacotherapeutics. Most current medications for schizophrenia are D2 antagonists or partial agonists that treat positive symptoms and treat other domains poorly and their side effects are serious. The CATIE, EUFEST and CUTLASS trials suggested that the first-generation antipsychotic drugs are as effective as 2nd generation antipsychotic drugs, but the latter are better tolerated. Thus, there is a need for new treatments for all domains with an acceptable side effect profile.

Dr. Kiel Svensson presented the mGLU2 receptor as a novel drug target for schizophrenia. Evidence for mGLU2/3 receptor agonists as treatments for schizophrenia is suggested by an early phase II trial with an mGLU2/3 agonist prodrug (LY 2140023 monohydrate) that showed statistically significant results in improving positive and negative symptoms compared to placebo (Patil et al., 2007). Also there is evidence that the mGLU2 allosteric potentiators (PAMs) are effective treatments for schizophrenia as they suppress glutamate activity during periods of enhanced but not normal glutamate release. PAMs may have favorable side effect profiles, with lower risk for tolerance/desensitization development compared to an agonist, and also blockade of D-amphetamine/pcp/ketamine hyperactivity and 5-HT2A agonist-induced behavioral effects (Marek et al., 2010). Studies with transgenic mice suggest that the effects of PAMs are mediated via the mGL2 receptor with no evidence for a direct interaction with the dopamine D2 receptor. Additional testing is needed to address whether potential differentiation exists between mGLu2/3 agonists and mGLU2 PAMs in efficacy and tolerability.

Dr. Christopher Schmidt discussed development of GlyT1 inhibitors for treatment of schizophrenia. NMDA antagonists (e.g. PCP) can produce positive, negative and cognitive symptoms in healthy volunteers and exacerbate those three symptoms in patients, so many current drug development programs for schizophrenia target mechanisms believed to augment NMDA receptor activity. GlyT1 inhibition produces neurochemical, neurophysiological and behavioral effects consistent with augmentation of NMDA receptor activity and treatment of schizophrenia. Also GlyT1 inhibitors may allow exploration of the entire continuum of NMDA receptors glycine site activation beyond that achievable with oral glycine.

Dr. Peter Hudson discussed the rationale for mGluR5 positive allosteric modulators as potential antipsychotics. He noted that there is genetic evidence for a link to schizophrenia: an mGluR5 allele (on chromosome 11) is associated with schizophrenia in some studies. Also the mGluR5 antagonist (MPEP) potentiates a PCP/methamphetamine induced deficit in PPI and locomotor activity and induces cognitive impairment in animals. Moreover, activation of the mGluR5 receptor with DHPG potentiates NMDA receptor currents in rat hippocampal CA-1 pyramidal calls, and GluR5 potentiators have antipsychotic like effects in rodent models.

Dr. Nicolas Brandon discussed the rationale for considering PDE 10A in schizophrenia. It is expressed in medium spiny neurons in striatum. Inhibition may increase striatal output and PDE 10A inhibition thus modulates neuronal activity in the striatum. PDE 10A is also found in hippocampus and cortex suggesting its potential to affect cognition and negative symptoms. WEB-3 was identified as a novel PDE 10A inhibitor and is described as a potent and specific brain permeable agent (1.2 B/P). MP-10 and WEB-3 showed evidence of antipsychotic activity in conditioned avoidance responding (CAR) in rats. They produced low levels of

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catalepsy indicating a low EPS risk. Also they enhanced retention of recognition memory in rats. MP-10 enhanced social odor recognition memory in MK 801 treated mice. It was efficacious in animal models for negative symptoms and had an attractive side effect profile.

5.4. Improving signal detection in schizophrenia clinical trials by multiple methods (reported by Hsiao Piau Ng)

Dr. David Daniel (United BioSource Corporation and George Washington University, Washington, DC) began by highlighting the various factors contributing to poor signal detection, namely inconsistent credentials of raters, inaccurate measurement, poor inter-rater reliability, poor interview technique, high placebo response, rater drift, sloppy ratings, rater bias and manipulation of ratings. An earlier study by Kalali et al. (2003) which demonstrated a marked difference in distribution of PANSS scores by US and European raters was cited as an example of such variability. According to Dr. Daniel, successful site based ratings usually require the following measures, namely i) careful selection of raters based on their credentials and past performances, ii) standardization of the measurement tool used, interpretation of symptoms and interview style, iii) site training in placebo response reduction, iv) periodic re-standardization of measurement technique and v) ongoing surveillance of patient ratings and feedback to raters. A comparison was made between common and best practices for preparing raters prior to a trial. Common practices are instructional slide presentation and rating videotaped interview to within acceptable limits. Suggested best practices provide greater challenges to candidates before they are being approved to rate. They involve challenging candidates with difficult cases, putting them through interview training, getting them to rate a broad range of symptoms and severities, having culture and language specific breakouts, as well as certifying the candidate's ability to elicit data effectively from an actor and score. The standardization of required rater credentials by sponsors should also be encouraged to reduce variations while rating. In addition to proper selection of raters, Dr. Daniel stressed that there is a need to maintain rater calibration over time as any shift from an entrenched practice tends to regress to usual practice over time and frequent data monitoring or reviewing of videotaped interviews produces sentinel effect. Periodic refresher or recertification procedures may also help to reduce rater drift and maintain quality data throughout the duration of a trial. Ongoing surveillance of patient ratings and feedback to raters should occur. He concluded with analyses from a complex multi-center clinical trial, which showed reduced ratings errors and rater drift, hence supporting the feasibility of these interventional approaches.

Dr. Janet Williams (MedAvante Research Institute) began by identifying two main causes of failed clinical trials, namely inappropriate subject selection, as well as inaccurate and variable outcome measures. The issue on rater drift was also raised by Dr. Williams and she quoted an earlier study by Kobak et al. (2007) which showed that a large percentage of the raters who were initially certified, failed the raters applied performance scale (RAPS) by study midpoint. It was then suggested that the use of remote blinded centralized raters and centralized monitoring by continuously calibrated reviewers may help to avoid the two main causes of failed clinical trials. Being remote meant that raters have no contact with the site, have no incentive to screen subjects in or out and will not develop relationships with subject which will influence ratings. When raters are blinded, they have no prior knowledge of inclusion criteria and hence eliminate the chances of expectancy bias. By having centralized raters, extensive training and continuous calibration, rater drift may be avoided. It was noted that assessment for psychosis through the use of videoconferencing is increasingly common. Patient satisfaction questionnaires indicate that video is often preferred in clinical settings as it means reduced travel time and less absence from work for both patient and family. Through the use of video, patients feel a greater sense of confidentiality and privacy. It also provides them with more immediate access to a psychiatrist and a potential for clinical improvement without hospitalization. To illustrate the effectiveness of having remote blinded centralized raters, Dr. Williams quoted schizophrenia trials where remote blinded raters detected change and onset of drug action from the first week, while site raters scored test drugs not differently from placebo. Thus, independent centralized and continuously calibrated reviewers for quality control monitoring play a role in obtaining and maintaining high quality assessments. It was also noted that no company has carried out both remote rating and site rating in the same study for the sole purpose of comparing their effectiveness.

Dr. John Harrison (Imperial College and CogState Ltd, London, UK) spoke on the best practice guidelines for cognitive test selection. He began by listing the cognitive processes which are of interest: i) memory, ii) visuo-spatial function, iii) language, iv) praxis, v) working memory, vi) executive function, and vii) attention and processing speed. The Measurement and Treatment Research to improve Cognition in Schizophrenia (MATRICS) initiative has identified seven domains of importance (speed of processing, attention, working memory, verbal memory, visual memory, social cognition, and reasoning and problem solving) in assessing the ability of new therapies to improve cognitive function in schizophrenia. Dr. Harrison also discussed the basic criteria for a good test which include being reliable, sensitive, valid, relatively immune to practice effects and previously used longitudinally. Additionally, the test should be capable of being used cross-culturally and be pharmaco-sensitive. In conclusion, Dr. Harrison stated that the MATRICS initiative has yielded excellent advice regarding which cognitive processes should be assessed. With the appropriate precautions, reliable and stable measurements of cognition can be achieved, thereby increasing the probability of detecting effects.

Dr. Nina Schooler (SUNY Downstate Medical Center, NY, NY) spoke on the use of functional outcome as a long-term treatment goal, the rationale for assessment of functional outcome, available measures, assessment models and how assessment can be improved. According to Dr. Schooler, there is increasing interest to assess functional outcome, as long-term trials are conducted to seek the “real-world” outcomes which refer to the critical everyday life functions that can be measured against a general population. As mentioned by Leifker et al. (2009), there are many available instruments for assessment of functional outcome and they can be broadly

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divided into hybrid scales (e.g. Heinrichs-Carpenter Quality of Life Scale), social functioning scales (e.g. Birchwood Social Functioning Scale) and everyday living scales (e.g. Life Skills Profile). The choice of instrument is dependent on the following factors: i) goal, ii) hypothesis and duration of clinical trial, iii) level of functioning in patient population, iv) clinical skill level of assessors, v) availability of informants, vi) inclusion of symptom measures in scale, vii) distinction between capacity and performance, and viii) collection of information in addition to selected scale. Assessment methods can be in the form of self report by the subject, clinical assessment based on interview with subject and clinical assessment based on interview with informant. The reliability of the assessment method can be improved by choosing an instrument with high reported reliability, getting assessors with clinical experience when clinical judgment is required and training assessors with multiple examples. In order to improve the validity of assessment, it is suggested that external validators of functional outcomes, such as living status and employment, be included and moderators of functional outcomes, such as social class and education, be assessed. In conclusion, Dr. Schooler stated that functional outcome assessment will continue to play an important role in clinical trials. There are many available measures but the choice of measure is dependent on its ability to detect changes in the patient population. Additionally, attention to assessment training is critical and assessment of moderator variables may enhance sensitivity to change.

5.5. New antipsychotic drugs in early-onset psychosis: a translational view (reported by Yousri El Kissi)

Psychotic disorders are less common in children and adolescents than in adults and thus antipsychotic treatment studies in this population are lacking. The aim of this session was to evaluate the evidence for existing antipsychotic treatment and the latest information on its effectiveness and side effects in children with schizophrenia and to identify the most urgent clinical questions in this area. Presentations were based on placebo-controlled trials and active trials of new antipsychotic drugs in children and adolescents. Developmental aspects were also examined through new animal data to improve understanding of age-related differences in side effect profiles of these drugs.

Dr. Christoph U Corell provided an overview of the available and emerging efficacy and safety data of antipsychotic drugs in young patients with schizophrenia. Fourteen randomized controlled studies ($n=1155$) were found (Corell, 2008a). All newer antipsychotic drugs showed superiority on the PANSS. The only group significant difference was that clozapine was better than haloperidol and olanzapine. While response rates were lower in adolescents compared to adults, pediatric patients were at higher risk for side effects such as EPS, prolactin elevation, sedation, weight gain and metabolic effects (Corell, 2008b). By contrast, tardive dyskinesia and akathesia were less prevalent (Corell and Kane, 2007). Although diabetes was rarely noticed, marked increase in insulin resistance and incidence of dyslipidemia are of great concern (Corell, 2008c).

As there are limited published controlled data on the long-term efficacy of antipsychotic drugs in adolescents, *Dr. Margaretta Nyilas* compared adolescent and adult short and long-term efficacy and safety of aripiprazole. A post hoc analysis was generated from three data: a six-week double-blind study (Findling et al., 2008a), which compared 10 mg and 30 mg to placebo in adolescents (13 to 17 years old) with schizophrenia, a 26-week open label extension in the adolescent (15 to 17 years old) schizophrenia population (Findling et al., 2008b), and a 52-week double-blind design study which compared 30 mg/day of aripiprazole to 10 mg/day of haloperidol in adult schizophrenic patients (18 to 65 years old) after an acute exacerbation (Kasper et al., 2003).

Comparable short and long-term efficacies were observed. Percent of adolescents achieving remission at 27–32 weeks (82%) was similar to that in adult studies at week 26 (76%) and at week 52 (79%). Remission was maintained at 27–32 weeks in 91% of adolescents who achieved remission at 6 weeks compared to 95% and 92% of adults after 26 and 52 weeks, respectively. Also, similar frequency and type of side effects were observed in adolescent and in adult patients. In summary, comparable response and remission rates were observed between adolescents and adults in both short and long-term studies. Extrapolation of adult long-term efficacy data has been validated. Similar tolerability and safety outcomes were noticed.

Dr. Sanij Kumra reported the results of controlled study comparing the effectiveness and safety of clozapine versus high doses of olanzapine in treatment-refractory adolescents (10 to 18 years old) with schizophrenia (Kumra et al., 2008). The research question was raised because early onset of schizophrenia under the age of 18 years was noticed in 50% of patients and was associated with increased severity and antipsychotic drug resistance (Kumra and Charles Schulz, 2008). Previously Kumra et al. (1996) demonstrated that clozapine was superior to haloperidol. Because olanzapine has been shown to have superiority to other agents in adults, the current study was thus carried out. The study consisted of a randomized double-blind trial of flexibly dosed treatment with clozapine ($n=18$) or high dose (up to 30 mg/day) of olanzapine ($n=21$). Significantly more clozapine-treated adolescents met response criteria (66%) compared to olanzapine-treated subjects (33%). Clozapine was superior to olanzapine in reducing negative symptoms. However both treatments were associated with significant weight gain and related metabolic abnormalities. These side effects were less for clozapine than for olanzapine, but more important for both compared with adult patients taking the same medications. Thus, this study supports clozapine as the agent of choice in treatment-refractory adolescents with schizophrenia.

In order to investigate age-related antipsychotic drug side effects, *Dr. Frank Tarazi* presented long-term effects of these drugs on neurons of developing versus mature rat brain. Juvenile [PD 22] and adult [PD 70] Sprague–Dawley rats were treated with first (fluphenazine) and second generation (clozapine, olanzapine and risperidone) antipsychotic drugs. At the end of treatment, animals were sacrificed and brain processed by dopamine (DA) and serotonin (5-HT) receptor autoradiography. Repeated treatment with fluphenazine, clozapine, or olanzapine decreased D1 receptors in cerebral cortex of juvenile but not adult rats. All of the antipsychotic agents increased D2 receptors in cerebral cortex of adult animals and in hippocampus of juvenile animals. The four

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agents also more profoundly increased D4 receptors in nucleus accumbens and caudate–putamen in juvenile than in mature rats. No effects on D3 receptors were observed. Clozapine, olanzapine and risperidone increased 5-HT1A receptors in juvenile, but not in adult animals. The same three agents decreased 5-HT2A receptors in both aged groups but with different magnitudes. These data suggest that young animals are more sensitive than adults to the long-term effects of antipsychotic drugs. Developmental differences in dopamine and serotonin receptor responses may account for differences in clinical effects of antipsychotic drugs between young and adult psychiatric patients.

5.6. New research in the early prediction of antipsychotic response in schizophrenia (reported by Gisele Huf)

Dr. Stefan Leucht summarized both his own and work of others in investigating the pattern of response in people with schizophrenia. For decades text books have been suggesting that the pattern of response is one of the delay and, after a series of weeks, of the increase in functioning and decrease in symptoms. From the datasets presented, Dr. Leucht suggested that early response can be expected within 2–3 weeks. He outlined the different trajectories of response: 1. Moderate—seen in 77% of people grouped (3 different groups), 2. Poor response—seen in 8%, characteristically these people were slightly older (in their forties) with chronic illness and high BPRS scores, and 3. Fast responders—15%, typified by younger, men with a more paranoid-type illness.

Dr. Christop Corell focused largely on the timing of response using data from studies of adolescents. The data presented showed that a 'good response' in week 3 (defined as a 20% decrease in PANSS) predicted a much higher odds (10) of 'overall response'. Again, 'good early response' predicted 'remission' (odds of 8). Overall, only a little data were available, but Corell thought that a 3 week cut-off was somewhat better than 2. There was no indication that 'non-response' was predicted by the adverse effects of weight gain and akathisia—but early EPS may be indicative of later poor response. In addition, data were presented on the value of the CGI in clinical practice. Although the PANSS may be of value in research, this measure is not widely used in clinical practice and therefore the CGI might be of more value. Although the CGI might not be as informative a measure, it may have more clinical utility. Finally,Corell cautioned that average results may be of great research use and interest, but how this is of value to the individual in the clinic is not entirely yet clear.

Dr. Bruce Kinnon presented data from a large risperidone study examining prediction of robust response. Again data indicates that response by 2 weeks seems to predict a response at 12. This holds true for 30% of the sample. This important subgroup could be highlighted at 2 weeks for the positive predictive value of 70% and a negative predictive value of 80%. The number of episodes in the last 2 years and baseline PANSS are good predictors of response. Further analysis of PANSS data suggested that these early responders can be divided into three groups: those who gain a true drop of 7 or more in two psychotic items on the PANSS, and then a further group defined as having a 2 point drop on excitement items on the PANSS, and if gains in either the psychotic or excitement items are not seen, the remainder are defined as non-improvers (929).

Dr. Shitij Kapur (London, UK) discussed issues around the mechanisms of delayed response and presented some data from past studies and even striatal d^2 occupancy—even within a few hours of administration of medication that may well be used to predict early improvement and PANSS scores a few weeks later. He went on to discuss the issue of the collective versus individual response. It is clear that average scorings are not a good reflection of what actually is happening. With rather elegant analysis, a "parsimonious trajectory fit" was undertaken on individual patient data. Again, as with other studies, 15% of the people who had a dramatic response to medication in a placebo-controlled trial, were independent of any placebo effect. However, any other level of response, even good or moderate response, seemed highly contaminated by placebo response and when these data were illustrated with what effect is absolutely discernable from placebo in these moderately responding or non-responding subgroups, there seemed to be no clear effect of the antipsychotics. The difference driving the overall effect of drug and non-drug was the effect in the 15% dramatic responders.

There were several comments and questions, and one recalled the history of how Jaansen in the 1950s had suggested that haloperidol may well have a response in a matter of hours. Two points were made that people who are non-responders, may have other issues that hamper response (i.e. family/social) and their non-response may well be a function of those rather than anything to do with how their neurotransmitters are treated. Although confounding variables are randomized evenly across groups, multiple analyses from week to week within a group could well result in confounding variables having profound effect on peoples' mental state and functioning, and these variables have not been measured in routine data collection.

5.7. Novel interventions (reported by Kristen A. Woodberry)

Data for 4 novel non-pharmacological interventions and longitudinal data related to diagnostic issues and treatment response in schizophrenia and related disorders were presented. Innovative strategies highlighted the use of new technologies such as electronic medication adherence monitors, transcranial direct current stimulation (tDCS), and biofeedback based on visual scan paths and neural signal from fMRI. Pilot data illustrated the potential of bottom–up approaches for remediating cognitive deficits in learning and social cognition and for testing causal models. Related research provided longitudinal follow-up of obsessive compulsive symptoms in first-episode schizophrenia, predictors of recovery and treatment response in first-episode spectrum disorders, and five-year follow-up of individuals at ultra-high risk for psychosis.

Presenters offered new strategies for long-standing challenges in the treatment of schizophrenia. For instance, "smart pill containers" (devices that remind patients not only when and what dose of medication to take but why they are taking it) are demonstrating promising effects on medication adherence, particularly in the context of Cognitive Adaptation Training (CAT), a manual-driven treatment using environmental

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supports to cue and sequence target behaviors in the home. In an effectiveness trial of CAT in a community mental health clinic, average medication adherence was almost 95% across 9 months. Discussion focused on the difficulty teasing out non-adherence versus malignancy in reasons for poor outcomes such as hospitalization and the fact that medication dosing is often managed without sufficient knowledge of how much a patient is actually taking.

Bottom–up approaches to refractory deficits also show potential for identifying new intervention targets and mechanisms. tDCS to the left dorsolateral prefrontal cortex may improve feedback learning for schizophrenia patients classified as "good learners"(*Dr. Cyndi Weichert*). Importantly, feedback learning demonstrated a moderately strong correlation to overall quality of life. *Dr. Kathryn McCabe* presented a work demonstrating that visual scan path remediation may have a positive impact on emotion recognition and raised the question of whether emotion recognition may be an "upward manifestation of early visual processing dysfunction" (e.g., Russell et al., 2008). Another bottom–up approach to improving emotion recognition was presented by *Sergio Ruiz*. Using real-time biofeedback from fMRI and brain computer interfaces, individuals with chronic schizophrenia were successfully taught volitional control of the neural signal of the anterior insula. This new capability was accompanied by changes in perception of emotional faces and enhancement of effective brain connectivity. Although fMRI has little practical treatment value due to cost, these techniques offer exciting opportunities for clarifying the neural pathways underlying behavioral functions.

Longitudinal data related to treatment response provided valuable information for shaping future treatment approaches, particularly for FES-spectrum patients. In a five-year follow-up, *Dr. Lieuwe de Haan* suggested that roughly half of these patients experience obsessive compulsive symptoms and these are significantly related to psychotic relapse, depressive symptoms, and worse social outcome. He did not support the suggestion that they reflected coping strategies. Also reporting on a five-year follow-up on a similar sample, *Dr. Nikolai Albert* identified predictors of recovery (Bertelsen et al., 2009). These included social capabilities, GAF, negative symptom dimensions, being male, not having a partner, increased age, and having children. Duration of untreated psychosis and a diagnosis of schizophrenia, although strong predictors of poor outcome, were not predictors of recovery. *Dr. Benedicto Crespo-Facorro* reported on an antipsychotic trial in first-episode psychosis (non-affective) suggesting that the degree of symptom reduction at week 3 provided the best distinction between responders and non-responders at week 6.

Dr. Barnaby Nelson presented longitudinal follow-up data on 75% of the 416 UHR individuals recruited to the PACE clinic over a 10-year period (1995–2005). Risk of transition to psychosis in this population extends 5 years and longer after initial identification. In light of decreasing transition rates for more recent cohorts, the possibility was raised that later cohorts, marked by reduced duration of symptoms at study entry, might not have moved through the greatest period of risk within the time frame of typical follow-ups. Cohort differences may include the possibility that earlier identification may facilitate more effective intervention and prevention. During the discussion, Nelson indicated that the severity of putative prodromal symptoms has not changed over the years, that some syndromes or disorders do remit over time, but that 70% have a non-psychotic diagnosis at follow-up. Eight of the nine deaths reported were due to suicide. Follow-up of individuals who refused research found a transition rate of 18%.

5.8. Vocational recovery in first-episode psychosis: international evidence for early intervention (reported by Hiroaki Hori)

Unemployment is a major problem facing individuals with psychotic illnesses, including both those with chronic mental illness and those with first-episode psychosis. The approach to vocational recovery that has the most empirical evidence is the Individual Placement and Support (IPS) model, a highly defined form of supported employment. Although IPS has been shown to be effective in chronically ill people through a number of randomized controlled trials, there has been only one randomized trial to date that has investigated the effectiveness of IPS in people with a recent-onset of psychosis (Killackey et al., 2008). This interesting session, chaired by Dr. Eóin Killackey (Melbourne, Australia), included four presentations applying IPS to people with first-episode psychosis.

Dr. Keith Nuechterlein (Los Angeles, CA) began by mentioning that the application of IPS to people with first-episode psychosis is novel. After briefly explaining the nature and principles of IPS, Dr. Nuechterlein mentioned several potential advantages it has, such as prevention of chronic disability, making the best of patients' eagerness to return to jobs/school, and shorter duration of interruptions of prior work or school history. He then introduced the UCLA Aftercare Research Program for young persons with recent-onset (first episode in last two years) schizophrenia-spectrum disorders including schizophrenia, schizoaffective disorder and schizophreniform disorder. This was an 18-month randomized controlled trial of combined IPS with Workplace Fundamentals Module (WFM) for enhanced work rehabilitation ($n=46$) versus equally intense brokered vocational treatment approach plus social skills training ($n=23$). To fit the age range of recent-onset schizophrenia, in this trial IPS was adapted to include supported education as well as supported employment (Nuechterlein et al., 2008). Dr. Nuechterlein explained that WFM, a recently developed group skills training approach designed for integration into mental health settings, involves motivational interviewing, video-assisted social learning, role-played solutions, and problem-solving methods, emphasizing skills needed to maintain a job after obtaining one. WFM focuses on 9 skill areas, including how work changes your life, learning about your workplace, identifying stressors, learning to solve problems, managing symptoms and medications, managing health and hygiene, social interactions to improve work, socializing with coworkers, and finding support and motivation. For the IPS-WFM group, the first 6 months involved 2.5 h weekly WFM plus weekly meetings with IPS specialists. Next 12 months involved less frequent WFM groups and continued meetings with IPS specialists, with frequency fading over time. At this point Dr. Nuechterlein stressed several issues that should be taken into consideration when adapting IPS to young patients in the initial period of their psychosis: 1) since

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many individuals with first-episode psychosis were in the midst of their education, return to education is as common desired goal as a job, 2) IPS workers need to learn the options for individuals with psychiatric disorders in various educational institutions, 3) IPS may include teaching effective study skills, monitoring early progress and adjusting plans, arranging extra time for school activities such as papers and tests, and 4) direct contact of IPS workers with employers or teachers, in particular the disclosure of having a psychiatric condition, is a sensitive issue and therefore IPS workers need to work within the levels of contact and of disclosure permitted by the client. Of note, by the end of this 18-month study, 74% approved and received direct IPS help in the community. All 69 participants in the 18-month study were receiving atypical antipsychotics, starting with oral risperidone at baseline. During the initial 6 months of intensive treatment, 83% of subjects in the combined IPS-WFM group returned to competitive work or regular school, in contrast to 41% in the comparison group (Wald $\chi^2 = 7.73$, $p = 0.005$). The IPS-WFM group continued to show advantages at the end of the 18-month trial relative to the comparison group (72% versus 42%), even after the intensity of treatment had been decreased. The IPS-WFM treatment was superior to the comparison treatment for "total percentage of participants in competitive work or regular school at any point over the 18 months" (90% versus 59%, $\chi^2 = 8.16$, $p = 0.004$) and for "duration of time in competitive work or school" (42 versus 26 weeks, $F = 8.43$, $p = 0.005$).

