The 2nd Schizophrenia International Research Society Conference, 10-14 April 2010, Florence, Italy: summaries of oral sessions.

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SUMMARIES FROM ORAL SESSIONS AT THE 2nd SCHIZOPHRENIA INTERNATIONAL RESEARCH SOCIETY CONFERENCE, 10-14 APRIL 2010, FLORENCE, ITALY

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Key Words: schizophrenia, diagnosis, genetics, brain imaging

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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 reviews on the most significant findings that emerged from each session and the discussions that followed. The following report is a composite summary of their reports. 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 would like an overview of current investigations and the state of the field of schizophrenia research.

INTRODUCTION:

This was the 2nd international conference on schizophrenia research with the theme of 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 discussed 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 and continues to rapidly emerge for finding causes for common disease. New treatments, both pharmacologic and non-pharmaocologic have continued to also be a focus so that ultimately the field is devoted to improving the quality of life for people with schizophrenia world-wide. Student travel awardees volunteered to serve as "Rapporteurs" of oral sessions to summarize the major findings that were reported and the conclusions in the discussions that followed.

I. DIAGNOSIS AND CLINICAL CHARACTERISTICS

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 considering modest changes in criteria for classification and major changes affecting the following: a] subtypes of schizophrenia; b] catatonia; and c] schizoaffective disorder. Domains of pathology with dimensions representing critical aspects of psychopathology is being considered for an addition to the DSM-V, which is intended to address syndrome heterogeneity and focus assessment on pathologies requiring clinical attention. Regarding a possibility of including other dimensions in diagnosing schizophrenia, Dr. Carpenter noted that the age of onset was now being discussed Furthermore, the question of whether bipolar disorders should be grouped with psychotic disorders or mood disorders will be addressed in the DSM-V. 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 highlighted a new focus on cognitive deficits in schizophrenia. Currently, there is little support for the idea that cognition should be included as a criterion A–type symptom that would differentiate those individuals with schizophrenia from individuals with other psychiatric illnesses. However, the role that cognitive function should play in diagnostic criteria for schizophrenia in the DSM-V is debated. It was noted that there would need to be training for those assessments, and it is unknown how feasible adding this new dimension would be. He highlighted the importance of cognitive function, however, for understanding functional status and outcome and to facilitate treatment planning. Third, Dr. Alex Hofner reviewed the previous findings in social cognition in schizophrenia and concluded that it had a strong relationship with functional outcome and should be regarded as a core symptom of this illness. Fourth, Dr. Dieter Naber cited a series of his own work and suggested that the quality of life and subjective wellbeing are distinct outcome dimensions in schizophrenia. Fifth, Dr. Kim Mueser suggested the clinical relevance of work outcomes as an outcome measure, which could 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 time course of illness (schizophrenia), which has not sufficiently been addressed in the DSM-IV.

2. DSM 5 debate
Reported by Anna-Karin Neubeck

The topic of the debate revolved around the proposal from the DSM working group to include a Psychosis Risk Syndrome (PRS) in the forthcoming 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, while Dr. John Kane was moderator.They represented three different points of view. Woods and Carpenter were in favor of the suggestion of including a Psychosis Risk Syndrome, Cornblatt and Yung were both against the proposal, while 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/ProposedRevision, 2010-04-08) and the potential benefit of establishing this category is that it will facilitate early intervention that may have long lasting benefit that is not achievable with later therapeutic intervention. However, some critical issues are raised that include the question of sensitivity and specificity of this as a separate category and issues related to stigma and potential harm of excessive treatment. Dr. Carpenter, stressed that it is necessary to include an at risk syndrome in order to identify these persons who do suffer and are in need of help. He argued that behaviors in an 'at risk state' would be stigmatizing in themselves, and even more stigmatizing than a label. Carpenter argued that it would be better to treat the persons and take away their odd behaviors. Dr. Woods further emphasized that the research criteria for these patients are reliable and valid. (Woods, et al, 2009) and that persons who meet proposed DSM-V clinical criteria are symptomatic, functionally impaired, and treatment-seeking, and many are cognitively impaired. This current clinical state should be sufficient for inclusion of the disorder in DSM 5, since no DSM 4 disorder accurately describes the diagnosis. Both Drs.Cornblatt and Yung argued against the proposal. Dr. Cornblatt expressed concern that potential negative consequences will outweigh the benefits given uncertainties still characterizing 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 including a PRS in DSM 5. 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 and illness and between normal and prodromal behaviors. Dr. Yung countered Carpenters argument stating that the young people she sees in the at risk clinics 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 PRS state would be treated with antipsychotics, with further risk of side effects and stigma. Dr.Yung further noted that young people with the PRS do need help for current problems, but emphasized that this does not justify including a heterogenous group with unproven validity and reliability in the DSM 5. A further issue brought labeled by Dr.Yung is that of "diagnostic creep". By this she refers to the situation in which the threshold for a diagnosis of RS gradually changes in response to clinical practice, political lobbying and other social forces. (Yung, et al, 2010, in press) "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 RS and "normality" (that is, just below the RS threshold) may be labeled as RS in order to access treatment and gain insurance coverage". Alternatively, someone previously diagnosed with schizophreniform or delusional disorder may be given a diagnosis of RS to reduce stigma while still enabling 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 (Yung, et al, 2010, in press).

Drs. Stephan Ruhrmann and Frauke Schultze-Lutter presented a third view constructing a new concept, a psychosis spectrum disorder, using the ICD 10 diagnosis of schizotypal disorder as a model (Ruhrmann, et al, 2010, in press). This suggested spectrum disorder does not preclude risk research, but is instead a broader approach that uses cognitive basic symptoms not covered by the current risk class criteria suggested and are important for prediction and diagnosis.

3.The Many Faces of Psychosis
Reported by Hsiao Piau Ng

The understanding of psychotic disorders is a major challenge to clinicians and researchers due to the complexity of these disorders. As introduced by Dr. Charles Schulz, chairperson, from University of Minnesota and Mind Research Network (MRN), psychotic disorders at times appear to be archetypal, while on other occasions seem to be combinations of disorders. The complexities faced in the study of psychosis and the approaches utilized by leading researchers in the field are presented 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 belonging to patients who have high and low level of symptoms based on PANSS scores. Participants were asked to stop at certain times and make notes of their experience and feelings at particular points in time selected at random, tenper day for six consecutive days. This method attempted to put participants in "real-life" scenarios and enabled the relating of mood and 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 the possibility of using deficits in brain derived neurotrophic factors (BDNF) as a neurobiological marker for vulnerability to psychosis. A number of previous BDNF studies have been reported and include decreased BDNF levels in post-mortem hippocampus and decreased BDNF mRNA expression in prefrontal cortex. He noted that clinical studies of BDNF were conducted on chronic and first-episode patients, but no study involving subjects at the prodromal stage has been conducted. In a study which compared BDNF levels in patients with first-episode pyschosis to that of normal controls, the patients displayed significant reduction in plasma BDNF levels. In another study, the role of BDNF in schizophrenia was explored through its receptor, TrkB. It was found that there was significantly increased gene expression of c-Cbl, which is associated with TrkB, in postmortem dorsolateral prefrontal cortex samples from patients with schizophrenia compared to normal controls. Dr. Buckley concluded from these data that BDNF is of pathological relevance to schizophrenia and stated that his group is continuing efforts to look into the role of plasma BDNF levels as a biomarker for schizophrenia.

Dr. Schulz presented data from multi-modality brain imaging studies, including diffusion tensor imaging (DTI), spectroscopy and functional imaging (fMRI).These modalities investigate the connectivity, chemistry and functioning of the human brain respectively. A multimodality imaging pipeline was set up within the MRN to investigate their relationship.Patients with first-episode psychosis, chronic schizophrenia and matched controls were recruited at MRN sites. All subjects underwent an MRI sequence 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 otherhand, 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 hypotheses for schizophrenia. Seagall 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 continue to unveil the relationship between different imaging approaches and progressive changes in brain measures over the course of illness.

4.Einheitspsychose? Comparison of schizophrenia and bipolar disorder across genes, brain and behaviour

Reported by Cali Bartholomeusz

This symposium, chaired by Drs. Melissa Green (University of New South Wales, Australia) and Jim 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 and colleagues (2004), who proposed that the only real 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 bipolar patients; Grozeva et al., 2010), may prove more useful for distinguishing between the two disorders. In line with this are findings suggesting strong genetic risk for schizophrenia, based on significant cognitive impairment in first-degree relatives (Snitz et al., 2006), while genetic risk for Bipolar Disorder tends to be weaker, based on minor executive functioning deficits in relatives (Arts et al., 2008). With respect to environmental factors, data suggests cannabis use increases the risk of co-morbid mania and psychosis, as does growing up in an urban as opposed to rural environment. However, urbanicity appears to be a risk factor specific to schizophrenia and does not independently increase the risk of mania alone, unlike migration. Further research is needed to determine whether cannabis use, or the experience of trauma, increases the risk for mania independently.

The 'symptom domains' model, posed by Krabbendam and colleagues (2004) suggests that psychometric risk states for schizophrenia (i.e. paranoia, hallucinations, first-rank delusions) and bipolar disorder (i.e. depression, somatic symptoms, mania) exist within the healthy population. Dr van Os highlighted that these domains are

inter-correlated 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 thenpresented 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. However, this enlargement tended to be more pronounced for patients diagnosed with affective psychoses (Garner et al., 2005; Pariante et al., 2005). Data further suggests this abnormality persists throughout the course of the illness in bipolar disorder(Takahashi et al., 2009) 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 regions of the anterior cingulate cortex was found to be reduced bilaterally in first episode schizophrenia(ACC; Fornito et al., 2008). In contrast, male (but not female) bipolar patients showed right-sided increases in the subcallosal limbic ACC (Fornito et al., 2009). A longitudinal study by Koo and colleagues (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 improvements in phenotypic and longitudinal characterisation, and stated that differences between the two disorders may even manifest peri-natally.

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 patients compared to the schizophrenia group. 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 that Dr. McIntosh discussed was an emotional memory task with images from the International Affective Picture System (36 neutral scenes, 36 emotionally positive scenes, rated on a 1-9 scale for emotional content). Contrasts of emotional versus neutral scenes resulted in significant differences in mean hippocampal cluster activation between patient groups and control group activation was between these 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 that concept that the two disorders may be placed at different locations along a continuum. Activation differences were most prominent in regions of the dorsal PFC and medial temporal lobe. Although findings suggest differing neural bases underlie these two disorders, Dr McIntosh commented that a continuum would be possible if evidence could show that the same networks were involved but that the load-response relationship differed between patient groups. Further research in this area is needed.

Dr Katherine Burdick (The Zucker Hillside Hospital-NSLIJHS, NY), continued the discussion of a continuum model by presenting 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 functions as 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 schizoaffective disorder within this model.

The discussion was led by Dr. Ulrich Schall (The University of Newcastle, Australia). Dr Burdick noted that her main goal was to highlight the importance of using intermediate phenotypes related to brain function, to better understand the inherent risk associated with, 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. This supports the abandonment of DSM-IV categorisation within clinical research of this kind. Dr Melissa 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 between both disorders, the differences in brain structural and neuropsychological abnormalities, which often manifest early on, are significant and do not support a continuum.

5. Psychotic symptoms in the community: Where are we today?
Reported by Yousri El Kissi

Population-based studies indicate that psychotic-like experiences (PLE) manifest in up to 30% of apparently healthy individuals. Understanding the relationship (or lack of it) between these experiences and mental illness which is much less prevalent is crucial. The overall aim of this session was to provide explanations for such a high prevalence of PLE in the community and to investigate their relationship with psychotic disorders.

Mari Dominguez aimed to determine the relationship between affective symptoms and psychotic-like experiences. She first reported evidence from clinical patient populations indicating that affective dysregulation is strongly associated with reality distortion which characterize psychotic symptoms. Attenuated forms of psychotic symptoms are found in up to 10% of the general population, with difficulty cuting 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 (hypo)manic 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 greater level of affective symptoms. The authors concluded that affective and non affective psychotic symptoms are correlated dimensions at the community level. In addition, affective dysregulation is not only an overlap but a direct impact on the persistence and clinical relevance of psychotic experiences.

Dr. Mary Cannon reported results from community study assessing prevalence of psychotic symptoms and of prodromal risk and among adolescents. As psychotic symptoms in the general population and prodromal syndrome or "at risk mental state" are both known to index an increased risk for psychotic outcomes, relationship between them was examined in 334 school children aged 11-13, using a 7-item psychosis screener. 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 were performed. 29% 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). 9 of them (53%) fulfilled criteria for prodromal risk syndrome. Risk factors were SIPS scores and current functioning state. Conclusions were that prodromal risk syndromes can be diagnosed in adolescents from community or school settings. Up to half of adolescent reporting strong psychotic type experiences fulfilled criteria for the prodromal risk syndrome. Specialized screening instruments and measures of current functioning are predictors of prodromal risk syndrome.

Dr. Marc Weiser provided evidence suggesting that psychotic experiences identified in non ill people signal risk for mental illness. He reported the results of 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 who had been screened in the 1980's were examined after a mean follow-up of 24 years. 25% of them reported at least one psychotic experience, screened by PERI (psychiatric Epidemiology Scale) and confirmed by SADS. 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. Psychotic experiences were not specific for psychotic disorders; they were correlated with varied types of psychological distress (depression, anxiety).

Dr. John McGrath examined the prevalence of psychotic-like experiences and their relationship with depression and anxiety in adolescents. He reported results from a community sample (n=8841) drawn from the mater-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 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, using the Composite International Diagnostic Interview (CIDI). Having a lifetime diagnosis of major depression or anxiety disorder was associated with higher PDI total scores and with any CIDI hallucination or delusion item. Psychotic symptoms were also associated with family history

of depression and anxiety. Psychotic-like experiences are, thus, not specific for continuum with psychotic disorders. They are also 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, biology), without medication interference. Studying psychotic-like symptoms in general population is then studying schizophrenia. 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, although may not have psychiatric disorders, are not well functioning.

6. Movement disorders should be a criterion for schizophrenia in DSM-V
Reported by Renan P Souza

Dr. Diederik Tenback (Maastricht University Medical Center) introduced the criteria for the inclusion of a motor symptom as a criterion in the DSM IV: (1) a minimum prevalence of 10% and ideally 30 to 40%; (2) having predictive value; (3) biological basis and (4) specificity. He thus presented evidence to support the inclusion of movement disorders as a criterion for schizophrenia. Movement disorders (e.g. dyskinesia and parkinsonism) are more often present in siblings of schizophrenia subjects than in controls (Koning et al., 2008). Further, antipsychotic-naïve schizophrenia subjects can present movement disorders although the prevalence is much higher in subjects who have received antipsychotics, especially first-generation antipsychotics. Dr. Tenback hypothesized that movement disorders in schizophrenia subjects would be associated with a model of gradual supersensitivity on which the severity of movement symptoms and the course of psychosis would be associated with a pandopaminergic sensitivity.

Dr. Bakker (Maastricht University Medical Center) outlined criteria to classify a trait as part of the illness spectrum that include heritability, co-segregation within families and biological and clinical plausibility. Previous findings have shown a familial occurrence of tardive dyskinesia (Koning et al., 2008) and there are biological hypothesis for these movement disorders (i.e.Pappa et al., 2009). He reported results from a genetic study of 199 subjects 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 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. The first mechanical instrument assess the force variability (Koning et al., 2010) and can identify dyskinesia and resting tremor (4-6 Hz). The second method is based in the velocity scaling or the ability to accelerate movement velocity when distances increased. It is known that control subjects would be able to spend the same amount of time to perform this task whenever the distance is doubled but subjects with bradykinesia would require twice as much time. Dr. Koning results clearly showed that in his sample no subjects presented Parkinsonism assessed using UPDRS but 30% of the siblings and 2% of the control subjects showed movement disorder symptoms

assessed by the 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 psychiatry particularly in schizophrenia and this relationship had been described over 100 years ago. After these basic assumptions, Dr. van Harten presented evidences indicating that movement disorders fulfill the criteria to be a DSM V criterion in agreement with Dr. Tenback. Moreover, he suggested that movement disorders should be added to the prodromal symptoms. Instrumental measurements are more objective, reliable and easier to learn. However, there are still some limitations. It is necessary to differentiate dyskinesia from drug-induced dyskinesias in this context. Further, dyskinesia and Parkinsonism prevalence measured with mechanical approaches may be dramatically different from the assessment done using clinical rating scales.

7. Schizophrenia and Homelessness
Reported by Gul A. Jabbar

Homelessness is a major worldwide problem facing individuals with schizophrenia. The dilemma of people with mental illness and homeless remains one of the least understood and most challenged service delivery problems in mental health today (Gonzalez & 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 behavioral health disorder diagnosis: 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 demonstrated 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 of people suffering from schizophrenia in a community-based system of care. 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. He investigated the relationship between socio-economic variables and psychiatric services use. The study, conducted in a well developed comprehensive community based mental health services in Northern Italy, 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 costs of patients' care. The sample, consisting of 4,420 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' services 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. Through multilevel analysis it was reported that patients diagnosed with schizophrenia (841; 19%) were the highest service users, and the effect of SES on service use was significant for patients starting a new episode after a period of no care >3 months. It was concluded that this SES score may be used as an alternate measure for planners to create specific polices for homeless people with psychotic disorders.

Founder and CEO of Pathway Housing 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 Pathway's discussed were the consumer choice philosophy, separation of housing and services, recover 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 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 individual need to relocate into another housing site, they don't lose their 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, Gulcur andTsemberis (2006) have found that dual diagnosed adults can remain stably housed without increasing 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 leading to reduction of their psychiatric symptoms. Identified in numerous research studies, pathways' is successfully growing through the United States, Canada and Europe.

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 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 (>80% adults are males, >80% children are males) people in SA are homeless with no shelter and on the streets (Kok et al., 2010) possibly due to political and social factors such as urban migration, landlessness and removal (Ward and Seager, 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% 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 rape is 117/100,000. HIV-AIDS is another relating factor in SA as 0.7% of the global population and 17% of the global burden of HIV infection. Life expectancy in SA is 48 years for males and 51 years for females with 84% mortality rate. Along with AIDS, 80% 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 concluded with the multiple risk factors for psychosis and homelessness such as HIV/AIDS, violence/trauma, migration, poverty and orphans. There is very little data on homelessness and psychosis making it most challenging and few mental health professionals, few community-based resources for mentally ill person and few resources for homeless population all partake in this challenge. Burns suggested that political, economic and social intervention strategies need to be implemented in order to address these multiple inter-linked factors.

II. COGNITION

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 in schizophrenia. Cognitive abnormalities are a core feature of schizophrenia. Cognitive dysfunction can be observed in early childhood, in non-affected family members of people with schizophrenia, and 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.

Donald Goff The first talk of this symposium was given by Donald Goff (Boston, MA) who 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 forerunner program to TURNS that addressed several obstacles to 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 and labeling. 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.

Donald Goff then discussed the evolution of MATRICS in to 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, highlighting the investigators, and identified seven widespread participating USA sites each with pharmacologists and neuropsychologists as Co-PIs. TURNS' selection of compounds was rigorous and formal, whereby the group voted based on drug efficacy, pharmacology, safety/tolerability, innovation and pharmokinetics. Of the initial 57 compounds that were nominated, 17 were accepted and a final six were pursued formally.

A first of these six compounds was Org 24448, a positive allosteric modulator of the AMPA glutamatergic receptor. Org 24448 provided some positive effects on cognition in animal studies, in particular, a sustained increase in performance in rats on the radial maze and delayed non-matching to sample tasks. Org 24448 was further shown to preferentially increase mRNA levels in the rat cortex in a dose dependent manner. However, on the eve of the clinical trial a toxicology concern arose, and the compound was withdrawn from further study. A second compound of interest was Ispronicline TC 1734, a partial agonist of the $\alpha 4$ and $\beta 2$ nicotinic receptors. This compound showed efficacy in animal models on several variables including passive avoidance, object

recognition and radial arm maze task performance, as well as an absence of tolerance. Importantly, TC 1734 was shown to ameliorate age associated cognitive impairment and mild cognitive impairment in human trials. This compound was eventually licensed to AstraZaneca and has most recently demonstrated high efficacy in a phase II trial in ADHD. The third pursued compound was 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. Fourth, AV965, an agonist for 5HT1, was initially pursued but ultimately aborted due to insufficient funds. Finally, two compounds completed clinical testing: MK-0777, a GABA A α2/α3 partial agonist, and the neuroprotective protein AL108 NAP. Donald Goff used these results to acknowledge that drug development is not for the faint of heart.

Daniel C. Javitt (Orangeburg, NY) was the second presenter and talked on a TURNS study of the effects of intranasal AL-108 (Davunetide) on neurocognition and functional outcome in schizophrenia. Davunetide is an intranasal drug product containing NAP, an 8 amino acid peptide fragment of Activity-Dependent Neuroprotective Protein (ADNP). The study of Davunetide as a cognitive enhancer in schizophrenia 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, 5mg and 30 mg AL-108. Patients were chronic and stable with controlled positive symptoms. In this study, the primary outcome measure was neurocognition as measured by the MATRICS Consensus Cognitive Battery (MCCB), 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. Daniel C. Javitt noted that because this was a Phase IIa study the implications of the results would be interpreted in terms of effect size rather than significance.

First, when considering MCCB total scores, a significant test-retest effect was observed in the placebo group between the 6 and 12 week assessments. Improvement in the 5mg and 30mg groups was observed between baseline and week 12, and this was a small effect size (d= .21). Considering the cognitive domains separately, the 30mg group displayed improved visual learning and worse verbal learning relative to the other groups; however, Daniel C. Javitt noted that the test-retest point may be influencing the results. Second, when considering UPSA scores, a significant treatment effect emerged in the 30mg group, though this may be due to their poorer baseline performance. The drug demonstrated no safety concerns and was well tolerated; no negative nasal side effects or change in body mass index were observed.

Daniel C. Javitt also discussed a separate study that examined the effect of Davunetide on neuronal integrity in the dorsolateral prefrontal cortex in 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 in the experimental group. Daniel C. Javitt concluded with the suggestion that compounds developed for treatment of Alzheimer's disease, like Davunetide, may be relevant to schizophrenia.

Robert W. Buchanan (Baltimore, MD) discussed another TURNS study which looked at MK-0777 for the treatment of cognitive impairments in people with schizophrenia. Dr. Buchanan began by discussing the neural mechanisms of GABA. GABA is the primary central nervous system inhibitory neurotransmitter and its mechanisms are important 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 $GABA_A$ α2 receptor activation. MK-0777 is a $GABA_A$ α2/α3 partial agonist, with no activity at α1 or α5 subunits and no known activity at other receptors. In a previous work, this compound was shown to enhance delayed memory in schizophrenia when compared to placebo, and improve performance on n-back reaction time, continuous performance test d' score and preparing to overcome prepotencies (Lewis et al., 2008).

Robert Buchanan next described the TURNS study of MK-0777, a double-blind, randomized controlled clinical trial with three treatment arms: Placebo, MK-0777 3mg BID and MK-0777 8mg BID. Participants in the study were schizophrenia patients on stable doses of second generation antipsychotics. A thorough set of restrictions regarding cognitive performance, positive symptom severity and medical status were applied. The dependent measures of interest were scores on the MCCB battery, UPSA and Schizophrenia Cognition Rating Scale (SCoRS).

One-hundred and nine patients provided signed informed consent and 46 were excluded, mainly for failing to meet medical (non-symptom) criteria. Considering cognitive performance, no significant beneficial effects of MK-0777 were observed on MCCB total scores. For the separate cognitive domains, a significant improvement on visual learning and reasoning and problem solving domains was observed in the placebo group only. On the UPSA, the only group difference that emerged was higher performance on the planning domain in the placebo group. No significant drug effects were observed for continuous performance test d' scores, or n-back 2-back reaction time or d' scores, and this is in contrast to findings in the Lewis et al. (2008) study. The drug was well tolerated, was not associated with cataracts, but did associate to a nuclear color grade safety concern in three participants (all study completers).

Robert Buchanan summarized that the results suggest that neither low nor high doses of MK-0777 improve cognition in people with schizophrenia. He hypothesized a potential explanation for the null result may be that MK-0777 is a relatively weak partial agonist, and a more selective agent with greater intrinsic activity at the $GABA_A$ α2 site may be a promising avenue for future research on the treatment of cognitive impairment in schizophrenia.