Dr. Barnaby Major (London, UK), opened his presentation with a brief summary of the background and rationale of the intervention for first-episode psychosis using IPS, such as far-reaching benefits of work and study, right to work, and its evidence of efficacy in chronic mental illness, but not in a first-episode psychosis cohort. These prompted Dr. Major and his colleagues to design a naturalistic prospective cohort study aimed to evaluate the effectiveness of a modified form of IPS in first-episode psychosis. An occupational-therapy led vocational intervention service was developed called VIBE, a locally-derived modification of IPS, which was embedded within a multidisciplinary early intervention team serving two relatively deprived London inner city boroughs. The intervention included comprehensive baseline assessment, flexible and assertive individual support, specific skills training and liaison with employment/education providers, all of which were given from the beginning, and within 3 years. VIBE is similar to IPS in many aspects, except that the former focuses more on education and has broader goals (i.e., not only rapid job search but also early recovery of psychosis). One hundred and fourteen individuals (mean age: 24 years, 62% males, 85% black minority ethnic group) with first-episode psychosis were consecutively enrolled in this study and followed up for at least one year. Primary outcome was defined as competitive employment or educational activity. Results indicated that their premorbid functioning was markedly impaired, their average duration of untreated psychosis (DUP) was 3 months, they had moderate positive/negative symptoms, and that 58% and 18% of them were diagnosed as having schizophrenia and bipolar affective disorder, respectively. A multivariate analysis revealed that several variables were significant predictors of vocational recovery during 12 months follow-up; having access to VIBE, being educated beyond secondary level, duration of untreated psychosis, 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 (OR = 3.53, 95% CI = 1.25 to 10.0). During the subsequent follow-up period up to 3 years, these results were generally unchanged. Dr. Major concluded with the following remarks: 1) modified IPS following first-episode psychosis is effective, 2) effect is additional to early intervention alone, 3) the present findings were consistent with emerging international data, and 4) findings were relevant to patients, clinicians, commissioners and politicians.

Dr. Eóin Killackey (Melbourne, Australia) described the current situation and recent changes in employment/unemployment and welfare status in Australia. In general, people with psychotic illnesses are among the worst of groups who are socially excluded from employment. Unemployment rates for first-episode psychosis and schizophrenia are 40% and 74%, respectively. Persons with psychological and psychiatric disabilities constitute the largest proportion of jobseekers participating in public funded disability employment services, but achieve the lowest proportion of durable open employment compared to other disability groups. Given these facts, clearly there is a need for a better approach to the vocational recovery of people with mental illness, in particular psychotic illness. Dr. Killackey listed a number of reasons for targeting young people with psychosis; 1) they are less removed from their original vocational trajectory, 2) they would be physically healthier than those with chronic schizophrenia, 3) they are more likely to have a peer group, 4) they are less likely to have serious forensic involvement, 5) they are relatively open to learning new skills, and 6) the potential gains in terms of vocational, symptomatic and social outcomes are much greater. A study by Ho et al. (1997) showed that patients with a first-episode psychosis are highly likely to become dependent on welfare benefits. Their education achievement is also poor, as indexed by the markedly lower rate of those with first-episode psychosis who achieve 12 years of education (Killackey et al., 2008), 31% as compared to the average rate in healthy populations of approximately 80%. Moreover, the extra costs due to non-working people with schizophrenia are enormous. To address all these problems, supported employment, or IPS, has been developed. Dr. Killackey showed a comparison of competitive employment rates between supported employment (mostly IPS) groups and control groups in 16 randomized controlled trials. It was obvious that supported employment was much more beneficial for achieving competitive employment. In his original study (Killackey et al., 2008) 41 people with first-episode psychosis were randomly allocated to IPS ($n = 20$) or treatment-as-usual (TAU, $n = 21$). The IPS group worked with an employment consultant as part of the clinical team, while the TAU group could access all normal clinical services and external vocational agencies. Assessments were made at baseline and six months. The results showed that significantly more of those in the IPS group became employed or enrolled in courses than those in TAU (17/20 versus 6/21, $p = 0.000$). When the outcome was confined to work only, there still remained a significant difference (13/20 versus 2/21, $p = 0.000$). The IPS group obtained a significantly larger number of jobs than the TAU (23 versus 4, $p = 0.006$).

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Participants in the IPS group had a significantly higher median income (AU$:2432 versus AU$:0, $p = 0.012$). In addition, the IPS group demonstrated reduced use of welfare benefits (80% to 56%), in contrast to the control group (57% to 57%).

Dr. Miles Rinaldi (London, UK), began by stating that employment/education rates in individuals with first-episode psychosis were quite poor in his country. Studies have shown that onset of schizophrenia is associated with a pronounced decrease in employment. His own study (Rinaldi et al., in press) in Southwest London was conducted in a naturalistic setting, i.e., in routine clinical practice. One hundred and sixty-six participants, most of whom were recent-onset schizophrenia patients, were enrolled. Only 13% of the participants were in open employment at the outset, but this figure rose to 48% at 24 months. There was no change in the proportion of those who were in mainstream education/training throughout the 24 month period. In contrast, the proportion of those who were unemployed showed marked reduction during the first 6 months and this effect was maintained during the subsequent 18 months. The intervention with IPS achieved high fidelity, an index of the degree of implementation of an evidence-based practice. Dr. Rinaldi mentioned some myths surrounding employment of the mentally ill and stressed that there still are stigma, prejudice and discrimination attached to schizophrenia. These negative attitudes, coupled with the recent recession in UK, have been making employment of schizophrenia patients very difficult. A review that has recently been completed (Rinaldi et al., 2010) shows that studies using IPS as a vocational rehabilitation approach for first-episode psychosis generally demonstrate a strong effect on vocational recovery including both education and employment. Finally, Dr. Rinaldi mentioned an International Consensus Statement (http://www.iris-initiative.org.uk/), which was launched in London at an event organized by the World Health Organization. This statement concerns the rights of young people with psychosis to pursue employment, education and training, the evidence which exists about interventions to help them do this, and ways in which individuals, organizations and governments can assist.

The discussant, *Dr. Kim Mueser* (Hanover, NH) first stated that supported employment for first-episode psychosis is a clearly important intervention that has the potential to affect the long-term trajectory of the disease. Dr. Mueser described Dr. Nuechterlein's finding as a very strong indicator of the beneficial effect of the unique combination of IPS with social skills training Workplace Fundamentals Module on vocational recovery. He noted that it would be interesting to try to replicate this finding in other populations since UCLA's program is based on a referral-based population, but not a catchment-area based population. Dr. Major's presentation, by contrast, targeted an extremely disadvantaged population in a naturalistic study and showed the feasibility of implementing supported employment and education. Since the number of those who were enrolled in education programs in both groups increased over the follow-up period, including in the control group that did not receive supported employment and education, there may be a natural inclination for young people to go back to school. In Dr. Killackey's presentation, a very strong controlled trial demonstrated the feasibility of implementing IPS in an already established program for individuals with first-episode psychosis in a relatively disadvantaged population. Dr. Rinaldi's presentation again demonstrated the feasibility of the routine implementation of IPS for first-episode psychosis in a natural setting. Dr. Mueser concluded with the remark that the feasibility of implementing supported employment, specifically IPS, in first-episode psychosis was demonstrated in all four presentations. Throughout the discussion, he stressed that the education component of the supported employment is central to the vocational rehabilitation of people with first-episode psychosis.

6. Neuroimaging

6.1. Brain abnormalities in emerging psychosis (reported by Christopher Chaddock)

In this session data were presented to show that during the prodromal and early phases of psychosis, observable changes of neurobiology and neurofunction exist, are present prior to the onset of psychosis, and are predictive of subsequent transition to psychosis.

The first speaker was *Dr. Stephen Lawrie*, who reported on progress from the Edinburgh High Risk Study (EHRS), where subjects were recruited who had at least two first-degree relatives with schizophrenia, providing an enriched sample of subjects at genetically high risk of developing schizophrenia. By the close of the study, 13% of the high-risk (HR) group developed schizophrenia. At baseline, the EHRS identified a number of regional alterations of brain structure including reduced GM volume in the HR sample compared to the control group within the left amygdala–hippocampal complex and bilateral thalamus (Lawrie et al., 1999). Within the same HR sample, a longitudinal study showed dynamic GM changes over an 18 month period, with marked GM reductions noted in both temporal and frontal regions, particularly in those subjects who experienced psychotic symptoms at one or both assessments (Job et al., 2005). A comparison of those HR participants who subsequently became ill (HR-P) and those that did not (HR-NP) showed greater GM volume loss over time in the left inferior temporal gyrus, uncus and cerebellum, with these reductions in GM density showing positive predictive values of around 60%–70% (Job et al., 2006). However, cortical gyrification patterns that are thought to reflect genetically programmed maturation patterns, showed the strongest neuroimaging predictor of subsequent transition to psychosis in the HR group (Harris et al., 2007).

Dr. Lawrie concluded with some unpublished data incorporating all scans from the EHRS, which have tracked the time course of brain changes during the progression to psychosis using up to 5 scans at multiple time points. *GroupXTime* interactions were observed in the prefrontal GM volume, in which an exaggerated loss of prefrontal volume was observed bilaterally in the HR-P group compared to the HR-NP. GM volume change correlated with positive symptom levels, which is suggestive that this relationship operates upon a continuum across the psychosis spectrum. A significant *GroupXTime* interaction also existed when assessing white matter volume, however in this analysis a specific abnormality was observed in the HR-P group, where a decrease in white matter volume was seen in the HR-NP

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group, and control subjects showed a pattern of increasing white matter volume. The white matter volume change was not seen to correlate with symptom levels. The cause of the white matter change is unknown, but could relate to genetic susceptibility (McIntosh et al., 2008).

Dr. Stephan Wood reported on findings from the Melbourne Ultra-High Risk (UHR) cohort. Unlike the Edinburgh study, these high risk subjects are selected by having attenuated psychotic symptoms, the history of a brief limited psychotic episode of less than one week, or a family history of psychosis with a cognitive or social decline. UHR cohorts typically show 20–35% transition rate within a two-year period from baseline assessment (Yung et al., 2003). The first published structural imaging study of the UHR state was from Melbourne in which they compared UHR subjects who did not develop psychosis (UHR-NP) with those who did (UHR-P). The latter had less GM in the right medial temporal, lateral temporal, and inferior frontal cortex, and in the cingulate cortex bilaterally (Pantelis et al., 2003). Between baseline and follow-up scans the UHR-P group showed a greater reduction in GM in the left parahippocampal, fusiform, orbitofrontal and cerebellar cortices, and the cingulate gyri (Pantelis et al., 2003). These findings, were further explored by investigating the cortical surface changes over time, with significantly greater brain contraction observed in the UHR-P group in comparison to the UHR-NP group (most marked in the right prefrontal region; Sun et al., 2009a). Region of interest studies have confirmed greater GM loss in the UHR-P group compared to the UHR-NP and control sample, both within the superior temporal gyrus (Takahashi et al., 2009b), and the Insula cortex (Takahashi et al., 2009a). A reduction in white matter volume has also been observed in the region of the left fronto-occipital fasciculus in the UHR-P group (Walterfang et al., 2008). Dr. Wood concluded by discussing possible causes of these structural changes, and whether they relate to i) medication exposure, which happens after transition to psychosis; ii) age and development effects, i.e. whether a normal developmental process is accelerated; or (iii) a biological discontinuity, i.e. stress or cortisol changes. He also discussed the importance of considering other psychiatric disorders, i.e. mood disorders as outcomes, moving away from the focus on the transition to psychosis as the only predictive of outcome.

Dr. Stephan Borgwardt presented research from the Basel early detection of psychosis study (FEPSY). Dr. Borgwardt's research assesses structural changes associated with transition to psychosis in an UHR sample. The first study was a cross-sectional design, and identified reduced GM volume in UHR subjects compared to a control group in the posterior cingulate gyrus and precuneus, with a trend for reduction in the left insula, bilateral superior temporal gyri, the left amygdala–hippocampal complex, and the right amygdala (Borgwardt et al., 2007). There were also GM differences between UHR-P and UHR-NP groups, with lower GM volume in the UHR-P group in a region that included the right insula and the adjacent part of the right anterior superior temporal gyrus, and at trend level in the anterior cingulate gyrus. Greater GM volume was seen in the ARMS-P group in the parahippocampal, fusiform, and medial occipital gyri, plus the posterior temporal, inferior parietal and postcentral cortex and also the thalamus and supramarginal gyrus (Borgwardt et al., 2007). Using a longitudinal design, GM volume was seen to decrease to a greater degree between the baseline and follow-up scans in the UHR-P group within the orbitofrontal cortex, the right inferior temporal, superior frontal, and superior parietal lobule, the left precuneus, and the right hemisphere of the cerebellum, whereas the UHR-NP group showed no change in GM volume (Borgwardt et al., 2008). Cortical thickness measurements were made within 41 anatomic regions; cortical thickness asymmetry distinguished a first-episode psychosis sample from a control group ($P = 0.0006$; sensitivity, 70.0%; specificity, 85.0%) with a trend observed for distinguishing the UHR group from controls as well ($P = 0.06$; sensitivity, 75.0%; specificity, 65.0%) (Haller et al., 2009).

Finally, Dr. Borgwardt presented a synthesis of UHR imaging studies, across varying methodologies, including neurochemical, neurofunctional and neurostructural studies. Twenty-five studies were reviewed. Structural MRI studies showed small to medium effect sizes of decreased prefrontal, cingulate, insular and cerebellar gray matter volume in UHR-P compared to UHR-NP. Meta-analysis revealed relatively larger whole-brain volumes in UHR-P compared to UHR-NP subjects. Compared to UHR-NP, UHR-P subjects showed by fMRI reduced brain activation in the prefrontal cortex, reduced neuronal density, and increased membrane turnover in frontal and cingulate cortex with medium to large effect sizes (Smieskova et al., 2010).

Dr. Nicolas Koutsouleris (Munich, Germany) also discussed his work on a UHR sample, with subjects recruited from the Early Detection and Intervention Centre for Mental Crises at the Ludwig Maximilians University. He showed that UHR subjects could be differentiated from healthy controls at baseline, with GM reductions found within prefrontal regions, including the medial and lateral prefrontal cortex, the orbitofrontal cortex and the anterior cingulate cortex. GM volume reductions were also observed in a right-sided temporal cluster involving the insular cortex, the inferior, middle and superior temporal gyrus (Meisenzahl et al., 2008). He also showed that the UHR-P group differed from the UHR-NP group, with a cluster identified in the prefrontal cortex that showed decreased GM volume in the UHR-P group in dorsomedial, anterior cingulate and orbitofrontal regions (Koutsouleris et al., 2009b). Another analysis addressed whether an individualized neurodiagnosis of psychosis is possible, using multivariate pattern classification. The previous analyses had considered each voxel independently, whereas pattern analysis takes information from all voxels to identify a complex morphological phenotype, rather than considering single brain regions. One particular advantage for pattern analysis is that it allows for the sensitivity and specificity of an analysis to be examined providing possible diagnostic utility. Koutsouleris et al. (2009a) showed the ability to discriminate UHR individuals from a control group in a case-wise basis with more than 86% of cases correctly classified. In addition it was possible to discriminate the UHR-P from the UHR-NP group with 82% accuracy (Koutsouleris et al., 2009a), based upon the classifier detecting a pattern of GM volume reductions involving the medial, lateral, and inferior temporal cortices, as well as the lateral prefrontal areas, the thalamus, and the cerebellum. Dr. Koutsouleris also discussed the possibility of

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using the original baseline classification results to predict brain deformation change over time, as there appears to be acceleration in GM changes over time in the UHR group in comparison to a control group.

In summary, these imaging studies reveal that cross-sectional and longitudinal abnormalities exist on at-risk individuals and first-episode patients and offer important insights into the brain pathology emerging during the transition from the prodromal state to full-blown schizophrenia. In addition, the recent advent of multivariate pattern recognition techniques in the neuroimaging field has opened up new possibilities to derive valid biomarkers that may allow for the individualized early recognition of the at-risk mental state and the prediction of disease transition.

6.2. Integration of structural, functional, and neurochemical brain changes prior to psychosis onset (reported by Renate Thienel)

Dr. Jon Roiser (Institute of cognitive neurology, London, UK) talked about aberrant salience in psychosis. The effect of incentive, motivational salience (like food, money etc.) is mediated by Dopamine (DA). Disruptions can lead to maladaptive incentive salience. The aberrant salience hypothesis (Kapur, 2003) constitutes a context-independent DA release with increased attribution of salience to neutral objects and internal representations. Cumulative aberrant salience experiences are thought to lead to delusions. Murray et al. (2008) demonstrated that aberrant salience is evident in psychosis. Schizophrenia patients showed enhanced responses to neutral stimuli and decreased responses to rewarded/punished stimuli. This was functionally correlated with bilateral temporal activation in the fMRI and interpreted as patients reading something into neutral situations.

The SAT (salience attribution test) utilizes a button press to squares on a screen. The faster the RT, the more money the subjects get. But money is only distributed 50% of the time, depending on a cue (cues have a color and shape dimension). While the color information codes for high versus low probability of gains, the shape information codes for no such difference. Roiser et al. (2009) demonstrated that patients showed a reduced adaptive salience, but equivalent aberrant salience as healthy subjects. When choosing only delusional patients though, the patients did show a reduced aberrant salience. Adaptive reward prediction (color stimulus) was associated with activations in VTA, thalamus, medial dorsal thalamus, and emotional limbic loop (DA mediated). The thalamus (pulvinar) has been associated with salience before. Aberrant reward prediction (by asking them if they expect shapes to be predictive) leads to bilateral DLPFC activation in healthy volunteers.

Roiser et al. (2010) demonstrated that differential dorsolateral PFC and middle temporal gyrus (MTG) responses in healthy subjects to cues with identical reward probabilities were very strongly correlated with the degree of aberrant reward learning. Participants who showed greater aberrant learning exhibited greater dorsolateral PFC responses, and reduced MTG responses to cues erroneously inferred to be less strongly associated with reward. Roiser also reported that non-medicated at-risk mental state (ARMS) subjects showed higher aberrant salience but normal adaptive salience. Aberrant salience correlated with CAARMS positive symptoms and thought content as well as with schizotypy. Activations in the right DLPFC in response to low probability stimuli were evident in at-risk subjects only. There was no difference in adaptive reward prediction. L-DOPA was higher in the associative striatum with aberrant reward prediction. There was a strong positive relationship between striatum activation in healthy subjects, and a negative correlation in ARMS subjects.

Dr. James Stone (Imperial College London, UK) reported that most risk genes for schizophrenia impact on glutamatergic NMDA receptors, which can be blocked by ketamine. As reviewed by Olney and Farber (1995) administration of NMDA antagonists leads to toxic changes in cortical regions in rats due to excitotoxicity, conditional upon disinhibition as NMDA receptors are expressed on gabaergic interneurons. Law and Deakin (2001) demonstrated a reduction in mRNA expression of NMDA receptors in the left hippocampus in un-medicated patients. NMDA receptor dysfunctions have downstream effects. Using Magnetic Resonance Spectroscopy (MRS) Theberge et al. (2007) showed elevated glutamate levels in first-episode patients in the anterior cingulate (AC). This might be associated with reduced gray matter in subjects that transitioned to psychosis and may be due to the excitotoxic action of glutamate. Using MRS one has to predefine a region and assess metabolites, such as glutamate/glutamine. Twenty-seven ARMS subjects, 6 receiving antipsychotic medication, plus age and sex matched controls were scanned by MRS using a 3 T scanner and AC, left thalamus, left medial temporal cortex plus gray matter voxel based morphometry was performed. Gray matter reductions in the medial prefrontal cortex and the AC were found and Glu reduction was present in the thalamus, and increased in the AC. NAA was reduced in the thalamus. Lower levels of Glu in the thalamus were correlated with smaller volumes in some brain areas. When evaluating Glu over time and how it is related to transition, the 3 subjects that underwent transition to psychosis of 18 demonstrated the same thalamic Glu baseline levels as subjects that did not transition to psychosis. Whereas at follow-up, those who transitioned to psychosis had lower thalamic Glu.

Dr. Thomas Whitford reported on infectious agents, i.e. viruses and parasites, as risk factors for developing psychosis. The family history of patients with psychosis often discloses environmental factors, like obstetric complications, or infectious agents. Patients show abnormally high levels of infectious agents like toxoplasma antibodies. But the mechanism is unknown. Infectious agents might change the structure of the brain, and these structural brain changes might increase the risk for psychosis. Therefore the study assessed whether subjects with an infection show differences in brain structure. Toxoplasma, the herpes viruses, and others were tested by determining seropositivity in subjects exposed to the agents in the past. Toxoplasma exerts its action through changes in brain chemistry, i.e. infected rats show increased dopamine (DA) levels in the amygdala. Rats lose their fear of cats when infected with Toxoplasma through changes in DA levels in the amygdala. This fear can be reintroduced by administration of antipsychotics.

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T1-weighted MRIs, using the VBM method with ROIs were collected in $N = 58$ high risk for psychosis subjects (aged 14–29 years). Subjects with seropositivity (IgG antibodies seropositivity) showed no difference in brain structure for all of the viruses (IgG flu, herpes, etc.). But there was a significant reduction in the limbic lobe for recent infection with toxoplasma determined by toxo-seropositivity. An increased toxoplasma infection rate in schizophrenia patients, could increase DA levels and trigger psychosis. However, note that the subjects in this study were IGM positive but IGG negative. In addition, seropositivity for toxoplasma is very high in the Australian general population and ranges up to 80%. Thus, these results could be false positives.

Dr. Paolo Fusar-Poli (Fabio University, Italy) evaluated whether neurocognitive prefrontal cortex (PFC) deficits are a trait of the prodromal state (Fusar-Poli et al., 2007). Striatal dopamine (DA) function is aberrant in schizophrenia. In order to examine the relation between striatal and PFC DA levels, F-DOPA PET plus fMRI scans were carried out on 16 healthy subjects compared to at-risk mental state subjects (aged 14–30 years). The study hypothesized that ARMS subjects show a higher striatal DA correlated with altered activation in PFC. A verbal fluency task was administered in a 1.5 T scanner. DA synthesis was assessed using F-DOPA-PET. The verbal fluency task leads to a greater left inferior frontal gyrus activation in ARMS subject when compared to controls representing an increased, exaggerated response in at-risk subjects. The Blood Oxygen Level Dependent (BOLD) signal increase was significantly correlated with psychopathological ratings on the CAARMS (perceptual abnormality subscale). An increased synthesis capacity was assessed with F-DOPA-PET. An elevation of subcortical DA function in the association part of the striatum was found. Furthermore striatal DA was correlated with the CAARMS-scale. A negative correlation was found between neurocognitive performance (verbal fluency) and subcortical DA. The fMRI and PET results, BOLD and striatal DA levels correlated positively in the left frontal cortex within the at-risk group only.

Dr. Shitij Kapur as the discussant quoted David Hull's book 'science as a process' (Hull, 1988) describing science as it develops through 3 stages: cataloging findings, correlating data, and finally integrating and synthesizing use the same terminology. Shitij Kapur underlined that this session showed that we are reaching stage 3, where we use the same terminology, and we are at the stage where we can start synthesizing. But he formulated two thoughts/questions. He said that there is a body of findings that have to do with DA and Glu. Thus, one could well ask whether UHR a just quantitatively smaller than schizophrenia or is it qualitatively different? If it was just a "little schizophrenia" we would not have different therapeutic targets. He asked the question whether we could predict conversion, hence whether the data is generating prediction or new strategies of intervention for prevention or just suppression. Dr. McGuire responded that UHR is not a "mini-schizophrenia", because Glu results on MRS are greater in the prodrome than in schizophrenia. Thus, a Glu treatment might be more useful in high risk than in clinical schizophrenia. Dr. Pantelis responded that interventions at early stages might be things such as targeting HPH-axis activity like pituitary body changes or cortisol changes, and these may not be relevant to treatment of chronic schizophrenia.

6.3. Making connections: abnormal white matter development in the early stages of schizophrenia (reported by Gabriela Novak)

Dr. Anthony James (Oxford, UK) discussed abnormalities in white matter tracks between early onset schizophrenia and early onset bipolar disorder. Bipolar disorder and schizophrenia share pathophysiological mechanisms (Craddock and Owen, 2010). Furthermore, previous research, which tracked the ongoing myelination process and the dynamic changes in cortical structures in children and adolescents using magnetic resonance imaging (MRI) revealed deviations from normal development, characteristic of schizophrenia and bipolar disorder, suggesting a neurodevelopmental cause (Gogtay and Thompson 2010).

Dr. James used MRI and DTI to study white matter (WM) and gray matter (GM) in 43 subjects with early onset schizophrenia, 15 with early onset bipolar disorder and 36 controls. Significant changes were found in both schizophrenia and bipolar disorder as compared with controls. However, in schizophrenia changes in white matter were found primarily in cortical, subcortical and cerebellar tracts, with reduced gray matter density in frontal and temporal lobes; while in bipolar disorder, white matter changes were observed in the corpus callosum and gray matter changes in the visual processing areas, and cerebellum. These patterns suggest that the neural abnormalities in schizophrenia and bipolar disorder differ, with only corpus callosum being similarly affected, at least in the early course of the disease during adolescence. In addition, gray matter loss was much less significant in bipolar disorder. This is in agreement with observed changes in multiple premorbid IQ domains, including verbal fluency. While there is a premorbid decrease in IQ in schizophrenia, no evidence for such decrease was found in bipolar disorder. However, working memory processing has been significantly affected in both disease states (Zanelli et al., 2010; Barrett et al., 2009).

Dr. Katherine Karlsgodt (UCLA, California, USA) discussed normal white matter development in general and in adolescents with high risk for psychosis. Current research using DTI shows a decrease in fractional anisotropy(FA) in white matter of first-episode schizophrenia patients, suggesting a disruption of white matter integrity, possibly predating the onset of the disease (Hao et al., 2006; Price et al., 2008). This abnormality seems to only become evident during adolescence, the most proximal stage of neurodevelopment to the onset of schizophrenia, at a time of significant reduction in gray matter through pruning and an increase in white matter during the final stages of myelination.

In 2008, in order to examine whether anatomical changes are present at the onset of schizophrenia, Dr. Karlsgodt applied a rigorous registration approach of Tract-Based Spatial Statistics (TBSS) to DTI to examine FA in the superior longitudinal fasciculus (SLF; Karlsgodt et al., 2008). The study showed that SLF integrity was disrupted by the first episode, therefore early on in the disease. In a next step, in order to assess whether white matter abnormalities are present prior to the onset of the disease, Dr. Karlsgodt analyzed the change

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in baseline white matter integrity in a cohort of individuals of ultra-high risk for developing schizophrenia (UHRS), recruited through the Center for Assessment and Prevention of Prodromal States (CAPPS; Karlsgodt et al., 2009). She again used TBSS to examine FA in six major white matter tracts. While controls showed an increase in FA (indicating an increase in white matter) with age, this was not observed in UHRS individuals, indicating that the normal myelination pattern may be altered. In fact, the baseline white matter integrity was predictive of social and role functioning 15 months later. In particular, verbal working memory performance was affected, and a cognitive deficit was observed in schizophrenia and known to be associated with this circuitry. In summary, her research shows that changes in white matter integrity are present very early in the disorder and possibly pre-date the illness and that patients fail to show a normal increase of white matter during adolescence. Dr. Karlsgodt suggested that these changes may arise through a disrupted developmental process, suggestive of a genetic influence on white matter microstructure.

Dr. Marek Kubicki (Harvard Medical School, Boston, MA, USA) discussed his recent DTI findings in first-episode schizophrenia, chronic schizophrenia and controls who were part of a Center for Intervention Development and Applied Research (CIDAR) consortium. The goal was to understand whether white matter abnormalities in schizophrenia are restricted to certain tracts or widespread, whether they are present at first episode, and whether they progress over time. Dr. Kubicki scanned 18 first-episode patients and 20 controls at high DTI resolution in 51 directions in order to add specificity to DTI measurements. He observed differences in a number of areas, in agreement with a meta-analysis that implicated changes in the uncinate fasciculus (UF) and cingulum bundle (CB) (Ellison-Wright et al., 2008). Using track-based spatial statistics, FA abnormalities were observed in both first episode and chronic schizophrenia, but Trace (a measure of mean diffusivity) was increased only in first-episode individuals. While progressive changes at first episode have been reported before, Trace increase in FA and its normalization in chronic patients were interesting. This finding was reported before, but only in a very small population (Garver et al., 2005). The most interesting is the correlation between increased Trace in first-episode schizophrenia patients and increased levels of anti-inflammatory cytokines (IL-6), since both Trace and cytokines normalized within 2 weeks after treatment.

The cytokines IL-2 and IL-6 are frequently abnormal in schizophrenia (review in Potvin et al., 2009) and are usually associated with an autoimmune response. Interestingly, cytokines can also increase dopamine release, and have cytotoxic effects on oligodendrocytes. Furthermore, cancer patients treated with cytokines exhibit hallucinations and delusions that respond to antipsychotic medication, which in itself has strong immunosuppressive properties. More research is needed to determine whether the Trace increase in first-episode schizophrenia patients is a sign of an autoimmunological response.

Dr. Gary Price (Institute of Neurology, London) performed a study of white matter tracts in first-episode schizophrenia and used a probabilistic tractography algorithm (Price et al., 2008), which provides an index of connectivity of white matter. He studied the corpus callosum (CC) and uncinate fasciculus (UF) in 18 patients with first-episode psychosis and 21 controls. He applied a multi-threshold approach to analyze the structure of the CC and showed that there is a decrease in CC FA in patients, but no overall change in UF. A change in UF was only present in a specific area of the left UF and the effect was sex-specific.

In summary, abnormalities in white matter observed using DTI suggest abnormalities in structural connectivity with strong sex effects. FA was reduced in patients compared to controls in tracts crossing the genu, and to a lesser degree in the splenium of the CC. However, there is yet no direct evidence for what FA signifies. There are some suggestions that it could be related to inflammation or other processes other than myelination. For a recent review of this topic see Frangou (2010).

6.4. Brain progression in schizophrenia: who, where, when, how? (Reported by Christopher Chaddock)

This session reported on brain structural changes that occur during the lifespan of a psychotic patient, whether they are apparent before onset, and whether they show continued progression after the illness onset.

The first presentation was by *Dr. Christos Pantelis*, who reported on findings from the Melbourne Ultra-High Risk (UHR) cohort, where subjects are at high risk of developing psychosis, and are selected due to the presence of attenuated psychotic symptoms, the history of a brief limited psychotic episode of less than one week, or a family history of psychosis with a cognitive or social decline. UHR cohorts typically show a 20–35% transition rate within a two-year period from baseline assessment (Yung et al., 2003). Past research has shown that cross-sectional studies of volunteers with established schizophrenia, show enlarged ventricles, and reduced gray matter (GM) in fronto-temporal, limbic and subcortical regions (Fornito et al., 2009a), with greater abnormalities observed in chronic compared to first-episode schizophrenia (FES) (Ellison-Wright et al., 2008). Indeed brain structural changes can be observed in the UHR state with UHR subjects who did develop the disorder (UHR-P) showing lower gray matter than those UHR who did not develop psychosis (UHR-NP) in the right medial temporal, lateral temporal, and inferior frontal cortex, and in the cingulate cortex bilaterally (Pantelis et al., 2003). Multiple time points are required to identify longitudinal changes in brain structure and increased GM loss has been seen in established psychosis (.e.g. Cahn et al., 2009; DeLisi et al., 1997; Ho et al., 2003; Lieberman et al., 2001). During the prodrome, longitudinal changes in gray matter development were observed between baseline and follow-up scans in the UHR sample, with the UHR-P group showing a greater reduction in gray matter compared to the UHR-NP group in the left parahippocampal, fusiform, orbitofrontal and cerebellar cortices, and the cingulate gyri (Pantelis et al., 2003). A further exploration of this dataset identified greater brain reduction in the UHR-P group in the right prefrontal region (Sun et al., 2009a), while in the FES sample, a similar finding of greater brain contraction was observed in the dorsal surfaces of the frontal lobe. Overall, brain surface reductions in patients and healthy controls show similar anatomical

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patterns, with the FES showing exaggerated progressive changes (Sun et al., 2009b). Subcortical brain structures have also been measured, with patients with chronic schizophrenia showing bilateral hippocampal volume reduction, FES displaying left hippocampal volume reduction and UHR patients showing normal baseline hippocampal and amygdala volumes (Velakoulis et al., 2006). The FES and chronic patients had significantly smaller anterior insular cortex at baseline than the controls. In a longitudinal comparison, the FES patients showed significant GM reduction of the insular cortex over time which correlated with symptom severity, while there was no difference between chronic patients and controls (Takahashi et al., 2009a). Similar findings have also been observed in those subjects at UHR, with UHR-P subjects showing greater gray matter reduction of insular cortex bilaterally compared with controls and UHR-NP subjects, indicating that insular cortex GM abnormalities in psychotic disorders may reflect a pre-existing vulnerability (Takahashi et al., 2009b). Dr. Pantelis concluded by placing these findings in a normal developmental context of maturational changes that begins during adolescence and continues to adulthood (e.g. Knickmeyer et al., 2010), and that an exaggerated normal maturational pattern may explain the brain structural changes. The discussion noted that the 2nd scan of a longitudinal study will be complicated by medication effects within the UHR-P group, however is unlikely to fully explain the differential pattern of development.

Dr. Robert McCarley (Harvard University, Boston, MA, USA) commented on whether a neurodevelopmental hypothesis of schizophrenia had to be mutually exclusive from the observation of progressive brain change (i.e. developmental GABA neuron excitotoxicity or other could lead to later brain changes). The study presented was undertaken at Mclean Hospital where a sample of first-episode subjects was scanned at baseline and also at a second time-point 1.5 years later. Medication began at the first episode approximately 2–3 weeks prior to admission. Twenty-one first-episode subjects and 23 healthy controls completed the baseline and follow-up scans. The DARTEL procedure as developed as part of the SPM software (Ashburner, 2007) was used to maintain accurate registrations both within and between subjects. As predicted, greater gray matter volume loss was observed over time in the first-episode sample in comparison to the control group, within the lateral prefrontal cortex, superior temporal gyrus, inferior and medial prefrontal gyri, left cingulate gyrus and bilateral insula. The change over time in positive symptom severity was negatively correlated to the change in gray matter volume in Heschl's gyrus bilaterally, indicating that greater gray matter loss was associated with worsening or less marked improvement in symptom levels. There was also a correlation observed between negative symptom severity and gray matter loss within bilateral prefrontal regions, the insula, and left supramarginal gyrus, while correlations to measures of cognitive functioning were much more widely distributed. Greater gray matter volume loss was seen in patients non-compliant with medication compared to those that were compliant. Therefore an accelerated gray matter loss is seen in the 1.5 years after onset of the illness, which relates to cognitive and clinical symptoms and does not appear to be due to medication. What is unknown is whether the rate of volume loss continues at a constant rate, or whether it occurs in a step wise manner with loss at each illness episode.

Dr. Kiyoto Kasai (University of Tokyo, Japan) began by stating that in some brain regions there is a known decline in gray matter volume in schizophrenia (e.g. Kasai et al., 2003a, b), but these changes may be greatest during transition from the UHR state to a first episode of psychosis. Dr. Kasai's research involves scanning the UHR sample at baseline and then one year later at follow-up and he presented some unpublished data from this sample. The first study was an fMRI facial imitation task in which subjects had to either imitate a facial expression by moving their own face, or observe a movie of a facial expression. Bilateral amygdala activation appeared lower on this task in the UHR group than in the healthy controls. The second study used MRS to measure glutamate levels, which appeared higher in the anterior cingulate in the ARMS group in comparison to a first episode and chronic sample. The third study used Near Infrared Spectroscopy (NIRS), which is a non-invasive and cheap measure similar to fMRI that can detect oxy/deoxyhaemoglobin changes at a depth of 2–3 cm beneath the skull (i.e. cortical). A finding of reduced fronto-polar activation in schizophrenia patients was observed, which was correlated with the degree of social functioning (Takizawa et al., 2008), and varied genetically as well (Takizawa et al., 2009).

Dr. Rene Kahn (University of Utrecht, Netherlands) discussed the dynamic brain changes that occur during a lifetime, and noted that these changes appear to be non-linear and differ in respect to the location within the brain. He presented data from a longitudinal study in which 96 patients and 113 controls were followed up during a five-year period. This data showed that there are brain changes occurring throughout the first 20 years of illness in schizophrenia, with greater GM volume decreases seen in patients (4.5%) than control subjects (2.5%). The gray matter loss was also accompanied by a larger increase of the third and lateral ventricular volumes. Patients show a different trajectory of gray matter volume with a negative linear relationship noted between volume and age of subject, while controls showed a non-linear relationship. The greatest rate of loss in schizophrenia appeared in frontal, temporal and occipital lobes. Those patients with a poor outcome showed a greater increase in lateral ventricle volume and a decrease in cerebral volume relative to good outcome patients. Patients medicated with olanzapine had a reduced rate of GM loss (van Haren et al., 2008).

Decreases in gray matter density were found in patients with schizophrenia in the left superior frontal gyrus, left superior temporal gyrus, right caudate nucleus, and right thalamus as compared to healthy individuals. The number of hospitalizations during the scan interval was significantly associated with a larger decrease in gray matter density in the left superior frontal gyrus, while cumulative clozapine and olanzapine intake per year significantly attenuated this loss (van Haren et al., 2007). In addition the total duration of psychosis was significantly related to the percentage of volume change in gray matter, lateral ventricle and third ventricle volume. There was no significant association between the total duration of psychosis and percentage of volume change in white matter (Cahn et al., 2009). New data

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also indicate that cortical thickness decreases significantly in patients over a five-year period in the superior temporal gyrus, inferior and middle prefrontal cortex. In those with a poor outcome, cortical thinning was seen in Wernicke's area, the post- and pre-central gyrus the paracentral gyrus and precuneus. In summary, the brain shows exaggerated gray matter loss in schizophrenia in addition to the plastic changes noted in healthy controls throughout the lifespan. Excessive cortical thinning appears clinically relevant, and medication with atypical antipsychotics appears to limit this loss. Due to non-linear brain changes within prefrontal regions, mapping the trajectory of brain changes during the transition to psychosis requires multiple time points.

Dr. Lynn DeLisi led the discussion by commenting that we now know that there are progressive changes in both gray and white matter in schizophrenia that are not solely caused by medication. There also appears to be a greater gray matter loss in poor outcome individuals, and gray matter loss is observed at the first episode and may be heritable. However what we don't know is when the brain changes begin deviating from normal maturation. While changes can be observed in the prodrome to psychosis, they may date back further even to infancy. We also still do not know the cause of these brain changes, whether they are due to abnormal maturation, abnormal neuronal metabolism, inflammation, or epiphenomena due to substance abuse, long-term medication, physiological changes unrelated to the illness or MRI methodological issues.

6.5. Brain maturation during adolescence and the pathophysiology of schizophrenia: relevance for understanding psychosis, cognitive dysfunction and implications for treatment (reported by Kristen A. Woodberry)

The talks during this session examined brain changes and the developmental context of early phases of schizophrenia. Longitudinal data and trajectories were emphasized with particular attention given to the timing of illness onset (adolescence). Speakers presented data suggesting brain deterioration proximal to the onset of schizophrenia, posing challenges for neurodevelopmental models to elaborating specific developmental processes during adolescence with possible relevance to mechanisms of psychosis onset.

In reviewing the evidence for progressive deterioration during the onset of psychosis (e.g., Borgwardt et al., 2008; Job et al., 2005; Pantelis et al., 2003; Takahashi et al., 2009a), *Dr. Christos Pantelis* argued that the timing of this deterioration must be considered within a developmental context and in relation to potential changes throughout the brain. He noted how the timing of brain changes had relevance to the possible prediction of later psychosis (Fornito et al., 2008a) and etiological models. For instance, although neurodevelopmental models would predict reduced hippocampal volume prior to the onset of psychosis, reduced hippocampal volume has not been found during the prodromal phase in subjects who later developed psychosis (Velakoulis et al., 1999, 2006).

A critical point made during the presentations and reiterated in the subsequent discussion was that current methods and findings cannot yet speak to whether progressive changes actually reflect pathophysiological processes in the causal pathway to psychosis or the consequence of illness on normal development (developmental "hit"). Developmental processes proposed to have possible relevance to illness onset were presented by *Dr. Cynthia Shannon Weickert* (maturation of inhibitory neurons and increases in stress responsivity) and Peter Uhlhaas (neural oscillation and synchrony). Cortical interneuron development has been targeted given the evidence of inhibitory neuron disruption in schizophrenia, its sensitivity to stress, and its relevance to prefrontal cortex development and function (e.g. Sinclair et al., 2010). Dr. Shannon Weickert argued for attention to migration and maturation of dendrite targeting and somatostatin positive interneurons in addition to parvalbumin positive interneurons. *Dr. Uhlhaas* illustrated the importance of normative data for understanding the timing of specific maturational processes in adolescence (Uhlhaas et al., 2009b, 2010b). He argued that the disruption of oscillation and synchrony during adolescence could lead to difficulties with information uploading and maintenance, symptom onset, and spatial working memory deficits.

Dr. Nitin Gogtay and colleagues' neuroimaging data have made an important contribution to clarifying patterns of cortical maturation in adolescence (Gogtay et al., 2004). One provocative finding arising from longitudinal imaging data has been the normalization over time of gray matter abnormalities in the siblings of individuals with childhood onset schizophrenia (Gogtay et al., 2007a). Longitudinal data for individuals with bipolar disorder relative to those with schizophrenia also suggest a possible role for brain maturational trajectories in differentiating these two disorders (Gogtay et al., 2007b). His work has also identified white matter loss in childhood onset schizophrenia (Gogtay et al., 2008). Possible mechanisms presented for progressive deterioration include stress and cannabis use (e.g., Yücel et al., 2008).

Dr. Patrick McGorry noted in his summary comments that good premorbid functioning is much more common than poor premorbid functioning in psychotic individuals, highlighting adolescence as the period during which most difficulties begin. At the time of identification of high risk (typically based on attenuated symptom onset or progression), however, subjects are already ill with global assessment of functioning (GAF) scores in the 40s and 50s. Evidence that maturational processes occur within a specific time or stage of development would support Max Birchwood's concept of a "critical period" (Birchwood et al., 1998). There is also uncertainty about how medications might influence changes in the brain (e.g., lithium may promote gray matter growth). McGorry argued that early intervention has the potential to facilitate "maturation out of risk".

There was some discussion about the apparent conflict between evidence implicating developmental processes during adolescence with the occurrence of childhood onset schizophrenia. Could this be considered evidence that abnormalities in brain maturation reflect a consequence rather than cause of illness? Additional comments noted that imaging findings remain non-specific and that early intervention is still exceedingly difficult, given the fact that prodromal symptoms predict diverse outcomes. Dr. McGorry argued that this very diffuseness of psychopathology supported a Youth Model of Care with less attention to specific diagnoses early on.

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7. Genetics

7.1. Genetics plenary session—clinical implications of recent genetic findings: GWAS, endophenotypes and commercial testing (reported by Naren P. Rao)

In this session, chaired by Drs. Lynn DeLisi and Ming Tsuang, panelists discussed recent findings in genetic research and their implications. *Dr. Michael J Owen* gave a summary on "Schizophrenia Genetics: What have we learned and where are we going?"*Drs. Mary-Claire King*, *Pablo Gejman* and *Peter Visscher* discussed Where the new GWAS has gotten us. *Drs. Lynn DeLisi* and *Dan Rujescu* debated the usefulness of the endophenotype concept in defining genes for schizophrenia. *Drs. James Kennedy* and *Thomas Lehner* ended with discussions of commercial DNA testing and whether it will ever be a useful tool in the clinic for schizophrenia.

Dr. Owen began by emphasizing the importance of studying risk genes in schizophrenia. Epidemiological studies have established a definite genetic role. However, the exact etiopathogenesis is still unknown. As genomic approaches do not require an understanding of pathogenesis, they have the potential to identify genes for common disease like schizophrenia. He later gave a brief account of the history of psychiatric molecular genetics and described different methods used in past, and present, predicting what could be used in future studies. While past studies examined linkage, candidate gene association, chromosomal abnormalities, the present studies are now Genome-Wide Association Studies (GWAS) and Genome-Wide Copy Number Variations (CNV). He predicted that whole genome sequencing will be the technology of future studies.

Dr. Owen also discussed the possibility of common diseases like schizophrenia being the result of a spectrum of risk alleles. While most alleles are common with small effects, some may be rare alleles with relatively large effects (Wang et al., 2005). Linkage studies assuming high penetrance and identify relatively rare alleles require large pedigrees for their identification. Candidate gene association studies identify genes which are typical of common diseases having low penetrance of very common variations. Thus there are multiple studies without conclusive results. False positive results could be due to small sample sizes and multiple testing. Thus, at present, findings from candidate gene studies have been disappointing. However, naturally occurring chromosomal abnormalities have identified some important genes implicated in schizophrenia but are relatively rare and very few genes have been identified by this method. He discussed the well known association of the deletion known as Velo-Cardio-Facial Syndrome (VCFS) on chromosome 22q11 and schizophrenia. The deletion includes such relevant genes as Catechol-O-Methyl Transferase. Another important gene identified this way is the DISC1 gene, located on chromosome 1. Interestingly, this gene is associated with visual and working memory deficits and has evidence for behavioral phenotypes in mouse models. Dr. Owen then summarized the findings of genetic studies up to 2007, then noted that a new era of schizophrenia genetics began in 2007, due to advances in technology which made genome-wide association studies and genome-wide detection of submicroscopic chromosomal abnormalities (copy number variations) possible. The advent of commercially available "Gene chips" facilitated these large-scale studies. GWAS detects common risk alleles with low penetrance. However, GWAS is not a strong method for finding individual genes and requires large samples. Lastly, he discussed the findings from his own studies in which he and colleagues identified and replicated ZNF804A as a risk allele in schizophrenia. Interestingly, strong associations from recent GWAS support genetic overlap between schizophrenia and bipolar affective disorder; ZNF804A and CACNA1C associations are found in both schizophrenia and bipolar disorder suggesting that common polygenic variation contributes to the risk of both schizophrenia and bipolar disorder (Ferreira et al., 2008; O'Donovan et al., 2008).

While GWAS detects common alleles with low penetrance, CNV can detect rare alleles with high penetrance. He enumerated the findings of different CNV studies in schizophrenia, including the association of a deletion in the Neurexin (NRXN1) gene in schizophrenia (also implicated in autism and MR). He then discussed ways in which the genetic findings can be translated to biologically meaningful outcomes. Genetic findings can be used to develop animal models which in turn can help in understanding disease mechanisms and potential drug targets. They are also useful in development of endophenotypes, biomarkers which may be of diagnostic and prognostic relevance. He explained the former with the examples of NRXN1 and DISC1 for which animal models have been developed. With the help of animal models, the functions of these genes are better understood. NRXN1 is essential in the development of synaptic plasticity and DISC1 is important in prenatal and adult neurodevelopment (Sudhof, 2008). He also explained the usefulness of identifying common low impact variants by using the example of the PPARG locus in type 2 Diabetes mellitus. However, future research needs to use new techniques, such as computational biology, modeling complexity, to bridge the gap between genetic findings and biological usefulness. He also mentioned that endophenotypes may be more helpful in characterizing the effects of alleles associated with the disease. However, endophenotype research assumes relative genetic simplicity and he cautioned that causality cannot be assumed by the thus far specifically chosen endophenotypes. He also suggested pooling clinical diagnoses to examine biology and used as an example, the findings of Craddock et al. (2010) on $GABA_A$ receptor gene variation in schizophrenia and bipolar affective disorder. When the diagnostic categories were retained, there was no significant difference for either group. However, a repeat analysis pooling both groups of patients revealed a significant difference between patients and controls. He concluded with prediction of potential uses of genetics in the future: defining more homogeneous groups and identification of possible shared mechanisms across diagnostic categories.

Dr. Mary-Claire King initiated the panel discussion on "Where have the GWAS gotten us?" The polygenetic model for schizophrenia was proposed many years back but still has not been clarified. GWAS is successful in identifying genes for some disorders like breast cancer and age-related macular degeneration where there is a presence of a rare variant of a haplotype or a functional common variant. However, there are many limitations and difficulties in interpreting the

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GWAS data in schizophrenia. The matching of cases to controls is not perfect and could lead to false findings. Since odds ratios are low, replication may be difficult.

Dr. Peter Visscher discussed "Narrowing the boundaries of the genetic architecture of schizophrenia" with the statement "Essentially all models are wrong, but some are useful". The model becomes useful if it can further be tested with new data. He discussed the concepts of genetic architecture and prediction models. Genetic architecture is made up of a number of causal variants, their effect size and their function varies. To be causal, the genetic variation should have a balance of frequency and effect size. Thus if a minor allele frequency is rarer then there should be a higher odds ratio and vice versa. But, with respect to genome-wide scans, if the locus effect is smaller, then there should be more number of variants and vice versa. Genetic architecture was traditionally analyzed using recurrence risk to relatives and then by pedigree studies. With the advances in technology, disease marker association studies within pedigrees were used, and now, disease marker association studies in populations are studied using genome-wide association. Different models have been used to predict the genetic risk of a disease. While evolutionary models are based upon assumptions that are hard to test empirically, a liability threshold model doesn't make any assumption and is consistent with observed risks in relatives, sporadic or familial cases, locus and allelic heterogeneity, phenotypic heterogeneity and multiple common and rare causal variants.