In the question period that followed Robert Buchanan was asked whether a first-episode schizophrenia sample should be targeted in cognitive enhancer studies. He replied that although a study in first-episode could rule of any effects of chronicity, antipsychotic mechanisms are the same in first-episode and chronic patients. Robert Buchanan was then asked whether a cross-over design will be undertaken in future, to which he replied that such studies in schizophrenia in general are unsuccessful, and time or carry-over effects of cognitive task performance may potentially mask any benefits of the drug.

Michael F. Green (Los Angeles, CA) gave the final talk on the validation of intermediate (co-primary) measures for clinical trials of cognition-enhancing drugs for schizophrenia. He first identified that 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), 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, 160 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 aims of VIM were threefold: 1) to examine the psychometric properties of the measures, including reliability and repeatability; 2) to examine the validity of the measures, including correlation with cognitive performance and measures of "real-life" functioning; and 3) practicality/tolerability of the measures, for example, tester training, assessment duration and participant satisfaction ratings.

Of 196 patients who consented to the study, 30 failed to pass screening and three provided invalid data. All full intermediate measures showed adequate reliability (ICC = .69 to .76). The UPSA showed the highest correlation with MCCB cognitive performance (r = .67), followed by the TABS (r = .61) and ILS (r = .51), while lower correlations emerged between the intermediate measures and community functioning (r = .12 - .30). All tests were tolerated satisfactorily, the UPSA was considered most practical and there were few missing data. A similar pattern of results emerged when considering results on the short forms of the intermediate measures. In particular, reliability on the intermediate measures was adequate (ICC = .69 - .70) though slightly lower than that of the long forms. The UPSA, TABS and ILS performance scores each correlated to MCCB cognitive performance at r = .53. Correlations between short form test scores and community functioning (r = .15 - .27) were comparable to those observed with the full measures.

Michael F. Green concluded by identifying the UPSA as the leading measure because it had 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. However, lower test-retest reliability was observed indicating that more participants would be needed compared to the full measures.

The discussant for this symposium was Wolfgang Fleischhacker. He raised the issue that a challenge to research on cognitive enhancing agents is to match targets to compounds that in fact affect the target. Further, it remains a challenge to find appropriate corresponding phenotypes, i.e., patients, for drug targets that have been identified. Science moves forward in part through falsifying hypotheses and the results of these studies may demonstrate that the above tested compounds should not be studied further; rather, new targets may be pursued. Wolfgang Fleischhacker suggested two avenues for future research. First, better rating instruments need to be developed that may show greater relevance or importance for studying cognitive-enhancing agents in schizophrenia. Second, at the pharmacological level, compounds that encourage neurogenesis should be pursued to optimize the effects on cognition.

2. Autistic and cognitive traits in the genetic understanding of the continuum in eurodevelopmental disorders and functional psychosis reported by Hanan D. Trotman

Despite the similar genetic and neurobiological mechanisms that likely underlie schizophrenia-spectrum illness and autism spectrum disorders the clinical overlap is rarely examined. 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. Adult-onset patients who demonstrated these delays 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 and patients, which 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 disorder should be used in genetic studies of schizophrenia.

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 KIAA1267 Gene MLL1 on chromosome 17q21.31. KIAA1267 has a role in transcriptional regulation through medication of histones. This study accounted for the context of the gene. Interestingly, as Fatjó-Vilas points out, the largest region of LD in the genome (CRHR1 and MAPT) is also located in this region. Fatjó-Vilas concluded that this was an important region with its effects through the modulation of age at onset and illness severity.

Rouleau described the large scale identification of rare, highly penetrant de novo mutations in genes coding for synaptic proteins (Synapse to Disease Project) in schizophrenia and related neurodevelopmental disorders. He points to the high rate of de novo mutations as an explanation for the high illness prevalence across cultures, despite reduced reproductive fitness. Although, this presentation was slanted in favor of the Multiple Rare Variant hypothesis, Rouleau acknowledged that the Common Disease/Common Variant hypothesis also likely applies. 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.

Collier presented data from a genome-wide search for schizophrenia-associated rare CNVs examining 9,878 transmissions from parent to offspring. He notes that common CNVs are not the best place to look for genetic determinants of schizophrenia. As in the prior presentation, he again highlighted that due to decreased fertility in schizophrenia, common variants are less likely to be casual explanations. 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. One CNV (15q13.33) can give rise to multiple problems.

3. International perspectives on group based approaches to treating cognition in schizophrenia Reported by Renate Thienel

Alice Medalia welcomed the audience by pointing out the relevance of this session's topic, given the strong link between cognitive impairment and patients' outcome. She also carried out that several meta-analytic studies showed moderate effect sizes of behavioural treatments. And finally because some clinical settings only allow for group settings, this conference session is going to report on such group samples, here from an international perspective.

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, which are mainly aimed at treating positive symptoms. Cognitive deficits tend to be generalised, with processing speed, attention, learning abilities, executive functioning being specifically impaired. Those cognitive symptoms have a very strong effect on social, functional and vocational, outcome. The effect sizes of cognitive training reported in a review from 2003 (Twamley et al., 2003: including 17 studies) vary between .3 on cognition, .26 on symptoms, .5 on functioning. A more recent review from 2007 including 26 studies reported similar effect sizes ranging from .4 for cognition, .28 on symptoms, and .36 on functioning.

Compensatory cognitive training uses different strategies, in order to use people's individual strengths, and to make use of different brain areas. As habits are difficult to forget, habit learning is used as a strategy. Strategies in general can be classified into internal and external strategies. An example for an internal strategy would be 'visual imagery' and for an external strategy 'note-taking' is an example. Important is that clients have to recognize that they have deficits with the internal ones in order to accept the need of using external ones, whereas with externals they may not generalize that much, and cues have to be 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 last 2 h with lots of time for practicing. Clients also get homework. The following cognitive domains are targeted: prospective memory (rationale: this is aiming to improve attendance, treatment adherence, task compensation with compensatory strategies like using calendars, reminders, linking tasks), conversational task vigilance (rationale: association with functional outcome, compensatory strategy: conversational skills, 'self-talk'), verbal memory, (rationale: association with functional outcome, compensatory strategy: reducing information, meaning, remembering peoples names, writing things down), executive functioning (rationale: linked to functional outcome, compensatory strategy: problem solving methods, brainstorming, hypothesis testing). N=89, baseline assessment for all subjects, thereafter 38 patients were randomised into the cognitive training and 31 into the standard pharmacological treatment. Follow up assessments were done after 3 months and 6 months. Inclusion criteria were no substance abuse, 21 years plus. A hierarchical linear modelling was used for analysis, effect sizes, for time, time x treatment interaction, attention, learning and memory, executive functioning and prospective memory are targeted cognitive domains, clinical ratings were done by PANSS and Hamilton. A functional capacity measure 'shopping task' was employed, also a quality of life interview was done. The sample was half sz, half schizoaffective. Mean age was 47, mean education 13 years, sick for 24 years and a CPZ equivalent of 335 mg. The attendance at classes was 82%.

No significant effects on positive and depressed symptoms, and the non-targeted cognitive symptoms. But there was a significant effect on the targeted cognitive symptoms (P= .046). Whereas the control group was better at the initial assessment, after 3, and 6 months the group receiving cognitive training was better. Results at 6 months follow-up were stable, hence indicated a consolidation. Functional capacity in the cognitive training group improved most extensively (P= .007). Negative symptoms also improved (P= .019), but after training they went back to baseline. Quality of life also increased in the cognitive training group (P= .039) while the control group showed a decline. Moderate effect sizes were achieved for visual memory (.6 effect size). The sample size was small, drop outs limit generalisability of results. The question remains whether the effects reflect reduced deficits or better compensation. Furthermore the follow up period was brief. Manuals are available: contact etwamley@ucsd.edu.au.

Questions from the audience: **1.** Some effects emerged at 3 month, some emerged at 6 month, why is that? Answer: Some effects get strongest at 6 months due to more practice, after 3 months, they still only try them out. **2.** Did people take drugs? Answer: We did not use pill counts, but only asked them if they have taken their medication. **3.** Question: A) Non- generalisation from targeted to non-targeted cognitive domains, why? B) Did you use the matrix battery? Answer: Matrix battery wasn't used, but verbal learning was in and one else, we did not expect generalisation, as we don't teach how to improve processing speed, for instance, but don't think that lack of generalisation is a surprise. **4.** Question: Was the sample baseline impaired? Answer: Yes they were.

Muhammed N.M. Alwi from Malaysia reported on a multisite study of a cognitive remediation program (CREP), in a developing country setting in Malaysia. CREP based on NEAR (a computerised program

developed by Alice Medalia), was officially launched 20 December 2005. Challenges were that computer programs had to be developed in malayian and that there are no neuropsychologists in Malaysia. Also the team had to overcome a certain resistance for change amongst clinicians. 85 patients diagnosed with schizophrenia were included to attend 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, 1hr/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 conducted at 5 centres with a cognitive training group versus a waiting list group. Furthermore additional so-called booster sessions (4 sessions) after a 2-week gap were including assessing whether this would have any enhancing effects on cognition? Clinical measures were BPRS, CGI, psychological functioning. Inclusion criteria: patients with schizophrenia between 16 and 50 years of age, no drugs, no electro convulsive therapy, no head injury or neurological disorder. 15 patients dropped out of the treatment group, 14 patients dropped out of the waiting control group. 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. (Caveat, as the clinicians where not blind). Booster sessions had no significant effect. The cognitive training was effective and this effect remained stable after 5 weeks.

Alice 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 as compared to the objective impairment, the subjective awareness is often poor (Medalia & 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% had impairments but only 40 % where aware of them. More precisely 52% had no awareness at all, a quarter had some awareness, and the other quarter full awareness. When asking for patients' attribution to illness 26 percent attributed them to the illness and 35% partially attributed their deficits to the illness. This data clearly stresses the need for psycho-education to inform patients. Unfortunately cognition very often is not part of psycho-education though. Alice Medalia was also referring to a handbook, available at www.omh.state.ny.us and to the work of Carol Dweck 'brain-check', which integrates cognitive screening in a psycho-educational group. These groups are run in 1 or 2 sessions and can be done in a group or individual setting. The sessions are interactive, and include a self-screening of cognitive skills, to get people aware and engage them. 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. Discussion points are: 'what does my score mean', 'illness causes decline in cognitive skills', 'attention deficits', 'ask participants if they experience that too?', 'malleability of cognitive skills', 'explain that one might be born with strength, and be able to improve weaknesses', 'what are strengths and weaknesses', 'and how can this be changed over time'. In a randomised control trial the study assessed whether a discussion session ('brain-check') can improve awareness. Targeted population: 18-60 year old subjects (mean age of 38 years) diagnosed with schizophrenia and schizoaffective disorder. In this ongoing study, so far 63 people were analysed (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), RECT (Receptiveness To Treatment). One to two brain-check sessions, and discussions were run. Subjects were excluded when their working memory index indicated they were unimpaired. None of the results were significant. But they are directing into the right direction. Relationship between awareness correlated with receptiveness to treatment. It is helpful to include cognition into psycho-educational programs, as there is some

evidence that awareness improves, and an association to receptiveness to treatment exists. Concerns: The awareness into cognitive disability is different to inside into the illness. As receptiveness to treatment is multi-determined, one session might be insufficient due to learning problems in that group. Therefore family members should for instance support people.

Questions from the audience: **1.** As a comment: Cognitive deficits often start during the prodromal stage and have a huge impact on vocational functioning. It is very important how people perceive their cognition as it can drag a mind set. If people believe that they are not able to do something this predicts cognitive failure. **2.** Cognitive strength in primary, cognitive ability in real life? Is it a leap to talk about real life or test results? Answer: We talk about test results and real life in the discussion. Generally it's the aim of the program to talk about real life.

Volker Roder -75-85% show long lasting cognitive deficits (Gray & Roth, 2007). Cognitive deficits predict 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 neuro- cognition and functional outcome, also treatment orientation is an intermediate factor (like motivation). Training of neuro-cognition, and social competence plus social cognition remediation and psycho-education help training treatment orientation. The Integrated Psychological Therapy (IPT) combines neuro-cognitive remediation with training in social cognition, social skills, and problem solving (Roder, Brenner & Kienzle, in press 2010). 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 .74-.84 in neuro-cognition, and social cognition. These results lead to further development of IPT towards an integrated neuro-cognitive training (INT). The framework for INT is resource orientation, empirical research and practical experience with IPT. The interventions content is: matrics categories, psycho-education, group processes, and therapeutic tools itself. Furthermore transfer to daily life and focus on intrinsic motivation. The INT includes 4 modules: highly structured exercises with Cogpack (a computer based cognitive training), social part with interactive groups, increase of complexity, and 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 when training twice a week. Multi side study of INT-training conducted in 3 countries including 9 centres. Inclusion criteria: IQ >80, duration of illness > 2 years, 15 weeks of training twice per week for 90 minutes, with a control group receiving treatment as usual (TAU). Follow up 3 times. N=170 patients were randomised into INT (N=88), and TAU (N= 82). The retention rate at the 1 year follow up was N= 50 (INT) and 47 (TAU). Mean age was 35 years, mean duration of illness was 9.9 years, and the mean number of hospitalisations was 3.54, mean IQ of 106, mean PANSS= 65, mean CPZ-equivalent of 352 mg, more males than females. Outcome measures were: TMT, COWAT, CPT, d2, and CVLT. Stronger effects at follow up compared to the immediate effect. Patients seem to need time to establish effects in social cognition and neuro-cognition modules. PANSS and GAF scores also improved. The effect sizes in the active INT-group were .36 for the immediate effect with an increase up to .52 at follow up. Duration of illness is a moderator - the longer the duration the less the effect size. Discussion: INT is well accepted, as the patients liked it a lot. Patients need time to show improvement, and the group therapy is a very helpful format. Email: roder@sunrise.ch.

Discussant Til Wykes: Pull things together- asking the question what effects groups have? Groups comprise the so-called non-specific beneficial effects of sharing experiences, and they have the potential to normalise by

sharing with other people. Also they help identifying common factors, and help sharing natural coping strategies. In general they provide a built in social support. These are important processes to use as part of therapy. Benefits/costs: within group settings more people can receive therapy, and groups can increase engagement. On the negative side there is to mention that groups are the less tailoring treatment to the individual. In general there is a need of group therapy expertise. Targets of the different studies reported on were cognition, and meta-cognition (like awareness, in Medalia's and Twamley's talks). When it comes 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. Til warned to not report interim analysis, and stressed out the importance of good trial designs with blind rating and treatment fidelity rating. She also asked to not talk about impairments or deficits but preferably rather refer to limitations, as we don't want the self-esteem to get poor. In a humorous conclusion Til summed up that as compared to the mean age of people of 32, Beth with her group of older (mean age 47) subjects showed that you can teach old dogs new tricks, the Malaysia study showed us that you can do more with less and Volker integrated modules, whereas Alice's study demonstrated again, that television (as within the waiting group) rots your brain.

General discussion: **1.** Group training is important. Group is therapy, and this requires specific training for the therapists. **2.** Was a generalisation effect followed up, like vocational skills, did they make more friends, functional outcome? Answer from Elizabeth Twamley: A meta-analysis showed that integration of a training into a psychosocial treatment works better, than a stand-alone cognitive training. I reported only on such a selective training of cognitive remediation. Furthermore in my study the timeframe was too short. Answer from Volker Roder: We need well trained therapists and have to think in terms of rehabilitation chains, where patients need continuous good relations to their therapist.

III. ANIMAL MODELS

1. New Directions for Animal Modeling in Schizophrenia
Reported by Gabriela Novak

Schizophrenia is a dynamic process and as such it is difficult to model. Based on current state of our knowledge, the disease is not caused by any one single gene, but rather by a complex interaction of etiopathological factors, with accordingly varied behavioural manifestations. The resulting phenotype reflects the interaction of genes, development and the environment. Therefore, in order to better understand the complex etiology of the disease, we need reliable approaches to quantify the behavioural output, ones that are transferrable between animals and humans. Such approaches have been discussed in this session.

Dr. Bita Moghaddam has highlighted the necessity for a conceptual shift from a the analysis of a static system of "risk" genes to "risk networks". But, because the same input can result in an array of behavioural outputs due to the complex nature of behavioural systems, it is important to understand the various aspects of behaviour, in order to be able to extrapolate to the complex network underlying such response. Therefore, we need to shift our focus to understanding the neural network and the interaction within it. An ideal approach would (1) identify behaviourally 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 of these circuits, confirm whether these are relevant to schizophrenia using measures common to both animals and humans. Dr. Moghaddam then discussed the role regulation of the cortical pyramidal network plays in the

"dynamic synapse hypothesis" of schizophrenia. In brief, 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, therefore, this excitatory input both stimulates the pyramidal neurons, as well as activates their inhibition by the GABAergic neurons. However, there is evidence that the GABAergic neurons are more sensitive to this stimulation as a result of a lower action potential threshold. This sensitivity of GABAergic neurons to excitatory input explains the pro-psychotic action of NMDA antagonists.

Dr. Akira Sawa then has set criteria, which should be fulfilled by a schizophrenia animal model. As mentioned earlier, schizophrenia is likely the result of multiple genes. Therefore, individual genetic mutations should be expected to model aspects of schizophrenia endophenotypes, rather than the full disease. They should be considered as useful models and essential tools used in dissection of the etiology of this disease. With that in mind, what criteria should a good model of the disease fulfill? It should reflect the etiology and pathogenesis of schizophrenia, reflecting the combination of genetic and environmental factors and involve the pathways identified to play a role in the disease.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.It should reflect the timecourse of the disease, involving early postnatal brain maturation and onset in early adulthood. As an example, Dr. Sawa presented his research involving the BACE1-NRG1-ErbB-Akt-DISC1 pathway (Niwa et al., 2010). The team 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 knock-down 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 also emphasized the necessary paradigm shift in schizophrenia research from gene or lesions to a "disconnectivity syndrome". Such shift in thinking would better reflect 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). What are the means currently available to us for understanding such complex processes? 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 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) as a result of aberrant neurodevelopment (Wright et al., 1999; Phillips & Silverstein, 2003; Uhlhaas et al, 2009b, 2010).

Synchrony depends on a balance of excitation and inhibition. Importantly, because indexes of this synchrony can be obtained both in animals and in humans, this approach it is ideally suited for analysis in 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 (Uhlhaas et al., Poster Nr 148). Kwon et al. 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, especially in the auditory cortex and particularly to stimulation of 40Hz (Kwon et al., 1999).

Another approach, one used to analyze coordination at a large scale level, was used 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 the millisecond range. In schizophrenia, between 200-300 msec, the synchronization between the two electrode sites is dramatically reduced, suggesting a strong impairment of large scale coordination (Uhlhaas and Singer, 2010).

These studies point to possible mechanisms involved in the deficits observed in schizophrenia, involving 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 areas of the brain.

Dr. Inna Gaisler-Salomon then 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 synapse, taken up by the glial cell, converted to glutamine and again taken up by neuron and converted glutamate. This glutamate to glutamine 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 FC. Interestingly, these mice do not show schizophrenia-like deficits. However, even though this is not a risk gene, and these mice do not represent a schizophrenia model, they are very useful for the study of a specific pharmacological aspect of schizophrenia (Gaisler-Salomon et al., 2009a).

Using an fMRI cerebral blood volume measurement developed by Dr. Small (Small, 2003), Dr. Schobel has shown that there is an increased activity in the CA1 and in the subiculum both in schizophrenia patients and in high risk individuals (Schobel, 2009). However, the GLS1 hetererozygous mice show a decrease in activity in the same subregions 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 behavioural 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, which is commonly used as a screening tool to asses the actions of antipsychotic drugs (Gaisler-Salomon et al., 2009a).

In conclusion, overexpression of glutaminase is not a model of schizophrenia, but interestingly enough, it seems to interact with other neurotransmitter systems, in particular other molecules in the glutamate system and the dopamine system, 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 then concluded the session with a discussion on the future of developmental animal models. Assessments at various end-points, including behavioural, electrophysiology, anatomy and other methods revealed remarkable convergence of evidence for defects in dopamine, glutamate and GABA interactions being affected in most of these models and highlight a disbalance in inhibition / excitatopn in these networks, as was discussed by Dr. Moghaddam.

This has also been shown by Dr. O'Donnell in animals treated prenatally with the antimitotic methylazoxymethanol acetate (MAM), which show loss of parvalbumin staining in the mPFC and ventral

subiculum of the hippocampus at adulthood, without loss of neuronal numbers. This indicates hypoactive GABA system (Lodge et al., 2009).

Using the neonatal ventral hippocampal lesion (NVHL) model (Tseng et al., 2009), the O'Donnell lab has shown that D2 agonist (quinpirole) enhances the excitability of interneurons from normal adult rats, but not in adult animals with NVHL. In fact, dopamine can have the wrong effect in NVHL animals (Tseng et al., 2008). This points to deficient interactions between dopamine and GABA in NVHL animals, but also that this interneuron deficiency is dynamic, since the anomaly is only revealed when they are challenged by dopamine.

Combining two models, an immune challenge and 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).

Therefore, as Dr. O'Donnell summarized, 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 maturation to adult. This does not seem to occur in many schizophrenia models.

Therefore, now we have a number of schizophrenia-relevant pathophysiology models, which integrate dopamine, GABA and glutamine. We can now analyze the pathways that mediate this phenotype. For example, why blocking NMDA can make interneurons misfunction, why do we get a schizophrenia phenotype with DISC1 manipulations or with lesions in areas that project to PFC, or even in the disease. Now we can attempt to more closely address the etiology of the disease and what other factors are involved, such as BDNF. Genetic models can provide us with much information to test these circuit-based models.

We can now start asking questions about the timing of the disease. What has changed in the system, compared to normal maturation of these cortical areas? We should also be able to see the equivalent of a prodromal stage in juvenile animals and design experiments to address mild cognitive dysfunctions in these animals and, perhaps, even model these. We can analyze environmental interactions, such as social isolation or cannabis use.

In Dr. O'Donnell's opinion, it is not necessary to choose one single model, many different models are applicable, as long as they provide the pathophysiological scenario that is consistent with the idea that there is a loss of excitation/inhibition balance.

As Dr. Uhlhaas showed, we can have ways to look at interneurons function and synchrony between cortical regions and these can be parallel in humans and in rodents.

Several models now give us a pathophysiological scenario that is quite consistent with what we know of schizophrenia and these are ideal for testing novel therapeutic approaches, such as mGluR2/3 agonists, GABAA agonists, phosphodiesterase, glycine transporter, D-serine, AMPA modulators, etc.

As an example, Dr. O'Donnell has shown results of his recent work. In animals with neonatal lesion (NVHL), DNA oxidation has been illustrated within parvalbumin-labeled neurons, indicating that the interneurons of mPFC undergo oxidative stress early on (Cabungcal, Lewis, Cuenod, Do, O'Donnell unpublished data).

Using an odor smelling test, the O'Donnell team showed that an increase in interneuron-dependent beta band oscillation frequency during decision making, which is present in normal rats, is not observed in rats with

neonatal hippocampal lesion. This effect is apparent during the time when dopamine cells fire bursts and implies that in animals with a lesion these interneurons cannot be driven by the release of dopamine.

As a last note, many of the available models likely affect pathways necessary for proper inhibition/excitation by interneurons, but we cannot always see the pathophysiology, because the neural circuits must first undergo maturation (O'Donnell 2010).