GWAS have revolutionized common disease research. In the last five years, a number of genes have been identified for different disorders with varying heritability. The International Schizophrenia Consortium (ISC) adopted a new strategy and used a less stringent *p* value and cross checked the results with independent study samples. The ISC findings are consistent with causal variants with small effects and both common and rare variants. However, it is not consistent with common variants with large effects. He concluded that GWAS have significantly contributed to narrowing the boundaries of genetic architecture and the empirical observations are consistent with a polygenic model. He ended with a cautionary note that precision of risk prediction doesn't depend on genetic risk alone but also on environmental risk factors. Thus if the heritability of the trait is low then genetic predictors alone may not be able to predict the phenotypic risk.

Dr. Pablo Gejman spoke on "Common variation in schizophrenia" with the note that heritability of schizophrenia is difficult to explain with existing genetic data. Copy number variations can explain some amount but not the whole. By comparing allele frequencies in cases versus controls we can search for a disease without clues to its pathophysiology. GWAS may result in identification of risk genes even though they are not implicated by pathophysiological hypotheses. As small genetic effects dictate large samples, we need to use clinical phenotypes, as other methods like brain imaging endophenotypes may not be cost effective.

He explained the results of their recently completed GWAS study. They examined 21,856 samples in a primary GWAS and 29,650 samples in a replication series. Thus a total of 52,156 samples of European ancestry were examined. The observed numbers of hits were more than expected. The results were consistent with the polygenic model and revealed six loci which crossed the GWAS threshold. The replication study confirmed five loci on chromosomes 6p21.3–22.1, 1p21.3, 18q21.2, 10q24.32 and 8q21.3. Out of these one was within the HLA region. Interestingly one was a gene for miRNA 137 responsible for gene regulation. The GWAS data show that there may not be deletions in important genes but there may be abnormalities in areas where there are no genes or in between exons. He concluded that schizophrenia is possibly a disorder of gene regulation.

Dr. DeLisi discussed the endophenotypes concept in schizophrenia research, with the question "Are there useful endophenotypes for Schizophrenia?" She began with the definition of endophenotype, as many investigators use the term with different meanings. She stated that endophenotypes should be intermediate phenotypes which are closer to the genes and thus help in the dissection of the genetic diathesis of schizophrenia, as they decrease the heterogeneity of the phenotype. For any marker to be called an endophenotype it has to show distinction between people with schizophrenia and controls; it should be heritable; and should segregate with illness within families, frequently also being present in unaffected relatives. She discussed the brain imaging findings in schizophrenia pointing to the differences between patients and controls, i.e. enlarged lateral ventricles, non-localized bilateral gray matter reductions, reduced white matter integrity, regional volume deficits, loss of normal asymmetries and developmental abnormalities, but there are few studies of heritability of these variables. An early landmark study (Reveley et al., 1984) compared monozygotic and dizygotic twins for ventricular size and found high heritability. She noted that there are few such studies examining the differences between MZ and DZ twins, which are very important to account for heritability of a candidate endophenotype. Current researchers suggest various structural and functional brain abnormalities as candidate endophenotypes. However, she emphasized that inability to differentiate whether these are intermediary in the disease pathway or the consequences of the disease is a major problem.

In summary, she noted that though there are numerous imaging and cognitive measures which distinguish patients with schizophrenia from controls, only some have been shown to be heritable and only a few segregate with illness within families. She stated that currently there is no clear endophenotype for schizophrenia. As a concluding comment, she discussed the limitations of studies using imaging genomics, as they use unsupported intermediate phenotypes and do not take into account errors due to multiple testing. Also, these studies do not account for the possibility of multiple genes contributing to single brain measurements or that measurements may change over time and scanner variability also occurs. Thus many of the clear differences shown in carriers of different common alleles could be spurious findings.

Dr. Dan Rujescu continued the discussion on endophenotypes by enumerating the different ways to find genes for schizophrenia. He discussed the importance of intermediate phenotypes in psychiatric disorders as they are more elementary when compared to heterogeneous clinical

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phenotypes. He explained the possibility of intermediary phenotypes being useful in identifying genes by using the example of Type 2 Diabetes. Genes were first identified that are associated with fasting glucose and later tested for association with type 2 DM. Two genes were associated with type 2 DM, however not all genes associated with fasting glucose were associated with type 2 DM. Interestingly, ADCY5 (Adenylate cylase 5) was associated with low birth weight and fasting glucose level, both risk factors for type 2 DM (Freathy et al., 2010). In schizophrenia, a major advantage is that animal models can be developed based on the endophenotype and tested. He gave the example of an animal model based on NMDA receptor hypofunction which was based on phencyclidine induced cognitive deficits. It was found that parvalbumin dependent interneurons were decreased in hippocampus and increased after treatment with haloperidol. This was also associated with decreased prepulse inhibition and poorer cognitive performance (Sohal et al., 2009).

However, there are many drawbacks to intermediate phenotypes. He reiterated the view of Dr. DeLisi that not all claimed endophenotypes are tested for the proposed intermediate phenotype criteria and it is not clear whether they are in the disease pathway or a consequence. Also, it is unclear whether they actually reduce the complexity of traits. Thus in the future, more accuracy is needed before naming something an intermediate phenotype. Also phenotypes which are plausible underlying biology should be prioritized and examined with sufficiently powered studies. He predicted that linking the whole genome data to physiology and disease will be a major future challenge. He also cautioned that epigenetics and many other mechanisms that are still not understood also need to be considered in addition to whole genomic sequence.

Dr. James Kennedy spoke on "commercial genetic testing for schizophrenia". Recently, different companies are marketing genetic tests for schizophrenia on the internet and thus it is important for clinicians to be aware of the implications this has. Technological advances have made a personal genome sequence possible and in the future it will become less costly, thus making these tests more popular. However, society's perception about genetic testing has been different from those of scientists who are developing the tests. He described his own unpublished survey on 900 medical students and undergraduates in which they were asked their opinions on genetic testing. Interestingly while a majority of people wanted to know their risk for disorders like cystic fibrosis, they did not want to know their risk for depression. In addition there was a difference between their opinions on whether genetic testing is needed for major psychiatric disorders in the general population (19% responding yes) versus for those with high responsibility jobs (37% responding yes). As the decisions to be taken by the patients and their families involve significant emotions he quoted that "scientists who are behind this technological revolution need to assume a prominent role in ensuring that its benefits are not mishandled".

There are different companies with web pages on the internet claiming to provide genetic information on different disorders, including schizophrenia. These genetic tests are based on several putative markers for schizophrenia and are claimed to quantify the risk for schizophrenia. However, there are differences in test results obtained between commercially available kits using the same person's DNA and thus he cautioned against direct consumer testing. In addition there is no clinically valid test for most psychiatric disorders, including schizophrenia and testing at this point could result in severe adverse consequences.

Beachamp and Childress have developed principles of biomedical ethics which takes into account respect for autonomy, beneficence, nonmaleficence and justice. Thus while autonomy and personal choice have to be respected one should also consider responsibility and concept of "do no harm". Taking the example of the ApoE gene for Alzheimer's disease, he discussed the benefits and harm of genetic testing. While the benefits like early intervention may exist, there is a risk of depression, suicide after finding out the testing results, and also adverse consequences to the family. As there is no proven early intervention for Alzheimer's disease at present, testing could result in more harm than benefit.

On the other hand, physician delivered test results may be beneficial in some scenarios, i.e. in 22q11 deletion syndrome. As there is a definite risk associated with this syndrome, this test could be added to newborn screening programs (Bales et al., 2010) provided good genetic counseling accompanies it. Advantage of this could be avoidance of a "diagnostic odyssey" and early treatment of associated problems. However, testing could also result in parents becoming more cautious about their children's psychiatric status. Further research is needed to consider the effect of epigenetic and other variations in the chromosomal regions of the non-deleted co-pair of this chromosome. He concluded that at present there are multiple genes with small effects for psychiatric disorders and we do not have mechanisms to combine them together. Thus considering the benefit versus harm, direct genetic testing is not recommended. In some rare cases physician delivered test results may be useful (i.e. 22q11 deletion syndrome and pharmacogenetic testing for side effects).

Dr. Thomas Lehner re-emphasized the views of Dr. Kennedy that the currently available tests for psychiatric disorders are not validated and one needs to be cautious in interpreting the results. On the other hand, testing could be more useful in the field of pharmacogenomics. He discussed the ongoing Exome sequencing project which may help to identify people at risk of developing side effects such as clozapine induced agranulocytosis.

The session generated active discussions. There was a query on heritability of schizophrenia and how much GWAS can predict about heritability. Dr. Gejman responded that what can be explained by GWAS is very low, and may be less than 5%, about 2–3%. In response to queries on why genetic studies based on the imaging endophenotypes can't be plausible Dr. DeLisi responded that they don't take into consideration that there can be many genes for the same brain function and don't control for multiple other gene variations.

7.2. Multiple mechanisms for the genetic basis for schizophrenia (reported by Renan P. Souza)

This session started with an interesting discussion regarding genomic approaches and whether genetic

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evaluations require or should take into account an understanding of the pathogenesis.

Dr. Marie Claire King (University of Washington, Washington, USA) opened this session emphasizing the human paradox that most of the human variation is ancient and shared, but most alleles are recent and individually rare. The observations regarding schizophrenia that are relevant for explaining its genetic architecture are: (1) family history increases risk for schizophrenia, but most of the cases are sporadic; (2) illness is common worldwide; (3) it persists despite reduced fertility of affected subjects; (4) older paternal age seems to increase risk; and (5) some rare chromosomal variants are known to increase risk. At this point, Dr. King introduced a possible hypothesis for the genetic basis of schizophrenia, that there would be an ongoing supply of new mutations inherited that would be rare (or unique) affecting neurodevelopmental pathways leading to the illness, but these variations would only survive a few generations. Her idea was followed up using an example of rare structural genetic variants that disrupt genetic in neurodevelopmental pathways in schizophrenia subjects (Walsh et al., 2008). None of the rare variants found in control subjects disrupted genes associated with neurodevelopment. However, one of the deletions (Δ399158bp) found in patients disrupted the exons 20 to 27 of the neuregulin receptor—Erbb4. It is known that neuregulin 1—Erbb4 complex regulates neuronal migration and differentiation, neurotransmitter receptor expression, glial proliferation and synaptic plasticity, and it is critical to the development of glutamate networks. It had been shown that mice with truncated Erbb4 had reduction in the number and structural changes in oligodendrocytes, reduced myelination and conduction of axon velocity, increased dopamine receptors and transporters and behavioral alterations (Roy et al., 2007). The other deletion that seems to be relevant in this context was observed in chromosome 5 (Δ502683bp). This deletion would lead to a chimeric protein coded by the SKP2-GLAST genes. No functional analysis has been conducted with this locus thus far. Other recent results were also highlighted indicating that most of the mutations are unique. These mutations have been identified frequently in some genomic areas: 1q21.1, 15q11.2, 15q13.3, 16p11.2, 16p12.1, 16p13 and 22q11.2. Some of these mutations are de novo, but some are inherited, recent and rare. It is of considerable interest that there are similar results in autism spectrum disorders indicating that there may exist a genetic overlap between both disorders (McClellan and King, 2010). Dr. King concluded with some critical questions for the field: (1) what would be the critical genes; (2) what functional alterations are caused by the observed mutations; (3) if there is a possible convergence of these mutations on specific pathways; and (4) how these results would affect treatment.

Dr. Sybille Schwab (University of Western Australia) continued the session with her talk on candidate genes from linked chromosomal regions and specifically where we are with Neuregulin and Dysbindin. She reviewed the history of linkage studies in schizophrenia. The results of these studies have not been consistent and linkage peaks were generally broad and in different positions from study to study. Although there was a considerable heterogeneity across linkage results, the regions located on chromosomes 6p and 8q seem to be the most consistently supported thus far. Dysbindin was the main gene associated with schizophrenia in the 6p region (Schwab et al., 2003; Straub et al., 2002), while neuregulin is located on 8q (Stefansson et al., 2002, 2003). The variant rs1011313 located in the dysbindin gene region received support for association from a meta-analysis (Allen et al., 2008). Other findings implicate dysbindin and neuregulin 1 function in phenotypes associated with schizophrenia. Dysbindin has reduced mRNA expression in schizophrenia (Weickert et al., 2004) and the haplotype associated with increased risk for schizophrenia is associated with reduced dysbindin expression (Bray et al., 2005). Moreover, dysbindin may be required for adaptive neuronal plasticity (Dickman and Davis, 2009; Ji et al., 2009). Likewise, neuregulin 1 signaling has been implicated in neurodevelopmental processes (e.g. neuronal and axonal guidance). However, no functional variants have been found in both genes.

Dr. James Kennedy (Centre for Addiction and Mental Health, Toronto, Ca) ended the session focusing on genes for antipsychotic action and asked whether patients who respond and those who do not respond to treatment could divide schizophrenia into a more homogenous subpopulation. This same idea was hypothesized for subjects who present antipsychotic-induced side effects: weight gain and tardive dyskinesia. He presented results for association of dopamine DRD1 and DRD3 receptor polymorphisms with treatment response; SNAP-25 and cannabinoid receptor 1 (CNR1) polymorphisms with antipsychotic-induced weight gain; and DRD2 and DRD3 findings with tardive dyskinesia. Although most of the associations still require replication in larger and independent samples, it appears that subjects who present specific treatment response or side effects are homogenous groups and genetic architecture may play a major role in determining these traits.

7.3. Gene–brain interaction in the pathophysiology of psychosis (reported by Diana Prata)

Dr. Ruben Gur (University of Pennsylvania, PA, USA) presented his latest research suggesting how endophenotypes based on expression and recognition of emotion may be at least as useful as cognitive ones for the study of schizophrenia. He began by discussing the evidence for sex differences in several tasks where schizophrenia patients generally perform worse (Censits et al., 1997): working memory, verbal, spatial and motor tasks and in emotion recognition. In the emotion recognition task, males were more inaccurate, slower and more inefficient as seen in regional brain activation (i.e. increased BOLD response for the same level of performance), than women (Derntl et al., 2009). In schizophrenia, his group found that patients showed a marked decrease in amygdala activation which was suggested to explain emotion processing deficits in the illness (Gur et al., 2007). Normally, amygdala activation increases with higher accuracy for sad and angry faces but in schizophrenia, accuracy goes down when amygdala activation increases (Gur et al., 2007). Furthermore, increased amygdala activation correlates with increased flat affect in schizophrenia patients, which suggests that the latter relates to overstimulation of the limbic system. A recent study

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(Satterthwaite et al., 2010) showed a positive correlation between symptom severity and activation in the amygdala and the orbitofrontal cortex during threat. In the same study, patients also showed a weaker coupling between the amygdala and cortical regions involved in cognition compared to controls, which indicates that abnormal processing of threat may exacerbate cognitive impairment in schizophrenia. His group also showed that schizophrenia patients are impaired in emotion recognition in voice (prosody), showing a significant difference in correct responses, which denotes decreased saliency, compared to controls, except for anger.

Dr. Alessandro Bertolino focused on prefrontal inefficiency as a heritable intermediate phenotype of schizophrenia, which is supported by studies that show inefficient prefrontal activation (compared to normal controls) in patients and their healthy siblings (Callicott et al., 2003). He explained that the effect of dopamine contributing to this can be direct, *in situ*, or indirect due to an imbalance in the striatum (which is connected to the prefrontal cortex via the thalamus (in a cortico-striatal-thalamic-cortical loop where the striatum may act as a filter of information; O'Reilly, 2006). Given that the dopamine receptor D2 (DRD2) is highly expressed in the striatum, DRD2 signaling is a very plausible participator in memory processing and performance and several pieces of evidence support this idea: i) prefrontal DRD2 agonism enhances tuning of pyramidal neurons during working memory (Wang et al., 2004); ii) DRD2 over-expression in the striatum induces working memory deficits (Kellendonk et al., 2006); and iii) DRD2 agonism and antagonism respectively improve and deteriorate spatial working memory (Mehta et al., 2004) and modulate prefronto-striatal activity (Mehta et al., 2003) in humans. In addition, there have been several positive genetic associations of DRD2 polymorphisms with schizophrenia, including a recent meta-meta-analysis (Allen et al., 2008). He asked what the effect of the DRD2 genetic variation on striatal pre- and post-synaptic dopamine signaling is and how it can relate to prefrontal activity during working memory. His team found that two intronic nucleotide polymorphisms (SNPs) in the DRD2 gene regulate gene expression and splicing in the prefrontal cortex and the striatum during working memory (Zhang et al., 2007). They also found these SNPs to be associated with working memory and attention load and to fronto-cortical and subcortical activation during working memory. Interestingly, the latter effect was found to be significantly different in patients with schizophrenia (Bertolino et al., 2009a). In another study (Bertolino et al., 2009b), they reported epistasis between the dopamine transporter and the DRD2 genes on prefrontal–striatal activity and volume, an interaction which was also demonstrated by immunoprecipitation in the striatum. In a more recent study, Bertolino et al. (2010) also showed that one of the above SNPs (rs1076560) affected receptor availability and that there was a positive correlation between striatal DRD2 signaling and prefrontal activation during working memory in the GG genotype group. The same SNP was also recently associated to personality dimensions (Blasi et al., 2009). In summary, functional variants of DRD2 seem to affect different brain phenotypes related to modulation of D2 signaling: mRNA expression, cortico-subcortical function during working memory, amygdala and prefrontal activity during emotion processing, striatal DRD2 binding, the relationship between DRD2 striatal binding and working memory activity, behavioral performance during working memory, attention and emotion processing, and possibly schizophrenia. It is by these systems-level brain effects that variants such as DRD2 SNPs may have influence on more complex phenotypes like diagnosis. He concluded that: "The endgame of research into genetic causes of schizophrenia is going to be identification of how, where and when these variants modify brain function."

Dr. Tilo Kircher spoke on how schizophrenia risk genes, and in particular the Dysbindin gene, can affect brain function, structure and personality. Dysbindin is involved in glutamatergic transmission (Owen et al., 2004) and it has been genetically associated with susceptibility to schizophrenia (Allen et al., 2008), schizotypy (Stefanis et al., 2007), attention (Stefanis et al., 2007), executive function (Luciano et al., 2009), intelligence (Luciano et al., 2009) and memory (Luciano et al., 2009). Reduced prefrontal Dysbindin mRNA levels have also been found in schizophrenia (Ji et al., 2009). In a large behavioral, functional and structural imaging study, the effect of several candidate psychosis risk genes was assessed. A polymorphism in the Dysbindin gene (rs1018381) was found to have an effect on activation of the right anterior cingulate and middle/superior temporal gyrus during verbal fluency (Markov et al., 2009) and on the middle frontal gyrus bilaterally during working memory (Markov et al., 2010) and on the left middle frontal gyrus and bilateral cuneus during encoding and the right inferior/middle frontal gyrus and inferior parietal lobule during retrieval of the episodic memory task (Thimm et al., 2010); in all cases the risk genotype group showed increased (i.e. putatively inefficient) activation. The same risk allele (A) has also been associated to lower scores on personality traits such as in the Schizotypal Personality Questionnaire and the Interpersonal Deficit subscale (Kircher et al., 2009). However, inconsistently, the same polymorphism had previously been associated to less schizotypal personality (Stefanis et al., 2008). Lastly, he presented activation brain-maps where associations of each of several genes/polymorphisms (CACNAC1, COMT, DTNBP1. NRG1, etc.) with corresponding regions were mapped for each task. His final suggestions on how to understand the existing intricate interactions between genes, brain activation, environment and disorder are to invest in using patient samples across diagnostic categories, longitudinal and multimodal studies, and further investigation of the impact of CNVs.

Dr. Michael Owen opened the discussion questioning whether imaging genetics has allowed us to find genes for endophenotypes that lie on the gene-to-disease pathway or for mere (risk indexing) epiphenomena of the disease. He suggested that it is potentially misleading to presume that variation in an endophenotype will depend upon variation in fewer genes than the more complex disease phenotype and therefore it will be more tractable to genetic analysis. Among the theoretical characteristics of endophenotypes, is that they occur at a higher frequency in individuals with the disease than in the general population and that this association should derive from shared genes. This means that they are heritable, co-segregate with the illness in multiply affected families, present in unaffected relatives of cases at a higher

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rate than in the general population, and ideally show evidence for shared genetic risk factors from twin studies. A genotype-to-endophenotype-to-illness causal pathway is suggested by the state-independence of the endophenotype and its presence before illness onset or in well relatives. These criteria render reverse causation unlikely. In terms of experimental characteristics, psychiatric phenotypes are generally believed to be surpassed by endophenotypes which have good psychometric properties (higher reliability and validity), sufficient sensitivity to detect individual differences and applicability to sufficient numbers. In summary, he cautioned that the above theoretical and experimental criteria are seldom satisfied and that even when they are, it is hard to determine that the "endophenotype" is on the disease pathway and is not an epiphenomena or a consequence of the disease (Walters and Owen, 2007). He pointed out that it is very hard to distinguish mediation from pleiotropy (i.e. does the endophenotype lie on the disease pathway or simply correlate with genetic variation that does?). An example was given in the case of copy number variants (CNVs): cognitive impairment may be mediating the effect of CNVs on schizophrenia or autism *or* coexist with schizophrenia and autism due to shared genetic liability. He then suggested that the solution to this may lie on the use of longitudinal studies, a more genetically informative design, and more appropriate statistical approaches which require larger samples. He also stated the problems using endophenotyes for initial gene discovery: they may be influenced by the illness course, drug treatment, smoking or the menstrual cycle, and have inter-laboratory variability. Also, they may not be decisively heritable or have shared genetic risk with disease, and may not be genetically simpler than the clinical phenotype (Flint and Munafo, 2007). Practical problems are that very large samples are needed (to prevent assumptions of higher penetrance) and that we may be at risk of increased multiple testing (Walters and Owen, 2007). However, the lack of evidence for mediation is not necessarily a problem for gene finding studies. It is useful if the endophenotype/trait simplifies the genetic architecture by defining a more genetically homogeneous disease subgroup or identifies carriers of the risk genotype among unaffected relatives, in which case the "biomarker" designation is more appropriate. In a criticism of an earlier review publication (Meyer-Lindenberg and Weinberger, 2006), he emphasized the problems with the use of endophenotypes for exploring mechanisms: genetic multiple testing, phenotypic multiple testing, small sample sizes (which potentiate the occurrence of false positives and may be based on incorrect penetrance assumptions), weak replication and pleiotropy (which is hard to exclude). Dr. Owen ended by presenting an unpublished study where it was possible to clarify whether an executive task or a social cognitive dysfunction task accounts for the association between COMT Val158Met polymorphism and antisocial behavior in ADHD. It was found that only the latter did (40%) and therefore can be taken to be an intermediate (or endo-) phenotype on the risk pathway, while the first was shown to be an epiphenomenon. He thus concluded that there are concerns about the use of endophenotypes both for gene finding and investigation of gene function.

Dr. Daniel Weinberger ended the session by stating that "given that changes in the brain have implications on how the brain works and that genes set the rules for how brain works, clearly genes have to do with changes in the brain. Any abnormality at the level of behavior is necessarily caused by an abnormality at the brain level". He defended that genes have more directly to do with changes in the brain than with behavior such as delusions or hallucinations which are epiphenomena. He mentioned the example of risk genes for Type I diabetes showing much stronger effect in the regulation of T cell activation than on risk for Type I diabetes. Thus, to avoid spurious findings, the real challenge should be, not in arguing whether endophenotypes will add value to understanding the disorder, but in choosing a good intermediate phenotype. (For instance, glucose level is not a good one for diabetes because unaffected relatives of ill subjects do not show it.) He argued optimistically that, with time, psychiatry will gain from gathering a list of powerful endophenotypes since in other areas of medicine they have shown to be extremely useful. Also, statistical correction tools which are currently widely used for endophenotype studies, are robust enough to avoid the false positive error (Meyer-Lindenberg et al., 2008). He ended by noting that it is very difficult to know how to validate or disprove mediation (e.g. discern mediators from epiphenomena). He also argued that we cannot ignore vast previous evidence that deficits in cortical function in schizophrenia pre-exist the onset of the illness, "…whether they are what has been measured in imaging, it is not certain, but for sure there is something in cortical development and function that is on the risk pathway to the emergence of schizophrenia later in life."