Question: What is the role of endocannabinoids, since we know that endocannabinoid receptors decrease form pre-birth to adulthood. Answer by Dr. Moghaddam: The CD1 endocannabinoid receptor is expressed prevalently in the cortex, but we know very little of their function. They are the focus of future research. Note: (see Harkany et al., 2008)

2. Gene Expression in Schizophrenia - animal models and postmortem studies - Reported by Moogeh Baharnoori

Genetic studies have been significantly contributed to our understanding of etiopathology and neurobiology of schizophrenia. More recently, extensive research effort has been dedicated to unravel the important changes in the epigenetic regulation of gene expression in the post mortem brains. The main focus of this special session, chaired by Dr. Amanda Law was to underpin the recent advances in gene expression profiling in schizophrenia combining the findings on the animal models and 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. In the beginning he gave an introduction about the critical role of neocortical GABA inhibitory system in the pathophysiology of schizophrenia. He talked about interneuron subpopulation, their differential laminar distribution and distinct electrophysiological properties. One of the most consistent finding 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 sub-population of GAD1-containing interneurons is also decreased in the prefrontal cortex of the schizophrenic subjects. Applying an endogenous mechanism for gene silencing, they succeeded to develop a transgenic mouse with down regulation in 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 the CHO and HEK293 cell lines and *in vivo* in the transgenic mouse brain. The cell lines were primarily incorporated with GAD1 and then co-transfected with the miRNA silencing construct. As the result, GAD1 protein was significantly decreased (>90%) in both cell lines. Furthermore, the transfected cell lines maintained the 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 was 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) implicating the transgene was selectively expressed in the NPY subpopulation of interneurons. The efficient reduction in GAD1 protein expression was also studied in the 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 specificity of this knockdown approach. At the end he discussed the several advantages of novel gene silencing technique. For example, these are cell type specific down regulation which can be visualized by eGFP reporter gene, the transgenic mice are cost benefit, generate rapidly and can be easily

crossed with other backgrounds. Importantly, the novel strategy can be used to generate various splice-variant-specific transgenic animals (due to the small size of silencing miRNAs). At the end, he argued the need for generating similar animal models such as NPY-GAD67 knockdown or NPY- PV-CCK driven GAD1 miRNA transgene mice in order to gain better understanding for the critical role of different interneuronal systems in the cortical neurotransmission, behavioural outcome and cognitive function. Second speaker Dr. Schahram Akbarian (University if Massachusettes Medical School, USA) presented data on the epigenome mapping in developing and diseased prefrontal cortex. The basic knowledge on epigenetic regulation of gene expression has significantly progressed in recent years. It is specifically important in the post mortem field for neuropsychiatric disorders, since the study of chromatin modifications allows us to focus on one aspect of transcriptional regulation within the human brain. Histone proteins are subject to different epigenetic modifications, among them histone methylations are particularly important because they 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 on the gene promoter region associated with transcriptional activations (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 significant increase in H3K4 methylation. Applying a chromatin precipitation assay (ChIP), he reported significant deficits in GAD1 mRNA and H3K4me3 levels 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. Thus, in addition to the active regulation during early brain development, certain histone methylations are also important in the molecular mechanism operating during different stages of a psychotic illness. In a separate experiment, they looked at epigenetic architecture of human prefrontal cortex aiming to map the genome wide distribution of H3K4me3 enriched sites (peak) during postnatal brain development using ChIP-Seq in conjunction with an Illumina Solexa sequencing platform. Interestingly, they found that H3K4me3 peaks at several high risk loci such as 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 changes in the prefrontal cortex as 600 H3K4me3 peaks are lost in first postnatal year (mainly through demethylation process). Next speaker Dr. Amanda Law (NIMH, USA) talked about the recent finding on the intracellular signalling pathway of a susceptibility gene for schizophrenia, Neuregulin1 (NRG1). NRG1 receptor, ERbB4 is also a candidate risk gene for schizophrenia suggesting that NRG1 signalling cascade might be involved in the pathophysiology of this illness. The expression of ErbB4 splice isoform containing exon 26 (CYT-1) and exon 16 (JM-a) are significantly elevated in the dorsolateral prefrontal cortex of schizophrenic patients. The increased expression of ErbB4 variants which activate PI3K pathway may explain the PI3K over activation observed in schizophrenia (Law et al., 2007). PI3K gene expression (PI3KCD), its intracellular signalling and cell migration were measured in lymphoblast cell line (LCL) derived from schizophrenia and healthy controls in relation to genetic variation to ErbB4 (rs7598440, rs707284, rs839523). The result showed that ErbB4 risk variation predicts Nrg1 mediated intracellular signalling and Nrg1 mediated cell migration. They also found impaired transmission of SNP alleles in PI3KCD in two independent family samples however; unlike LCL the PI3KCD is not increased in the brains of schizophrenic patients probably due to antipsychotic treatment. In conclusion, their finding provide the direct evidence certain gene risk variation in ErbB4 are able to induce significant functional outcome for PI3K pathway at the molecular and cellular level and further confirmed that an aberrant Nrg1/ErbB4 signalling is an upstream effecter of impaired PI3K function in schizophrenia. The last speaker in

the is symposium, Dr. David Porteous (University of Edinburgh, UK) talked about DISC1 a most convincing susceptibility gene for schizophrenia, originally identified at a breakpoint of a chromosome t(1;11) in a large Scottish family with major mental disorders such as schizophrenia and mood disorders (Millar et al., 2001). At first he described behavioural phenotype and predictive validity of two DISC1 missense mutant models. Q3IL mice exhibited depressive like behaviours (forced swim test) that were reversed by the antidepressant treatment, while the other mutant, L100P display schizophrenia like behaviours (prepulse inhibition and latent inhibition) that were again reversed by antipsychotic treatment These finding 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 molecular mechanisms underlying abnormal phenotype in these mutants. They also conducted a global analysis of the common SNP variants of DISC1 and it common binding partners (PDE4, and NDE1) in gene expression in human LCLs. The analysis of data revealed that these genetic variants specifically regulate synaptogenesis, neurodevelopment and sensory perception proteins. Importantly, they identified seven psychoactive drug targets within the DISC1 pathway that can be used as reliable predictors of individual response to therapeutic agents.

3. **Mutant models and psychosis at the crossroads: a critical re-evaluation of techniques and translation**
   Reported by Aurelie Boucher

As schizophrenia is thought to be a polygenic disorder and recent progress has been made in identification of candidate genetic risk factors, the four speakers of this symposium reviewed new developments in the generation and evaluation of mutant models of schizophrenia.

In his presentation entitled “Novel developments in genetic mouse models: a DISC1 story”, Mikhail Pletnikov from *Johns Hopkins University, Baltimore, Maryland, USA* exposed the neurodevelopmental and schizophrenia-like phenotypic manifestations of mice mutant for disrupted-In-Schizophrenia 1 (DISC1), a strong candidate gene for major mental diseases including schizophrenia. The inducible expression of mutant DISC1 demonstrates the particular interest of using genetic manipulations in cell-specific, time-dependent and brain region-restricted manners. Using Tet-off system, the expression of the transgenes is inducible in different time points of neurodevelopment of forebrain regions such as in the cortex, hippocampus, striatum but not in the cerebellum. While there was no gross effect/abnormalities in those mice, enlargement of lateral ventricles was observed. At a molecular level, decreased DISC1 was observed in mutant showing a dominant-negative effect. Behaviourally, they reported 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. The evaluation of the effect of different timings of expression was done using a standard and well developed model that has however not really been applied in the psychiatric context. Four different groups were analysed 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 shown an increased aggressiveness in pre+post, decreased social interaction in pre+post and in post, increased response to the psychostimulant MK-801 on beam breaks in pre+post, and increased immobility in a model of depression, the forced swim test, only in females post. When evaluating monoamines alterations, they observed decreased dopamine (in all mutants), serotonine (females post) and parvalbumin (in all mutants). In addition, enlargement of lateral ventricules were also observed in pre+post and post mutants, as well as increased spine protusions in pre+post. In conclusion, schizophrenia-like behavioural alterations have prenatal origin in males DISC1 mutants. Depression-like behaviours depend on post natal for females, and structural brain adnormalities on post. The limitations of mice

models include temporal or regional expression, mutations in regulatory regions of the gene, target multiple genes and combine with environmental factors.

The second speaker, John Waddington from *Royal College of Surgeons, Dublin, Ireland,* presented a "Psychopathological, cognitive and morphological phenotypes in schizophrenia risk gene mutants: challenges and the example of neuregulin". Mice mutant for a lot of different genes have been studied, and NRG1 will be used here as an example. The first challenge is the phenotypic assessment. While a focused and approached evaluation (thus an "*a priori*" method) is more often used, it is important to also use a broad, hierarchical method (with no "*a priori*") to allow diversify screening. The second challenge is to assess mental health in the mouse using social behaviour, cognition or prepulse inhibition. The third challenge is the multiple and rare copy number variations in the different genes involved in schizophrenia. The fourth challenge is that most mutants are not models of schizophrenia *per se*, so there is a need in creating model of the functional role of genes associated with schizophrenia. The fifth challenge is that a) there are several genes of small effects so are their effects additive or independent? and b) are we expecting the similar phenotype from one mice to another or different ones? There are different mutants for NRG1 and also transgenic over-expressing type 1 NRG so the sixth challenge is that antipsychotics increase NRG1 expression. The results from NRG1 mutant mice showed that they had an increased locomotor activity. However it is important to consider the ethological assessment of phenotyping and examine what is the animal actually doing by checking all behaviours. While the general locomotor activity was increased, only rearing free was increased as opposed to rearing seated, to the wall or sniffing that were unchanged compared to control mice. In addition difference in behaviours such as grooming was dependent on gender. While no difference in sociability was observed, no social novelty preference was seen in females and male NRG1. In the Barnes maze, all groups succeeded in this spatial learning task, but male NRG1 displayed an increased latency on the first day only. This showed that this effect was confounded by hyperactivity or anxiety and independent of a spatial learning deficit. In the Y maze, no spatial working memory deficit was observed. In conclusion, it is interesting that NRG1 mice showed disrupted social novelty but no working memory, while COMT mutant show intact social behaviour but selective disruption in working memory. The seventh challenge is that there are sex differences so it is important not to generalize to both gender. In other social behaviours, there was an increased aggressiveness but not in non aggressive social infarction. Orofacial dyskinesia was observed in NRG1 mutants (increased chattering) showing that it is interesting to add new phenotypes that you would not think of. Using fMRI, a small but significant decreased in the total ventricles volume was observed in NRG1 mutants. When investigating gene by environment interactions, adolescent social defeat is different in NRG1 mutants compared to WT. In addition, an acute PCP challenge decreased hyperactivity in NRG1 compared to vehicle. In animals subchronically pretreated with PCP, an increased activity sensitization was observed in NRG1 compared to controls. The ninth challenge is the "bottom up" approach to genetic modelling, trying to find new genes instead of using the ones discovered from clinical schizophrenia research. For example, mutant mice for semaGA, that is involved in thalamocortical connectivity, show hyperactivity that is reversed by clozapine.

The third presentation was untitled "Copy number variation in schizophrenia: modeling 22q11" by Maria Karayiorgou from *Columbia University, New York, USA* presented a new mouse model of copy number variants on the 22q11.2 microdeletions, that leads to very high risk to develop schizophrenia. The common allele hypothesis or the rare allele hypothesis are trying to understand this genetic role. There is a missing link in animal models between genetic mutations and disease: there are deficits at the molecular, cellular, synaptic, systems level and behavioural and cognitive levels. Thus different tests are used to study each cognitive

function. In mice, hyperactivity, light-dark, decreased prepulse inhibition, fear conditioning, working memory, alteration in spine density, impaired dendritic growth, transcriptome alterations in prefrontal cortex and hippocampus can be used. The knockout mice generated are Dgcr8 deficient (a segment syntenic to the human 22q11.2 locus). They showed affected prepulse inhibition and water maze performance, but no difference in locomotor activity and fear conditioning. In addition, Dgcr8 deficiency affected dendritic spine development but not size. Thus Dgcr8 haploinsufficiency induced cognitive impairments accompanied by and neuronal abnormalities and dysregulation of synaptic genes.

The last speaker was Bart Ellenbroek from *Evotec Neurosciences, Hamburg, Germany* who presented "The dopamine D1 mutant rat: A novel approach to modelling negative and cognitive aspects of schizophrenia" which exposed the development of a knockout rat model. Dopamine has long been implicated in the neuropathology of schizophrenia, thus were created dopamine D1 mutant rats (by replacing an isoleucine by a serine that disrupt the interaction between the third and fourth transmenbrane domains). The decreased D1 labelling in the homozygous mutants was confirmed by autoradiography. The advantage of using mutant rat is first the fact that there is a huge evolution gap between mice and rats (a rat is not a big mouse). Second, 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 performances. Third, there are pharmacological differences between them but not a lot of studies compared both. For example, D1 and D2 have different effects on prepulse inhibition between rat and mice where D1 works in mice and D2 in rats. The results obtained from the mutant rats showed that amphetamine and cocaine-induced hyperactivity was reduced in the mutants. The mRNA level of Arc, increased with cocaine, was not observed in mutants. In the paw test, catalepsy induced by SCH was not observed in the mutants. Sucrose intake was decreased in mutants compared to WT on day 1. Social behaviour was decreased in mutants especially play behaviour in young rats. In the Morris water maze, spatial learning was affected as seen with an increased latency in mutants, but they did learn over time. In the egocentric task of the water maze (more specific to dopaminergic frontostriatal implication) where the platform change all the time, mutant rats did not learn this task. Finally, decreased prepulse inhibition was observed in the mutants. In conclusion, while the study of endophenotypes is not a model of schizophrenia, this model is interesting to study especially the negative and cognitive symptoms of schizophrenia.

IV: TREATMENT

1. Psychosocial session: An update on psychosocial treatment of schizophrenia – Reported by Juan Gallego

The first speaker was Dr. Lisa Dixon (Maryland, US) who spoke about first episode psychosis and the 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 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 has also some benefits in terms of 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 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) has found superior outcomes with a blended ACT program with a vocational specialist as compared to a traditional ACT program and McFarlane et al. (2000) found superiority with blended ACT compared to conventional vocational rehabilitation. In terms of substance use, there were no clear advantages of ACT enhanced with substance use expertise compared to traditional ACT or clinical case management (Essock et al. 2006). Mixed evidence has been found in terms of forensic ACT having arrests and jail days as outcomes (Lamberti et al. 2004)

Dr. Dixon's talk then focused on the NIMH Recovery After Initial Schizophrenia Episode (RAISE) project. This project looks to test whether early, aggressive, and pre-emptive intervention can slow or halt clinical and functional deterioration in schizophrenia. Two separate 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. 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, whose primary investigator is Jeffrey Lieberman, MD. They expect to enroll 330 to 370 participants. The subjects will be aged 15-35 with diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, psychosis NOS and 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 condition. The Connection Team condition is a comprehensive multi-element approach with a clinician team leader, a psychiatrist, a supported employment/education specialist and a skills training specialist. The Connection Partnership condition 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 around 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. To conclude her talk, Dr. Dixon stressed that the ACT team remains a stable evidence-based practice within US and that the relevance of a team-based treatment for persons experiencing first episode of psychosis is to be tested in US system.

The second talk was conducted by Dr. David Kingdon (Southampton, UK) and his topic was 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. He also argued that one of the key differences with other approaches is that psychosis is viewed on a continuum between normal and ill, rather than all or nothing. The benefits of CBTp are multiple but the most important are that it has a powerful normalizing effect on patients; it does not require acceptance of 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). The meta-analysis by 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 – 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), 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). As limitations Dr. Kingdon mentioned that CBTp is not available in many countries because of the difficulties in implementation. At the end of the talk one member of the audience asked whether a continuum in psychosis meant a continuum in schizophrenia to which Dr. Kingdon replied that schizophrenia could be part of the psychosis continuum as opposed to being two different phenomena.

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 explained in detail on two recent meta-analyses done on cognitive remediation. The first meta-analysis (McGurk et al. 2007) included 26 studies with 1151 clients. The results showed that cognitive remediation was associated with significant improvements, 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 (under review) showed moderate effect sizes on overall cognitive improvement on functioning (functional outcomes). As a summary she concluded: 1) the adjunctive psychiatric rehabilitation is a moderator of functional outcomes; 2) the positive effects of cognitive remediation are seen in the presence of adjunctive rehabilitation; 3) cognitive remediation helps with cognitive functioning, 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 practices alone.

During the discussion a member of the audience asked Dr. McGurk if she thought that the benefits shown by cognitive remediation in presence of psychosocial rehabilitation were due to the effects of psychosocial rehabilitation or if cognitive remediation alone can be helpful by itself. Dr. McGurk replied that there was evidence that cognitive remediation added additional value above and beyond psychosocial rehabilitation.

Dr. Pitschel-Walz was the fourth speaker in the session and her talk was titled “family psychoeducation”. She 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 interventions were combined with CBT the rates of rehospitalization were lower at 5 and 8 years follow up. Bauml et al. (2007) and Hornung et al. (1999) found lower rates of rehospitalization in patients who received psychoeducation compared to patients 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 Bauml et al. (2007) showed that the reduction of number of hospital days could signify a reduction of the cost of 37.500 Euros after seven years of follow up. In terms of effectiveness, Dr. Pitchel-Walz mentioned that only 0 to 8% of the patients in US and Spain received any kind of family intervention (Glynn et al. 2006). Barriers such as the increased workload, the higher costs, the insufficient knowledge and the 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 and some of them have a "real-world" or effectiveness approach (Magliano et al. 2006; Rummel-Kluge et al. 2007). Family-based peer programs are also being explored (Pickett-Schenk et al. 2006) and special target populations are also being examined such as substance abuse population (Mueser et al. 2009) and first episode of psychosis population (Gleeson et al. 2009; Lyse et al. 2007).

Two questions arose during the discussion. The first question was regarding the difference between family psychoeducation and family therapy. Dr. Pitchel-Waltz pointed out that family therapy occurs over a long period of time and it has a more therapeutic emphasis whereas psychoeducation is shorter and does not look to treat but to educate. Dr. Lisa Dixon answered a second question from the audience. It was asked whether peer to peer programs could help disseminate family psychoeducation programs and she noted that a family to family approach is effective for family outcomes but not for client outcomes. She stressed that one of the barriers is that families sometimes do not want to be involved in therapy which makes dissemination difficult.

Dr. Mueser was the next speaker and he started his presentation with explaining 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 search, 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 the vocational/rehabilitation programs. It has been suggested that cognitive impairment is associated with less response to SE and that cognitive remediation improves cognitive functioning, therefore 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 outcomes but the main question remained whether or not cognitive remediation can improve outcomes in non-responders to supported employment. He continued his presentation by explaining that social skills training (SST) is 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 session, with training individualized to each client based on personal goals. He emphasized that 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 with schizophrenia (Bartels et al. 2004), for patients with schizophrenia and 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). His presentation then was directed to the NIMH RAISE project. Dr Mueser is a co-investigator in The Feinstein Institute for Medical Research team. The trial looks to incorporate about 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 and 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 (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.

One question was brought up during the discussion. A member of the audience asked why a specific treatment or approach has not been developed for mothers with psychosis or mothers who have family members with a psychotic illness. He mentioned the importance of "mothering" in mental health and mentioned that he did not understand why it has been overlooked. Dr. Mueser replied that he agreed with him and that this area of research has been neglected so far but that it would be a very important area to investigate further.

Dr. Wykes started 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 (Wykes et al. under review) work. She also expressed 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 neither 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 to be proven. She pointed out that there are several limitations for this. 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, CRT). She stated that expectations are high for early interventions and she wondered what the field should do in case the RAISE studies fail to show any differences and what to make of it in the context of the trial. 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 the biggest challenges is that health and social care services have limited budgets but that patients have high expectations.

2. **Early intervention services for five years?**
   Reported by Hanan D. Trotman, Ph.D.

Malla and Nordentoft chaired a fundamental 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, Norman & Manchanda, 2002; 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, gave the first presentation, which 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 and 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 patient 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 reportedly predicted outcome better than relapse alone. Malla concluded the presentation, with the suggestion that longer intervention trials were needed, as two years was not long enough to determine whether extended specialized care was better than regular care for the long-term outcome in early psychosis.

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). OPUS patients spent less time in supported housing than the standard group. Positive and negative effects were reduced, but the effect was not maintained at 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. (See Pskiatrifonden.dk).
Vazquez-Barquero tackled the problem of the length of time that first episode patients should take medication in a sample from Northern Spain. Central to this presentation was the problem of lack of clarity in discontinuation criteria due to the limited number of investigations related to medication withdrawal. Patients had to be symptom free for 18 months to be eligible for this intervention. 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 against relapse. Vazquez-Barquero concluded that better predictors of successful discontinuation are needed.

Verhaegh's discussion of function assertive community treatment (FACT) and results from a trial of assertive community treatment (ACT) in community treatment in two mental health groups. Essential features of the program included vocational training, and supported education, 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 39-50 percent. 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.

In Birchwood's excellent discussion of the four presentations, he 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. He raised a second point, that a patient's long-term trajectory is formed within the first couple of years. Long DUPs and disability is already present at that point. Further, early intervention services do not solely account for individual trajectories and follow a "one size fits all" paradigm. He suggested a probable enhancement from the combination of early intervention services and methods for decreasing DUP. A third point, raised by Birchwood was to ask, how is change sustained? What are the specialized long-term structures that are needed? Malla response to these "reflections" was that patients remain engaged then they attain skills that help them cope.

3. An update on the Next Wave of Schizophrenia Therapeutics
Reported by Nashaat Mohamed Abdel-Fadeel

This session included an introduction and 3 talks. It examined the new wave of schizophrenia therapeutics that differs from current available medication. As all current therapies for schizophrenia are D2 antagonists or partial agonists, so they treat positive symptoms but they treat other domains poorly and their side effects are serious. ATIE, EUFEST and CUTLASS studies reported that the first generation antipsychotic drugs are as effective as 2nd generation antipsychotic drugs, but atypicals have advantage in tolerability.

So, there is a need for new treatments to treat all domains with an acceptable side effect profile.

Kiel Svensson presented the first talk regarding the mGLU2 receptor as a novel drug target for schizophrenia.

Evidences of mGLU2/3 receptor agonists for treatment of schizophrenia have been reported in early clinical testing in a 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 mGLU2 allosteric potentiator (PAM's) for treatment of schizophrenia as it suppresses glutamate activity during periods of enhanced but not normal glutamate release.

PAM's may have favorable side effect profile with lower risk for tolerance/ desensitization development compared to agonist, and also blockade of d-amphetamine/ pcp/ ketanie hyperactivity and 5-HT2A agonist-induced behavioral effects (Marek, 2010 for review).

In addition studies with transgenic mice suggest that the effects are mediated via the mGL2 receptor with no evidence for a direct interaction with dopamine D2 receptor in vitro or in vivo.

Also, additional testing is needed to address questions around potential differentiation between mGLu2/3 agonists and mGLU2 PAM's in terms of efficacy and tolerability.

Christopher Schmidt has 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 schizophrenis 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.

Finally the presenter recommended confirmation of clinical activity with a second GlyT1 chemotype and that will provide support not only for the potential utility of GlyT1 inhibitors in the treatment of schizophrenia but will also validate other approaches targeting NMDA receptor.

Peter Hudson presented "mGluR5 positive allosteric Modulators as putative antipsychotic agents".

The rationale of mGluR5 positive allosteric modulators is through that there is genetic evidence of link to schizophrenia: mGluR5 allele association on chromosome 11 and enhanced message encoding mGluR5 in PFC.

Also mGluR5 antagonist (MPEP) potentiates PCP/ methamphetamine induced deficit in PPI and locomotor activity and induces cognitive impairment in radial arm maze.

Moreover, activation of 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.

Finally, Nicolas Brandon discurssed "PDE 10A and schizophrenia". The rationale is that PDE 10A is expressed in medium spiny neurons in striatum suggesting potential therapeutic indications as inhibition may treat psychosis by increasing striatal output, also, PDE 10A inhibition modulates neuronal activity in the striatum.

PDE 10 A is also found in hippocampus and cortex suggesting potential to affect cognition and also PDE 10A inhibitor therapeutic profile is antipsychotic, pro-cognitive and affects negative symptoms.

WEB-3 was identified as a novel PDE 10A inhibitor and is described as a potent and specific PDE 10A inhibitor brain permeable agent (1.2 B/P).

MP-10 and WEB-3 showed evidence of antipsychotic activity in conditioned avoidance responding (CAR) in rats, also they produces low levels of catalepsy indicating low EPS risk.

Also they enhance retention of recognition memory in rats. MP-10 enhances social odor recognition memory in MK 801 treated mice; also, it is efficacious in animal models relevant for negative symptoms.

Finally PDE 10A inhibitors improve all symptoms in preclinical models with attractive side effect profile.

4.Improving Signal Detection in Schizophrenia Clinical Trials by Multiple Methods - Reported by Hsiao Piau Ng

This symposium was chaired by Dr. Wolfgang Fleischhacker from Medical University Innsbruck. The first speaker was Dr. David Daniel, from United BioSource Corporation and George Washington University, who started by highlighting the various factors contributing to poor signal detection namely inconsistent credentials of the 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 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 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. The talk was concluded with analyses from a complex multi-center clinical trial, which showed reduced ratings errors and rater drift, hence supporting the feasibility of these intervention approaches. A question was raised on whether the inter-rater reliability was done between regions or within regions. The reply was that the reliability test was carried out between and within regions. A comment was made on an observation where severity rating decreases with experience. This implies that given a similar severe case, an experienced rater might give a less severe rating compared to a less experienced rater as the former has probably seen worse cases.

The second speaker of the symposium was Dr. Janet Williams, from MedAvante Research Institute, who began her presentation by identifying two main causes of failed clinical trails, namely inappropriate subject selections 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, has no incentive to screen subjects in or out and will not develop relationship with subject which will influence ratings. When raters are blinded, they have no prior knowledge on inclusion criteria and hence eliminate the chances of expectancy bias. By having centralized raters, extensive training and continuous calibration, rater drift may be avoided. Going along the line of having centralized, remote and unbiased raters, 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 meant reduced travel time and less absence from work for both patient and family. Through the use of video, patients feel 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 signal of test drug and onset of action from first week, while site raters scored test drugs no differently from placebo. Dr. Williams concluded her talk by emphasizing that inappropriate subject selection and inaccurate outcome measures are major sources of risk to clinical trials. Traditional rater training, along with minimal monitoring, is insufficient to minimize these risks. Highly-trained blinded remote centralized raters can improve subject selection and administration of outcome measures. Independent centralized and continuously calibrated reviewers for quality control monitoring play a role in obtaining and maintaining high quality assessments. A question was posed on whether the consistency of ratings should be monitored over one scale or more and the reply was that it should involve more than one scale and the scales should be correlated. When asked if there are known symptoms related to rating over video, Dr. Williams quoted an interesting example where increased video bandwidth resulted in more accurate ratings by rater. In response to another question, 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. The issue of maintaining the motivation in raters to provide accurate rating was also raised, and Dr. Williams provided some examples where raters were given the opportunities to take on other work to help them stay motivated.

The third speaker of this symposium was Dr. John Harrison from Imperial College and CogState Ltd in London, who spoke on the best practice guidelines for cognitive test selection. He began his talk by listing the cognitive

processes which are of interest and they are: i) memory, ii) visuo-spatial function, iii) language, iv) praxis, v) working memory, vi) executive function, 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, reasoning and problem solving) in assessing the ability of new therapies to improve cognitive function in schizophrenia. Dr. Harrison also discussed the basic criteria of a good test which include it 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 measurement of cognition can be achieved, thereby increasing the probability of detecting effects.

The last speaker of this symposium was Dr. Nina Schooler from SUNY Downstate Medical Center and The Zuckler Hillside Hospital. Her talk on the use of functional outcome as a long-term treatment goal covers the rationale for assessment of functional outcome, available measures, assessment models and how assessment can be improved. According to Dr. Schooler, there is an 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 general population. As mentioned by Leifker et al. (2009), there are many available instruments for assessment of functional outcome and they can be broadly 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, 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 of origin and education, be assessed. In conclusion, Dr. Schooler states that functional outcome assessment will continue to play an important role in future clinical trial. 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. A question was raised on whether it is possible to come up with a particular instrument that is suitable for all clinical trials. The reply to this was that some of the concepts often involved in clinical trials are similar and these could be used to design an instrument that caters to them.

5.Newer 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. Thus, antipsychotic treatment studies with informative samples in this population are lacking. The overall aim of this session was to evaluate the evidence for existing antipsychotic treatment and the latest information on its effectiveness and side effects in order to improve the design and conduct of clinical trials in pediatrics schizophrenia and to identify the most

urgent clinical questions in this area. Presentations were based on placebo-controlled trials and active comparator trials of newer antipsychotic drugs in children and adolescents. Developmental aspects were also examined through new anima data to improve understanding of age-related differences in side effect profiles of these drugs between young and adult patients.

Christoph U Corell presentation **a**imed to provide an overview of the available and emerging efficacy and safety data of antipsychotic drugs in young patients with pediatric schizophrenia. 14 randomized controlled studies (n=1,155) were found (Corell, 2008a). All newer antipsychotic drugs showed superiority on PANSS all studied doses. The only group significant differences were in favour of Clozapine compared to 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 akathisia were less prevalent (Corell and Kane, 2007). Although diabetes was rarely noticed, marked increase in insulin resistance and incidence of dyslipidemia were of great concern (Corell, 2008c).

As there are limited published controlled data on the long term efficacy of antipsychotic drugs in adolescents, Margaretta Nyilas presentation aimed to compare between the adolescent and adult short and long term efficacy and safety of Arirpiprazole. A post hoc analyses 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 efficacy were observed. Percent of adolescents achieving remission at 27-32 weeks (82%) on open label treatment was similar to that in adult study at week 26 (76%) and at week 52 (79%) on double blind trial. 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.

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 age of 18 years- was noticed in 50% of patients and was associated to increased severity and antipsychotic drug resistance (Kumra and Charles Schulz, 2008). A previous study of Kumra et al. (1996) has 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 design consisted of randomized double-blind trial with flexibly dosed treatment with clozapine (n=18) or high dose (up to 30 mg/day) olanzapine (n=21).

Significantly more clozapine-treated adolescents met response criteria (66%) compared to olanzeapine-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 important for clozapine than for olanzapine and more important for both than those noticed in adult patients

undertaking the same medications. The study seems to support clozapine as the agent of choice in treatment-refractory adolescents with schizophrenia.

In order to investigate age-related in antipsychotic drugs side effects between young and adult patients, Frank Tarazi presented long term effects of these drugs on neuronal elements in 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, subjects were sacrificed and brain were collected and processed for in dopamine (DA) and serotonin (5-HT) receptor autoradiography. Repeated treatment with fluphenazine, clozapine olanzapine decreased D1 receptors in cerebral cortex of juvenile but not adult rats. All four antipsychotic agents increased D2 receptors in cerebral cortex of adult animals and in hippocampus of juvenile animals. The four agents also increased more profoundly 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 and 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.

6. New Research in the Early Prediction of Antipsychotic Response in Schizophrenia Reported by Gisele Huf

Stefan summarised both work of others and his own 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 delay and, after a series of weeks, of gentle increase in functioning and decrease in symptoms. From the datasets presented, and accompanied by clear argument, Dr Leucht suggested that early response can be expected within a matter of 2-3 weeks. Stefan outlined five different trajectories of response: moderate - seen in 77% of people grouped (3 different groups), poor response - seen in 8%, characteristically these people were slightly older (in their forties) with chronic illness and high BPRS scores, Fast responders - 15%, typified for being younger, men and with a more paranoid-type illness.

Stefan drew attention to three randomised controlled trials of switching for early non-responders as now there is an argument that, should non-response be clearly identified in a matter of a few weeks, switching maybe indicated. The data on these ongoing trials are not all available but clinical implications of this work are considerable.

Questions and answers ranged around issues as regard whether a dysphonic response predicted outcome. Stefan felt that this was a distinct possibility. There are issues as regards as what does happen to poor responders over time and Stefan thought that these groups may well continue to improve slowly - but this is not clear as mostly data are from naturalistic studies. Another question suggested and was asked whether length of illness really predicted the course and outcome - Stefan suggested that the first episode sample of trajectories are few and it is too early to be sure but more studies in this area needed. A question suggested that the anxiolytic affect of antipsychotics maybe what is being seen early on, but Stefan noted that a pivotal study by Kapur looked specifically at the antipsychotic affect and it does seem to explain the whole affect of what is going on.

Christop Corell: This presentation focussed largely around the same question - was there people who responded early - but using data from studies of adolescents. Convincing 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, data were somewhat thin but Corell thought the 3 week cut off was somewhat better than the 2. In addition, data were presented on the value of CGI in clinical practice. Although the fine-grain measures of PANSS may be of value in research, this measure is not be widely used in clinical practice and therefore the crude arrestment of CGI would be of more value. This hypothesis was supported by the evidence presented. Although the CGI might not be quite so informative a measure, it nevertheless, may be one with more clinical utility. There was not a clear indication that 'non-response' was predicted by the adverse affects of weight gain and akathisia - but early EPS maybe indicative of later bad response.

Questions and answers: Again questions were wide ranging but a key issue was that these 'collective data' were averages - population means - and not at all indicative of individual prediction per person. Corell left us with a warning that the average results may be of great use and interest but how this is of value to the individual in the clinic is not entirely yet clear.

Bruce Kinnon: Data were presented from large risperidone case series as regards prediction of robust response. Again data indicates that response by 2 weeks seem to predict a response at 12. This holds true for 30% of the sample. This important sub-group 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 high baseline PANSS seem to be good at suggesting the likelihood of being a poor responder. What was noticeable about this presentation was that there was an "explosion of response" in a "broad spectrum of domains" and measures of self-rating of mood of improvement and quality of life also seemed to reflect the early gain in mental state measures. 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 of PANSS (445), and then, even if those items are not fulfilled. - a further group can be defined as a 2 point drop on excitement items of PANSS (interim group, 120). - Finally should the gains in either the psychotic items or excitement items not be seen the remainder are defined as non improvers (929).

Questions and answers: One question asked as regards whether patients could then be trusted to actively tell their physician when they were not better - and therefore predict their own response rather than needing a rating scale - Dr Kinnon seemed to concur with the idea that we can indeed believe what people are saying about their own mental states.

Further question asked if the early responses hold true across different drugs. Dr Kinnon suggested that this was a good question and important but there were too few data on whether it should be true. Again Dr Kinnon was asked as to whether the MADRAS suggested that the early cycles in mood rather than anything else and he did suggest that this indicated the importance of depression in early response, but nevertheless still underlined the broad cascade effect across several domains and measures.

Shitij Kapur: Kapur discussed issues around the mechanisms of delay and tried to relate and further support the ideas that dopamine and that early response can be confidently expected. He presented some data from past studies and even striatal d^2 occupancy - even within a few hours of administration of medication - may well be

able to predict early improvement and PANSS scores a few weeks later. Kapur went on to discuss the issue of the collective response versus the individual. Interesting data where the average data are presented was disaggregated back to each individual person's trajectory - and categorised into improvement or lack of improvement. It is clear that the average scorings are not a good reflection of what actually is going on. With rather elegant analysis [it wasn't entirely explained], a "parsimonious trajectory fit" was undertaken on individual patient data. Again, as with other studies, the 15% of people who had a dramatic response to medication [and this, from the placebo controlled data], seemed quite independent of any placebo effect. Rather humbling was that any other level of response, even good or moderate response, seemed highly contaminated by placebo response and when these data were illustrated with what affect is absolutely discernable from placebo in these moderately responding or non-responding sub-groups, there seemed to be no clear affect of the antipsychotics whatsoever. The difference driving the overall effect of drug and non drug was the effect in the 15% dramatic responders.

Questions and answers: Kapur was asked as to whether shorter trials could be possible and it was suggested that they would be. It was asked if clozapine data were available and Kapur said that there are few clozapine data but there is an indication that there may be a slightly longer lag time to an effect - but again this is not entirely clear as to whether this is the result of titration of the clozapine dose. Kapur was asked as to whether there was any data as regards non-commercial trials. He answered that, currently, such trials were not big enough or not available. There was also questions as to whether patients had already had a selection process into going into trials, had been self-selected or been selected by the situation of the trial to produce this pattern - there was no real answer to that. Another elegant comment suggested that if in search of new d^2 blockers, we had 50 people and 5 don't respond to a possible i d^2 blocker n a matter of a couple of weeks, we therefore would not have the sought-after d^2 blocker. Although Kapur suggested that probably no one is quite looking for pure d^2 blocker anymore, this was a point well met and well made.

Summing up - John Kane: John Kane made a short comment just reminding us that nothing is new under the sun. I presume he was quoting David Sackett reminding the audience that 50% of what they are taught is incorrect and it's just hard to tell which 50%. [The more accurate quote from Sackett suggests that this is the situation after only 5 years after qualification]. Kane ended the afternoon on an upbeat note saying that this brings back into focus issues about high blood levels of drug can be helpful identifying people who are at least receiving and physiologically utilising antipsychotics and that shorter trials may indeed be possible. He said that it also raises issues as to why first episode studies are not quite so convincing - this may well be a more indigenous group or a better response could be expected anyway in this group.

There were several further comments and questions as regards remembering our history and how Jaansen in the 1950's had suggested that haloperidol may well have a response in a matter of hours. Two points very well made were that, where it comes to people who are non-responders, there are many other issues at the same time (family/social) and their non-response may well be a function of those other issues rather than anything purely to do with how their neurotransmitters are treated. This point was underlined several times by questioners. One questioner made the point that how, even in the rarefied population that enters a trial, although confounding variables are randomised evenly across groups, multiple analysis 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 by routine data collection.

7. Novel Interventions
Reported by Kristen Woodberry

Data for 4 novel non-pharmacological interventions and longitudinal data related to diagnostic issues and treatment response in schizophrenia (SCZ) and related disorders. 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 (OCS) in first episode SCZ (FES), predictors of recovery and treatment response in FES-spectrum disorders, and five year follow-up of individuals at ultra high risk (UHR, "prodromal") for psychosis.

Presenters offered new strategies for long-standing challenges in the treatment of SCZ. 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 supports to cue and sequence target behaviors in the home. In an effectiveness trial of CAT with a community mental health clinic sample, average medication adherence was just shy of 95% across 9 months. Discussion focused on the difficulty teasing out non-adherence vs. 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" (Weickert, April 13, 2010). Importantly, feedback learning demonstrated a moderately strong correlation to overall quality of life. Kathryn McCabe presented 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 connectivities. 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, Lieuwe de Haan suggested that roughly half of these patients experience OCS and that OCS are significantly related to psychotic relapse, depressive symptoms, and worse social outcome. He did not support the suggestion that OCS reflected coping strategies. Also reporting on a five-year follow-up and similar sample, Nikolai Albert presented data identifying predictors of recovery (Bertelsen, 2009). These included social capabilities, GAF, negative symptom dimensions, being male, not having a partner, increased age, and having children. Interestingly, duration of untreated psychosis and a diagnosis of SCZ, although strong predictors of poor outcome, were not predictors of recovery. Benedicto Crespo-Facorro reported on antipsychotic trial data in FEP (non-affective). In contrast to recommendations for antipsychotic trials of 4-8 weeks, the analyses reported suggested that the degree of symptom reduction at week 3 provided the best distinction between responders and non-responders at week 6.

In closing, 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 putatively 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%.

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 as well as 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 by four speakers who have been applying IPS to people with first episode psychosis.

The first speaker, Dr. Keith Nuechterlein (Los Angeles, CA), began his presentation by mentioning that the application of IPS to people with first episode psychosis is a pioneering area and that this session is, ironically, almost equivalent to the world literature until now. After briefly explaining the nature and principles of IPS, Dr. Nuechterlein mentioned several potential advantages of application of IPS to first episode psychosis, 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. Then he went on to introduce their study at 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) vs. equally intense brokered vocational treatment approach plus social skills training (n = 23). To fit the age range of recent-onset schizophrenia patients, 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 on 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, first 6 months involved 2.5 hours weekly WFM plus weekly meetings with IPS specialists. Next 12 months involved less frequent WFM groups and continued meetings with IPS specialist, 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 many individuals with first

episode psychosis were in the midst of their education, return to education is as common a 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, etc., 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% vs. 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% vs. 59%, $\chi^2 = 8.16$, $p = 0.004$) and for "duration of time in competitive work or school" (42 vs. 26 weeks, $F = 8.43$, $p = 0.005$). In addition, the intensive IPS-WFM treatment program to urge return to competitive work or school, as compared to the comparison treatment, did not lead to any increases in dropouts from treatment (treatment dropouts over 18 months: 26% vs. 39%).

The next speaker, 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. Due to a disparity in funding, the VIBE service was available only in one borough. 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. Of the 114 potential participants, 44 (39%) had access to VIBE, and 40 of the 44 (91%) received the intervention. 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 (but insufficient numbers as yet to reach statistical significance). 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.

The third presentation was given by Dr. Eóin Killackey from Melbourne, who was the chair of this session. As the introductory part of his speech, Dr. Killackey described the current situations and recent changes of employment/unemployment and welfare status in Australia. In general, the employment outcomes of those with psychotic illnesses are among the worst of socially excluded groups, i.e., unemployment rates for first episode psychosis and schizophrenia are 40% and 74%, respectively. It is also reported that, in Australia in 2001, persons with psychological and psychiatric disabilities constituted the largest proportion of jobseekers participating in public funded disability employment services, but achieved 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 then 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 like 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. By referring to the study by Ho et al. (1997), Dr. Killackey next explained that those with first episode psychosis are highly likely to become dependent on welfare benefits. The level of education is also poor in these populations, as indexed by the markedly lower rate of those with first episode psychosis who achieved 12 years education in the study of Killackey et al. (2008) (31%) as compared to the average rate in healthy populations (approximately 80%). Moreover, the extra costs due to non-working people with schizophrenia are enormous. To address all these problematic situations, supported employment, or IPS, has been developed. Dr. Killackey showed a figure where competitive employment rates were compared between the supported employment (mostly IPS) group and control group in 16 randomized controlled trials. From this figure it was obvious that supported employment was much more beneficial in achieving competitive employment. Then he went on to the presentation on their original study, which has recently been published (Killackey et al., 2008). In this study, 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 collocated with the clinical team while the TAU group could access all normal clinical services and external vocational agencies, and assessments were made at baseline and six months. The result for the global outcome showed that significantly more of those in the IPS group became employed or enrolled in courses than those in TAU (17/20 vs. 6/21, p = 0.000). When the outcome was confined to the work only, there still remained a significant difference (13/20 vs. 2/21, p = 0.000). The IPS group obtained significantly larger number of jobs than the TAU (23 vs. 4, p = 0.006). Participants in the IPS group had a significantly higher median income (AU$:2432 vs. AU$:0, p = 0.012). In addition, the IPS group demonstrated reduced use of welfare benefits (80% to 56%), in contrast to no change in the control group (57% to 57%). As a concluding remark, Dr. Killackey stated that to "mind the gap" between healthy people and those with mentally ill would be important in the vocational recovery.

The final speaker, Dr. Miles Rinaldi (London, UK), started his presentation by stating that employment/education rates in individuals with first episode psychosis were quite poor in their country. Studies have shown that onset of schizophrenia is associated with a pronounced deterioration in employment outcomes. Then, Dr. Rinaldi introduced their study (Rinaldi et al., in press) in South west London, which 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 in this study. Only 13% of the participants were in open employment at the outset, but this figure rose to 48% at 24 months. There was no remarkable change in the proportion of those who were in mainstream education/training throughout the 24 months 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. In general, a transition from education to employment was observed. This intervention with IPS achieved high fidelity, an index of the degree of implementation of an evidence-based practice. After describing his study, Dr. Rinaldi mentioned some myths surrounding employment of the mentally ill (e.g., "people with severe mental health conditions cannot work" or "our job is to protect the public and individual") 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 by Dr. Rinaldi, Dr. Killackey and their colleagues (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 International Consensus Statement (http://www.iris-initiative.org.uk/), which was launched in London at an event organised by World Health Organisation. 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, organisations and governments can assist the attainment of these ends.

The discussant of this session, Dr. Kim T. Mueser (Hanover, NH), provided a clear and well-balanced account of the above 4 presentations. Dr. Mueser 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. He then commented upon each of the four presentations in the order of presentation. As for the Dr. Nuechterlein's presentation, Dr. Mueser described that the finding from this study was a very strong signal demonstrating the beneficial effect of the unique combination of IPS with the 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. Based on the result that 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, Dr. Mueser pointed out that there may be natural inclination to go back to school in young people. For Dr. Killackey's presentation, a very strong controlled trial demonstrated the feasibility of implementing IPS in already established program for individuals with first episode psychosis in a relatively disadvantaged population. Dr. Rinaldi's presentation again demonstrated feasibility of 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, in particular IPS, in first episode psychosis was demonstrated in all four of the presentations. Throughout the discussion, Dr. Mueser stressed that the education component of supported employment is central to, and thus should be a prominent focus on, the vocational rehabilitation of people with first episode psychosis.

There was a comment from an audience member that this was a great session as it focused on an area that was both important and under-explored. There was also a comment about the length of time which people keep their jobs. This is an important point as most IPS research in both first episode psychosis and chronic illness has

concentrated only on getting people into work, and has not focused on how long they keep their job for. In the future studies will have to examine this outcome. In addition, there was a lot of debate about the modifications necessary to IPS to include supported education. Dr. Major's study, for example, showed that more in the intervention arm achieved competitive employment, but not necessarily any more got into education. Furthermore, there was panel discussion about what is supported education, can you adapt supported employment in this way, or should a different model be developed to help these young people back into education.

V. NEUROIMAGING

1. Brain abnormalities in emerging psychosis
Reported by Christopher Chaddock

This session aims were to present research to show that during the prodromal and early phases of psychosis, observable changes of neurobiology and neurofunction exist, that are present prior to the onset of psychosis, that are predictive of subsequent transition to psychosis, and that show dynamic changes over this early period of illness.

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 thalamaus (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, especially 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 the diagnostic properties of these reductions in GM density showing positive predictive values of around 60% - 70% (Job et al., 2006). However, cortical gyrification patterns that are though 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 that 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. G*roupXTime* 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, with GM volume change seen to correlate 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 whilst the HR-NP 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, and therefore is not seen in those with fleeting psychotic symptoms. The cause of this highly specific white matter change is now under investigation, and could relate to genetic susceptibility genes (McIntosh et al., 2008).

The second speaker was **Dr Stephan Wood**, who reported on findings from the Melbourne Ultra High Risk (UHR) cohort. Unlike the Edinburgh study, these high risk subjects 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 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 during the cross-sectional baseline comparison, compared with UHR subjects who did not develop psychosis (UHR-NP), those who did develop the disorder (UHR-P) 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 how the cortical surface changes over time, with significantly greater brain contraction observed in the UHR-P group in comparison to the UHR-NP group, with this contraction marked in the right prefrontal region (Sun et al., 2009). 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 within the UHR-P group (Walterfang et al., 2008).

Dr Wood concluded his talk, by discussing what the cause of these structural change may be, as to 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) via a biological discontinuity, i.e. stress or cortisol changes. Dr Wood also discussed the importance in considering outcomes that also includes other psychiatric disorders including mood disorders, moving away from the focus upon positive symptomatology, as transition to psychosis is not necessarily predictive of outcome.

The third speaker was **Dr Stephan Borgwardt**, who presented research from Basel early detection of psychosis study (FEPSY). Dr Borgwardt's research assesses structural changes associated with transition to psychosis from an UHR sample. The first study was a cross-sectional design, and identified reduced GM volume in UHR subjects compared to a control group within the posterior cingulate gyrus and precuneus, and at trend level in the left insula, bilateral superior temporal gyrus, the left amygdala-hippocampal complex 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. Whilst 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). Extending the analysis from GM volume, cortical thickness measurements were made within 41 anatomic regions, with cortical

thickness asymmetry able to distinguish a first episode psychosis sample from the control group (P = .0006; sensitivity, 70.0%; specificity, 85.0%) with a trend observed in distinguishing the UHR group from control subjects (P = .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 neuro-chemical, neurof-unctional and neuro-structural studies. Twenty-five studies met the inclusion criteria for this systematic review. 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 in functional imaging studies reduced brain activation in prefrontal cortex, reduced neuronal density, and increased membrane turnover in frontal and cingulate cortex with medium to large effect sizes (Smieskova et al.).

The final speaker was **Dr Nicolas Koutsouleris** from Munich, who discussed his work, which has again focused on the UHR sample, with subjects recruited from the Early Detection and Intervention Centre for Mental Crises at the Ludwig Maximilians University. The first study presented showed that UHR subjects could be differentiated from healthy controls at baseline, with GM reductions found within prefrontal regions, including 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). The second study 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). The third analysis addressed whether an individualized neurodiagnosis of psychosis is possible, using multivariate pattern classification. The previous analyses had considered each voxel independently (mass-univariate model), 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 and colleagues (2009) 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. These findings indicate the possible utility of imaging research to base clinical judgments upon. Dr Koutsouleris also discussed the possibility of using the original baseline classification results to predict brain deformation change over time, as there appears to be an acceleration in GM changes over time in the UHR group in comparison to a control group. In addition the discussion following the presentation allowed for the consideration that white matter changes may also accompany and/or cause the grey matter changes.