7.4. Plenary session—On the matter of neuroimaging in the context of schizophrenia genetics (reported by Diana Prata)

Dr. Daniel Weinberger (Bethesda, MD, USA) reviewed the findings supporting prefrontal efficiency as an intermediate phenotype for schizophrenia. Unaffected relatives of schizophrenia patients show intermediate BOLD activation/performance between controls and patients (Callicott et al., 2003). This was also found for temporoparietal P300 amplitude (Winterer et al., 2003). He stressed that the field of "imaging genetics" can have applications in several ways: for genetic association with brain structure and function, genetic dissection of complex functional systems, for understanding brain mechanisms of genetic risk of disease, for understanding of genetic mechanisms of variable outcomes of CNS disease, for understanding genetic variation in brain development and aging, and for pharmacogenetic mechanisms in brain and characterization of biological epistasis. He gave the example of the effect of COMT Val158Met on cortical function during working memory (Egan et al., 2001) which has been replicated several times. Genes that emerged from GWAS research on bipolar disorder (CACNAC1) and schizophrenia (ZNF084A) have now been positively associated with brain function as well: i) the CACNA1C with hippocampal activation during declarative memory and with prefrontal activation during executive function (Bigos et al., in press) and ii) the ZNF084A with differences in functional connectivity of the dorsolateral prefrontal cortex (DLPFC) across hemispheres and with the hippocampus (Esslinger et al., 2009). Most genes are likely to impact on brain function and a link between genetic association with brain function and neural

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mechanisms of clinical risk requires demonstration that the association is with a heritable, susceptibility-related phenotype. Prefrontal–hippocampal functional connectivity has been detected at an intermediate level in healthy relatives compared to their schizophrenic siblings and unrelated controls and may therefore be a heritable phenotype. Dr. Weinberger added that thinking about complex diseases one SNP at a time is not helping us finding the missing heritability of complex diseases because the effect of genetic variation depends on genetic context. One way to try to tackle this, he suggested, is to investigate epistasis (i.e. interactions within a gene or a protein pathway) with imaging genetics to elucidate complex biological mechanisms on the brain and to biologically validate clinical genetic interactions. As an example, AKT1 has been associated with schizophrenia (Norton et al., 2007), is inactivated by D2 signaling (Beaulieu et al., 2007) and its expression is influenced by a coding SNP (Tan et al., 2008). The same SNP interacts non-linearly with COMT Val158Met to mediate prefrontal activity (Tan et al., 2008). Imaging genetics can be used for biological validation of genetic association with risk. Imaging genetics has supported previous statistical epistases associated with schizophrenia risk where COMT was shown to affect the risk for schizophrenia associated with other genes such as G72, DISC1, GRM3 and GAD1 (Nicodemus et al., 2007). Specifically, epistases between COMT (Val158Met) and GRM3 (Tan et al., 2007), between COMT and DAOA and between COMT and GAD1 have been demonstrated by his group to impact on prefrontal efficiency. In addition, CIT has been shown to interact with DISC1 and with NDEL1 using machine learning algorithms as well as using fMRI (Nicodemus et al., 2010). This has also been demonstrated for epistases in the NRG1–ERBB4–AKT1 pathway (Nicodemus et al., 2010) where the same interaction was found on prefrontal activation with risk allele directionality. Thus, Dr. Weinberg concluded that comparing phenomenological neuroimaging data of patients with controls is not likely to yield further important insights, but characterization of cortical network dynamics will help refine brain-based intermediate phenotypes associated with schizophrenia susceptibility.

Dr. Alessando Bertolino focused on epigenetics, emphasizing the possible role of changes in DNA methylation and chromatin structure on the heritability of schizophrenia. This is suggested by the increase of epigenetic differences during the lifetime of monozygotic twins (Fraga et al., 2005). DNA methylation modulates transcriptional plasticity, with many genes demonstrating an inverse correlation between the degree of methylation and the level of expression. Typically occurring in adult somatic cells, the methylation of CpG sites is overrepresented in CpG islands of promoter regulatory regions. This disrupts the binding of transcription factors and attracts methyl binding proteins that initiate chromatin compaction and gene silencing. This mechanism has been shown to play a role in epigenetic programming by early life events, since maternal behavior may affect CpG methylation of the glucocorticoid receptor (GR) gene promoter in rats (Weaver et al., 2004). Furthermore, early life stress can dynamically control DNA methylation in postmitotic neurons to generate changes in arginine vasopressin (AVP) gene expression in mice (Murgatroyd et al., 2009). Importantly, epigenetic programming is dynamic and can be reversed even in fully differentiated brain cells: for example, methyl supplementation can reverse the maternally programmed stress response (Weaver et al., 2005). Investigating the link between epigenetic processes and schizophrenia may be particularly intriguing because DNA methylation has been shown to play a role in cognitive functioning. The rs4680 SNP in the COMT gene has been associated with prefrontal cortex-dependent cognition and activation (Egan et al., 2001). Interestingly, differences in methylation among monozygotic twin pairs have been reported for two CpG sites in the promoter region of the COMT gene (Mill et al., 2006). Methylation level at these CpG sites seems to be associated with rs4680, with Val158 homozygotes exhibiting lower levels of methylation than Met158 homozygotes, suggesting a different methylation pattern for different alleles (Dempster et al., 2006). Notably, SNP rs4680 creates or abolishes a CpG site so that the Val158 allele has one more CpG site than the Met158 allele. Dr. Bertolino and colleagues examined the relationship between stress, COMT methylation and working memory performance as well as related brain activity in healthy subjects. They measured % methylation of 4 CpG islands in the COMT exon 4 (rs4680) region and 3 CpG islands in the COMT promoter. They found that COMT methylation is affected by stress and may affect working memory performance as well as brain activity and that these effects depend on the rs4680 genotype. Moreover they demonstrated how the interaction between COMT methylation, SNP rs4680 and stress may affect working memory brain activity in PFC. He concluded that COMT methylation could be a potential modulator of intermediate phenotypes and might explain at least part of the "missing heritability" by epigenetic mechanisms.

Dr. Philip McGuire (London, UK) presented a novel research on the at-risk mental state (ARMS) as well as other imaging genetic findings using case–control comparisons, gene × gene interactions and gene × environment interactions. He emphasized the potential of using neuroimaging in the ARMS population since the same individual can be studied before and after the onset of psychosis to identify baseline findings and longitudinal changes associated with the onset of illness. Another advantage is that there are no confounding effects of previous illness or treatment. Recent findings have emerged from this approach. Prefrontal inefficiency, measured with fMRI, in the ARMS is much higher in the ones that become psychotic than in the ones that do not (Allen et al., 2010). Increased striatal dopamine function, measured with PET, in the ARMS is intermediate between controls and 1st episode patients (Howes et al., 2009). Through integrating these two imaging modalities, it was found that altered prefrontal activation is correlated with striatal presynaptic dopaminergic activity (Fusar-Poli et al., 2009). A new longitudinal neuroimaging study in ARMS where subjects were scanned during the prodromal phase and re-scanned at the first episode revealed an increase in dopamine function associated with the onset of psychosis. Longitudinal volume reductions were previously reported to be associated with the onset of psychosis (Pantelis et al., 2003). As an example of how genes implicated in risk for schizophrenia based on case–control studies also show predictable variation at the level of cortical efficiency in normal subjects, he presented the first study finding an effect

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of DISC1 Ser704Cys on prefrontal efficiency in humans (Prata et al., 2008). An example of how the effect of genetic variation depends on genetic context was the finding that effects of COMT Val158Met on brain activation during verbal fluency varied according to the DAT 3′UTR VNTR (Prata et al., 2009b). In fact, the effect of genetic variation may also depend on diagnostic status: an opposite effect of variation in COMT Val158Met was found in schizophrenia compared to controls during verbal fluency in the right peri-Sylvian cortex (Prata et al., 2009a). Environment alone also has an effect on brain activation: acute induction of psychotic symptoms correlates with an increase in accumbus activation after THC administration (Bhattacharyya et al., 2009). However, the same authors showed that the increase in psychotic symptoms and in striatal activation associated with the drug also varies with COMT Val158Met genotype (the increase being greater in Val homozygotes). With the goal of characterizing cortical network dynamics to help refine brain-based intermediate phenotypes and biomarkers related to schizophrenia susceptibility, probabilistic machine learning has also recently been employed (Koutsouleris et al., 2009a).

Dr. Andreas Meyer-Lindenberg (Mannheim, Germany) mentioned the large overlap of common genetic risk, besides the overlap in symptoms, between schizophrenia and bipolar disorder (Lichtenstein et al., 2009), although this may not be the case for rare variants. ZNF804A may be one of those common genetic risk genes. A novel study found that activation of the theory of mind network is altered in healthy risk allele carriers of the rs1344706 SNP in the ZNF804A gene. Interestingly, this was also verified in areas which are part of the human analogue of the mirror neuron system. A different study investigating another genome-wide-supported risk gene, CACNA1C for bipolar disorder, has found the risk allele to be associated with increased amygdala activity in response to reward (Wessa et al., 2010). Turning to a long-investigated functional SNP in a psychosis candidate gene, Meyer-Lindenberg described evidence for a neural substrate supporting an interesting pleiotropic role for the COMT Val158Met polymorphism. A recent meta-analysis (Mier et al., 2010) detected this polymorphism to have strong and opposing effects for executive cognition paradigms (favoring Met allele carriers) and emotional paradigms (favoring the Val allele). This pleiotropic effect was suggested to have an evolutionary explanation: since both alleles were adaptive, each on its own trait (executive function and emotional stability), they were kept by natural selection in very similar frequencies in the human population.

Dr. Steven Potkin (Irvine, California, USA) presented a novel study showing that DRD1 alleles predict brain circuitry (covariance patterns) in the dorsolateral prefrontal cortex and the inferior parietal lobule in schizophrenia (Tura et al., 2008). He suggested that brain imaging data could be used as a quantitative trait (QT), instead of in a case–control design, to increase power and reduce needed sample sizes. This can be especially useful in a genome-wide association study including controls and schizophrenia patients. One such study (Potkin et al., 2009) used mean BOLD activation in the dorsolateral prefrontal cortex during a working memory task. As a result, significant SNP by diagnosis interactions were found for genes/regions involved in neurodevelopment and response to stress. This approach is a useful genome-wide screening method to identify novel SNPs related to schizophrenia risk. Systems biology approaches used to clarify the role of new risk candidate genes and the networks in which they participate should bring further insight into the illness and lead to the development of new pharmacological targets.

Dr. Si Tianmei (Beijing, China) provided an overview of recent research on brain structural differences in schizophrenia and on how they may be influenced by antipsychotic treatment. Compared to controls, patients demonstrated reduced volume bilaterally in superior temporal gyrus gray matter but not in white matter and increased mean diffusivity bilaterally in superior temporal gray matter and in left superior temporal white matter (Lee et al., 2009). Moreover, the latter effect showed a significant correlation with auditory hallucinations and attentional impairments (Lee et al., 2009). Type-dependent effects of antipsychotics on brain structure have also been reported (Navari and Dazzan, 2009). Brandt and Bonelli (2008) in a review suggest that there may be decreased caudate volume in first-episode psychotic patients, whereas studies on chronic patients reveal volume increases in the caudate, putamen and pallidum. Data from longitudinal studies suggest that atypical and typical neuroleptics may produce different effects on brain morphology and that these changes are dynamic (Crespo-Facorro et al., 2008). Indeed, antipsychotics can affect neuronal structure and function through neuroplasticity, neurotoxicity, gene expression and apoptosis (Dean, 2006) and they may have differential effects on neurotrophic factors such as BDNF or the NRG1–ErbB pathway and in turn could affect myelination (Bartzokis et al., 2007). She concluded that antipsychotic treatment potentially contributes to the brain structure changes observed in psychosis (type-dependent, time-dependent and dose-dependent) and that further research is needed to take into account these potential effects.

The discussion began with a focus on the observation of large variances in the associations being found. Dr. Weinberger suggested that it is due to measurement error, as well as to epigenetics and interactions between genetic variants that we are not yet taking into account. Dr. Bertolino added that methylation may be a factor that will explain the “spread” of BOLD signal within one genotype group such as Val homozygotes. However, he said, studies of methylation are usually in lymphocytes so their application to neuroscience is limited. Even in the brain, different cell types are differently methylated. Dr. Weinberger added that his group has used the available GWAS database to replicate their previous findings of epistasis but in some cases SNPs of interest are not genotyped or tagged and high probability imputation is not possible. He also added that genotype by diagnosis interactions could be genotype by drug interactions. To conclude, he stated that even though there are epigenetic and environmental factors playing a role, there is evidence that at two weeks of age, one can predict the temperament present 10 years later. “Expression (not only sequence) of genes is ancestry-dependent. We can predict something even though there is complexity and… complexity is inherited too.”

7.5. Gene–environment interactions in the prediction of psychosis (reported by Alex Fornito)

This session included a diverse range of talks concerned with the role that various environmental risk factors play in

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the pathogenesis of psychosis. *Dr. Daryl Eyles* opened by focusing on the link between developmental vitamin D deficiency (DVD) and the ontogeny of the brain's dopamine system. Low prenatal levels of vitamin D have been proposed as a potential risk-mediating mechanism that can explain a diverse range of epidemiological findings in schizophrenia (McGrath, 1999). Dr. Eyles presented data from animal studies suggesting that rats with DVD show a range of dopamine-related changes, including increased mitosis and decreased apoptosis perinatally (Ko et al., 2004), reduced conversion of dihydroxyphenylacetic acid (DOPAC) to homovanillic acid (HVA) and a corresponding reduction of catechol-O-methyl transferase (COMT) expression (Kesby et al., 2009), and reduced dopamine neuron number in the substantia nigra in adulthood. He noted similarities between the DVD and the Nurr1 +/− phenotypes (Zetterstrom et al., 1997), suggesting that DVD may affect DA neuron ontogeny primarily through the Nurr1 transcriptional pathway.

Two talks were concerned with the relationship between cannabis and schizophrenia. *Dr. Jenny Ceccarini* described the results of a relatively large [^{18}F]MK-9470 positron emission tomography (PET) study of CB1 receptor (CB1R) availability in patients who were either antipsychotic-naïve, drug free, or on stable monotherapies with various antipsychotics. Her findings indicated that both medicated and unmedicated patients showed increased CB1R binding relative to controls, with the mean increase being greater in unmedicated patients across most regions studied. The differences were particularly pronounced in dorsal anterior cingulate, ventral striatal and insula regions. Different monotherapies were associated with distinct changes in CB1R binding, suggesting that they may exert differential effects on the endocannabinoid system. Regional binding levels were also correlated with symptom and cognitive measures in patients. She interpreted these findings as evidence that schizophrenia is associated with hyperactivity of the endocannabinoid system. This hyperactivity is directly related to symptom expression and is down-regulated by administration of antipsychotics in a treatment-specific manner.

Dr. Monica Rais (Utrecht, Netherlands) presented work examining how cannabis use relates to longitudinal gray matter loss in schizophrenia. Her findings indicate that cannabis-using patients show increased gray matter loss over a 5-year period when compared to controls and non-using patients (Rais et al., 2008). In addition, cannabis-using patients show excess cortical thickness reduction over time most prominently in lateral prefrontal and anterior cingulate cortices, regions rich in cannabioid receptors. She concluded that cannabis use is associated with excess gray matter loss in schizophrenia, possibly as the result of a neurotoxic effect of exogenous cannabinoids, and that this may be related to poorer outcome in cannabis-using patients.

In a complimentary work, *Dr. Neeltje van Haren* (Utrecht, Netherlands) presented research trying to determine whether genetic or environmental factors can explain the association between schizophrenia liability and smaller brain volume. This work was conducted as part of the Schizophrenia Twins and Relatives (STAR) consortium, which pooled MRI data from twin pairs with and without schizophrenia collected and/or processed across six sites in Europe and the US. Multivariate modeling of the data indicated that additive genetic factors accounted for approximately 57% of the phenotypic correlation between gray matter volume and schizophrenia liability, with no such association being observed for white matter. These findings suggest that there are common genetic influences affecting liability for schizophrenia and brain volume.

Drs. Eve Johnstone and *Larry Seidman* continued the theme of imaging research in genetic high-risk cohorts. Dr. Johnstone presented structural MRI findings from the Edinburgh High Risk Study. The findings of this study suggest that longitudinal brain changes, particularly in the uncus and cerebellum, are most predictive of which high-risk individuals make the transition to schizophrenia, being associated with positive and negative predictive powers of 0.83 and 0.75, respectively. She presented data from recent additional follow-up scans acquired in this cohort suggesting that high-risk individuals subsequently diagnosed with schizophrenia show excess prefrontal gray matter volume reductions over an approximate 10-year follow-up period. In addition, reductions in prefrontal white matter volume were apparent after illness onset.

Dr. Seidman presented the findings of an fMRI study of activation and deactivation during the n-back working memory task in schizophrenia patients and unaffected relatives (Whitfield-Gabrieli et al., 2009). Patients showed increased activation of fronto-parietal regions, and reduced deactivation of the so-called default-mode network, a collection of brain regions typically showing reduced activity during cognitively demanding tasks (Shulman et al., 1997). Unaffected siblings showed intermediate changes in activation and deactivation. The finding was interpreted as a failure to suppress activity in brain regions associated with self-reflective thought, resulting in less cognitive resources available for task performance and a potential blurring of the internal and external world. In addition, patients and their relatives showed hyper-connectivity of the default-mode network during both rest and task performance. These changes were also associated with psychopathology ratings.

Dr. Matthew Kempton (London, UK) presented the results of a meta-analysis of 13 longitudinal studies of ventricular enlargement in schizophrenia. The results suggested significant, yet moderate progressive enlargement in patients compared to controls, with a pooled effect size of 0.45 (95% CI: 0.19–0.71). There was no evidence of publication bias, although there was considerable study heterogeneity. Subgroup analysis revealed that this effect was significant in chronic, as well as first-episode patients. Meta-regression revealed no associations with inter-scan interval, patient age at baseline, the proportion of female patients, duration of illness at baseline, age of illness onset, or proportion of patients using typical or atypical antipsychotics. Dr. Kempton concluded that the data suggest that progressive ventricular enlargement may begin even prior to illness onset, either perinatally or during the prodrome.

Adopting an epidemiological focus, *Dr. Pirjo Maki* (Finland) presented data from a 1985–1986 Finnish birth cohort aimed at identifying precursors of schizophrenia onset in later life. Assessments at approximately 8 and 15 years were conducted using a variety of screening questionnaires examining various aspects of psychopathology, with clinical outcomes being obtained from the Finnish discharge register.

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Measures of antisocial symptoms were associated with lower risk for psychosis, but higher risk for non-psychotic disorders, whereas measures of neuroticism were associated with elevated risk for both psychotic and non-psychotic illnesses. In contrast, measures of both positive and negative psychotic symptoms, as assessed using a screening instrument for prodromal symptoms, were specifically associated with the subsequent onset of psychotic illness. However, there was a generally high incidence of prodromal symptoms in the wider population, suggesting that they may be poor predictors of relatively rare disorders such as psychosis.

7.6. Gene–environment interactions in schizophrenia: advancing basic and clinical research (reported by Aurelie Boucher)

The aim of this symposium was to address how to study complex gene by environment interactions with both clinical and animal data.

Andreas Meyer-Lindenberg (Mannheim, Germany) spoke on how gene by environment interactions affect the brain. There is a relation to function, for example to dopamine in the prefrontal cortex. Indeed, prefrontal dysfunction in schizophrenia is related to striatal dopamine disinhibition. This in turn relates to symptoms by which a dopamine burst in the midbrain will produce reward and salience through efferences from the prefrontal cortex. Schizophrenia is a chaotic disorder where salience is observed when it should not. fMRI studies showed activation of the prefrontal cortex with both reward anticipation and reward. There is a complex path from genes to behavior. For example, COMT is linked to cannabis and prefrontal and executive function. This difference can also be seen in the brain. The warriors (met) versus worriers (val) model suggests that the met carriers have more executive function and val have more emotional processing. The environmental risk factors for schizophrenia such as urbanicity or social status are proxies for people with genetic vulnerability. The problem is to know what these proxies are. For example, social status is a good model because it is highly relevant for mental health. It is also present throughout the animal kingdom and it interacts with genetic risks for schizophrenia. In the study presented, people performed a task for a monetary reward. They were rated with stars depending on performance, under stable hierarchy (where social rank positions where unchanged) or under unstable hierarchy (where the hierarchy was changed dependent on performance). Results using fMRI showed that, with an unstable hierarchy, additional emotional regions such as the amygdala and the medial prefrontal cortex were activated.

Dr. Ruud van Winkel (Maastricht University, Maastricht, Netherlands) spoke on "Momentary Assessment Technology" to assess gene–environment interactions and the underlying endophenotype of stress sensitivity. The momentary assessment study examined stress sensitivity using the experience sampling method. They were able to show an interaction between COMT polymorphisms, stress and psychosis, particularly in Met/Met patients where an increase in delusions was observed. In an attempt to find which genes are involved in the cannabis association with psychosis, they studied 740 unaffected siblings of patients with psychosis. No effect of COMT was observed, but 3 other genes showed an effect including AKT1. Interestingly, AKT1 is downstream from D2 and has previously been linked to the effects of cannabinoids.

Dr. Jonathon Arnold (Sydney, Australia) presented an animal model of a gene–environment interaction to examine the role of NRG1 in cannabis associated schizophrenia. The effect of cannabis was studied on NRG1 treated mice, a model of susceptibility to schizophrenia. The acute administration of THC (the main psychotropic constituent of cannabis) to these mice improved prepulse inhibition. In addition, THC increased c-Fos expression, a marker of neuronal activation, selectively in the ventrolateral septum of the NRG1 mice. This showed that stress was necessary for this effect. In another experiment, repeated stress triggered a prepulse inhibition deficit in NRG1 mice. The relationship between cannabis and schizophrenia is stronger in heavy, long-term cannabis users. Similarly, the effects of repeated administration of cannabis on those mice induced an accelerated tolerance to cannabinoid-induced locomotor suppression and hypothermia. Experiments on CB1 receptor binding showed no difference in CB1 receptor expression, but NRG1 showed reduced cannabinoid-stimulated G-protein activation. In prepulse inhibition, different effects were observed on the first day, where an increased was seen in NRG1 mice and a decrease in the wild-type mice. Both groups became tolerant to these effects. In a light–dark experiment, an anxiogenic effect was observed with cannabinoid on the first day for both groups, and NRG1 mice did not become tolerant to this effect. Repeated cannabinoid exposure also increased FosB/delta-FosB in the ventrolateral septum of NRG1 mice. In another experiment, repeated adolescent THC exposure induced differential CB1 receptor expression levels in the substantia nigra. In conclusion, NRG1 confers altered neurobehavioral responses to acute and repeated cannabinoid exposures and thus provides an animal model of genetic vulnerability to cannabis-induced psychosis.

Another mouse model was presented by *Dr. Mikhail Pletnikov* (Johns Hopkins University, Baltimore, Maryland, USA). The aim was to study the molecular underpinnings of gene by environment interactions, but this has been difficult due to the paucity of relevant experimental approaches such as genetic models and identifiable and measurable environmental factors like infection and immune activation. The Tet-off system was used to generate transgenic DISC1 mouse models with inducible expression of the transgenes in forebrain regions. This was expressed during development like endogenous DISC1. Mutants showed enlargement of lateral ventricles. Here, maternal immune response as a leading pathogenic factor, using Poly IC as the environment factor to mimic some aspect of the viral response *in vivo*, was studied. Behavioral results showed an increased peripheral activity (anxiety), decreased time in the open arm of the elevated plus maze and increased immobility in the forced swim test in poly IC mutants. Abnormal social interaction was only observed in mutants exposed to poly IC during pregnancy. Stress reactivity was decreased in mutant mice suggesting that the HPA axis may be deficient. However, no increased volume of the lateral ventricles was observed. Poly IC in the mutants also decreased GFAP. Those results show that prenatal expression was necessary to see those effects as they are not shown in DISC1 mutants after birth. In conclusion, an interaction between DISC1 mutants and

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immune activation produced the behavioral alterations previously unseen in DISC1 mutant males.

7.7. Dynamic brain changes in schizophrenia across the lifespan: influence of genetic and environmental factors (reported by Alex Fornito)

Dr. Nitin Gotgay (Bethesda, Md., USA) presented work examining the developmental trajectory of gray matter changes in childhood onset schizophrenia (COS), largely based on structural magnetic resonance imaging (MRI) data acquired at five time points from pre-adolescence to early twenties. This work suggests that children with COS show a similar pattern of gray matter loss as healthy children throughout adolescence, but the magnitude of the loss is exaggerated, suggesting an acceleration of normal neurodevelopmental processes (Thompson et al., 2001; Gogtay et al., 2004; Greenstein et al., 2006). A similar, albeit attenuated, pattern of change was observed in unaffected sibs of patients. In both groups, the most pronounced changes occurred in fronto-temporal regions early in development and attenuated by the early twenties, having completely normalized in the sibs. The findings in the sibs suggest that the gray matter changes are related to genetic vulnerability to COS. Individuals homozygous for the high-risk Val allele of the catechol-O-methyl transferase (COMT) gene were found to demonstrate the greatest degree of change over time. These changes appeared to be diagnostically specific. Children with bipolar disorder showed a qualitatively different pattern of brain development from that seen in COS or controls (Gogtay et al., 2007a,b). Children initially presenting with COS, but whose psychotic symptoms resolved after medication wash-out, showed no gray matter changes.

Dr. Andrew McIntosh continued the emphasis on longitudinal brain changes, focusing on MRI studies of white matter in adult schizophrenia and bipolar disorder. He cited meta-analytic data suggesting that schizophrenia patients show excess longitudinal white matter reductions in frontal, temporal and parietal regions, when compared to healthy controls. Work from his group has also shown that white matter changes are apparent in patients with bipolar disorder (Sussmann et al., 2009), and that these are related to genetic risk for both illnesses, as revealed by studies of unaffected siblings (Munoz Maniega et al., 2008). In addition, white matter integrity across diffuse regions of the brain was found to correlate with cyclothymic personality traits, suggesting that white matter deficits are related to bipolar symptoms even in unaffected individuals. Dr. McIntosh's group has begun to study the molecular genetic basis for these changes, showing that putative risk variants in the NRG-1 and Erb4 genes are related to white matter integrity of the anterior limb of the internal capsule and anterior thalamic radiation (McIntosh et al., 2008; Sprooten et al., 2009).

The other two talks in the session continued the genetic theme. Dr. Hilleke Hulshoff Pol addressed the question of whether longitudinal reductions in schizophrenia result from genetic or environmental influences. She described results from a longitudinal twin study of schizophrenia suggesting that patients and their co-twins show excess reductions in whole-brain volume over time compared to controls (Brans et al., 2008). However, the changes were not as pronounced in the unaffected co-twins, suggesting an effect of both genetic risk and illness onset on brain volume reductions. Multivariate modeling showed that the correlation between schizophrenia liability and brain volume reductions over a 5-year period showed significant additive genetic influences for whole-brain (66%), frontal (76%) and temporal (79%) lobe measurements. Shared environmental factors implicated in the disease explained another 23% (non-significant) of the variation in whole-brain volume loss in schizophrenia. Unique environmental factors did not significantly contribute to the progressive whole-brain volume change found in patients (approximately 11%). These findings point to common genetic influences on schizophrenia liability and longitudinal brain volume reductions. Point-wise analyses of cortical thickness measures confirmed that the most robust findings were in frontal and temporal regions.

Dr. Andreas Meyer-Lindenberg considered the relationship between genes and brain connectivity in schizophrenia and bipolar disorder. In collaboration with Dr. Ed Bullmore's group, his team has found that the brain has a so-called small-world architecture, characterized by a combination of locally clustered and globally integrated connectivity, which provides an optimal balance between segregated and integrated information processing (Bassett et al., 2006). The brains of people with schizophrenia also show small-world properties, but the wiring patterns are altered, being characterized by increased limbic but decreased lateral cortical hierarchical connectivity (Bassett et al., 2008). Unaffected sibs of patients show a similar pattern, suggesting that this trend may reflect a connectivity-based intermediate phenotype. Work by his group has also shown that specific risk variants are related to brain connectivity changes that mirror findings of studies of the global connectome. They have found that the rs1344706 SNP polymorphism near the ZNF804 gene, a genome-wide supported risk variant for psychosis, exerts a pronounced effect on lateral prefrontal cortex connectivity during working memory and basic emotion processing, modulating prefrontal–hippocampal connectivity during the former and prefrontal–amygdala connectivity during the latter (Esslinger et al., 2009). They have also demonstrated an effect of CACNA1C, a genome-wide supported risk gene for bipolar disorder, on connectivity between subgenual prefrontal cortex and the medial temporal lobes.

In summary, the findings presented in this session suggested that schizophrenia is associated with pronounced brain changes that worsen over time and which are likely related to inter-regional connectivity deficits. Some of these changes interact with genetic risk for the illness, and can be traced back to the effects of specific risk variants. Some of these changes are also apparent in bipolar disorder.

7.8. Genetic, epigenetic, and molecular aspects of GABA function in the pathophysiology of schizophrenia (reported by Melanie Föcking)

Dr. Daniel Weinberger (NIH/NIMH Bethesda, MD, USA) spoke about genetic variation in GAD1, and its effects on GAD67 expression, GABA levels in living human brain, and the imposed risk for schizophrenia (Lewis and Gonzalez-Burgos, 2008). He questioned whether GABA findings are an epiphenomenon or primary to the disease. Focusing on the

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association of genetic variation in GAD1 and the risk for schizophrenia, his group identified distorted transmission of single-nucleotide polymorphism (SNP) alleles in two independent schizophrenia family-associated samples (Straub et al., 2007). Employing different approaches, they found that the GAD1 risk associated genotypes predict increased cingulate cortex GABA levels in normal subjects. They also observed evidence of statistical epistasis between the functional COMT Val158Met variant and SNPs in GAD1, suggesting a potential biological synergism indicating an increased risk. This epistatic interaction was confirmed in normal subjects on fMRI measures of cortical inefficiency. They then tested the effects of the six risk associated SNPs in GAD1 and the COMT variant on GABA levels in the anterior cingulate cortex by magnetic resonance spectroscopy. There was a significant effect of genotype on GABA for three GAD1 SNPs and for COMT. Surprisingly, risk alleles for schizophrenia in GAD1 were associated with higher GABA levels and Val–Val homozygotes for COMT had higher GABA with a GAD1 risk than a non-risk genotype. 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.

Dr. Iris Cheung (University of Massachusetts, Boston, MA, USA) continued this theme by describing the evidence for an aberrant epigenetic regulation of GAD1 in schizophrenia. After a short digression into epigenetic control of gene expression and post-transcriptional inhibition via microRNA-mediated mechanisms, that play a role in the underlying pathophysiology, she immediately focused on a specific examination of histone H3-lysine 4 methylation (Huang et al., 2007). She argued that GAD1 and H3K4me3 levels are developmentally regulated in human prefrontal cortex, associated with transcriptional activity and regulation of promoters, dynamically regulated at sites of GABAergic gene promoters, and altered in some cases with schizophrenia. Other GABAergic mRNAs frequently dysregulated in schizophrenia show less robust chromatin changes in diseased tissue. Recent data on GAD2 show no significant changes in schizophrenia in an initial post-mortem study. The aim is to develop a method for mapping the epigenome in neurons of the prefrontal cortex, delivering a model to separate neuronal from non-neuronal changes. In conclusion, she suggests 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.

Dr. Karoly Mirnics (Vanderbilt University, USA) described how post-mortem studies revealing GABA system disturbances in schizophrenia led to a new generation of transgenic mice lines. As one example, the cell-type specific down-regulation of GAD67 protein in interneurons, using exon-embedded miRNA to study downstream effects of GABAergic neurotransmitter dysfunction was mentioned. His group generated several transgenic mice lines with cell-type specific down-regulation of GAD67 protein in the NPY+, CCK+ and PV+ interneurons using exon-embedded miRNA. This transgenic approach allowed rapid, cell-type specific *in vivo* down-regulation of the transcripts of reduction of GAD67 in these interneuronal subpopulations. Analysis of the dopamine system and turnover was altered in the NPY-BAC/GAD67 miRNA transgenic mice. Whether the observed mouse phenotype is related to human schizophrenia needs to be determined. The Mirnics lab offers these mice and the constructs used to anyone interested (http://mirnicslab.vanderbilt.edu/mirnicslab).

Dr. Alessandro Guidotti (University of Illinois at Chicago, USA) discussed new pharmacological strategies to correct GABAergic dysfunction in schizophrenia. He focused on GAD67, Reelin and other gene expression in schizophrenia. DNA methyltransferase (DNMT1) has been found to be highly expressed in cortical GABAergic interneurons (Veldic et al., 2007). DNMT1 mRNA was found to be over-expressed, while GAD67 mRNA was less present (Ruzicka et al., 2007). He proposed two principal strategies: first the enhancement of defective GABAergic transmission by drugs active as selective positive allosteric modulators of GABA action at pertinent $GABA_A$ receptor subtypes, possibly using DNA methylation inhibitors that are used in cancer research phase I–III trials. Secondly, he proposed the use of drugs acting to correct chromatin remodeling abnormalities due to dysregulated epigenetic mechanisms. His data suggest that valproate's and clozapine's efficacy is on the GAD67 and the Reelin promoter. Clozapine down-regulates promoter demethylation of Reelin and GAD67 in cortical and subcortical regions. In addition, the up-regulation of putative DNA methylases is caused by clozapine and valproate. He concluded that these data suggest that chromatin remodeling mechanisms may become an important focus in studying the new generation of antipsychotics.

8. Predicting development of schizophrenia

8.1. Pathways to psychosis and neurochemistry (reported by Olasunmbo O. Owolabi)

Dr. George Awad (University of Toronto, Canada) discussed subjective tolerability to antipsychotics, referring to how the person feels on a medication. In other words, it is the person's subjective interpretation of the physiological changes taken place after receiving a medication. In an era dominated by objective scientific enquiry, study of “subjective tolerability” has been until recently relegated to “soft science”, difficult to measure or quantify. He stated that, objectifying “subjective responses” includes development of a conceptual model and development of measuring tools with sound psychometrics to demonstrate the reliability of self report. He described the development of the Drug Attitude Inventory (DAI), which continues to be in use since its introduction in the 1970s, and is the standard for measurement of subjective responses to antipsychotics. This includes: subjective positive response, subjective negative response, health/illness, physician, control, prevention and harm. Relevance of negative subjective tolerability to clinical management includes: medication defaulting, predication of clinical outcome, co-morbid substance use, quality of life, suicide behavior and health cost.

He then discussed co-morbid substance abuse in relation to its implication on subjective response to medication. He observed that neuroleptic dysphoria has subjective responses related to alterations in dopamine functions. Thus, patients with lower dopamine functioning are those vulnerable to dysphoric responses when further given potent dopamine

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blocking antipsychotics. Awad cited Voruganti et al. (1997), who proposed that neuroleptic dysphoria may be the missing link between schizophrenia and substance abuse. Based on their findings, those patients with schizophrenia that experienced neuroleptic dysphoria have a higher likelihood to develop co-morbid drug abuse compared with non-dysphoria patients (odds ratio: 4.08; $X^2 = 21.8$; $p < 0.0001$). Alpha-para-aminotyrosine (AMPT) dopamine depletion SPECT study showed an inverse link in the relationship between dysphoric negative subjective responses and dopamine binding ratio in the nucleus accumbens and the nigrostriatal area in medication free persons with schizophrenia (Voruganti et al., 2001). Dysphoric responses were the earliest behavioral experiences because they occur within the first 2 h, and usher in a cascade of behavioral alterations in the affective state, cognitive, motor, extrapyramidal, motivational changes. These can serve as clinical markers.

Dr. Award concluded by saying, that subjective tolerability both in its negative and positive experiences has significant implications in the management of schizophrenia, and the development of co-morbid addictive states are important to new drug development. He further stressed that subjective tolerability is central to understanding the addictive liability of many drugs and has led to significant research interest particularly in the addiction field.

Dr. Gabriela Novak (University of Toronto, Canada) discussed hyperactive mice that show elevated D2 receptors, a model for schizophrenia that are calcium/calmodulin-dependent kinase II alpha knockouts. CaMKII is an important enzyme in schizophrenia, and makes up 2% of total protein in the hippocampus; it is a molecular decoder of Ca^{2+} signal amplitude duration and frequency. It also forms memory of the signal. CaMKII is known to interact with more than 30 specific substrates of which are: AMPA-R, NMDA-R, DAT, and GABA-R. CaMKII is a holoenzyme that has 14 subunits, alpha and beta. The beta and alpha ratio is responsible for its kinetic activity, autophosphorylation rate and Ca2+–CaM affinity, and substrate interactions (localization of substrate affinity) which determine the properties of the enzyme. CaMKII beta levels are 27% higher in schizophrenia (Novak et al., 2006). CaMKII beta up-regulation and an increase in CaMKII beta and alpha ratio may be important in a schizophrenia-like phenotype. Heterozygous CaMKII alpha knockout mice show 50% reduction in CaMKII alpha, which leads to an increase in CaMKII beta:alpha ratio. CamKII alpha heterozygous knockout mice exhibit severe spatial working memory deficits (hippocampal), enhanced activity-dependent dopamine release during repeated stimulation, decreased anxiety-like behavior and high levels of aggression, reduced paired-pulse facilitation ratios and hyperlocomotion (Yamasaki et al., 2008). In mice that showed increased D2 receptors, an increased proportion of dopamine receptors in their high affinity state was observed. All schizophrenia models tested to date exhibit increase in D2 (Seeman et al., 2006). Higher beta and alpha ratio indicated that CaMKII beta is sensitive to weaker Ca^{2+} signals than CaMKII alpha; it induces phosphorylation of alpha subunits by a beta neighbor at lower Ca^{2+} concentration. There is higher affinity for Ca^{2+}/CaM. Synapses are usually oversensitive to low Ca^{2+} and are easier to trigger (Brocke et al., 1999; Thiagarajan et al., 2002).

Pathology of the CaMKII ratio could be observed at different stages. 1) During neurodevelopment (prenatal/early postnatal), 2) during puberty, and 3) in the adult. Dr. Novak concluded that up-regulation of CaMKII beta or an increase in CaMKII beta and alpha ratio is likely a key component of schizophrenia. The model used may be able to explain many phenotypic observations in both animal models of schizophrenia and in humans with the disease. The elevated levels of $CaMKII^{\beta}$ mRNA in the striatum suggest that this enzyme may increase D2 in animals and possibly in schizophrenia itself.

Dr. Philipp Csomer (University Hospital Zurich, Switzerland) described the impact of neurochemical manipulation on sensory gating in healthy subjects with low gating levels. Gating is a fundamental feature of information processing, an ability to inhibit, filter out, or gate external stimuli, allowing attending to salient features of the environment. Prepulse inhibition (PPI) is the attenuation of the reflexive startle reactions elicited by an intensive pulse by a weak prepulse stimulation. P50 suppression is the first stimulus (S1) which does not only produce an auditory evoked potential approximately 50 ms after stimulation (P50 wave), but also activates gating processes, resulting in a suppression of P50 AEP to the second stimulus. Low gating models from rodent to man was highlighted. Clozapine was found to improve PPI in naturally low gating healthy humans (Vollenweider et al., 2006). Healthy humans with low gating exhibiting low PPI in normal populations might be viewed as a surrogate marker for the reduced gating in clinical populations. To bridge preclinical and clinical research an approach has recently been developed to investigate differential effects of antipsychotics on gating in healthy human subjects exhibiting low levels of gating, rather than in patients (Csomor et al., 2008; Vollenweider et al., 2006; Swerdlow et al., 2006). A proof of concept study was used to determine the effect of three different antipsychotic treatments, on sensorimotor gating (PPI), sensory gating (P50 suppression) and various cognitive domains assessed in healthy human subjects with low and high P50 gating levels. The validation process included three neuropharmacological compounds without antipsychotic properties. Antipsychotic compounds used included: aripiprazole, risperidone, and amisulpride. Compounds used for negative control treatments were: lorazepam, modafinil, and valproate. The antipsychotic, aripiprazole, but not risperidone and amisulpride exhibited the potential to improve PPI in subjects with low baseline sensorimotor gating. In negative control treatments, none of the negative control treatments improved PPI in low or high gating subjects. Lorazepam and modafinil reduced sensorimotor gating (main effect of treatment). In the P50-gating antipsychotics, all antipsychotics improved P50 gating in subjects exhibiting low levels of P50 suppression. For P50 gating: negative control treatments, lorazepam and modafinil impaired P50 suppression in subjects with high baseline gating; valproate did not significantly affect P50 gating. In conclusion, in the application of the low/high gating model in a phase 1b trial, the low gating subgroup can be considered as a surrogate patient group, while the high gating group can represent a respective “control group”.

Dr. Deepak Cyril D'Souza (Yale University School of Medicine, USA) provided data on how glycine transporter inhibition attenuates the psychomimetic effects of ketamine in healthy

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human subjects. He discussed the glutamate hypothesis of schizophrenia, in which the facilitation of NMDA receptor function is beneficial. Subjects used in this study were: 9 Caucasians, 5 Asian, and 1 African American. Compounds under study were ORG25935 and ORG25935x ketamine. The results showed no effect of ORG25935 or interaction of ORG25935x ketamine on a number of feelings/emotional states. Dr. D'Souza noted that GLY-T inhibition reduces some, but not all of the effects of ketamine relevant to psychosis. None of the behavioral effects of ketamine was increased by GLY-T inhibition pre-treatment. He concluded that there is preliminary support for antipsychotic potential of GLY-T inhibitors.

Dr. Douglas L. Noordsy (Dartmouth Medical School, USA) spoke on synergistic interactions between antipsychotics medications and psychosocial rehabilitation. He illustrated this using evidence from a double-blind randomized trial of risperidone versus olanzapine among participants in vocational rehabilitation.

Dr. Ruchika Gajwani (University of Birmingham, UK) described the developmental pathways to emotional dysfunction in young people at ultra-high risk (UHR) of developing psychosis. He emphasized that the purposes of the study were 1) to elucidate the nature and prevalence of emotional dysfunction in ultra-high risk group; and 2) to elucidate the developmental risk factors for emotional dysfunction in childhood trauma attachment dysfunction. The study revealed that increased levels of comorbid symptoms of anxiety and/depression, social anxiety/phobia which were associated with the occurrence of positive symptoms in the "at-risk" group. Childhood trauma was studied with respect to suicidal thinking to see if adverse life event would have an impact on dissociative experiences. Emotional neglect was found to be high, sexual abuse was reported, but childhood trauma was found to be less prevalent. Other factors considered were parental attachment, social phobia, and adult attachment. Emotional dysregulation was prevalent in all, with levels of neuroticism having a significant association with client distress and positive symptoms.

Dr. Ulrich Reininghaus (Queen Mary, University of London, London, UK) concluded the session with a discussion on sociodevelopmental pathways to psychosis. He and colleagues used data from the AESOP study (Aetiology and Ethnicity in Schizophrenia and Other Psychosis) to evaluate social adversity and psychosis. In childhood adversity and psychosis, physical, sexual, emotional abuse, parental separation and loss, and bullying were evaluated. The cohort consisted of people between ages 16 and 64 residing within a specific catchment area. During data collection for childhood adversity, factors taken into consideration were long-term separation from one or two parents before age 16 and death of parents (one or both). The adult adversity indices used were: index of social disadvantage and isolation, employment, housing, living arrangements, social networks education and premorbid IQ. The study revealed that there was a strong effect of parent separation and showed that early adversity leads to adult adversity then to psychosis.

8.2. Pathway to psychosis and factors in childhood (reported by Darryl C. Smith)

This session provided the opportunity to explore factors in childhood that promote the development of psychosis. *Dr. Bartels-Velthuis* opened the session by discussing voice hearing in childhood. This was based upon a study of 3870 children in the Netherlands (Bartels-Velthuis et al., 2010a,b). These children had a 1-year prevalence rate of auditory hallucinations of 9%. Of those reporting auditory hallucinations, 15% reported the voices as distressing while 19% endorsed cognitive effects. Both male and female subjects were equally likely to hear voices, but the girls reported increased rates of anxiety and somatic complaints as a result. In a 5-year follow-up of these children, the continuation rate of auditory hallucinations was 24% with a 5-year incidence rate of 9% and 1-year prevalence of 7% (Bartels-Velthuis et al., 2010a,b). New hallucinations were more common in children in urban settings and those with religious affiliation. It was noted that there was an individual range of pathology. This is most-likely due to more significantly traumatic and stressful life events during earlier childhood. In general, hearing voices in childhood is rather common and benign in nature. The vast majority of children discontinue hearing voices.

Dr. Zammit furthered the discussion of psychosis and urban environments in a study investigating whether individual, school, or area level characteristics could explain the relationship between the two (Zammit et al., 2010). The study was a Swedish population-based, multilevel, and longitudinal study which included all individuals born in Sweden in 1972 and 1977. The results showed that most of the variance was at an individual level and explained by school-level social fragmentation. Social fragmentation explains the effects of urbanicity and increases the risk of psychosis independent of individual effects (Zammit et al., 2010). There was also some evidence that individual effects are also context dependent. These findings were particularly important in that they display the significance of socioeconomic position in the development of a disease process. If attempts are made to rectify these injustices, then there remains a potential to decrease disease burden. Dr. Zammit offered the idea that increased social fragmentation helps explain the association between urbanicity and psychosis. Urban environments and social fragmentation can lead to increased stress levels. Bartels-Velthuis stated that early-onset stress, particularly when continuous can lead to hearing voices during childhood. Tineke Lataster addressed whether sensitivity to stress is a marker of genetic risk, how this risk is linked to the psychosis symptom dimensions, and whether this sensitivity clusters within families (Lataster et al., 2010b). The study was conducted using the Experience Sampling Method to measure daily life stress as well as Community Assessment of Psychotic Experiences and PANSS scales to evaluate psychotic symptoms. It was found that stress sensitivity is an indicator of genetic risk for psychosis, particularly with regard to positive symptoms, and is found to be clustered in families. With these findings, novel interventions focused on decreasing daily stress levels may be helpful in decreasing the manifestation of psychotic disorders in those at increased risk.

Dr. Johan Lataster also explored the effects of early adverse events as childhood trauma in the subsequent development of psychosis. He suggested that these early events increase the risk for psychosis when individuals face stressful situations later in life. In addition to genetic factors, early-onset environment × environment interactions could make one

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more vulnerable to psychosis when presented with future trauma (Lataster et al., 2010a). Stilo also considered environment in her study of the role of social disadvantage in the development of psychosis. For years, there has been discussion on whether schizophrenia leads to social disadvantage and isolation or vice versa. Using a case–control study method of first-episode psychosis, comparing indicators of current and long-term social disadvantage and isolation (living alone, single, employment status, and educational status) to healthy subjects, it was determined that at one year and five years from onset, the cases were 5.47 (CI 3.29–9.10) and 3.39 (CI 2.05–5.61) times more likely than controls to report social disadvantage and isolation (Stilo et al., 2010). Despite efforts to study gene–environment interaction, sufficient data is still needed due to lack of accurate measurement of many environmental exposures (Mortensen et al., 2010).

Beyond the factors that contribute to the development of schizophrenia, the goal shifts from prevention to improving mortality and morbidity. For years, it has been held that the lifetime suicide rate in schizophrenia patients is 10% (Miles, 1977). However, according to Dutta, what few realize is that these figures are based upon prevalence rather than incidence cohorts and based upon data from severely ill patients (Dutta, 2010). The 10% figure more accurately reflects proportional mortality and not lifetime risk. Her study, a follow-up of three incidence cohorts, used Standardized Mortality Ratio calculations in order to gain a more accurate understanding of suicide risk in these individuals. It was determined that although proportional mortality was 11.9% (53/444) in her sample, actual case fatality was lower than expected at 1.9% (53/2723) (Dutta, 2010). Suicide rates were higher in the first year after initial presentation, however there were also cases which occurred a decade later. These findings suggest that schizophrenic patients should be monitored closely from initial onset, as well as later in life in order to decrease mortality from suicide.

In conclusion, several risk factors for early-onset psychosis were discussed. Early adverse events, increased stress levels, and social fragmentation and isolation are a few important variables that have modifiable potential. It is important to consider them in the development of the Psychotic Risk Syndrome in DSM-V. As the literature expands, perhaps the evidence will be even stronger and new risk factors will be discovered. In the meantime, it is probably beneficial for clinicians to implement interventions which decrease these factors and increase efforts to monitor these patients for long-term suicidality. In addition, the development of policies that would help decrease social disadvantage would also aid in decreasing the burden of disease.

8.3. Predicting the development of psychosis (reported by Lisa Buchy)

Dr. Timothea Toulopoulou (London, UK) focused on endophenotypes. In schizophrenia, cognitive deficits are among the most promising indicators of liability to schizophrenia; they appear to be present before psychosis onset, are present at first-episode, appear to remain stable across the course of illness, and are found among non-affected relatives. Dr. Toulopoulou presented results from a large combined family and twin study, which aimed to quantify the covariance between schizophrenia and cognitive function due to shared genetic and environmental influences. She present a trivariate genetic statistical model that visually depicted the hypothesis that a considerable proportion of the variance in memory and IQ could be explained by genetic influences, that in turn would share substantial genetic variance with schizophrenia. Delayed recall showed a greater genetic link than immediate recall, but was the less heritable of the two. Intelligence showed a similar genetic correlation with schizophrenia to delayed recall but was also more heritable. No domain was more genetically correlated with schizophrenia than others. Finally, 89% of the phenotypic covariance between schizophrenia and IQ was due to shared genetic factors, and similar estimates were found for the two memory factors and schizophrenia. Taken together, her genetic model showed that a substantial proportion of the phenotypic correlation between schizophrenia and memory and IQ is due to the same genetic influence. She ended with the caveat that over 50% of the genes that influence the liability to schizophrenia do not affect cognition; as such, the genetics of schizophrenia are not restricted to the genetic determinants of cognitive impairment.