In summary, these imaging studies reveal that cross-sectional and longitudinal abnormalities exist in at-risk individuals and first-episode patients. These findings have offered important insights into the brain pathology emerging during the transition from the prodromal state to the full-blown clinical picture of schizophrenia. Thus, the accumulating brain alterations described by recent neuroimaging studies may be interpreted within the concept of a late neurodevelopmental process that evolves when higher-order cortical areas are placed "under functional demand" during the critical transition from adolescence to adulthood. Beside these advances in the basic science of psychosis, 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. Further work is required to map the longitudinal time course of changes over a larger window, allowing for multiple data-points prior to and after the transition to a psychotic state.

2.Integration of structural, functional, and neurochemical brain changes prior to the onset of psychosis
Reported by Renate Thienel

Jon Roiser, from the Institute of cognitive neurology in London 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. This can be demonstrated when rewards are presented at fixed times but the animal stands in the cage and thinks its behaviour shown at the time of the reward given is conditional for the reception of the reward. This effect is called 'superstitious condition effect'. Amphetamine increases non–reward related responses. The aberrant salience hypothesis (see review by Kapur, 2003) constitutes a context-independent DA release with increased attribution of salience to neutral objects and internal representations. Cumulative aberrant salience experiences can lead to delusions. Murray, et al. (2008) demonstrated that aberrant salience is evident in psychosis. Sz 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) utilises 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 colour and shape dimension). While the colour information codes for high vs. 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 (colour stimulus) was associated with activations in VTA, thalamus, medial dorsal thalamus, emotional limbic loop (DA mediated). 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.

Here Roiser reported on non-medicated at risk mental state (ARMS) subjects, who 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 was evident in at risk subjects only. There was no difference in adaptive reward prediction. There was a correlation between aberrant reward prediction (within the limb, assoc., and motor striatum). L-DOPA was higher in the associative striatum with aberrant

reward prediction. And finally there was a strong positive relationship between striatum activation in healthy but negative in ARMS subjects.

1. Chris Pantelis: Do you have data on converters versus non-converters. Answer: The sample was too small for this differentiation as we only had 2 converters.

James Stone, from the Imperial College London reported that most risk genes for schizophrenia impact on glutamatergic NMDA receptors, which can be blocked by ketamine. As reviewed by Olney & 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 gabaergig interneurons.

Law and Deakin (2001) could demonstrate 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 were found in the anterior cingulate (AC). This might be associated with reduced grey matter in subjects that made a transition and may be due to excitotoxic action of glutamate. Generally using MRS one has to predefine a region and assess metabolites, here glutamate/glutamine.

N=27 (6 ARMS subjects received antipsychotic medication), plus age and sex matched controls. 3T scanner, MRS in AC, left thalamus, left medial temporal cortex plus grey matter voxel based morphometry. Grey matter reduction in medial prefrontal cortex and the AC. Glu reduction in thalamus, Gln in AC increased. NAA reduced in thalamus. Correlation of lower levels Glu in thalamus with smaller volumes in some brain areas.

The reduction of Glu in the thalamus could be due to disinhibition after access Glu release had an excitotoxic effect. When evaluating Glu data over time and how it is related to transition the 3 subjects that underwent transition (3 of 18) demonstrated same thalamic Glu baseline levels as subjects that did not transition. Whereas at follow up transitioned subjects had lower thalamic Glu levels. The Glu levels correlated with global assessment of functioning (GAF) scores as well as with the general subscale score of the Positive and Negative Syndrome Scale (PANSS). Questions: 1. Were there no differences in clinical measures at baseline between transition and non-transition subjects? The thalamic and AC results could be related to clinical measures? Yes, correct. There were no differences at baseline.

Thomas Whitford reported on infectious agents, like viruses and parasites as a risk factor in developing psychosis. The family history of patients with psychosis often discloses environmental factors, like obstetric complications, or infectious agents. Patients show abnormal 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. The parasite toxoplasmosis, and the herpes viruses, and others were tested by determining seropositivity in subjects exposed to the agents in the past. Toxoplasma is a parasite. Toxoplasma-infected rodents stay closer to cats because they loose fear and are even attracted. Toxoplasma makes rodents liking cats so that it gets back into cat's stomach, the only way to survive. The mechanism through which toxoplasma works is through changes in brain chemistry as those rats show increased dopamine (DA) levels in the amygdala. Hence rats loose their fear of cats through changes in DA levels in the amygdala. This fear can be reintroduced by administration of antipsychotics.

T1-weighted MRI's, using the VBM method with ROI's 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 resent infection with toxoplasma determined by toxo-seropositivity. With an elevated toxoplasma rate in sz patients, could toxoplasma increase DA levels and trigger psychosis? Limitations: The subjects in this study were IGM positive but IGG negative. Therefore they might be false positives and might have been infected by another infectious agent.

Questions: **1.** Shitij Kapur: Why have so many people in your sample seropositivity for toxoplasmosis? What is the standard Australian number for this demographic? Answer: They range up to 80 percent in the standard population so this is a reasonable number. **2.** Is the DA increase in amygdala in rats replicated in the limbic lobe? Answer: We did not find changes, but evidence that the toxoplasma infection in humans changed human fear behaviour, as there was an increased risk taking behaviour demonstrated in toxoplasma affected people.

Paolo Fusar-Poli from the Fabio University in Italy evaluated whether neuro-cognitive prefrontal cortex (PFC) deficits are a trait of the prodromal state (for review see Fusar-Poli et al., 2007). Striatal dopamine (DA) function is aberrant in schizophrenia. In order to examine the relation between striatal and PFC DA-level F-DOPA PET plus fMRI scans were carried out in the currently presented study. 16 healthy subjects were compared to at risk mental state subjects (aged 14-30 years). The study hypothesised that ARMS subjects show a higher striatal DA correlated with altered activation in PFC. The task used was a verbal fluency task administered in a 1.5T scanner. Furthermore synthesis was assessed using F-DOPA-PET. The verbal fluency task lead to a greater left inferior frontal gyrus activation in ARMS subject when compared to controls representing an increased, exaggerated recruitment in at risk subjects. 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 striatum in particular was revealed. Furthermore striatal DA was correlated with the CAARMS-scale again. A negative correlation was revealed between neurocognitive perfomance (verbal fluency) and subcortical DA. The fMRI and PET results – hence BOLD and striatal DA levels- correlated positively in the left frontal cortex within the at risk group only.

Questions: **1.** Did the correlation with the CAARMS symptoms occur between the change in symptoms and the change in neuroimaging variables? Answer: Yes, I was talking about the longitudinal correlations between the change in prefrontal activation and change in symptoms. **2.** Was there any association with other CAARMS symptoms? No. **3.** Any other correlations? How do you interpret that? Answer: Maybe the sample size was too small.

Shitij Kapur: David Hull's book 'science as a process' (Hull, 1988) describes science as it develops through 3 stages. 1. Catalogue findings, 2. When data starts to cohere we correlate, and finally 3. Integrating and synthesizing with the need to 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 2 thoughts/questions. He said that there is body of findings, that have to do with DA and Glu, but one could well ask the question as we used to be looking at schizophrenia, is UHR a little schizophrenia? Just quantitatively smaller or is there anything qualitatively different? Not only quantitatively? That would be useful, because if it were just a little schizophrenia we would not have different therapeutic targets. And he asked the question whether we could predict conversion, etc., hence whether the data is

generating insides for prediction or new strategies of intervention, referring to new intervention strategies not just antipsychotics, which is not prevention, but maybe only suppression.

Is UHR a mini schizophrenia or something qualitatively different? 2. Is it telling us something different that we could not learn from schizophrenia research?
McGuire's answer: " UHR is no mini schizophrenia, because Glu specs are larger in the prodrome than in sz. Hence a Glu treatment might be more useful in high risk than in frank schizophrenia".

Pantelis' answer: "Interventions at early stages should they be different? What intervention should we use? Measures that might be abdicative of HPH- axis activity like pituitary body changes, cortisol changes. And this is not apparent in chronic schizophrenia. So this differs between the prodrome and schizophrenia".

Comment on discussion whether the prodromal / UHR- state is qualitatively different? Must it be one or the other? Couldn't it be qualitatively plus quantitatively different? Answer from Shitij Kapur: If you compare this with hypotension, with it's arbitrary threshold, before reaching that threshold it's a mini hypotension. But stroke for instance, everything before stroke is a different state not a mini stroke. Pantelis: Trajectories allow you to address that, sudden versus gradual changes allow you to go from the 'hypotension'- to the 'stroke'- model.

Comment/critic from the audience: Reliance on p-values is critical, not enough studies report on effect sizes, and mention the power. Maybe a lot of the study results are underpowered? Shitij's answer: .05 threshold is generating huge amount of results but on grounds nothing changes. Many results are not replicable. Goodman (1999) wrote about this, pointing out that for replicability we need p-values of .00013. But Shitij Kapur pointed out that on the other hand if we are too stringent, we might loose findings. Therefore he agreed with the commenter in the audience that Journals should ask for power.

Questions from the audience: 1. Question: Do we find similar results of decreasing Glu in subjects under ketamine challenge? Answer: 1 study using ketamine, showed no thalamus voxel changes but an increase in AC glutamine. 2. Question: Re follow up results in transitioners: Why do they show further decrease, is that a dichotomous response, or is it a continuous change? Answer: The numbers are too small, to answer this but a further reduction indicates a worsening of condition.

Comment from the audience: Very early symptoms are very unspecific. Brain equivalent of a very unspecific symptom would then also be such a very unspecific one. Hence a non specific treatment may work.

3. Making Connections: Abnormal White Matter Development in the Early Stages of Schizophrenia
Reported by Gabriela Novak

Dr. Anthony James (Oxford) discussed abnormalities in white matter tracks between early onset schizophrenia and early onset bipolar disorder. Bipolar disorder and schizophrenia share pathophysiological mechanisms (reviewed by (Craddock and Owen 2010). Tracking the ongoing myelination processes 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, which suggest a neurodevelopmental cause (Gogtay and Thompson 2010).

Dr. Anthony James used MRI and DTI to study white matter (WM) and grey matter (GM) in 43 subjects with early onset schizophrenia, 15 with early onset bipolar disorder and 36 controls, comparing observation of pathology in SZ and in BP disorder. In both, SZ and BP disorder, significant changes were found. However, in SZ, changes in WM were found primarily in cortical, subcortical and cerebellar tracts, with reduced GM density in the frontal and temporal lobes, while in bipolar disorder WM changes were observed in the corpus callosum and GM changes in the visual processing areas, and the cerebellum. These patterns suggest that the neural abnormalities in schizophrenia and bipolar disorder differ, with only corpus callosum being affect in common, at least in the early course of the disease during adolescence. In addition, GM loss was much less significant in BP disorder.

This is in agreement with observed changes in multiple premorbid IQ domains, including verbal fluency, which has show that while there was premorbid decrease in IQ in schizophrenia, no evidence for such decrease was found in BP disorder. However, working memory processing has been significantly affected in both disease states (Zanelli et al., 2010)(Barrett et al. 2009).

An essential aspect of the analysis used in this study is the quality of preregistration (alignment with mesh of control points). In order to obtain clear visualization of the tracts, the Tract-Based Spatial Statistics (TBSS) protocol was used (Smith et al. 2006). This protocol allows for alignment of images from multiple subjects using a projection onto an "mean fractional anisotropy (FA) skeleton". The disadvantage of this protocol is the possibility of not detecting some changes; this, however, can be corrected by using tractography. Even though this study had a limited sample size, its strength is the robustness of the method used.

Dr. Katherine Karlsgodt (UCLA) discussed normal white matter development and white matter development in adolescents with high risk for psychosis.

Current research using DTI shows a decrease in fractional anisotropy in white matter of first-episode schizophrenia patients, suggesting a disruption of white matter integrity, possibly predating the onset of the disease (Hao at 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 due to final stages of myelination.

In 2008, in order to examine whether anatomical changes are present at onset of schizophrenia, Dr. Karlsgodt applied a rigorous registration approach of Tract-Based Spatial Statistics (TBSS) to DTI to examine FA, an indicator of white matter integrity of the superior longitudinal fasciculus (SLF). The analysis was performed in 12 young adult patients with recent-onset schizophrenia and 17 matched controls (Karlsgodt et al. 2008). The study showed that SLF integrity was disrupted in first episode, therefore early on in the disease and that SLF relates to WM performance.

In a next step, in order to asses whether white matter abnormalities actually preexist the onset of the disease, Dr. Karlsgodt analyzed the change 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. The study was performed in 36 UHRS participants and 25 controls. In accordance with continued myelination, controls showed an increase in FA (indicating an increase in white matter) with age, while 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 moths later. In particular verbal

working memory performance was affected, which is a cognitive deficit commonly 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. Furthermore, the WM developmental trajectory is predictive of later social and role functioning. Dr. Karlsgodt suggested that these changes may arise through a disrupted developmental process, suggestive of genetic influence on white matter microstructure.

Marek Kubicki (Harvard Medical School) discussed his recent findings using DTI scans of first episode schizophrenia patients, chronic subjects and controls who were part of the Center for Intervention Development and Applied Research (CIDAR) consortium. The goal was to understand whether WM 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 patients after first episode of schizophrenia 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 study, which showed changes in WM in uncinate fasciculus (UF) and cingulum bundle (CB) (Ellison-Wright 2008).

Using track-based spatial statistics, FA abnormalities were observed in both first episode and chronic schizophrenia patients, but trace (measure of mean diffusivity) increased only in first episode individuals. In conclusion, both measures (axial and radial diffusivity) reflect changes in Trace, rather than specific axonal and myelin related abnormalities. FA and Trace might indicate two separate, independent processes.

While progressive changes at first episode have been reported before, Trace increase in FA and its normalization in chronics was interesting, since it's rarely analyzed. This finding was reported before, but only in a very small population (Garver et al., 2005). Most interesting is the correlation between increased Trace in first episode schizophrenia patients and its correlation with increased levels of anti-inflammatory cytokines (IL-6). Especially, since both Trace and cytokines normalized after a treatment (within two weeks).

The cytokines IL-2 and IL-6 are frequently abnormal in schizophrenia (review in Potvin et al., 2009) and are usually associated with autoimmune response. Interestingly, cytokines can also increase dopamine release, as well as 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 Trace increase in fist episode schizophrenia patients is a sign of an auto-immunological response.

Gary Price (Institute of Neurology, London) performed a study of white matter tracts in first episode schizophrenia. Dr. Price used probabilistic tractography algorithm (PICo) (Price et al. 2008), which provides an index of connectivity of WM in order to study 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 an increase in FA in controls. However, there was no overall change in UF. A change in UF was only present in a specific area of the left UF and the effect was gender specific.

In summary, abnormalities in WM observed using DTI suggest abnormality in structural connectivity in the core of the WM tract, but with strong gender effects. FA was reduced in patients compared to controls in tracts crossing the genu, and to a lesser degree in the splenium.

A member of the audience pointed out that in neonates FA measures indicate WM, yet we know that no myelin is present. Therefore, how can we be certain that the FA changes reflect changes in WM structure.

Answer by the panel: They agreed that the FA changes we see can be from a number of sources, both trajectory or inflammation related. Therefore, the cellular changes we are observing may be related to other myelin effects and need to be investigated further. Therefore, the FA measures still need to be correlated with myelin structure.

For a recent review of this topic see (Frangou 2010).

4. Brain Progression in Schizophrenia: who, where, when, how? Reported by Christopher Chaddock

The session aims were to report on brain structural changes that occur during the lifespan of a psychosis patient, whether they are apparent before onset, and whether they show continued progression after the onset of a first episode and on to a chronic phase of illness.

The first presentation was by **Prof. 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 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 grey matter (GM) in fronto-temporal, limbic and subcortical regions (Fornito et al., 2009), 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 GM 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 GM development were observed between baseline and follow-up scans in the UHR sample, with the UHR-P group showed a greater reduction in GM 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 contraction in the UHR-P group in the right prefrontal region (Sun et al., 2009a), whilst in the FES sample, a similar finding of greater brain contraction was observed in the dorsal surfaces of the frontal lobe. Overall, brain surface contraction in patients and healthy controls show similar anatomical 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, those FES displaying left hippocampal volume reduction and UHR patients showing normal baseline hippocampal and amygdala volumes (Velakoulis et al., 2006). Measuring Insula volumes at baseline,

the FES and chronic patients had significantly smaller anterior insular cortex than the controls. In longitudinal comparison, the FES patients showed significant GM reduction of the insular cortex over time which correlated with symptom severity, whilst there was no difference between chronic schizophrenia patients and controls. (Takahashi et al., 2009a). Similar findings have also been observed in those subjects at UHR, with UHR-P subjects showing greater GM reduction of insular cortex bilaterally compared with controls and UHR-NP subjects, indicating that insular cortex GM abnormalities in psychotic disorders may reflect pre-existing vulnerability (Takahashi et al., 2009b).

Prof Pantelis concluded by placing these findings in a normal developmental context of maturational changes that occurs during adolescence in to adulthood (e.g. (Knickmeyer et al.)), 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.

The second presentation was by **Prof. Robert McCarley**, from Harvard University. In his introduction, Prof McCarley commented on the role of whether a neurodevelopmental hypothesis of schizophrenia had to be mutually exclusive to the observation of a progressive brain changes, as a neurodevelopmental cause (such as GABA neuron excitotoxicity) could lead to later brain changes. The study presented was undertaken at Mclean Hospital where a sample of FES subjects were scanned at baseline and also at a second time-point 1.5 years later. Medication was started in the first episode sample approximately 2-3 weeks prior to admission; minimising prior exposure at the baseline scan. 21 FES subjects and 23 healthy controls completed the baseline and follow-up scans. To accurately normalize scans to allow for a voxel-based comparison of GM volume differences, the DARTEL procedure as developed as part of the SPM software (Ashburner, 2007) was used derive normalization parameters that maintain accurate registrations both within and between subjects.

As predicted, greater GM volume loss was observed between the two scans in the FES 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 (thinking disturbance, unusual thought content and severity of hallucinations) were seen to be negatively correlated to the change in grey matter volume in Heschl's gyrus bilaterally, indicating that greater GM loss was associated with worsening or a less marked improvement in symptom levels. There was also a correlation observed between negative symptom severity and GM loss within bilateral prefrontal regions, the insula, and left supramarginal gyrus, whilst correlations to measures of cognitive functioning were much more widely distributed. Greater GM volume loss was seen in those non-compliant with medication compared to those compliant with antipsychotic medication. Therefore an accelerated GM loss is seen in the 1.5 years after onset of the illness, which relates to cognitive and clinical symptoms. What is unknown is whether the rate of volume loss may proceed at a constant rate, or whether it occurrs in a step wise manner with GM loss at each illness episode.

The third presentation was Dr Kiyoto Kasai from the University of Tokyo. Dr Kasai began by stating that in some brain regions there is a known decline in GM volume within schizophrenia patients (e.g.(Kasai et al., 2003a; Kasai et al., 2003b)), but these GM changes may be greatest during the transition from the UHR state to a first episode of psychosis. Dr Kasai's research involves scanning an UHR sample at baseline and then one year later at follow up and he presented some unpublished data from this sample. The first reported 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 the healthy controls. The second reported 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 2-3cm beneath the skull (i.e. cortical). A finding of reduced fronto-polar activation in schizophrenia patients was observed, which was related to the degree of social functioning (Takizawa et al., 2008), with modulation also observed via genetic variation (Takizawa et al., 2009). The benefit of NIRS in that it would be an excellent biomarker as it is cheap and the machines portable, however much more work is needed in order to characterize changes over time.

The final presentation was by Prof Rene Kahn, from the University of Utrecht, Netherlands. Prof Kahn introduced his talk by discussing the dynamic brain changes that occur during our life, with these changes appear to be non-linear and differ in respect to location within the brain (Brans et al.). Prof. Kahn 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 GM loss was also accompanied by a larger increase of third and lateral ventricular volumes. It appears that patients show a different trajectory of GM volume with a negative linear relationship noted between volume and age of subject, whilst controls showed a non-linear relationship, and GM volume was seen to be decreased in schizophrenia patients during this time period, with the greatest rate of loss shown in frontal, temporal and occipital lobes. Those patients with a poor outcome showed the largest increase in lateral ventricle volume and largest decrease in cerebral volume relative to the good outcome patients, whilst the degree of olanzapine medication used reduced the rate of GM loss (van Haren et al., 2008)

Assessing GM volume loss during the 5-year interval using a voxelwise test, excessive decreases in GM 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, whilst 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 GM, 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 presented here also indicated that cortical thickness was seen to decrease significantly in patients over a five year period in the superior temporal gyrus, inferior and middle prefrontal cortex, and 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 does appear to show exaggerated grey matter loss in schizophrenia in addition to the plastic changes noted in healthy controls throughout their life. Excessive cortical thinning appears clinically relevant, and medication via 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. The discussion highlighted the fact that approximately 1/3 of the schizophrenia sample showed a significant reduction in GM loss, possibly due to GABA/glutamate levels.

The final discussion by Prof Lynn DeLisi summarised that we now know that there are progressive changes in GM volume (and white matter changes) that are not solely caused by medication. There also appears to be a greater grey matter loss in poor outcome individuals, and GM loss is observed at the first episode, and may be heritable. However what we don't know is when the brain changes start deviating from normal maturation, as

changes can be observed in the prodrome to psychosis, but tehse may be apparent during infancy. In addition, are these structural changes able to explain the full spectrum of psychosis symptoms or are they secondary to other changes in neural functioning. We also don't know the causes of these GM changes, which may be due to abnormal maturation, atypical metabolism, substance abuse, medication or methodological issues.

5. Brain Maturation During Adolescence and the Pathophysiology of Schizophrenia: Relevance for Understanding Psychosis, Cognitive Dysfunctions and Implications for Treatment Reported by Kristen 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 dominant neurodevelopmental models, and elaborating specific developmental processes during adolescence with possible relevance to mechanisms of psychosis onset.

In reviewing evidence for progressive deterioration during the onset of psychosis (e.g., Borgwardt et al., 2008; Job et al., 2005; Pantelis et al., 2003; Takahashi , Wood, Yung, Phillips, et al., 2009, Takahashi, Wood, Yung, Soulsby, et al., 2009), 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., 2008) 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 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 evidence of inhibitory neuron disruption in schizophrenia, its sensitivity to stress, and its relevance to prefrontal cortex development and function. 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., 2009, 2010). Identifying an increased reliance on oscillation and synchrony during adolescence, he argued that the disruption of these processes could lead to difficulties with information uploading and maintenance, symptom onset, and spatial working memory deficits.

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 imagining data has been the normalization over time of gray matter abnormalties 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 included stress and cannabis use (e.g., Yücel et al., 2008).

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 onset. 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 40's and 50's. 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). Yet there is ongoing 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 consequence rather than cause of illness? Dr. Shannon Weickert suggested that interneuron pathology might be primary rather than secondary. Reductions in GAD-67 mRNA are among the most ubiquitous changes found and work by Bita Moghaddam suggests that NMDAR blockers, known to trigger psychosis in normals and to exacerbate symptoms in people with schizophrenia, may include loss of inhibition as part of their mechanism.

Additional comments noted that imaging findings remain mysterious and that early intervention remains exceedingly difficult, especially given that prodromal symptoms predict diverse outcomes. Pat McGorry argued that this very diffuseness of psychopathology supported a Youth Model of Care with less attention to specific diagnoses early on.

VI: GENETICS

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 Dr. Lynn DeLisi and Dr. Ming Tsuang panelists discussed about the recent findings in Genetic research and their implications. The session generated interest and active discussions. The talks covered the following topics: (a) Dr. Michael J Owen gave the key address on "Schizophrenia Genetics. What have we learned and where are we going?" b) Dr. Mary Claire King, Dr. Pablo Gejman and Dr. Peter Visscher discussed on "Where have the new GWAS gotten us?" c) "Is the endophenotype concept useful in defining genes for schizophrenia?" was discussed by Dr. Lynn DeLisi and Dr. Dan Rujescu. d) Dr. James Kennedy and Dr. Thomas Lehner were the panelists for "Will commercial DNA testing ever be a useful tool in the clinic for schizophrenia?"

Dr. Ming Tsuang gave the introductory remarks and introduced Dr. Michael J Owen of Cardiff University. Dr. Owen began his talk on "Schizophrenia Genetics - what have we learned and where are we going?" emphasizing the importance of studying risk genes in Schizophrenia. The epidemiological studies have established a definite genetic role in the pathogenesis of Schizophrenia. However, at present, we don't know the exact etiopathogenesis of this disorder. As genomic approaches do not require understanding of pathogenesis,

genetic studies have the potential to identify genes for common disease like schizophrenia. He later gave a brief account of history of Psychiatric molecular genetics and described different methods used in past, present and predicted what could be used in future studies. While the past studies were examining linkage, candidate gene association, chromosomal abnormalities, present studies are Genome Wide Association Studies (GWAS) and Genome wide Copy number Variations (CNV). He predicted whole exome sequencing and whole genome sequencing will be the technology in future studies.

Dr. Owen later 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 have high penetrance and identify relatively rare alleles but require large pedigrees for their identification. Candidate gene association studies identify genes which are atypical of common diseases having high penetrance but they are very common variations. There are multiple studies without conclusive results; these false positive results could be due to small sample sizes and multiple testing. Thus, at present, findings from candidate gene studies have been disappointing. Chromosomal abnormalities have identified some very important genes implicated in schizophrenia but are relatively rare and very few genes have been identified by this technique. He discussed the well known example of association of Velo-cardio-facial syndrome (VCFS) and schizophrenia, which led to the identification of genes like Catechol-O-Methyl Transferase on chromosome 22q11. Another important gene identified by this technique 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. He then summarized the findings of genetic studies till 2007; Schizophrenia is a highly heritable disorder with complex but uncertain genetic architecture but there are no definitive findings from linkage or candidate gene studies. Studies of chromosomal abnormalities revealed some genes like DISC1 and 22q11 deletion.

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 sub microscopic chromosomal abnormalities (using genome wide copy number variations) possible. The advent of commercially available "Gene chips" made GWAS possible which can detect common risk alleles with low penetrance. However, GWAS is not a strong test for individual genes and requires large samples. Then he discussed the findings from their studies in which Dr. Owen 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; genes like ZNF804A, CACNA1C are found in both schizophrenia and bipolar disorder suggesting common polygenic variation contributes to the risk of both schizophrenia and bipolar disorder (Ferreira et al., 2008; O'Donovan et al., 2008).

While the GWAS detect common alleles with low penetrance, CNV can detect rare alleles with high penetrance. He enumerated the findings of different CNV studies in schizophrenia importantly association of deletion of Neurexin (NRXN1) gene in schizophrenia. Neurexin gene is implicated in autism and MR also. Large deletions (>100kb) of this gene are associated with schizophrenia with high significance. In addition to 22q11, many loci have been found which contain multiple genes but with incomplete penetrance. Dr. Owen also illustrated the interesting differences between GWAS and CNV studies. While there is an overlap between schizophrenia and BPAD in GWAS, there is evidence for discontinuity between schizophrenia and bipolar disorder. Thus at present, while some findings challenge diagnostic categories, others support.

Continuing his talk he discussed about the ways in which these genetic findings can be translated to biologically meaningful outcomes. He opined that genetic findings can be useful 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 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 taking the example of PPARG locus in type 2 Diabetes mellitus. However, future research needs to use new techniques like computational biology, annotation gap and modeling complexity to bridge the gap between genetic findings and biological usefulness. Further in his talk, he discussed about endophenotypes and opined that endophenotypes may be more helpful in characterizing the effects of alleles associated with the disease rather than for gene discovery. He was of the opinion that endophenotype researchers assumed relative genetic simplicity and caution was required before assuming causality as many genetic effects are pleiotropic. Future studies need to look at the neural mechanisms of these genetic findings as seen in a recent study by Esslinger and colleagues (Esslinger et al., 2009). In this study authors examined the neural mechanism of genes implicated in psychosis namely ZNF804A, rs1344706. In risk allele carriers, there was increased functional coupling of right amygdale and reduced connectivity in right dorsolateral prefrontal cortex.

Dr. Owen discussed the findings of study by Craddock and colleagues (Craddock et al., 2010) on GABA-A receptor gene variation in schizophrenia and bipoalr affective disorder. When the diagnostic categories were retained and patients with schizophrenia and bipolar disorder were analyzed separately, there was no significant difference. However, a repeat analysis pooling both groups of patients revealed a significant difference between patients and controls. He summarized his talk and concluded with the prediction of potential uses of genetics in future: defining more homogeneous groups and identification of possible shared mechanisms across diagnostic categories.

Dr. Mary king initiated the panel discussion on “Where have the GWAS gotten us?” The polygenetic model for schizophrenia was proposed many years back but still we have not been successful. GWAS is successful in identifying genes for some disorders like breast cancer and Age related macular degeneration where there is presence of a rare variant of a haplotype or a functional common variant. However, there are many limitations and difficulties and thus before interpreting the GWAS data in schizophrenia, one need to remember some facts about GWAS. Though matching cases to controls is good it is still not perfect as individual hypervariable Single nucleotide polymorphisms (SNPs) may pose problem. As odds ratios are low, replication may be difficult. Also, one needs to be cautious before inferring GWAS as we need to compare the results with variability in general population.

Dr. Peter Visscher started his talk on “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 the number of causal variants, their effect size and their function. The genetic variation to be causal should have a balance with 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 the population are studied using genome wide association studies. Different models have been used to predict the genetic risk of a disease. While evolutionary models like neutral evolutionary model are based upon assumptions that are hard to test empirically, 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.

He opined that 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 and not with synthetic association model. ISC predicted that if larger sample sizes are taken then it will explain more variation with fewer SNPs and narrow boundaries of genetic architecture.

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 predictor 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. He opined that, by comparing allele frequencies in cases versus controls we can search for a disease without clues to its pathophysiology. As we don't know the pathogenesis of schizophrenia at present, 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 phenotype as other methods like brain imaging may not be cost effective.

He explained the results of their recently completed GWAS study. They examined 21,856 samples in primary GWAS and 29,650 samples in replicator series. Thus a total of 52,156 samples of European ancestry were examined. The observed numbers of hits were more than the expected number of hits. 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 gene for HLA and another was gene for transcription factor 4. Interestingly one was gene for miRNA 137 responsible for gene regulation. The GWAS data shows 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 about the endophenotypes concept in schizophrenia research, with the question “Are there useful endophenotypes for Schizophrenia?” She began with definition of endophenotype as different people use the term endophenotype with different meanings. She opined that endophenotypes are intermediary phenotypes which are closer to the genes and help in dissection of genetic diathesis of Schizophrenia, as they decrease the heterogeneity of phenotype. For any marker to be called as endophenotype it has to show distinction between people with schizophrenia and controls, it should be heritable, should be present in unaffected siblings. Another important criterion which many researchers do not give importance is that it should segregate within families,

regardless of whether some unaffected siblings have them. She discussed the brain imaging findings in schizophrenia pointing to the differences between patients and controls like enlarged lateral ventricle, non localized bilateral gray matter reductions, reduced white matter integrity, regional volume deficits, loss of normal asymmetries and developmental abnormalities. She discussed the findings of a landmark. study (Reveley et al., 1984) comparing monozygiotic and dizygotic twins for ventricular size which found high heritability. She pointed that there are very less number of such studies looking at the differences between MZ and DZ twins, which is very important to account for heritability of candidate endophenotype. Current researchers suggest various structural and functional brain abnormalities as candidate endophenotypes. However, she opined that inability to differentiate whether these are intermediary in the disease pathway or the consequences of the disease is the major problem with these findings.

Summarizing the talk she emphasized 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 in the illness. She opined that there is no clear endophenotype for schizophrenia at present. On a concluding note, Dr. DeLisi discussed the limitations of studies using imaging genomics, like 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 measurement. She concluded with a cautionary note that the imaging genomics findings may be spurious.

Dr. Dan Rujescu continued the discussion on endophenotypes by enumerating the different ways to find out genes for schizophrenia. He discussed the importance of intermediate phenotypes in psychiatric disorders as they are more elementary when compared to the heterogeneous clinical phenotype. He explained the possibility of intermediary phenotypes being useful in identifying genes by taking example from Type 2 Diabetes. Dupius and colleagues first identified the genes associated with fasting glucose and later tested whether these genes were associated with type 2 DM. Two genes were associated with type 2 DM, however not all genes asociated 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, the major advantage is animal models can be developed based on the endophenotype and tested. He gave the example of animal model based on NMDA receptor hypofunction which was based on the Phencyclidine induced cognitive deficits. Authors found that parvalbumin dependent inter-neurons 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 for intermediary 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 consequence. Also, we do not know whether we can reduce the complexity of traits. Thus in future, more accuracy is needed before naming something as intermediate phenotype. Also phenotypes which are close to 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 challenge in future. He also cautioned that epigenetics and many other mechanisms which are still not understood also need to be considered in addition to whole genomic sequence.

Dr. James Kennedy gave his talk on “commercial genetic testing for schizophrenia”. Recently, different companies are marketing genetic tests for schizophrenia in internet and thus it is important for clinicians to be aware of the same. Technological advances have made a personal genome sequence possible and in future it

will become still cheaper which can make these tests more popular. However, the society's perception about these genetic tests has been different from those of scientists who are developing these tests. He discussed this with their own unpublished survey on 900 medical students and undergraduates in which they asked the about student's 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 opinion on whether the genetic testing is needed for major psychiatric disorder in general population (19% responding yes) versus for those with high responsibility job (37% responding yes). As the decisions to be taken by the patients and their families involve significant emotions he quoted "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 providing genetic information resources in internet which claim to provide the genetic information on different disorders, including schizophrenia. These genetic tests for schizophrenia are based on several markers for schizophrenia and are claimed to quantify the risk for schizophrenia. However, there are differences in test results between commercially available kits for the same person's DNA and thus he opined direct consumer testing is not recommended in current scenario. Currently there are no clinically valid tests 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, beneficience, 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 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 in patients and also adverse consequences in their family settings. As there is no proven early intervention for alzheimer's disease at present, testing could result in more harm than benefits.

On the other hand physician delivered tests may be beneficial in some scenarios, for example 22q11 deletion syndrome. As there is a definite risk associated with 22q11 deletion syndrome, this could be added in newborn screening programs (Bales et al., 2010). Advantage of this could be avoidance of "diagnostic odyssey" and early treatment of associated problems. However, this could result in parents becoming more cautious about their children's psychiatric status. He concluded that it could be useful to include this in neonatal screening, with good genetic counseling. However, further research is needed to consider the effect of epigenetics and other variations in non deleted 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 but in some cases physician delivered tests may be useful (like 22q11 deletion syndrome and pharmacogentic testing for side effects).

Dr. Thomas Lehner agreed with the views of Dr. Kennedy that the currently available tests for psychiatric disorders are not validated and one need to be cautious in interpreting the results. On the other hand, testing could be more useful in the field of pharmacogenomics. He discussed about the ongoing Exome sequencing project which may help to identify people at risk of developing side effects like 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, may be less than 5%, around 2-3%. In response to another query, will GWAS help to derive biological interpretations? he responded liability threshold model may explain. In response to queries on why genetic studies based on the imaging endophenotypes can't be plausible Dr. DeLisi responded they don't take into consideration that there can be many genes for the same brain function and don't control for multiple corrections. The panelists and the chairperson hoped that further research into these factors would provide better understanding of schizophrenia genetics in near future.

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 evaluations require or should take into account the understanding of the pathogenesis to be conducted. Further, if biological hypothesis were not required to conduct the first set of analysis, should we perform analysis later based on functionality?

Dr. Marie Claire King (University of Washington) opened this session with the talk entitled "Schizophrenia: Multiple Rare Alleles in a Genetically Heterogeneous Disease". Dr. King started her talk emphasizing the human paradox that most of the human variation is ancient and shared but most alleles are recent and individually rate followed by observations regarding schizophrenia that are relevant to discuss its genetic architecture: (1) family history increases risk to 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; (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: 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 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). Out of the findings presented in the paper from Walsh et al. none of the rare variants found in control subjects disrupted genes associated with neurodevelopment. However, one of the deletions (Δ399158bp) disrupted the exons 20 to 27 of the neuregulin receptor – Erbb4. It is known that neuregulin 1 – Erbb4 complex regulate 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 of the number and structural changes in the 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 the chromosome five (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. Part of these mutations is 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 may exist a genetic overlap between both disorders (McClellan et al., 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 in specific pathways; (4) how these results would affect treatment and clinical trial design.

Dr. Sybille Schwab (University of Western Australia) continued the session with her talk entitled "Candidate genes from linked chromosomal regions: What happened to Neuregulin and Dysbindin". Dr. Schwab started her talk reviewing 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 at chromosome 6p and 8q seem to be the most consistently supported thus far. Dysbindin was the main gene associated with the schizophrenia in the 6p region (Schwab et al., 2003; Straub et al., 2002), while neuregulin is located in the 8q (Stefansson et al., 2003; Stefansson et al., 2002). The variant rs1011313 located in the dysbindin gene region received support for association from a meta-analysis (Allen et al., 2008). After the association studies, other findings implicated dysbindin and neuregulin 1 function in phenotypes associated with schizophrenia. Dysbindin has reduced mRNA expression in schizophrenia subjects (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 et al., 2009; Ji et al., 2009). Likewise, neuregulin 1 signalling 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) ended the session with his talk entitled "Genes for Clinical Antipsychotic Action in Schizophrenia". He opened his talk asking whether schizophrenia subjects who respond and those who do not respond to treatment would 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. Dr. Kennedy 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 the genetic architecture may play a major role in determining these traits. However, after discussion with the public, there was not a consensus whether these subpopulations would help to understand the genetic make up of the disease per se.

3.Gene-brain interaction in the pathophysiology of psychosis
Reported by Diana Prata

At the start of the session, Ruben Gur presented us with his latest research suggesting how endophenotypes based on expression and recognition of emotion may be at least as useful than cognition ones for the study of schizophrenia. Indeed, emotion expression and recognition are highly conserved in evolution being similar across species. This is more so than higher cognitive functions which emerged only in *homo sapiens*, and therefore may have a greater underlying genetic and neuropshysiological basis. The speaker started by exposing us to evidence of differences between genders 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, man showed to be more inaccurate, slower and more inefficient in terms of regional brain activation (i.e. increased BOLD response for the same level of performance), than women (Derntl et al., 2009). In what concerns schizophrenia, the speaker's team found patients showed a marked decrease in amygdala activation which was suggested to explain emotion processing deficits in the illness (Gur et al., 2007). Also, in normality, amygdala activation increases with higher accuracy in sad and angry faces but decreases

with higher accuracy in happy faces recognition (Gur et al., 2007). However, 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 (Gur et al., 2007) which was thought to suggest that the latter relates to overstimulation of the limbic system. Consistently, a recent study (Satterthwaite et al., 2010) has detected 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 was suggested to indicate that abnormal processing of threat may exacerbate cognitive impairment in schizophrenia. Leitman et al (in prep) have shown 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.

Alessandro Bertolino gave us examples of functional imaging being used to access how functional variation in dopamine related-genes has an effect in schizophrenia risk. His work has 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., 2003b). 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 on 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 overexpression in the striatum induces working memory deficits (Kellendonk et al., 2006); 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 from a recent meta-metanalysis (Allen et al., 2008). Arising from that, the speaker asked the (more refined) question "What is the effect of the DRD2 genetic variation on striatal pre- and post-synaptic dopamine signaling and how can it 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 sub-cortical activation during working memory. Interestingly, the latter effect was found to be significantly different (in fact, in the opposite genotype-wise direction) in patients with schizophrenia (Bertolino et al., 2009a). In a different study (Bertolino et al., 2009b), they have reported epistasis between the dopamine transporter and the DRD2 on prefrontal-striatal activity and volume, an interaction which was also demonstrated by immunoprecipitation in the striatum. In a more recent study, Bertolino and collaborators (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 sum, 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 virtue of these systems-level brain effects

that variants such as DRD2 SNPs may have penetrance on more complex phenotypes like diagnosis. As the speaker concluded: "The endgame of research into genetic causes of schizophrenia is going to be identification of how, where and when these variants modify brain function."

Tilo Kircher exposed to us how schizophrenia risk genes, and in particular the Dysbindin gene, can affect brain function and structure and personality. Dysbindin is involved in glutamatergic transmission (Owen et al., 2004) and it has been genetically associated with susceptibility to schizophrenia albeit not consistently (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) and reduced prefrontal mRNA levels have been found in schizophrenia (Ji et al., 2009). In a large behavioral and 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 Schizotypal Personality Questionnaire and the Interpersonal Deficit subscale (Kircher et al., 2009). However, inconsistently, the same polymorphism had previously been associated to a less schizotypal personality (Stefanis et al., 2008). Lastly, the speaker presented us with activation brain-maps where associations of each of several genes/polymorphisms (CACNAC1, COMT, DTNBP1. NRG1, etc) with corresponding regions were mapped, for each task. Some pertinent final suggestions on how to tackle the issue of existing intricate interactions between gene, fmri paradigm, brain activation, environment and disorder on imaging genetics studies were to invest on: i) using patient samples across diagnostic categories, ii) longitudinal and multimodal studies and iii) further investigation of the impact of CNVs.

With his pertinent and timely presentation, Michael Owen opened the discussion on 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 started by pulling attention to the potential inaccuracy of the former which is a common key assumption in imaging genetics studies. In his opinion, the other potentially misleading pre-assumption is that variation in an endophenotype will depend upon variation in fewer genes than the more complex disease phenotype and therefore are 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 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 sum, Michael Owen believes 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, i.e. a consequence of the genes as much as the disease is (Walters et al., 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 as resultants due to shared genetic liability. He then went to suggest 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. The speaker also stated the problems with endophenotyes being used for initial gene discovery: they may be influenced by the illness course, drug treatment, smoking or the menstrual cycle, 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 et al., 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 et al., 2007). However, the lack of evidence for mediation is not necessarily a problem for gene finding studies. It is useful if the endophenoytpe/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 to an earlier review publication (Meyer-Lindenberg et al., 2006), Michael Owen also alerted for problems with the use of endophenotypes for exploring mechanisms: genetic multiple testing, phenotypic multiple testing, small samples 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). The speaker ended by presenting an unpublished study where it was possible to sieve out whether an executive task and a social cognitive dysfunction task account for the association between COMT Val158Met polymorphism and antisocial behaviour 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. In sum, the speaker concluded that there are concerns about the use of endophenotypes both for gene finding and investigation of gene function.

Subsequently, the above presentation ignited a discussion on the utility of current endophenotype studies in psychiatry. Alessandro Bertolino said that they are more useful than diagnostic categories which have no biological validity and phrased suspicion on whether the question of the presence or absence of the endophenotype in the causal pathway to disease gcan be addressed, to which Michael Owen replied that unless this is addressed, any interpretation remains speculative. "It is important to distinguish which (endo)phenotypes are mediators, which ones have nothing to do with the illness and which ones can only be biomarkers" said the speaker. Daniel Weinberger finalized the session arguing that "given that changes in the brain have implications on how the brain works and that genes set the rules on 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 behaviour 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.) Also, the endophenotype has to be genetically associated and not merely associated to a genetic association. Daniel Weinberger 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 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."

4. Plenary Session - On the matter of neuroimaging in the context of schizophrenia genetics Reported by Diana Prata

At the start of the plenary session "On the matter of neuroimaging in the context of schizophrenia genetics" Daniel Weinberger presented a plethora of recent imaging genetics studies. First, he recapitulated robust findings of prefrontal efficiency as an intermediate phenotype for schizophrenia where unaffected relatives of schizophrenia patients show intermediate BOLD activation / performance between controls and patients (Callicott et al., 2003a). This was also found for temporoparietal P300 amplitude (Winterer et al., 2003). He stressed that imaging genetics can have applications on several grounds: on genetic association with brain structure and function, genetic dissection of complex functional systems, understanding of brain mechanisms of genetic risk of disease, understanding of genetic mechanisms of variable outcome of CNS disease, genetic variation in brain development and ageing, pharmacogenetic mechanisms in brain and characterization of biological epistasis. He then brought to mind the pillar 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). May this be a neural system mechanism explaining the association of the gene with schizophrenia? Most genes are likely to impact on brain function and a link between genetic association with brain function and neural mechanisms of clinical risk requires demonstration that the association is with a heritable, susceptibility-related phenotype (i.e. intermediate phenotype). Prefrontal-hippocampal functional connectivity have indeed been detected at an intermediate level in healthy relatives compared to their schizophrenic siblings and unrelated controls (Rosetti et al, *under review*) and may therefore be a heritable (intermediate) phenotype. Daniel 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). Still in the realm of epistasis, the speaker then went on to describe examples of how 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 background was shown to affect the risk for schizophrenia associated with other genes such as G72, DISC1, GRM3 and GAD1 (Nicodemus et al., 2007). Specifically, epistasis between COMT (Val158Met) and GRM3 (Tan et al., 2007), between COMT and DAOA (Nixon et al, under review) and between COMT and GAD1 (Callicot et al, submitted) have been demonstrated to impact on

prefrontal efficiency. In addition, CIT has been shown to interact with DISC1 and with NDEL1 using machine learning algoritms 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, in press) where the same interaction was found on prefrontal activation with risk allele directionality. Daniel Weinberg concluded the session suggesting 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. "Imaging genetics is a unique and powerful method for studying the biological effects of genetic variation and gene interactions on brain structure, function and chemistry. Neuroimaging in schizophrenia research has finally begun to approach indentifying pathogenic mechanisms based on the application of imaging genetics."

Alessando Bertolino has exposed us to exciting new research on epigenetics, emphasizing the possible role of changes in DNA methylation and chromatin structure on the 'missing heritability' of schizophrenia. In fact, 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 the epigenetic programming by early life events, since maternal behaviour may affect CpG methylation of the promoter of 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). The speaker stressed that investigating the link between epigenetic processes and schizophrenia maybe particularly intriguing because DNA methylation has been shown to play a role in cognitive functions. The rs4680 in the COMT gene (a clear functional candidate gene for schizophrenia) has been associated with prefrontal cortex-dependent cognition and activation (Egan et al., 2001). Interestingly, differences in monozygotic twins methylation 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 in either allele (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. Alessandro Bertolino and colleagues evaluated potential associations between the above mentioned variables. In particular they 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 in COMT exon 4 (rs4680 region) and 3 CpG in 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 (unpublished data). Moreover they demonstrated how the interaction between COMT methylation, SNP rs4680 and stress, may affect working memory brain activity in PFC (unpublished data). The speaker 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.

Philip McGuire has presented novel research on the at risk mental state (ARMS) as well as other imaging genetics findings using case-control comparisons, gene x gene interactions and gene x environment interactions. He emphasized the potential of using neuroimaging in the ARMS population since it has proved difficulty to study how psychosis develops after illness is well established. By focusing on the ARMS, we can study the same individual 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 finding emerging from this approach been reported. Prefrontal inefficiency, measured with fMRI, in the ARMS is much higher in the ones that transit to psychosis than the ones that do not (in which they are very similar to normal controls) (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 prodromal fase and re-scanned at first episode revealed an increase in dopamine function associated with the onset of psychosis (Howes et al, in prep). Longitudinal volume reductions has previously also been 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, the speaker presented the first study finding an effect 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 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 accumbal 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 depending on the 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., 2009)(Fu et al, under review).

Andreas Meyer-Lindenberg has mentioned the large overlap of common genetic risk, besides the overlap in symptms, between schizophrenia and bipolar disorder (Lichtenstein et al., 2009) at least for the common variants. This may not be the case for the rare ones, he suggested. ZNF804A rs1344706 may be one of those common genetic risk genes. After its association with (Esslinger et al., 2009). A novel study has 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 recently 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. A recent metanalysis (Mier et al., 2009) detected this polymorphism to have strong and opposing effects for executive cognition paradigms (favoring Met allele carriers) and emotional paradigms (favoring Val). This pleitropic effect was suggested to have an evolutionary explanation: since both alleles

where 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.