Dr. Romina Mizrahi (Toronto, Canada) used PET neuroimaging to examine stress-induced dopamine release in participants at clinical high risk for psychosis and patients with psychosis. Schizophrenia has been associated with dysregulation of the biological stress response, and this is hypothesized to be due to increased dopamine and HPA hormones in response to a repeated stressor, known as sensitization. The goal of Dr. Mizrahi's study was to explore whether this relationship is detectable before psychosis onset in clinically high-risk participants and in antipsychotic-naïve patients with psychosis, relative to healthy participants. To achieve this goal, participants completed two cognitive tasks, namely, the Montreal Imaging Stress Test (MIST) and the Sensory-Motor Control Task (SMCT), while simultaneously undergoing PET. Results revealed that relative to healthy controls, participants at clinically high risk for psychosis and those with psychosis showed significantly greater stress-induced dopamine release in the associative striatum. No group differences emerged in the limbic or sensorimotor striatum. Results support the hypothesis that stress-induced dopamine dysregulation is observable in schizophrenia, and suggests that dopamine sensitization may be a possible risk factor.

Dr. Elaine Walker (Atlanta, GA, USA) discussed potential genetic and epigenetic mechanisms influencing glucocorticoid secretion in the emergence of psychosis. She described the role of glucocorticoids in the expression of genes governing neuronal function, and that glucocorticoid receptors are key to HPA axis function. In psychotic disorders, a relationship exists between HPA hyperactivity and symptom severity. Dr. Walker's longitudinal study examined whether heightened cortisol secretion precedes the onset of psychosis, and evaluated potential contributing genetic risk factors. Her sample consisted of 14 prodromal adolescents who converted to psychosis, 34 who did not convert and 38 healthy controls. The data revealed that adolescents who converted to psychosis showed the greatest increase in cortisol secretion between baseline and 1-year assessments. When examining potential genetic risk factors, individuals with a COMT Met/Met polymorphism showed elevated cortisol compared to

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individuals with Met/Val or Val/Val genotypes. These results support a role for HPA axis dysregulation in psychosis and extend previous work by demonstrating that HPA axis dysregulation is present at the time of conversion to psychosis.

Dr. Ashleigh Lin (Melbourne, Australia) focused on neurocognitive markers of transition to psychosis and poor functional outcome in a large sample of individuals identified as ultra-high risk for psychosis. She presented results from neurocognitive assessments collected at program entry to the PACE clinic 7 to 14 years prior. Forty-two percent of the sample experienced a psychotic episode and poorer visual memory ability significantly predicted the transition to psychosis (OR = 0.94). Interestingly, the data revealed a number of individuals with poor functional outcome who did not transition to psychosis. When separating these individuals into high and low functioning groups, 63% of the low function group had experienced a psychotic episode (37% having received a diagnosis of schizophrenia). The remainder of the poor functioning individuals had never had a psychotic episode, but was functioning very poorly later in life. The poor functioning group was further characterized with poorer verbal memory ability (OR = 0.70), greater mania, higher SANS and BPRS scores. The most striking result was that participants with baseline verbal IQ and verbal memory scores ≤1 SD below the mean were significantly more likely to be functioning poorly (OR = 6.30, OR = 14.0, respectively) at follow-up. Taken together, these data identified a substantial proportion of individuals who do not transition to psychosis yet experience poor functional outcome. Dr. Lin concluded by suggesting that using transition to psychosis as a primary outcome measure may be misleading; a shift in the current framework for measuring outcome is needed to include individuals who do not convert to psychosis yet function poorly.

Dr. Abraham Reichenberg (London, UK) talked about static and dynamic cognitive deficits in childhood that precede adult schizophrenia. He presented data from a 30-year longitudinal study that investigated 1) the developmental course of cognitive deficits, 2) whether all premorbid cognitive deficits follow the same course, and 3) whether premorbid cognitive deficits are specific to schizophrenia or are shared by other psychiatric disorders. A large cohort of participants was followed from birth to age 32. Cognitive development was compared in three resulting groups: participants who developed schizophrenia, participants who developed depression, and healthy participants. First, children who developed schizophrenia showed early and persistent cognitive deficits on verbal and visual knowledge acquisition, reasoning and conceptualization. This result supports the "developmental deficit" hypothesis of cognitive deficits in schizophrenia. Second, children who later developed schizophrenia displayed a slower rate of growth in processing speed, attention, working memory and visual–spatial problem solving. This second result supports the "developmental lag" hypothesis of cognitive deficits in schizophrenia. Neither of these two premorbid patterns of cognitive performance emerged in children who later developed depression. Taken together, the findings point to two possible etiologies of cognitive dysfunction in schizophrenia: a static neuropathology and a later developmental lag. The findings have further implications for schizophrenia nosology, as evidenced by clear distinctions in the developmental processes that lead to cognitive dysfunction.

Dr. Eileen Joyce (London, UK) focused on disentangling the influence of working memory versus speed of processing deficits on planning abilities in first-episode schizophrenia. Her first-episode patients and healthy controls performed a computerised version of the Tower of London task (CANTAB SOC). In this task, participants were first required to plan and execute a series of moves to match a test arrangement of balls to a goal arrangement. The second task was a control task which required the participant to copy the computer in performing the same series of ball movements performed in task 1. Tasks one and two allowed for evaluation and comparison of thinking and motor execution speed, respectively. Third, other cognitive variables were tested including working memory, processing speed, visual memory and IQ. Relative to controls, patients showed lower IQ, working memory and visuo-spatial recognition memory. Patients also spent less time planning their movements and greater time executing movements, indicating faster initial thinking times and slower subsequent thinking times, respectively, compared to controls. This "plan as you go strategy", i.e., reduced planning and increased execution times, significantly correlating to working memory but not to processing speed. Dr. Joyce concluded that cognitive enhancement strategies in psychosis should target working memory rather than processing speed.

Dr. Manuela Russo (London, UK) reported on neuropsychological functioning and its relation to symptom dimensions in first-episode psychosis. She presented baseline data from the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study in which patients were tested on six cognitive domains: verbal and visual memory, processing speed, executive functions/working memory, language; as well as current and premorbid IQ. The relationship between the above cognitive domains and five symptom dimensions (mania, reality distortion, depression, negative and disorganization) were examined. The results showed that negative and manic symptom dimensions shared a statistically significant relationship with cognition. In particular, most severe negative symptoms were associated with poorer IQ, verbal memory and processing speed. Furthermore, the mania symptom dimension was associated in an inverted U-shape to executive functioning/working memory and processing speed: mild manic symptoms were related to better cognitive performance compared to low or severe manic symptoms. Symptom severity accounted for approximately 5% of the variance. Dr. Russo used these findings to suggest that in people with a first-episode psychosis, symptom severity and cognitive ability are not independent, suggesting a common underlying brain system.

Dr. Larry J. Seidman (Boston, MA, USA) discussed cognitive performance as a predictor of conversion to psychosis. Dr. Seidman highlighted several important reasons to study cognition in the prodrome, including the fact that cognitive impairments are central to schizophrenia, and are well established as vulnerability indicators for the disorder based on family (genetic) high-risk research. A model was presented in which cognitive deficits comprise part of a biological vulnerability to schizophrenia, and cognition was

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thus conceptualized as a window into the pathophysiology of the disorder. Dr. Seidman's study described data from the NAPLS-1 project, an 8-site study with a large sample of clinically high-risk individuals, including converters and non-converters, individuals at risk with a family history of psychosis, and control participants. All participants were tested on an extensive neuropsychological battery and on IQ. Group comparisons showed that compared to individuals at clinical high risk who did not convert, converters had widespread baseline cognitive deficits, most pronouncedly in verbal memory and processing speed. Individuals with a familial risk displayed worse vocabulary than both clinically high-risk groups, whereas the latter groups showed poorer verbal memory than the familial risk group. Taken as a whole, converters with a family history of psychosis show the greatest cognitive impairments. Interestingly, when collapsing across all three experimental group scores on cognitive domains, the effect size ($d = 0.07$) appears to be half of 60% of the effective size of cognitive deficits in first-episode samples. This pattern of results may suggest that cognitive impairment increases during the late prodrome and first psychotic episode, and perhaps beyond.

8.4. Risk factors in the development of psychosis: common pathophysiological variables provide insight into the etiology and treatment of schizophrenia (reported by Gemma Modinos)

Dr. Anthony Grace (University of Pittsburgh, USA) presented a neurodevelopmental disruption model of schizophrenia in rats based on prenatal administration of mitotoxin methylazoxymethanol acetate (MAM) during gestation. The finding of hyperresponsivity of the dopaminergic system in MAM-treated rats aligns with studies of patients with schizophrenia. Furthermore, there is evidence to suggest hippocampus hyperactivity in patients, which appears to be correlated with levels of symptomatology. MAM-treated rats showed a similar pattern of elevated activity in hippocampus, reflecting an increase in the number of neurons that are firing spontaneously. Through hippocampal inactivation, it was found that dopaminergic neurons could be brought back to normal levels of firing. Dr. Grace additionally reported that context-dependent processes dependent on the hippocampal subiculum are also affected by stress, in terms of increased dopamine neuron firing, which was found to be hyperresponsive after 2 h of stress. After inhibition of the subiculum, this hyperresponsivity was observed to return to normal levels. He thus suggested that an abnormal increase of tonic dopamine neuron population activity in the hippocampus is a relevant factor in conditions of stress or drug abuse. Interestingly, both amphetamine sensitization and stress activate the ventral subiculum–nucleus accumbens pathway, leading to increased dopamine neuron population activity, and to hyperresponsivity to amphetamine. Finally, he reported that peripubertal administration of diazepam prevents dopamine overdrive in the MAM developmental model of schizophrenia. Thus, Dr. Grace suggested that treatment of the heightened responsivity to stress in at-risk individuals might be an effective means to circumvent the onset of psychosis.

Dr. Patrick McGorry (University of Melbourne, Australia) discussed Hippocampal-Pituitary-Adrenal (HPA) axis function in first-episode psychosis (FEP). He examined the cortisol response to the administration of low (0.5 mg) and very low (0.25 mg) doses of dexamethasone to neuroleptic-naïve FEP patients, and its relationship to childhood trauma. The Dexamethasone Suppression Tests (DST) revealed that, at 0.25 mg, there were 33% of FEP patients with an increased rate of cortisol hyper-suppression. At 0.5 mg, there were 63% of hyper-suppressors. Dr. McGorry concluded that there might be distinct profiles of HPA axis dysfunction in FEP, with some patients displaying enhanced cortisol suppression. In a second, prospective study, Dr. McGorry collected blood cortisol and Dehydroepiandrosterone sulfate (DHEAS) from patients with FEP and controls. Assessments were repeated after 12 weeks. DHEAS is known to exert a protective effect on hippocampal tissue against glucocorticoid-induced toxicity. Thus, this hormone is thought to be involved in neuroprotective processes. Under conditions of stress, an increase in DHEAS is regarded to be beneficial, and may play a role in resilience and adaptation to stress. Under chronic stress, DHEAS decreases and cortisol increases. In their study in patients with FEP, Dr. McGorry and colleagues observed that, at baseline, there were no significant differences between groups in cortisol, DHEAS, or the cortisol/DHEAS ratio. Nevertheless, within FEP patients, decreases in cortisol levels and in the cortisol/DHEAS ratio over time were associated with symptomatic improvement. In controls, perceived stress significantly correlated with DHEAS and the cortisol/DHEAS ratio. This association was not observed in patients. He concluded from this study that, in FEP, there might be an impaired hormonal response to stress, in terms of exhausted or depleted adrenal release of DHEAS due to toxicity. Taken together, these studies suggest involvement of the stress system in the pathophysiology of psychotic disorders, with relevant implications for potential treatment strategies modulating these neurosteroids.

Dr. Petra Habets (University of Maastricht, the Netherlands) presented results from a study on putative associations between cannabis use, trauma and brain alterations in psychosis. The study included 274 participants, comprising 89 patients with non-affective psychosis, 98 healthy siblings, and 87 controls. Brain alterations were examined with a measure of cortical thickness, which involved 34 regions per hemisphere. Childhood trauma was assessed with a questionnaire that measured different types of trauma: emotional, physical, sexual abuse and neglect. Cannabis use was measured with the Composite International Diagnostic Interview (CIDI). A multilevel regression was carried out to examine interactions between Group and Trauma, and between Group and Cannabis. There was a significant Trauma by Group interaction, with patients with more trauma showing less cortical thickness, and siblings with more trauma showing more cortical thickness (although not significantly different relative to controls). In addition, there was a significant Cannabis by Group interaction, with patients and siblings using cannabis showing less cortical thickness relative to controls. Dr. Habets concluded that increased cortical thickness in siblings with trauma could serve as a resilience mechanism. Thus, she interpreted this as evidence for GxE underlying the association between cannabis and psychosis. Dr. Habets proposed a model by which trauma would cause hypersensitive glucocorticoid release and/or abnormalities in glucocorticoid receptors, which then change

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HPA axis functioning causing increased dopamine in the mesolimbic system, which then cause volume reductions in the hippocampus and the prefrontal cortex. Finally, Dr. Habets related the present findings to a theoretical framework postulating a common pathway for trauma and cannabis, which is involved in assigning salience to otherwise innocent stimuli, which leads to the genesis of hallucinations and delusions.

Dr. Robin Murray (Institute of Psychiatry, London, UK) focused on integrating the epidemiology and the pathogenesis of schizophrenia. In particular, he presented a number of epidemiological facts and how they relate to research on the pathology of dopamine. Fact 1 referred to schizophrenia being more common and severe in men than in women. Interestingly, sex differences in striatal dopamine release have been reported, with men releasing significantly more dopamine than women, which could make them more prone to schizophrenia. Fact 2 referred to the maximum onset of schizophrenia being in early adulthood, with a decline in its incidence in later stages. Of note, an age-related change in midbrain dopamine synthesis and prefrontal activation has also been reported. Fact 3 referred to relatives of patients being more likely to develop schizophrenia. Noteworthy, first-degree relatives show relatively increased dopamine uptake and increased capacity for dopamine synthesis. Fact 4 referred to the fact that stimulant drugs and Dopa can produce a schizophrenia-like picture, particularly inducing positive symptoms. As Fact 5, obstetric complications (e.g., hypoxia) are known to increase risk for schizophrenia. Of note, such events impact on the dopamine system. For instance, hypoxia may cause lesions in the hippocampus, which impact on the dopamine system, similar to the MAM model presented by Dr. Grace during his talk. Finally, as Fact 6, it is known that social adversity augments the risk for schizophrenia, such as parental deprivation, child abuse, migration, or social isolation. Interestingly, there is evidence to suggest that poor parental maltreatment is associated with increased dopamine release. To conclude, Dr. Murray postulated that the pathophysiology of striatal dopamine explains the epidemiological characteristics of schizophrenia. Nevertheless, he acknowledged that there are a number of related questions yet to be answered, such as the determination of genetic risk, which is too poorly defined at the moment to be characterized in terms of effects on dopamine, and of whether cannabis increases striatal dopamine.

8.5. Dysregulation of the dopamine system: the final common pathway to schizophrenia? (Reported by Igor Riecansky)

This symposium addressed the role and importance of dopamine system dysregulation in the pathophysiology of schizophrenia. The first speaker, *Dr. Anthony Grace* (University of Pittsburgh, PA, USA), summarized recent findings on a developmental animal model of schizophrenia (the 'MAM rat model'). See last symposium discussed previously. He described how damage to the hippocampus during development resulted in changes in dopaminergic function that became apparent in adult rats, mirroring a number of findings in schizophrenia, including increased sensitivity to amphetamine. Dr. Grace reported that hyperactivation of hippocampal pyramidal cells resulted in increased tonic activity in the ventral tegmental area (VTA) and rendered the VTA to be more sensitive to pedunculopontine input signals evoked by behaviorally salient stimuli. Interestingly, an increase in tonic VTA activity was observed also in rats chronically treated with amphetamine. Inactivation of the ventral subiculum (VS) reversed the increased activation of the VTA and prevented exaggerated behavioral response to amphetamine. These results support the view that disinhibition of pyramidal neurons in VS could play a major role in the pathophysiology of schizophrenia. Dr. Grace also noted that increased VTA activity in amphetamine-sensitized animals evolved quickly and persisted for several months. Therefore, these mechanisms could underlie increased risk of psychosis in human individuals abusing psychostimulant drugs.

Dr. Alain Dagher (McGill University, Ca), focused on the association between the dopamine system and psychosocial stress. In the neuroimaging studies reported by Dr. Dagher, subjects were scanned during performance of a stressful mental arithmetic task (Montreal Imaging Stress Task, MIST), in which time pressure is imposed individually by an adaptive procedure. Dr. Dagher showed that task-related dopamine release in the striatum was higher in subjects who had experienced poor maternal care during the childhood and was associated with increased cortisol stress response. Subjects with negative schizotypy (physical anhedonia) had higher stress-related dopamine release than subjects with positive schizotypy (perceptual aberrations) and healthy controls. In an fMRI study, increase in serum cortisol level was associated with deactivation of several limbic structures, including hippocampus, hypothalamus, amygdala and orbitofrontal cortex. This indicates higher baseline activity in these regions in subjects with high stress response. Overall the data Dr. Dagher presented showed that environmental factors in early childhood and later life could increase dopamine release, and this was particularly the case in people with schizophreniform traits.

Dr. Oliver Howes (Institute of Psychiatry, KCL and Imperial College London, UK) addressed the question whether striatal hyperdopaminergia leads to psychosis or can be considered as a schizophrenia endophenotype. His recent results show that subjects with at-risk mental state for the development of psychosis had increased dopamine synthesis in the striatum, particularly in the associative subregion targeted by projections from the prefrontal cortex, and that this dopamine overactivity increased further in those individuals who went on to develop psychosis. On the other hand, the latest data from Dr. Howes' group indicate normal striatal dopamine synthesis in the well co-twins of schizophrenia patients. This suggests that disturbance of the dopamine system might be a state, rather than trait-dependent feature, and the finding that dopamine overactivity increased further only in those that developed psychosis provides further support for this.

Dr. Abi-Dargham (Columbia University, NY, NY, USA) summarized the evidence for dopamine dysregulation in schizophrenia and linked radiotracer studies with clinical symptomatology. The emerging view is that positive symptoms are directly related to striatal dopamine release, while cognitive symptoms may be associated with striatal dysfunction or frontal cortical dysfunction. Supporting the former, Dr. Abi-Dargham presented results of a recent study, which showed that intrasynaptic DA release is selectively increased

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in the associative, but not limbic and sensorimotor striatum. In agreement with the data presented by Dr. Howes, this finding suggests that impaired processing at the level of the striatum of input from the DLPFC may play a pivotal role in schizophrenia. Little is known about the associations between dopamine signaling and negative symptomatology in schizophrenia, but data from patients with substance dependence indicate that negative symptoms could be specifically associated with a decreased dopamine release in the limbic striatum.

In summary, the papers presented at this symposium provided converging evidence to link striatal dopamine overactivity to the development of schizophrenia, and particularly psychotic symptoms. Furthermore the data presented shows how developmental and environmental factors could lead to dopamine overactivity. This provides a mechanism to link established developmental and environmental risk factors for schizophrenia to a final neurochemical abnormality. Dr. Grace and Dr. Dagher's findings highlighted the likely role of the hippocampus in acting to dysregulate dopamine function. Discussant to this symposium, *Dr. Shitij Kapur* (King's College London), remarked that after more than 20 years of studies of the dopamine system one could have hardly expected new findings to appear, but that in fact recent development in radiotracer imaging had provided a step change in understanding of dopamine's role in schizophrenia. Methodological advances make possible novel insights into the pathophysiological mechanisms and indicate new targets for drug development. Dr. Kapur suggested that dopamine system disturbance could be regarded as a final common pathway to psychosis rather than schizophrenia as such. A vivid discussion followed. Professor Murray reformulated the question of the symposium title and asked if the dopamine system dysregulation could be regarded as a necessary condition for schizophrenia. Is psychosis without striatal hyperdopaminergia possible? Dr. Abi-Dargham replied that her data indicated it was possible since the overlap between patients and control in the measures of dopamine release was substantial. On the other hand, as noted by Dr. Dagher, inter-subject variability of the measured variables was very high and could mask subtle within-individual state-related changes. Thus, within-individual change in the dopamine function could to be of major importance.

9. Neuropathology

9.1. Future directions for the neuropathology of schizophrenia (reported by Melanie Föcking)

This symposium summarized the value of post-mortem brain research in schizophrenia and discussed possible future directions. There continues to be a need, to use integrative approaches and for detailed neuropathology employing newer technologies, and the necessity to study multiple cortical regions.

Dr. James Meador-Woodruff (University of Alabama at Birmingham, USA) focused on the glutamate hypothesis of schizophrenia and suggested that recent data point to abnormalities of glutamate receptor trafficking, delivery, dendritic localization, recycling, and degradation in the brain in schizophrenia (Beneyto and Meador-Woodruff, 2008; Kristiansen et al., 2010). In a study comprising both the anterior cingulate and the dorsolateral prefrontal cortex, they extended findings of abnormalities of intracellular trafficking of the AMPA subtype of glutamate receptor in schizophrenia and identified a lack of significant differences in the levels of AMPA-R subunits. Both GluR2 and GluR4 are sensitive to enzymatic de-glycosylation. He concluded that abnormalities of glycosylation in schizophrenia may be more extensive, as there are preliminary results suggesting abnormalities of N-glycosylation of NMDA subunits and two of the glutamate transporters. His results suggest 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 promising targets for drug treatment.

Dr. David Cotter (Royal College of Surgeons in Ireland, Dublin, Ireland) spoke on using proteomic studies of the post-mortem brain, to get a snapshot representative of the disease and getting direct insights into the pathogenesis of schizophrenia at the level of protein expression. He showed data (Pennington et al., 2008a,b; Behan et al., 2009; English et al., 2009) that elucidate how the different approaches all confirm changes in synaptic, cytoskeletal and metabolic functions across studies, and that different brain areas are affected by schizophrenia. He pointed out that there is evidence for NMDA receptor hypofunction in their datasets, and that clathrin mediated endocytosis related proteins seem to play an important role in this regard. He validated this finding by conducting a review of all brain proteomics studies published so far. David Cotter suggested extending this even further, by using a systems biology approach (Sauer et al., 2007) or an epigenetic viewpoint (Rutten and Mill, 2009). He concluded that there is a demand for further more integrative approaches, incorporating the findings relating to environment, genome, transcriptome, in addition to the proteome.

Dr. Maree Webster (SMRI, Washington, USA) underlined the importance of research on post-mortem brain tissue in order to identify relevant disease-related pathways. She introduced the recently established, publicly available, Stanley Neuropathology Consortium Integrative Database (SNCID; http://sncid.stanleyresearch.org) (Kim and Webster, 2010). This database integrates datasets from neuropathology studies using 12 different brain regions and genome-wide expression microarray datasets of three independent studies using frontal cortex and cerebellum. All data are derived from schizophrenia, bipolar disorder, severe depression cases, and unaffected controls. She pointed out that one limitation might be the inhomogeneity of laboratory practice and therefore the datasets present technical variation. Among other strategies it is envisioned to include SNP, microRNA, and methylation array data from the same cohort as well as similar data of another cohort of brains. She hopes that researchers using the database will come up with new hypotheses, concluding, that such applications of the database could potentially lead to the identification of molecular targets for drug development.

Dr. Karoly Mirnics (Department of Psychiatry, Vanderbilt University, USA) presented his exploration of the future of post-mortem research, stating that brain collections are an

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incredibly valuable resource, and none of the disease animal models is likely to be an adequate model to mimic the pathophysiological processes that occur in the diseased human brain. He addressed five points, namely i) confounds, with regard to post-mortem interval, medication, lifestyle, co-morbidities etc. ii) what should be analyzed: i.e. many different brain regions, different substructures of those brain regions, different cell types, and different cell compartments iii) how should it be analyzed, he went from RNA to DNA to -omics strategies, functional assays, Chip on Chip and SNP analyses that should become compulsory for any brain series iv) data integration according to Mirnics (Pongrac et al., 2002) has been overlooked and is a challenging area to explore. Finally he addressed the very valuable point of v) resource integration making it mandatory for all brain banks to share their resources to overcome difficulties, for instance of limited sample size, and improving on meaningful genotype–phenotype comparisons. He concluded by stating that investigating the same samples with many different tools (e.g. expression arrays, SNP chips, epigenetic modifications, etc.) may be a very powerful strategy, with all data 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 to subgroup patients into biological subphenotypes of the disease.

10. Cannabis use

10.1. Cannabis, amphetamines and early psychosis: evaluating the risks for progression, neurobiologic models of interaction and implications for treatment (reported by Bonga Chiliza)

Dr. Andrea Auther (NY, USA) presented data from a study conducted in New York under the auspices of the RAP (Recognition and Prevention) program. She and colleagues prospectively examined the relationship between cannabis use and prodromal symptoms of psychosis. People meeting the criteria of critical high risk for development of psychosis were compared to normal age-matched controls. The patients were comprehensively assessed using standard instruments (e.g. the Structure Interview for Prodromal Symptoms—SIPS, and the Scale of Prodromal Symptoms—SOPS) for attenuated positive and negative symptoms and non-specific symptoms. The study found that baseline predictors of psychosis conversion were the total number of positive symptoms and the level of social functioning. Cannabis use was not predictive of psychosis conversion. Cannabis users had no change in positive symptoms and functioning stayed the same during the follow-up period. Dr. Auther concluded that similar to other prospective prodromal cohorts (Cannon et al., 2008) there was no relationship between cannabis use and psychosis conversion.