Steven Potkin 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). One of the highlights of his presentation was the advantage of using brain imaging as a quantitative trait (QT), instead of 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 where found for genes/regions involved in neurodevelopment and response to stress. This approach revealed to be a useful genome-wide screening method to identify novel SNPs related to schizophrenia risk. One of those genes was TNIK which when knocked-down by a shRNA decreases glutamate levels. Also, DISC1 knockdown by shRNA increases glutamate and reverses the effects of loss of TNIK (Wang et al, under review). Systems biology approaches used to clarify the role of new risk candidate genes such as TNIK and the networks in which they participate will bring further insight into the illness and lead to the development of new pharmacological targets.

Si Tianmei has provided an overview of recent research on brain structural differences in schizophrenia and on how it 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 et al., 2009). A review study (Brandt et al., 2008) suggests there is possibly decreased caudate volume in first-episode psychosis patients whereas studies on chronic patients mostly reveal volume increase 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 which could affect myelination (Bartzokis et al., 2007). The speaker concluded that “antipsychotic treatment potentially contributes to the brain structure changes observed in psychosis (type-dependent, time-dependent and dose-dependent). Future research should take in to account these potential effects and use suitable subjects”

The discussion started with a focus on the observation of large variance in the associations being found. Daniel Weinberger suggested it is due to measurement error, and to epigenetics and interactions between genetic variants that we are not yet taking into account. Alessandro Bertolino added that, for example, methylation may be a factor that will explain the “spread” of BOLD signal within a genotype group such as the Val homozygotes. However, he said, studies of methylation are usually in lymphocytes so their application to neuroscience is limiting. Even in the brain, different cell-types in the brain are differently methylated. Daniel Weinberger added that his group has used the GWAs available 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. Alessandro Bertolino added that it is good news that imaging genetics results from Philip McGuire’s group have shown consistency with Steve Potkin’s results showing different effects of genetic variants in different diagnostic groups. Daniel Weinberger added that genotype by diagnosis interactions could be genotype

by drug interactions. To conclude, Daniel Weinberger stated that even though there are epigenetic and environmental factors having a role, there is evidence that at two weeks of age, one can predict the temperament of 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.”

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 risk factors play in 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 peri-natally (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 varying 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 they may exert differential effects on the endocannabinoid system. Regional binding levels were also correlated with symptom and cognitive measures in patients. Dr Ceccarini interpreted these findings as evidence that schizophrenia is associated with hyperactivity of the endocannabinoid system, which is directly related to symptom expression and is downregulated by administration of antipsychotics in a treatment-specific manner.

Dr Monica Rais presented work examining how cannabis use relates to longitudinal grey matter losses in patients. Her findings indicate that cannabis-using patients show increased grey 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 reductions 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 grey matter loss in schizophrenia, possibly as the result of a neurotoxic effect of exogenous cannabinoids, and that this may be related to the poorer outcomes of cannabis-using patients.

In complimentary work, Dr Neeltje van Haren 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 grey matter volume and schizophrenia liability, with no such association being observed for white matter volume. This finding suggests that there are common genetic influences affecting liability for schizophrenia and brain volume.

Dr Eve Johnstone and Dr Larry Seidman continued the theme of imaging research in genetic high-risk samples. 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 .83 and .75, respectively. She presented data from recent additional follow-up scans acquired in this cohort, which suggested that high-risk individuals subsequently diagnosed with schizophrenia show excess prefrontal grey matter volume reductions over a ~10-year follow-up period. In addition, reductions in prefrontal white matter volume were apparent after illness onset. Some of the changes observed in high-risk individuals were found to parallel those seen in individuals at elevated risk for schizophrenia due to cognitive impairment.

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). Relative to controls, 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, suggesting these differences may reflect an intermediate phenotype. 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 relative hyper-connectivity of the default-mode network during both rest and task performance. These changes were associated with psychopathology ratings, suggesting a direct link with patients' symptomatology.

Dr Matthew Kempton 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 moderate to high study heterogeneity. Sub-group analysis revealed that this effect was significant in chronic, but not 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. Citing other meta-analytic evidence of ventricular enlargement in first-episode patients, Dr Kempton concluded that the data suggest that progressive ventricular enlargement may begin prior to illness onset, either peri-natally or during the prodromal period.

Adopting an epidemiological focus, Dr Pirjo Maki 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. Measures of anti-social 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 promdromal symptoms in the wider population, suggesting they may be poor predictors of relatively rare disorders such as psychosis.

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 experimentally study complex gene by environment interaction with both clinical and mouse data.

The first presentation, "Mechanisms of GEI in schizophrenia" was presented by Andreas Meyer-Lindenberg from *Central Institute of Mental Health, Mannheim, Germany*. Either genes or environment can be linked to clinical evidence, but how do gene by environment interaction relate to the brain? There is a relation to function, for example dopamine in the prefrontal cortex. Indeed, prefrontal dysfunction in schizophrenics is related to striatal dopamine disinhibition. This relates to symptoms, for example delusions (and anhedonia?) where 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 behaviour, for example, COMT is linked to cannabis and prefrontal and executive functions. But is this difference seen in the brain? The warriors (met) versus worriers (val) model showed that the met have more executive function and val 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, people performed a task for a reward that was money. 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, in the unstable hierarchy setting, additional emotional regions such as the amygdale and the medial prefrontal cortex were activated.

The second presentation by Ruud van Winkel from *Maastricht University, Maastricht, Netherlands*, was entitled "Momentary Assessment Technology to Assess Gene-Environment Interactions Underlying the Affective Intermediary Phenotype of Stress Sensitivity in Schizophrenia". The momentary assessment study examined stress sensitivity using the experience sampling method. The effects were much stronger in participants with co-twins with affective dysregulation, compared to those without co-twin affective dysregulation. A study using experience sampling method showed an interaction between COMT polymorphism and stress and psychosis especially in Met/Met patients where an increased delusions were observed. The effect of cannabis is difficult to assess as it is difficult to give it to patients so it's useful to study natural variation of recent use with urinalysis. No significant increase in schizotypy was found but increase in unaffected siblings. In the attempt to find which genes are involved, it was found that in 740 unaffected siblings of patients with psychosis, no effect of COMT were observed but 3 genes showed an effect including AKT1. Interestingly, AKT1 is downstream from D2 and it has been linked to the effects of cannabinoids. In conclusion the proximity between gene and environment is essential in research of gene by environment interaction.

The third speaker, Jonathon Arnold from *University of Sydney, Australia* presented "An Animal Model of a Gene-Environment Interaction: The Role of NRG1 in Cannabis-Induced Schizophrenia". To model gene by environment interaction, the effect of cannabis was studied on NRG1 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 NRG1 mice. This showed that stress was necessary to 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. Thus 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 effect were observed on the first day, where an increased was seen in NRG1 mice and a decreased in WT. Both groups became tolerant to these effects. In the light-dark, an anxiogenic effects was observed with cannabinoid on the first day for both groups, and NRG1 mice did not become tolerant to this effect. Repeated cannabinoid also increased FosB/deltaFosB 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 neurobehavioural responses to acute and repeated cannabinoid exposure which provide an animal model of genetic vulnerability to cannabis-induced psychosis.

The final presentation was "Gene-environment interactions in schizophrenia: a new mouse model" by Mikhail Pletnikov from *Johns Hopkins University, Baltimore, Maryland, USA.* The aim was to study the molecular underpinnings of gene by environment interaction, but this has been difficult due to the paucity of relevant experimental approaches such as genetic models like DISC1 and identifiable and measurable environmental factors like infection and immune activation. The Tet-off system was used to generate transgenic mouse models with inducible expression of the transgenes in forebrain regions. This was expressed during the development course like endogenous DISC1. Mutants showed enlargement of lateral ventricles. Here was studied 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. Behavioural results showed an increased peripheral activity (anxiety), decreased time in 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. Also, 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 immune activation produced the behavioural alterations previously unseen in mutant male DISC1.

7. Dynamic brain changes in schizophrenia across the lifespan: Influence of genetic and environmental factors.
Reported by Alex Fornito

Dr Nitin Gotgay opened the session by presenting work examining the developmental trajectory of grey 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 grey matter loss to healthy children throughout adolescence, but that the magnitude of the losses 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 suggested the grey matter changes were in part related to genetic vulnerability to COS, and 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, as children with bipolar disorder showed a qualitatively different pattern of brain development form that seen in COS and controls (Gogtay, et al., 2007), whereas children with psychosis NOS showed grey matter reductions primarily localized to temporal regions. Children initially presenting with a diagnosis of COS, but whose psychotic symptoms resolved after medication wash-out, showed no grey 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 form his group has also shown that white matter changes are apparent in patients with bipolar disorder (Sussmann, et al., 2009), and that these white matter changes 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 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 (approximately11%). 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 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

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 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, a key brain interaction involved in emotion regulation.

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 largely overlap 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.

8. Genetic, epigenetic, and molecular aspects of GABA function in the pathophysiology of schizophrenia
Reported by Melanie Föcking

Daniel Weinberger (NIH/NIMH Washington, DC, USA) gave catching talk about genetic variation in GAD1, and its effects on GAD67 expression, GABA levels in living human brain, and the imposed risk for schizophrenia.

Coming from the genetic regulation of GABA activity (Lewis and Gonzalez-Burgos 2008) he questioned whether GABA findings are an epiphenomenon or primary to the disease. Focussing on the association of genetic variation in GAD1 and the risk for schizophrenia, related biologic intermediate phenotypes, interactions with other genes related to GABA neuronal activity and GABA levels measured in vivo in human brain, they identified distorted transmission of single-nucleotide polymorphism (SNP) alleles in two independent schizophrenia family-associated samples (Straub, Lipska et al. 2007). Employing different approaches, they found that the number of SNPs in schizophrenia patients predict, the GABA levels in the prefrontal cortex and also that 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. Testing 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 when on a GAD1 risk than on a non-risk genotype background. These coincident results implicate GAD1 in the etiology of schizophrenia and suggest that the mechanism involves altered cortical GABA inhibitory activity, perhaps modulated by dopaminergic function.

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 histone methylation with a special view on histone H3-lysine 4 methylation (Huang, Matevossian et al. 2007). In her opinion GAD1 and H3K4me3 levels are developmentally regulated in human prefrontal cortex, associated with transcriptional activity and regulation of promoters, and 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 from GAD2 show no significant changes in schizophrenia so far, as she puts it, but this might be due to a non representative post-mortem tissue sample as of yet. 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 of these findings 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.

Karoly Mirnics (Vanderbilt University, USA) presented data on how post-mortem studies revealing GABA system disturbances in schizophrenia have been the starting point to the 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 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 clarified as he confesses. On a final note, the Mirnics lab offers these mice and the constructs used to generate them for anybody interested in this research (http://mirnicslab.vanderbilt.edu/mirnicslab).

Alessandro Guidotti (University of Illinois at Chicago, USA) discussed new pharmacological strategies to correct GABAergic dysfunctions in schizophrenia. He delivered an interesting lecture by initially asking what the cause of GAD67, Reelin and other genes expression in schizophrenia could be. DNA methyltransferase (DNMT1) has been found to be highly expressed in cortical GABAergic interneurons (Veldic, Kadriu et al. 2007). DNMT1 mRNA was found to be over-expressed, while GA67 mRNA was less present (Ruzicka, Zhubi et al. 2007). He proposed two principal strategies: firstly the enhancement of defective GABAergic transmission by drugs active as selective positive allosteric modulators of GABA action at pertinent GABAA receptor subtypes, even though the mechanism of DNMT1 upregulation is not fully understood one ,suggested, possible approach is to study 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. The presented data suggest that valproates and clozapine‘s efficacy on GAD67 and the Reelin promoter. Clozapine down-regulates promoter demethylation of Reelin and GAD67 in cortical and subcortical regions and the up-regulation of putative DNA methylases is caused by clozapine and valproate. He concluded that this data suggest that chromatin remodeling mechanisms may become an important focus in studying the new generation of antipsychotics.

Dennis Grayson as the discussant summarized the talks by stating that a number of single gene studies support these findings, but the story is still out. A lot of studies have looked at methylation but what needs to be done is to define the regulation, when the gene is down-regulated, one sees a higher amount of methylation and vice versa.

VII. PREDICTING DEVELOPMENT OF SCHIZOPHRENIA

1.Pathways to Psychosis and Neurochemistry
Reported by Olasunmbo.O. Owolabi

There were eight presentations in this session on Pathway to Psychosis and Neurochemistry: George Awad (University of Toronto, Canada), Gabriela Novak (University of Toronto, Canada), Philip Csomor (University Hospital Zurich, Switzerland), Deepak Cyril D'Souza,(Yale University School of Medicine, USA) Douglas Noordsy (Dartmouth Medical School,USA), Ruchika Gajwani (University of Birmingham, UK), Andrew Thompson (Orygen Youth Health,Melbourne, Australia), Ulrich Reininghaus (Queen Mary, University of London, London).

George Awad presented on subjective tolerability to anti-psychosis in Schizophrenia. He explained that subjective tolerability refers 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 injection of 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" include development of conceptual model, development of measuring tools with sound psychometrics (DAI, PETIT) to demonstrate the reliability of the majority of the psychiatric patients to report their feelings. He stated that vulnerability to dopamine is part of positive dysfunction and a number of scales developed were ushered by the development of Drug attitude inventory (DAI), which still continues since it was introduced in the 1970's to be the standard measures for subjective responses to anti-psychotics.The standard measures include: 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 behaviour and health cost.

He described that co-morbid substance abuse in relation to its implication on the quality of life by describing subjective response of those that have compliant and non compliant behaviour. A good correlation between subjective tolerability and quality of life was observed when predicted group membership based on discriminant analysis of DAI response was taken between the compliant and non compliant behaviour. He observed that neuroleptic dysphoria has subjective responses related to alterations in dopamine functions and vulnerability to dopamine is part of its dysfunction. This means, patients with lower dopamine functioning are those vulnerable to dysphoric responses when further given potent dopamine blocking antipsychotics.

Awad cited Vorugati (1997), who proposed that neuroleptic dysphoria may be the missing link between schizophrenia and substance abuse.Based on their findings, those patient 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 of schizophrenia (Vorugati and Award, 2001).

Dysphoric responses were the earliest behavioural experiences because they occur within the first two hours, and usher in a cascade of behavioural alterations in the affective state, cognitive, motor, extrapyramidal, motivational changes. These can serve as clinical markers.

He further revealed that towards a new synthesis in neuroleptic dysphoria and co-morbid drug abuse in schizophrenia, negative subjective response and neuroleptic induced dysphoria can be confirmed on one hand as negative reinforcements, while the use of stimulant could be used as a positive reinforcement in the same neuronal circulatory. Dopamine activity in the nucleus accumbens has been implicated in the mechanism of reinforcement for almost all drugs of abuse, (Koob et al, 2004). Hyperdopaminergic state proposed in schizophrenia can disrupt the adaptive mechanism of the dopamine neurons in response to novel rewards, as well as hyperdopaminergic state produced by dysfunctional cortical hippocampal input to nucleus accumbens, can lead to continuous neural representation of rewards as novel stimulus a mechanism central to initiation and maintenance of addictive behaviour.

Dr Award concluded by saying, subjective tolerability both in its negative and positive experiences has significant implications in the management of schizophrenia, the development of comorbid addictive state is important in 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 contributing to the evolvement of a potential new science: subjective tolerability disorders. Someone from the audience asked whether there is correlation between dopamine receptor binding and dysphoric disorder. He answered that there is a low dose dopamine binding ratio of dysphoria.

Gabriela Novak discussed hyperactive mice show elevated D2 ^{high} receptor, a model for schizophrenia: Calcium/ calmodulin-dependent kinase II alpha knockouts. CaMKII is an important enzyme in schizophrenia, its importance lies in the fact that it 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, autophosphrylation rate and Ca2+ - CaM affinity, 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). She pointed out a hypothesis which states that CaMKII beta up regulation and/increase in CaMKII beta and alpha ratio is an important factor in a schizophrenia-like phenotype.She further stated that heterozygous CaMKII alpha knockout mice show 50% reduction in CaMKII alpha which leads to an increase in CaMKIIbeta: alpha ratio. **CamKII**alpha **heterozygous knockout Mice exhibits**:-Severe spatial working memory deficit (hippocampal), enhanced activity-dependant dopamine release during repeated stimulation, decreased anxiety-like behaviour and high levels of aggression, reduced paired-pulse facilitation ratios and hyperlocomotion (Yamasaki et al, 2008).

In Mice that showed D2 high receptors, an increased proportion of dopamine receptors in their high affinity state were observed. All schizophrenia models tested to date exhibit increase in D2 high (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 neighbour at lower Ca^{2+} concentration. There is higher affinity for Ca^{2+}/CaM. Synapses are usually over sensitive to low Ca^{2+} and are easier to trigger (Brocke et al, 1999; Thiagarajanet et al, 2002).

Pathology of CaMKII ratio could be observed at different stages. 1) During neurodevelopment (prenatal/early postnatal), CaMKII beta triggers the establishment of AMPA, NMDA, and GABA signalling pathways and at adulthood stabilizes dentritic structure. CaMKII beta increases arborisation, motility, filopodia extension, synapse number and retention of contacts.Beta and alpha expression ratio of CaMKII controls development and density of glutamatergic synapse and towards adulthood it controls glutamatergic neurons and later interacts with dopaminergic neurons via inhibitory, GABAergic interneuron. 2) Puberty:- at pre-puberty LTD is mostly involved, it initiates a change in decoding parameters and enhances some neural connections and elimination of others. At post puberty, LTP is mostly involved and causes a lower synaptic charge, increase signally frequency. There is higher responsiveness to NMDA reactivity, enhanced inhibition by AMPA reactivity an immature neuronal phenotype which means synapse is easily triggered at a low Ca^{2+} levels. All these are mediated by CaMKII Ca2+ independent activity. 3) Dopamine release in adult:-CaMKII mediated dopamine transporter in sensitized animal's schizophrenics through DAT. From the study, Novak observed that CaMKII beta is elevated in both humans in schizophrenia and in all animal model of the disease. CaMKII alpha knockouts satisfy a large list of behavioural parameters of a schizophrenia animal model.CaMKII alpha knockout have elevated $D2^{high}$, a biomarker present in all schizophrenia animal models examined thus far. Inhibition of CaMKII is the only method to date, which reduces the level of D2 high.Novak, concluded that, up regulation of CaMKII beta or 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 CaMKIIβ mRNA in the striatum suggest that this enzyme may increase $D2^{High}$ in animals and possibly in schizophrenia itself.

Philipp Csomer described the impact of neurochemical manipulation on sensory gating in healthy subjects with low gating levels-a validation study. He illustrated the traditional drug discovery cycle to include: construct, relevant effects on animal models, adverse events and pharmacokinetics healthy human volunteers (phase 1), proof of concept in small cohort of patients (phase II), Proof of concept in large cohort of patients (phase III+), Approval and introduction into market

Operational measures of gating involves: Gating: - A fundamental feature of information processing, ability to inhibit, filter out, or gate external stimuli and allowing attending to salient features of the environment. Prepulse inhibition (PPI):- This 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 50ms 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 population. Widely available and compliant studies can be conducted, cost effective in short amount of time. Confounding effects of previous medication used and the wide range of symptomatology were eliminated. To bridge preclinical and clinical research an approach to 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, 2008a, Vollenweider et al,2006, Swerdlow et al,2006).

Proof 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 humans subjects with low and high P50 gating levels.The validation process includes three neuropharmacological compounds without antipsychotic properties per se. These serve as negative control treatment in the validation process of the model. Antipsychotic compound used includes: Aripiprazole, risperidone, amisulpride. Compounds used for negative control treatments were: Lorazepam, Modafinil, and Valproate. Study design employed is: Control 1: Treatment 1 received aripiprazole (15mg .p.o) n=27. Treatment 2 received risperidone (2mg .p.o) n=26, Control 2: Treatment 1 received amusulpride (400mg .p.o) n=22, Treatment 2 received lorazepam (2mg .p.o) n=22, Control 3: Treatment 1 received modafinil (200mg p.o) n=29, Treatment 2 received valporoate (500mg .p.o) n=29, Subjects used were healthy male volunteers of Caucasian race aged between 18-40 years; subjects were without family history of psychiatric disorders. Each subject received two different treatments and placed in a counter balanced order. Electrophysiological assessment was conducted at time of peak drug effect, stratification of the subjects into two groups of either low or high gating was done according to placebo gating values. For the antipsychotics**,** 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. Relationship between PPI and cognitive performance showed that the strategy in SMW task was significantly better in the high than in the low PPI group. Moreover, Pearson correlation analysis revealed a significant correlation between strategy score and %PPI at SOA60 in the placebo condition (#=0.65, P<0.0004). This indicates the presence of superior strategy formation in subjects with high PPI values (Csomor, et al, 2008a). A high score represent poor use of strategy and vice-versa. The presenter concluded that, 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 represents the respective "control group". The model used has the potential to provide supplementary information.

Deepak Cyril D'Souza, provided reports on how glycine transporter inhibition attenuates the psychomimetic effects of ketamine in healthy 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, 1 African american. Compounds under study were ORG25935 and ORG25935xketamine. The results showed No effect of ORG25935 or interaction of ORG25935xketamine on a number of feelings/ emotional states.

D'Souza noted that GLY-T inhibition reduces some, but not all of the effects of ketamine relevant to psychosis. None of the behavioural effects of ketamine were increased by GLY-T inhibition pre-treatment; there is a preliminary support for antipsychotic potential of GLY-T inhibitors. He suggested future directions on the study, that there is need for replication, lower class and clinical trial

Question from the audience: 1) How were they able to decide whether the effects were not related to sedation or do they have any EIPS. 2) If any data was available where antipsychotics, either typical/atypical were used along with the treatment?

Answer: 1) No there was no time to determine that. 2) Typical antipsychotics like haloperidol do not block the effects of ketamine.

Douglas L. Noordsy spoke about are there synergistic interactions between antipsychotics medications and psychosciocial rehabilitation? He illustrated using evidence from a double-blind randominised trial of riperidone vs olanzapine among participants in vocational rehabilitation. He explained that study was used to test the following hypothesis: 1) if antipsychotics improved negative and cognitive symptom causes. 2) If negative and cognitive symptoms mediated acquisition of skills in PSR and translation into functional outcomes. 3) If antipsychotics and PSR should interact synergistically when provided simultaneously.

The MRRS study design was used in this study. The MRRS design includes:

Medication Portion: Which comprises of Consent, baseline measures, Cross taper to OLZ or RSP, Maintaining 2+ year, Glucose, Lipids, BMI, Intent to treat.

Vocational Portion: comprises benefits counselling, baseline measures, IPS, Job start, WPFM or none x, maintenance, IPS 2 years.

Medication Treatment Outcome where: N=107, 12 mo continuation: 36% RSP, 43% OLZ, 18 mo continuation: 31% RSP, 37% OLZ, Median duration: 470d RSP, 695d OLZ, 18 mo all-cause discontinuation: 69% RSP, 63% OLZ. All were not significant.

The MRRS side effects shown between group effects include: BMI:- RSP= 1.11year, OLZ+65/year, P<0.02. glucose, lipids were not significant.Treatment emergent TD: 3RSP; 3OLZ. Combined time effects were HDL increase trend P=.08

Question : Is there any measures used in the control of psychosocial clinical trials? Answer: There is need for standardization in such trials.

Ruchika Gajwani described the development pathways to emotional dysfunction in young people at ultra-high risk (UHR) of developing psychosis. He emphasized that the purpose of the study was to elucidate on. 1) Nature and prevalence of emotional dysfunction in ultra-high risk group. 2) Developmental risk factors for emotional dysfunction in childhood trauma attachment dysfunction. Batteries of measures used in this study to access each client includes: Depression- (BDI), social anxiety/phobia (SIPS); generalized anxiety (ABA), Childhood trauma (CTQ), Parental attachment (PBI/MOPS), Adult attachment (RAAS).

The study revealed 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 of psychosis. And very little or no correlation was found between counts of existing psychotic correlation.

Childhood trauma was taken into consideration while observing suicidal thinking to see if adverse life event would have an impact on dissociative experience. A level of emotional neglect was found to be high, sexual abuse was reported, childhood trauma was found to be less significant. Other factors considered were parental attachment, social phobia, and adult attachment.Emotional dyregulation was prevalent in all, with levels of neuroticism having a significant association with client distress and positive symptoms.