Dr. Donald Linszen presented results of a recently published study (Korver et al., 2010) examining the relationship between cannabis use and symptoms and neuropsychological functioning in ultra-high risk subjects compared to healthy controls. Dr. Linszen noted past literature showing significant association between cannabis use and later onset of psychosis. He also supported the theory that early cannabis use is a risk factor for psychosis in young adults. Dr. Linszen then presented the findings from a cross-sectional study which used commonly used instruments like the SIPS, and the Bonn Scale for Assessment of Basic Symptoms. The neuropsychological testing consisted of the finger tapping test, continuous performance test, California verbal learning, and verbal fluency. The study found that cannabis-using ultra-high risk patients had more symptoms than non-using patients and controls. The cannabis-using controls had more basic symptoms than non-using controls. The study also found that the neuropsychological functioning was highest in the non-using controls. When they examined the frequency of cannabis use, they found that the higher the frequency of use, the poorer the scores. Dr. Linszen emphasized that otherwise healthy controls who were cannabis users had significant symptoms, which has important implications for public health policy.

Dr. Tania Lecomte presented a study conducted in Vancouver, Canada, examining the profile of methamphetamine psychosis. Methamphetamine abuse has become an international health problem. In Vancouver, a large percentage of young people obtain methamphetamine on the streets and it is relatively inexpensive. Dr. Lecomte presented literature showing that a significant number of 'first-episode psychosis' patients have methamphetamine psychosis with up to 30% in some samples (e.g. Bühler et al., 2002). In her study she included people presenting at an emergency room with methamphetamine psychosis and followed them up for six months. There were 295 subjects at baseline and ended up with 158 who completed the follow-up. The results showed that the majority of the subjects had either a family history of mental illness, commonly schizophrenia, or a past history of mental illness. Approximately 20% of the sample had a previous diagnosis of schizophrenia or depression and up to a third had been previously diagnosed with Attention Deficit Hyperactivity Disorder and were, in fact, prescribed Ritalin. Almost half the sample (49%) met clinically significant criteria of Post Traumatic Stress Disorder. Other common diagnoses were major depression and antisocial personality disorder. On follow-up, a third of the patients had consistently high psychotic symptoms on the BPRS over the six months. Factors that predicted persistence of psychosis were the number of years of methamphetamine use and severe depression scores. Dr. Lecomte concluded that methamphetamine users clearly present with a plethora of issues and that their needs need to be addressed.

Dr. Douglas Noordsy explored whether clozapine could be used for cannabis-using first-episode psychosis patients. Dr. Noordsy discussed the reward deficiency model which hypothesizes that there are similar abnormalities in neurocircuitry in people with schizophrenia and substance use disorders. Further, studies have shown that second generation antipsychotics can reverse mesocorticolimbic abnormalities in animal models of schizophrenia. And more specifically some studies have demonstrated the positive impact of clozapine on substance abuse (Drake et al., 2000b). Therefore Dr. Noordsy's group compared risperidone to clozapine on cannabis-using first-episode psychosis patients. Patients were included in the study if they had schizophrenia, had less than 16 weeks of antipsychotic treatment, and were not in remission. They also had to meet the criteria for cannabis use disorder. Dr. Noordsy then presented four case examples of people with good and poor response to clozapine and/or risperidone. There are currently 7 patients in each arm of the

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study with average doses of clozapine at a mere 75 mg daily and risperidone at 3 mg daily. Three patients were discontinued early on due to poor tolerability on clozapine. These early results suggest that clozapine may be a useful treatment for first-episode psychosis patients with cannabis abuse. Dr. Noordsy also noted that the patients responded to a much lower dose of clozapine than expected.

Dr. John Kane (NY, USA) as discussant raised the issue that cannabis maybe an independent risk factor for schizophrenia and not the cause. He also said that the previous studies raise other questions about alcohol, as an example. Where do we fit alcohol in the substance abuse spectrum? What are the effects of concurrent alcohol and nicotine abuse? This may be important as nicotine affects permeability of the blood brain barrier. He also suggested that examining cannabis and conversion in the prodrome is perhaps not the best place to look for the effects of cannabis, as at that stage it may have already significantly progressed.

11. Outcome

11.1. Improving overall outcomes—extending CBTp to complex problems (reported by Jessica Merchán-Naranjo)

CBT has been accepted as treatment for affective disorders and has been fully integrated in Mental Health Services since 1980. Nevertheless, despite the case-studies by Beck (1952) and Shapiro (Shapiro and Ravenette, 1959) in the fifties, no randomized controlled studies assessing the intervention for specific schizophrenic symptoms appeared until the nineties. From 1990, 40 studies have been published, 8 are in the process of being conducted and a total of 15 manuals are available.

The results from the most recently published meta-analysis on cognitive behavior therapy in psychosis (CBTp) (Wykes et al., 2008) suggest a moderate effect size. This may lead to a recommendation for these therapies to be used routinely in Mental Health Services. Findings indicate that supervision, not therapist-education, is what actually drives the outcome of CBTp (Steel et al., 2010). A recent review on CBTp suggested that a good therapeutic alliance, therapeutic expertise, prolonged therapy, and the presence of care-givers improve therapeutic outcome. Additionally, more studies assessing the effect of memory problems or other cognitive changes on therapeutic outcome are necessary (Peters, 2010).

CBTp can be used to treat different schizophrenic subtypes, i.e. prodromal symptoms (McGorry et al., 2002), first and second episodes (Tarrier et al., 2004), acute psychosis (Lewis et al., 2002), treatment resistance (Tarrier et al., 1999), negative symptoms (Rector et al., 2003), and command hallucinations (Trower et al., 2004). Auditory hallucinations are among the most treatment-resistant schizophrenic symptoms. Command hallucinations are the auditory hallucinations that imply the greatest risk for the patient and his/her environment, being the most treatment resistant and frequent (53% of all voices) (Byrne et al., 2003; Shawyer et al., 2003). The auditory cognitive model (Birchwood et al., 2004; Van der Gaag et al., 2003) has demonstrated that patients perceive voices as damaging and humiliating if commands are not carried out. Carrying out the orders given by the voices leads to conformist behavior and produces fear and depression.

Hacker et al. (2008) developed a program that helps the patient to question the omnipotence and power of the voices and as such reduces fear and conformist behavior. The MRC COMMAND (Trower et al., 2004) is a randomized and controlled multi-center study assessing the effect of CBT in patients that recently caused severe damage to themselves and/or their environment because of auditory command hallucinations. This study suggests a reduction of conduct problems by equilibrating the patient's own voice and externally generated voices (Max Birchwood, 2010). Another method is competitive memory training (COMET) which is a technique that employs the memory of gratifying moments of the patient's life to reduce the negative emotions induced by the voices' content. The results of this study show that the power that patients attribute to the voices can be reduced, that the voices can be accepted by the patient as a cognitive phenomenon, with patients being less submissive and with increased auto-esteem (Van der Gaag et al., 2010).

11.2. Performance-based assessment of disability: validity across different cultures and age-ranges (reported by Cali Bartholomeusz)

Over the last decade the influence of treatment on functional outcome in schizophrenia has become a primary focus, thus calling for more ecologically valid tools for assessing this domain across cultures. This symposium, chaired by *Dr. Phillip D. Harvey* (Emory University, Georgia) and *Dr. Dawn Velligan* (UT Health Sciences, Texas) was proposed in light of the recent FDA requirement that all treatment trials aimed at enhancing cognition also include a co-primary outcome measure of functional capacity (defined as the ability to perform everyday functioning skills in structured assessments).

Dr. Philip Harvey, addressed the broad issue of 'how' to measure functional disability, given that real-world outcomes (e.g. marriage, employment, and residential status) are somewhat unrealistic targets in research. He highlighted that a measure of 'competence', that is, whether or not an individual is 'able' to do something, may better reflect disability. The UCSD Performance-based Skills Assessment (UPSA) measure, which requires participants to role-play and simulate functional skills such as reading a utility bill or making an emergency phone call, has previously been shown to predict residential status/independent living in schizophrenia patients with 75% accuracy (Mausbach et al., 2008). It has also consistently been shown to correlate positively with cognitive performance (e.g. Twamley et al., 2008). To test the validity of this measure across westernized cultures, the short version (UPSA-B) was administered to 244 and 146 schizophrenia patients in the United States and Sweden, respectively. There were no significant differences between Swedish and American patients on the UPSA-B, even after stratifying patients by residential status. However, when the same measure was administered to a Chinese sample of patients with schizophrenia ($N=274$), unipolar ($N=51$) and bipolar disorder ($N=60$), and compared to healthy controls ($N=282$) in Beijing, a biasing effect was observed. Specifically, although the schizophrenia group performed more

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poorly than controls, age, level of education and height were significantly correlated with UPSA-B scores in healthy individuals but not in the schizophrenia sample. When healthy individuals with 6 or fewer years of schooling were removed from the analysis the correlation disappeared. Dr. Harvey proposed that the relationship between UPSA-B performance and education, and height potentially reflects lifelong nutritional status and rural upbringing. He concluded that this increases the likelihood of Type I errors in clinical trials that do not include a control group, and suggested cultural adaptation of the UPSA-B is needed, plus obtaining normative data for such performance-based measures in developing countries such as China.

Dr. Dawn Velligan presented validation data on the cross-cultural adaptation of intermediate measures of functional outcome (VIM study), which was collected as part of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative. These measures included the UPSA, Independent Living Scale (ILS), Test of Adaptive Behavior in Schizophrenia (TABS), and the Cognitive Assessment Scale (CAI). The Cross-Cultural Adaptation Rating Scale (C-CARS) was a 10-item measure developed for administrators to evaluate the acceptability of each subtest within the above-mentioned intermediate measures. Each item was scored using a 7-point scale (1 = doesn't work at all, 7 = works extremely well), and reflected how comfortable raters thought participants would be with the content, and how appropriate it was, given their culture in the context of gender, ethnicity, geographic region, and socio-economic status. Fifty-five expert raters across Germany, Russia, India, China, Spain, Argentina, Mexico and the US completed the C-CARS for each of the intermediate measures. Each measure overall was rated within the acceptable range (except for the UPSA) within each country, with the CAI being rated most favorably. Dr. Velligan suggested this may be due to the CAI being interview-based as opposed to performance-based, and that judgements regarding the cognitive difficulties associated with everyday activities may be more easily made across cultures.

Numerous subscales of the UPSA received a rating below the cut-off (<5) in China, India and Mexico, particularly. For example, within the communication subtest, patients are asked to read an appointment reminder from the doctor and take the necessary steps for rescheduling that appointment. However, many people in non-westernized countries do not a) have access to a phone b) receive reminders in the mail, c) make appointments (i.e. they use walk-in services) or d) have a health insurance card, making this a difficult and culturally irrelevant task to perform. Certain subtests within the other measures (e.g. money in the ILS and medication in the TABS) also failed to meet the cut-off in specific countries (e.g., India and Spain), implying that they are not cross-culturally valid items and would need to be adapted. Overall, China, India and Mexico were the countries that provided the lowest scores on 'adaptability' of the measures. Dr. Velligan proposed two potential ways of overcoming these issues; 1) develop a hybrid measure using the acceptably rated subscales from multiple intermediate measures, and 2) create a functional capacity measure designed specifically for a non-westernised country such as India, and adapt that measure for use in the US.

Dr. Delfina de Achával (University of Buenos Aries, Argentina), continued discussions of the Validation of Intermediate Measures study by reporting on specific results that came out of Argentina. Overall, each of the independent measures, including the UPSA and UPSA-B, was rated within the acceptable range (5 or above) on the C-CARS. This was also the case when raters considered subgroups of Argentinians based on gender, socio-economic status, ethnicity and geographical region (urban/rural). However, there were some subscales within each measure that did not meet criteria, such as the transportation subtest from the UPSA (where participants must look at a bus schedule and maps to plan use of public transport), and the medication subtest from the TABS (where participants must fill a pill container for weekly use, recognize there are not enough pills to do this, and demonstrate how to refill a prescription and phone the pharmacy). Dr. Achával suggested simple and practical ways to adapt this measure to make them suitable for administration in Argentina. Dr. de Achával went on to present preliminary findings on the impact of functional outcome and cognition on quality of life in schizophrenia patients in Argentina. In comparison to healthy controls, schizophrenia patients, aged 18–65 years, displayed significant functional disability as reflected in UPSA and TABS scores, which were positively correlated with the Mini Mental-State Exam. Despite functional difficulties, plus significant cognitive impairments, patients' rating of perceived quality of life (using the MOS 36 short Form Health-Survey) was similar to that of healthy controls. With a larger sample, Dr. de Achával hopes to gain insight into the relationship between general cognitive abilities and functional capacity in the Argentinean culture.

Dr. Elizabeth Twamley (University of California, San Diego) presented data on the effects of language and acculturation on the measurement of functional capacity in schizophrenia. She first acknowledged the pros and cons of performance-based measures and noted that direct observation in a non-contrived/simulated environment, although not always possible, is the gold standard. She then went on to describe her study comprising 210 English-speaking and 29 monolingual Spanish-speaking patients with a schizophrenia-spectrum disorder. All participants completed the UPSA, the Social Skills Performance Assessment (SSPA) and the Medication Management Ability Assessment (MMAA). While groups were similar in age and symptom severity, Spanish-speakers were significantly less educated, had a later age of onset, lower Dementia Rating Scale (DRS) score, lower antipsychotic dose and were more likely to be female. Overall, Spanish-speakers performed better on the MMAA, but worse on the UPSA in comparison to English-speaking patients. However, after pooling the two groups together, regression analysis revealed that DRS score and language were significant predictors of UPSA performance. When the Spanish-speaking sample was analyzed separately, higher levels of education and acculturation were related to better UPSA performance, but these factors did not explain variance beyond that of cognitive (i.e. DRS) performance. It was concluded that measurement of functional capacity can be strongly influenced by language of test administration for monolingual Spanish-speaking schizophrenia patients. Dr. Twamley ended with the note that 'language' is not a stand-alone factor and is

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intricately intertwined with acculturation, literacy, education and cognitive abilities, increasing the difficulty of creating reliable cross-cultural intermediate measures of functioning.

Discussant *Dr. Richard Keefe* (Duke University Medical Centre, North Carolina) began by stating that, "not surprisingly, 'functioning' will mean different things for different people". In reference to the new FDA regulation described earlier, he pointed out that "we (researchers) are on the glacial academic timeline" and that the drug companies want a functional capacity measure (i.e. the UPSA) available for use now. He suggested that some sort of compromise may need to be reached to satisfy both parties. Dr. Keefe stated that the UPSA (already being used in a treatment trial in Singapore) is remarkably consistent, despite a few items that may not work so well across cultures. He also commented on the "pediatric" nature of some feedback regarding the measures' adaptability, where raters had reported, for example, that an item would not be acceptable in their culture because the phone number was 10 digits instead of 9, hence a minor detail than can easily be modified. He noted that the UPSA is already being used in several industry trials.

During the discussion, it was asked whether these measures had been tested in an adolescent ultra-high risk or first-episode psychosis population. While the functional capacity measures discussed within this symposium had not been tested in either of these groups, a shopping/errands task that is being used in the NAPLS study was suggested as a good measure of functional capacity in young people. Another questioner asked about practice effects on tasks such as the UPSA. Dr. Harvey's response was that the UPSA is a measure of 'state-dependent functional disability' rather than a specific cognitive ability (measures of which can often be influenced by repeated practice). He also stated that performance can improve on the UPSA with treatment. In conclusion, the constituents of real-world functioning naturally differ across cultures, where variations in educational opportunities, access to technology, and general everyday living requirements add to the challenge of creating valid cross-cultural measures. Given the new FDA regulation, and the implication that medication may enhance cognitive abilities and in-turn functional outcome, the responsibility placed on these measures of functional capacity to be reliable indicators of real-world functioning is substantial.

11.3. Update on duration of untreated psychosis (reported by Juan Gallego)

This session, chaired by *Drs. Lex Wunderink* (Leeuwarden, the Netherlands) and *Max Birchwood* (Birmingham, UK), consisted of four talks with *Dr. Max Marshall* (Preston, UK) as discussant. In the first talk Dr. Max Birchwood mentioned how earlier intervention services for psychosis have been increasing dramatically and that despite the increase of those services the duration of untreated psychosis (DUP) has not reduced. He commented, for example, that in the early intervention program he leads (YouthSpace, Birmingham) the mean DUP was 272 days. He also noted that DUP and self harm were linked in a group of 92 first-episode psychosis patients (Upthegrove et al., 2009). In a trial called REDIRECT, general practitioners in 55 sites were trained to detect first-episode psychosis more readily and were compared to general practitioners in another 55 sites that were not trained. The outcome measure was the number of referrals made by each group and interestingly the results did now show any differences in the number of referrals made by trained general practitioners compared to non-trained general practitioners (Lester et al., 2009). These findings of a persistent elevated DUP, even after adequate training of general practitioners, have led various investigators to examine the various factors that can contribute to a persistently elevated DUP. Brunet et al. (2007) examined the route timelines of 256 first-episode psychosis patients and found that the involvement of the community mental health teams was associated with a significant delay in the initiation of treatment. The mean DUP when the community mental health teams were involved was 609 days compared to 184 days when clients were referred directly by general practitioners via home treatment to the early intervention services. Three possible reasons could explain this: 1) community mental health teams may lack an assertive outreach for patients who are more difficult to engage; 2) some of them have a "three no-shows and discharge policy"; and 3) they may fail to recognize emerging psychotic symptoms on those patients. Dr. Birchwood therefore proposed that avoiding community mental health teams could help decrease the elevated DUP.

Another reason for a longer DUP in Birmingham, according to Dr. Birchwood, could be that some areas of the city, show a higher DUP compared to other areas. The presence of specific ethnicities has been associated with this and it was noted that Muslims families, for example, will not seek medical attention before they consult with the leader of the mosque or "Imam". When interviewed, Imams confirmed they were often consulted by clients with psychotic-like experiences and that these experiences would be framed as a spiritual problem or "Jinn" by the Imams. Dr. Birchwood then stressed the importance of involving the community and the religious leaders in the detection and referral of clients experiencing a first episode of psychosis and he suggested the use of radio programs. Finally, Dr. Birchwood stated that the high DUP in Birmingham could also be an outlier problem since some cases have a very long DUP which increases the mean disproportionately. To conclude, he proposed that it could be possible to decrease DUP by avoiding community mental health teams, working with ethnic communities' care pathways (Mosques) and raising psychosis awareness with direct access to early intervention programs.

Dr. Nynke Boonstra (Leeuwarden, the Netherlands) spoke of her recent meta-analysis that related duration of untreated psychosis with negative symptoms. She mentioned that a shorter DUP is associated with earlier and better level of remission (Malla et al., 2002a,b; Wunderink et al., 2006), better chance of recovery (Wunderink et al., 2009), lower relapse rates (Altamura et al., 2001; de Haan et al., 2003), less cognitive deterioration (Amminger et al., 2002), better social functioning (Drake et al., 2000a; Harris et al., 2005), less positive symptoms (Black et al., 2001; Bottlender et al., 2003; Larsen et al., 2000) and less evidence of negative symptoms especially at longer follow-up (Perkins et al., 2004; Simonsen et al., 2007). On the other hand, she emphasized that the relationship between negative symptoms and DUP is not well known. Prior studies have shown that negative symptoms at

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baseline are highly prevalent (Malla et al., 2004b) and are associated with poor functional outcome (Malla et al., 2004a), more resistance to treatment (Edwards et al., 1999), more cognitive deficits (Heydebrand et al., 2004), more social dysfunctioning (Addington and Addington, 1993; Petersen et al., 2008; Schmitz et al., 2007) and poor quality of life (Schmitz et al., 2007). She noted that positive symptoms are more responsive to treatment and have less impact on outcome. She performed a pubmed search from 1998 to 2009 with the Boolean operators "duration" and "untreated" and "psychosis" or "DUP" and also checked cross references. She ultimately included 14 studies. The aim was to explore the relationship between negative and positive symptoms and DUP in recent first-episode studies. She included only first-episode patients where a quantitative assessment of DUP was assessed using a validated instrument, and that had assessments at baseline and at least one follow-up assessment at 12, 24, 60 or 96 months. PANSS, SANS/SAPS or BPRS scores were also examined. She found that DUP is associated with positive symptoms and even stronger with negative symptoms. She also found that DUP together with negative symptoms at baseline predicts negative symptom severity up to 96 months of follow-up. She concluded that: 1) it is likely that by reducing DUP the severity of symptoms may also be reduced, 2) early detection should also focus on negative symptoms, and 3) further research is needed to clarify the relationship of untreated positive symptoms and emerging negative symptoms.

Dr. Paola Dazzan (London, UK) focused on brain changes following the first psychotic episode and the role of treatment. She began by noting that brain changes, especially in the prefrontal and medial temporal areas, are present even before the first episode. She suggested that it could be possible to differentiate very early on, even at the prodromal phase, patients who will ultimately develop psychosis or mood symptoms based on some of those changes. Additional evidence suggests that the thalamus, amygdala, insula, and anterior cingulate have already been compromised at the onset of the disease, as well as in chronic stages. Additionally, it has been shown that longer DUP is associated with smaller gray matter in cingulate, frontal, temporal and insular cortex (Lappin et al., 2006). To examine whether poorer outcome is mediated by the brain structural changes, Dr. Dazzan investigated changes in brain volume and outcome after 6 years of treatment in 49 patients with a first psychotic episode and compared them to 49 controls. She found that there was no relationship between DUP and global volume or change in volume over time, although she did find that DUP was independently associated with worse clinical and functional outcome. Dr. Dazzan also found that at the time of their first episode, patients had significantly smaller gray matter volume and significantly larger ventricular volumes. She mentioned that at first contact patients with longer DUP have already suffered more brain changes and are destined to have a worse clinical and functional outcome. Furthermore, at follow-up she found that patients with poorer outcome had larger ventricular changes and a longer exposure to antipsychotic medications. She concluded from these findings that patients at first contact who have larger ventricles are destined to spend more time on antipsychotics and to have a continuous illness course. In a further analysis, she used the support Vector Machine (Mourao-Miranda et al., 2007), which is a multivariate pattern recognition analysis of structural MRI data. Using this method she was able to differentiate between patients who will go on to have a continuous illness course from controls with a sensitivity of 0.68, specificity of 0.68 and accuracy of 0.68 with a $p = 0.001$. She was also able to discriminate between patients with an episodic course of illness versus a continuous illness with a sensitivity of 0.61, specificity of 0.71 and accuracy of 0.66 with a $p = 0.005$. She proposed the possibility of using neuroimaging to establish the correct treatment algorithm early in the course of illness.

Dr. Ingrid Melle (Oslo, Norway) mentioned that the relationship between DUP and outcome has been well demonstrated (Marshall et al., 2005; Perkins et al., 2005). She then briefly reviewed the results from the OPUS study, in which patients with a first episode of psychosis who received specialized integrated treatment had less psychotic, negative and disorganization symptoms at a two-year follow-up (Petersen et al., 2005) but the difference in symptoms disappeared at the 5 year follow-up assessment. Of note, the integrated treatment was discontinued after two years and all patients received standard treatment from then on (Bertelsen et al., 2008). She continued with a description of the TIPS study design. The study hypothesis was that early intervention will lead to a decrease in DUP followed by lower and more rapid remission of positive symptom, lower levels of negative symptoms, reduced level of complications/suicide and sustained low levels within the first two years. To be able to separate the effect of DUP from mediating factors affecting both DUP and outcome, the investigators examined the differences between patients who were treated in an area with an early detection (ED) program with patients who were treated in an area with standard psychiatric services. The ED program distributed information campaigns in paper, radio, cinema ads and information leaflets to the general public with the addition of targeted campaigns directed towards schools, general practitioners and social services. They had low threshold teams taking direct referrals, assessing within one day (Johannessen et al., 2001). Two hundred and eighty one patients were recruited from 1997 to 2000. One hundred and forty patients came from the early detection area and one hundred and forty came from a non-early detection area. The results showed that there was a statistically significant difference between the two areas with a mean DUP of 16 weeks in non-early detection area and 4.5 weeks in the ED area (Melle et al., 2004). At the start of treatment patients on the ED area had less positive, negative, depressive, suicidal symptoms (Melle et al., 2005, 2006). To control for confounding factors specific to a particular geographical area the investigators also compared patients from the ED area with a historical group derived from the same catchment area prior to the creation of the ED program. The mean DUP in pre-ED group was 26 weeks, during the ED group was 5 weeks and the post-ED was 15 weeks (Larsen et al., 2001). Additionally, ED patients had fewer symptoms across all domains compared to the pre-ED, post-ED and no ED. She concluded that it was possible to decrease DUP through an early detection program and that at baseline reductions in symptoms follow reductions in DUP. After five years of treatment she found that the effect of timing appears more prolonged and more

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specific for other areas (negative, cognitive, and depressive) than positive symptoms and she posed the unanswered question of why an intervention targeting and shortening positive symptoms affect mainly negative symptoms.

In the discussion, Dr. Marshall (Preston, UK) commented that it is critical to be able to understand the pathways to care, and how differences in culture and ethnicity could explain differences in DUP. He was also struck by the long time that community mental health teams will take to refer patients to early intervention services.

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Conflict of interest

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