Andrew Thompson discussed predictive validity of clinical variables in “at risk” for psychosis population: international comparism with results from the North American Prodromal longitudinal study (NAPLS).

Ulrich Reininghaus concluded the session with a discussion on sociodevelopmental pathway to psychosis? New evidence from the AESOP study. Reninghaus 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, bullying were evaluated. While for the adult adversity and psychosis, social economy and social isolation were considered. How adversity got combined across life course in the genesis of psychosis was taken into consideration by studying a socio-developmental pathway to psychosis. In studying aetiology and ethnicity in schizophrenia to psychosis, people used were between ages 16 to 64, presence of first episode psychosis was noted and people residing within a catchment were used. During data collection for childhood adversity, factors taken into consideration were long term separation from one or two parents before age 16, death of parents (one or both). For the adult adversity, indices used were; Index of social disadvantage and isolation, employment, housing, living arrangements, social networks education and pre-morbid IQ. Methods used were multiple analysis product co-efficient approach with biography. The study revealed that, there was a strong effect from parent separation. Early adversity leads to adult adversity then to psychosis. The presenter stated that the limitation of the study was that the temporal precedence measured was confounding.

2. **Predicting the Development of Psychosis**
   Reported by Lisa Buchy

Timothea Toulopoulou (London, ENG) was the first to present her study "Impaired intellect and memory, stepping stones between genetic risk and schizophrenia". The focus of her research group is endophenotypes of schizophrenia, which can be conceptualized as lying on the pathway between genetic variation and the clinical disorder. In schizophrenia, cognitive deficits are among the most promising indicators of liability to schizophrenia; they appear to be present before psychosis onset (citation), are present at first-episode (citation) and appear to remain stable across the course of illness (citation), and are found among non-affected relatives (citation). In her talk, 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 would be explained by genetic influences, that in turn would share substantial genetic variance with schizophrenia. Results showed that 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 the 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 identified that a substantial proportion of the phenotypic correlation between schizophrenia and memory and IQ is due to the same genetic influences. She ended with the caveat that more than 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.

Romina Mizrahi (Toronto, ON) used PET neuroimaging technique 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 participants with psychosis showed significantly greater stress-induced dopamine release in the associative striatum. No group differences emerged in the limbic striatum or sensorimotor striatum. Results support the hypothesis that stress-induced dopamine dysregulation is observable in schizophrenia, and suggests dopamine sensitization may be a possible risk factor for schizophrenia.

Elaine Walker (Atlanta, GA) discussed potential genetic and epigenetic mechanisms influencing glucocorticoid secretion in the emergence of psychosis. She first described the role of glucocorticoids in the expression of genes governing neuronal function, and indentified that glucocorticoid receptors are key players in HPA axis function. In psychotic disorders, a relationship exists between HPA hyperactivity and symptom severity (citation). Dr. Walker's longitudinal study examined whether heightened cortisol secretion precedes the onset of psychosis, and evaluated potential contributing genetic risk factors. Her sample comprised 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 individuals with Met/Val or Val/Val genotypes. These results support a role for HPA axis dysregulation in psychosis and extend previous works by demonstrating that HPA axis dysregulation is present at the time of conversion to psychosis.

The fourth talk of this session was given by Ashleigh Lin (Melbourne, AU), who 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 seven 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 = .94). Interestingly, the data revealed a number of individuals with poor functional outcome who did not transition to psychosis. When separating these individuals in to 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 nevertheless were functioning very poorly later in life. The poor functioning group was further characterized with poorer verbal memory ability (OR = .70), greater mania, higher SANS and BPRS scores. The most striking results was that participants with baseline verbal IQ and verbal memory scores $\leq$ 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. Ashleigh 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.

Abraham Reichenberg (London, ENG) 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 set 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. In concert, the findings point to two possible etiologies of cognitive dysfunction in schizophrenia: static neuropathology and a later developemental lag. The findings have further implications for schizophrenia nosology, as evidenced by clear distinctions in the developmental processes that lead to cognitive dysfunction.

Eileen M. Joyce (London, ENG) 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 computerized 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 visuospatial recognition memory. Patient participants 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 correlated 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.

Manuela Russo (London, ENG) 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 memory, 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 symptoms dimensions (mania, reality distortion, depression, negative and disorganization) were examined. The results of her study 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. Manuela Russo used these findings to suggest that in people with a first-episode psychosis symptom severity and cognitive ability appear not entirely independent, and this may suggest a common underlying brain system.

The final talk was presented by Larry J. Seidman (Cambridge, MA) who discussed cognitive performance as a predictor of conversion to psychosis. Dr. Seidman highlighted several important reasons to study cognition in the prodrome, including that cognitive impairments are central to schizophrenia (citation), 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 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 family risk displayed worse vocabulary than both clinically high risk groups, where as the latter groups showed poorer verbal memory than the family risk group. Taken as a whole, converters with a family history of psychosis show the greatest cognitive impairments. Interestingly, the effect size when collapsing across all three experimental groups scores on cognitive domains, the effect size (d=.07) appears to be half to 60% of the effective size of cognitive deficits in first-episode samples (d=1.4) (citation). This pattern of results may suggest that cognitive impairment increases during the late prodrome and first rank psychotic episode, and perhaps beyond.

3. **Risk Factors in the Development of Psychosis: Common pathophysiological variables provide and insight into the etiology and treatment of schizophrenia**
   Reported by Gemma Modinos

This symposium comprised four presentations: Antony Grace (University of Pittsburgh, USA), Patrick McGorry (University of Melbourne, Australia), Petra Habets (University of Maastricht, the Netherlands) and Robin Murray (Institute of Psychiatry, London, UK).

Prof. Grace presented a neurodevelopmental disruption model of schizophrenia in rats based on prenatal administration of mitotoxin methylazoxymethanol acetate (MAM) during gestation. Their findings of hyperresponsivity of the dopaminergic system in MAM-treated rats align with studies in patients with schizophrenia. Furthermore, there is evidence to suggest hyperactivity in hippocampus 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, this study found that dopaminergic neurons were brought back to firing at normal levels. Prof. 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 two hours of stress. After inhibition of the subiculum, this hyperresponsivity was observed to return to normal levels. Thus, Prof. Grace highlighted 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 hyper-responsivity to amphetamine. Finally, Prof. Grace reported that peripubertal administration of diazepam prevents dopamine overdrive in the

MAM developmental model of schizophrenia. Thus, Prof. 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.

Prof. McGorry discussed Hippocampal-Pituitary-Adrenal (HPA) axis function in first-episode psychosis (FEP). In a first study, Prof. McGorry examined the cortisol response to the administration of low (0.5mg) and very low (0.25mg) doses of dexamethasone to neuroleptic-naïve FEP patients, and its relationship to childhood trauma. Dexamethasone Suppression Tests (DST) revealed that, at 0.25mg, there were 33% of FEP patients with an increased rate of cortisol hyper-suppression. At 0.5mg, there were 63% of hyper-suppressors. Prof. 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, Prof. 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, Prof. McGorry 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, suggesting an impaired hormonal response to stress in FEP patients. Prof. McGorry 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. Finally, results from the two studies were summarized as lending support to the involvement of the stress system in the pathophysiology of psychotic disorders, with relevant implications for potential treatment strategies modulating these neurosteroids.

Dr. Habets presented results from their 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 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 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.

Prof. Murray 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 Prof. 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, Prof. 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.

Following the talks by the panelists, the session was brought to a conclusion by the discussant, Elaine Walker (Emory University, Atlanta, USA) who provided an overview of the most relevant contributions from each talk. Prof. Walker emphasized the importance of Prof. Grace's animal model, which is able to mimic the final common pathway in humans. Prof. Walker also highlighted Prof. McGorry's results on critical maturation processes that affect the HPA dysfunction, which in turn Prof. Grace's model emulates in animals. Special attention was placed on the finding that that different FEP patient subgroups seemed to respond differently to the environment. Furthermore, Prof. Walker drew attention on the issue of reverse causality, raising the possibility that, in Dr. Habets study, brain abnormalities might have predated cannabis use and might thus be a risk factor, as opposed to a consequence. Prof. Walker finished her discussion stating the need to be cautious, for schizophrenia is a complex disorder, not likely to be related to a single gene, or to simple one-way or two-way interactions.

Finally, the discussion of questions from the audience was opened. The first question noted that the talks had been directed to evidence in relation to positive psychotic symptoms, and inquired how would this relate to negative and cognitive symptoms of schizophrenia. Prof. Murray agreed that such issues are of interest yet they remain to be answered. The next question referred to the role of other neurotransmitters aside from dopamine, to which Prof. Murray responded that his talk mainly focusing on dopamine was not to say that glutamate, or GABA, do not have an effect; rather, he underlined that dopamine is the final common pathway to psychosis. A further question highlighted that animal models also suggest an early common pathway, not only a final one. The question was based on evidence from early models of psychosis suggesting that neural migration may already be affected in the disorder. Prof. Murray, in response, noted that people with no neurodevelopmental insult do as well develop psychosis. Therefore, not all schizophrenia can be neurodevelopmental, but also late developmental factors play a role. Another question from the audience referred to dopamine being also involved

in disorders other than schizophrenia. Prof. Walker concisely replied that psychosis most likely consists of a dopamine increase in a vulnerable individual with a vulnerable dopamine system. In addition, Prof. Murray proposed that patients with schizophrenia might be thought of as developmentally compromised bipolars, in terms of shared social adversity but having a distinct developmental compromise. Prof. Grace finally added that psychosis is likely to represent impaired resiliency to stress, given that a normal individual has the capacity to enter and leave stressful states successfully, a capacity that appears to be deficient in patients with schizophrenia.

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

This symposium addressed the role and importance of the dopamine system dysregulation in the pathophysiology of schizophrenia. The first speaker, **Dr. Anthony Grace** (University of Pittsburgh), summarized recent findings from his experimental lab on a developmental animal model of schizophrenia (the 'MAM rat model'). 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. In reply to a question posed by Professor Murray, Dr. Grace mentioned 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 psychostimultant drugs.

The next speaker, Dr. Alain Dagher (McGill University), focused on the associations 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) 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 an increased synthesis of dopamine 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, latest data from Dr. Howes's workgroup indicate normal striatal dopamine synthesis in the well twins of schizophrenia patients. These suggests that disturbance of the dopamine system might be a state- rather than trait-dependent feature- and his finding that dopamine overactivity increased further only in those that developed psychosis provides further support for this. In reaction to this presentation, Dr. Bertolino pointed to an association between polymorphism of the D2 receptor gene and schizophrenia and asked how these findings could be reconciled with Dr. Howes's results. Dr. Howes argued that in his studies presynaptic dopamine synthesis capacity had been determined, which may be most relevant for the phasic rather than tonic dopamine release than D2 receptor signaling.

Dr. Abi-Dargham (Columbia University) was the final speaker of the symposium. She 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 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 sum, 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. 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 also by Dr. Dagher, inter-subject variability of the measured variables was very high and could mask subtle within-individual state-related changes. Dr. Grace agreed that within-individual change in the dopamine function seemed to be of major importance. Dr. Kapur concluded that the talks and discussion warranted research topics for the next 20 years.

VIII. NEUROPATHOLOGY

Future directions for the neuropathology of schizophrenia **Reported by Melanie Föcking**

The symposium summarized "the value of post mortem brain research in schizophrenia" and discussed "possible future directions of work in this area". Regarding to the organizers there is a need, to use integrative approaches and active perception, that there is a continued demand for (1) detailed neuropathology employing newer technologies, and (2) the necessity to study multiple cortical regions aswell, as 3) assessing different developmental time periods.

The symposium commenced with a lecture by James Meador Woodruff (University of Alabama at Birmingham, USA) who stated that "it is 20 years down the line in pathology and it is time to translate the excitement in genetics".

He employed the "glutamate hypothesis of schizophrenia" as an example of recent data pointing to abnormalities of glutamate receptor trafficking, delivery, dendritic localization, recycling, and degradation in the brain in schizophrenia (Beneyto and Meador-Woodruff 2008; Kristiansen, Patel 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 AMPAR 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. In his opinion, these results suggest that there are changes in glutamate receptors in schizophrenia that involve abnormalities of intracellular processes that effectively reduce receptor function, even though total cellular levels of these receptors may be normal. Such findings should be considered to be important, because they point to the complexity of molecular and intracellular abnormalities in schizophrenia and highlight novel sites, that may be promising targeted for drug treatment.

David Cotter (Royal College of Surgeons in Ireland, Dublin, Ireland) impressed with an interesting lecture 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 from published as well as unpublished studies (Pennington, Beasley et al. 2008; Pennington, Dicker et al. 2008; Behan, Byrne et al. 2009; English, Dicker et al. 2009), that elucidate how the different approaches, with and without enrichment, all confirm, changes in synaptic, cytoskeletal and metabolic functions across studies, and different brain areas, are affected by schizophrenia. He continued pointing out that there is evidence for NMDA receptor hypofunction in their datasets, and that clathrin mediated endocytosis related proteins seem to play and important role in this regard. He validated these finding by conducting a review of all brain proteomics studies published so far (paper in press). David Cotter suggested to extend this even further, by using a systems biology approach (Sauer, Heinemann et al. 2007) or alteration of the angle of view, to look from an epigenetics point (Rutten and Mill 2009). He finally concluded that there is a demand for future work in schizophrenia to apply more integrative approaches, incorporating the findings relating to enviroment, genome, transcriptome in addition to the proteome.

Following on from the previous two talks, 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, publically 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 inhomogenity of laboratory practice and therefore the datasets present technical variation. Among other strategies it is envisaged to include SNP-, microRNA, and methylation array data from the same cohort as well as similar data of another cohort of brains. She persued by focusing on some examples that show the integrative analysis yielded novel candidate genes for the abnormalities including a glutamine transporter. Maree Webster 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, too.

Karoly Mirnics (Department of Psychiatry, Vanderbilt University, USA) presented his exploration of the future of post mortem research, stating that brain collections are an incredibly valuable resource, and none of the disease animal models are likely to be an adequate model to mimic the pathophysiological processes that occur in the diseased human brain. He addressed five points, namely i) confound, where he was addressing challenges in post-mortem research with regard to post mortem interval, medication, lifestyle, co-morbidities etc. ii) what should be analyzed and answered this with many different brain regions, different substructures of those brain regions, different cell types, different cell compartments and 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 regarding to Mirnics (Pongrac, Middleton et al. 2002) has been overlooked and is a challenging area that so far has failed to be achieved. 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, as for instance limited sample size, improving on meaningful genotype-phenotype comparisons.

He closed the circle 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, supposing, all data are 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.

Joel Kleinman in his role as discussant summarized the main points from the presentations, concluding that there is a starting point and the need to advance in the field as it is obvious that if there would be no human brain material, this research would be impossible. It was suggested that the GWAS studies could be used as the starting point and continuous post-mortem studies will help to find out how the genes work and then it could be achieved to tackle the disease properly.

IX. CANNABIS USE

1. Cannabis, amphetamines and early psychosis: evaluating the risks for progression, neurobiologic models of interaction and implications for treatment
Reported by Bonga Chiliza

Andrea Auther started the session by presenting data from their study conducted in New York under the auspices of the RAP (Recognition and Prevention) program. The study prospectively looked at 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 commonly used 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 then concluded that like other prospective prodromal samples (Cannon et. al. 2008) there was no relationship between cannabis use and psychosis conversion.

Don Linszen presented results of their recently published study (Korver et. al. 2010) looking at the relationship between cannabis use and symptoms and neuropsychological functioning of ultra high risk subjects compared to healthy controls. Dr Linszen started with the highlights of the 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 their 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 the fact that otherwise healthy controls who were cannabis users had significant symptoms which has important implications for public health policy.

Tania Lecomte presented their study conducted in Vancouver, Canada, looking at the profile of people presenting to the emergency room with methamphetamine psychosis. Methamphetamine abuse has become an international health problem. In Vancouver close to 60% of street children use methamphetamine as, amongst other attractions, 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. Buhler et. al. 2002). In their study they included people presenting at an emergency room with methamphetamine psychosis and followed them up for six months. They had 295 subjects at baseline and ended up with 158 who completed follow up in six months. 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 we need to take cognizance of their needs.

The last presentation of the session was by Douglas Noordsy which explored whether Clozapine could be used for cannabis using first episode psychosis patients. Dr Noordsy discussed the reward deficiency model which hypothesize 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. 2000). 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 study with average doses of clozapine at a mere 75mg daily and risperidone at 3mg daily. Three patients were discontinued early on due to poor tolerability on clozapine. These early results suggest that clozapine is a possibility for first episode psychosis patients with substance abuse. Dr Noordsy also noted that the patients responded to a much lower dose of clozapine than expected.

John Kane was the discussant in the session. He raised the issue that cannabis maybe an independent risk factor for schizophrenia but one needs to be careful about how we convey that message to family members of people with schizophrenia as they may unfairly blame patients. He also said these 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. Dr Kane also raised the point that looking at cannabis and conversion in the prodrome is perhaps not be the right place to look as the illness may have already significantly progressed.

X. OUTCOME

1. Improving overall outcomes- Extending CBTp to complex problem
Reported by Jessica Merchan Naranjo

CBT has been accepted as treatment for affective disorders and has been fully integrated in Mental Health Servives since 1980. Nevertheless, despite the case-studies by Beck (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 behaviour 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 caregivers 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 employed to treat different schizophrenic subtypes such as prodromal symptoms (McGorry et al, 2002), first and second episodes (Tarrier et al, 2004), acute psychosis (Lewis et al, 2002), treatment resistant patients (Tarrier et al, 1999), negative symptoms (Rector et al, 2003), and command hallucinations (Trower et al, 2004) amongst others.

Auditory hallucinations are amongst 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 cognive model (Birchwood et al, 2004; Van der Gaag et al, 2003) has demonstrated that patients

perceive voices as damaging and humilliating if commands are not carried out. Carrying out the orders given by the voices leads to conformistic behaviour and produces fear and depression.

Hacker et al. (2008) developed a programme that helps the patient to question the omnipotence and power of the voices and as such reduces fear and conformistic behaviour. The MRC COMMAND (Trower et al, 2004) is a randomized and controlled multicenter 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 conductual problems by equilibrating the patient's own voice and externally generated voices (Max Birchwood, 2010). Another method is competitative 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, 2010).

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 Prof Phillip D. Harvey (Emory University, Georgia) and Prof Dawn Villigan (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).

The first speaker, Prof Harvey, began by addressing the broad issue of 'how' to measure functional disability, given that real-world outcomes (e.g. marriage, employment, 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 westernised 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 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. Further, when healthy individuals with 6 or fewer years of schooling were removed from the analysis the correlation disappeared. Prof 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 in needed, plus re-norming of such performance-based measures in developing countries such as China. During questioning, Prof Harvey was asked his opinion as to

why the Heinrich- Carpenter Quality of Life scale was not found to correlate with the UPSA in a recent study, discussed in Prof Michael Green's talk as part of another symposium earlier in the week. His refutation was that none of the other functional capacity measures correlated with the Henrichs-Carpenter measure either, and suggested this was possibly due to the scale being more focused on negative symptomatology than functional disability.

Prof Velligan was the second speaker and 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 Behaviour in Schizophrenia (TABS; co developed by Prof Velligan), 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 Likert-type 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 favourably. Prof Vellign 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-westernised countries do not a) have access to a phone or voicemail, 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, Medication in the TABS) also failed to meet the cut-off in specific countries (e.g., India, 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. Prof 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.

The third speaker, Dr Delfina de Achával (University of Buenos Aries, Argentina), continued discussions of the above-mentioned 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, were rated within the acceptable range (5 or above) on the C-CARS. This was also the case when raters considered subgroups of Argentines based on gender, socio-economic status, ethnicity and geographical region (urban/rural). However, again 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, recognise 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 these 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 (n=12), schizophrenia patients (n = 13, 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 context of Argentinean culture.

The final speaker was Prof Elizabeth Twamley (University of California, San Diego) who presented data on the effects of language and acculturation on the measurement of functional capacity in schizophrenia. Prof Twamley 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 analysed 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. In summary, it was concluded that measurement of functional capacity can be strongly influenced by language of test administration for monolingual Spanish-speaking schizophrenia patients. Prof Twamley ended with the note that 'language' is not a stand-alone factor and is intricately intertwined with acculturation, literacy, education and cognitive abilities, increasing the difficulty of creating reliable cross-cultural intermediate measures of functioning.

Discussant Prof 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, Prof Keefe went on to point 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. Prof Keefe stated that the UPSA (which is already being used for 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 "paediatric" 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. Prof Keefe highlighted that the UPSA is currently being used in several industry trials, and suggested that data regarding this measure would be extremely useful if the tight security, and reluctance of the companies to release such data, could be overcome.

When discussions were opened to the audience I 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 member of the audience queried the issue of practice effects on tasks such as the UPSA. Prof 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, providing that individuals were functionally impaired to begin with. In conclusion, the constituents of real-world functioning naturally differs 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.

3. Update on duration of untreated psychosis; its impact on outcome, and finding ways to its reduction

Reported by Juan Gallego

This session, chaired by Dr. Lex Wunderink (Leeuwarden, the Netherlands) and Max Birchwood (Birmingham, UK), comprised of four talks and the discussant was Max Marshall (Preston, UK). In the first talk titled: "Reducing DUP in a large urban, multicultural city: why we need to use and understand data on pathways to care" 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 remained elevated. 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, has led to various authors 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"; 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 of Birmingham, such as the east area of the city, show a higher DUP compared to other areas of the city. 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 gave as an example 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. At the end of the session there was one question from the audience in regards to whether or not these clients with long DUP had received any sort of treatment prior to the initiation of the antipsychotics and Dr. Birchwood replied that some of these patients had not received any treatment because they were very difficult to engage while others were indeed treated with other psychiatric medications like antidepressants or benzodiazepines for depressive or anxiety symptoms.

Dr. Nynke Boonstra (Leeuwarden, The Netherlands), in her talk titled: "Duration of untreated psychosis and negative symptoms: how do they relate?", spoke of her recent meta-analysis (Boonstra et al. in preparation) that related duration of untreated psychosis with negative symptoms. As part of the introduction she mentioned that a shorter DUP is associated with earlier and better level of remission (Malla et al. 2002; 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. 2000; Harris et al. 2005) and 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 so well known. Prior studies have shown that negative symptoms at 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). Dr. Boonstra reminded the audience that positive symptoms are more responsive to treatment and have less impact on outcome. She went on to describe the methodology employed for her meta-analysis. 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. All scores were transformed to normalized T scores. 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 predict negative symptom severity up to 96 months of follow up. She concluded: 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. Dr. Dazzan started by explaining 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 points out that the thalamus, amygdala, insula, and anterior cingulate are compromised at the onset of the disease as well as in chronic stages. Recent findings have also suggested that treatment can reduce the time spent with psychiatric symptoms and that a longer period of untreated illness is associated with a poorer outcome. Additionally, it has been shown that longer DUP is associated with smaller grey matter in cingulate, frontal, temporal and insular cortex (Lappin et al. 2006). Dr. Dazzan then mentioned that a very important question to answer is to determine whether the poorer outcome is mediated by the brain structural changes. To answer that question 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 (Lappin et al. in preparation) and 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 those 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. She questioned whether there was a point in trying to know how much the brain changed over time, or if individualized prediction of outcome was already possible at illness onset. To help with the analysis she used the support Vector Machine (Fu et al. 2008; 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 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. During the discussion Dr. Lex Wunderink asked if she was implying that antipsychotics were making worse the clinical picture and Dr. Dazzan replied that there was an association between large ventricles and antipsychotics but that it was not possible to dictate the direction of that association.

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 that 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). Her presentation 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 1997-2000. 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; Melle et al. 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 preED, 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 specific for other areas (negative, cognitive, depressive) than positive symptoms and she posed the unanswered question of why an intervention targeting and shortening positive symptoms affect mainly negative symptoms.

The discussion was led by Dr. Marshall (Preston, UK). He commented on Dr. Birchwood's talk saying that it is indeed 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 the early intervention services. About Dr. Boonstra's talk he expressed that she was able to expand on the link between DUP and negative symptoms, which he himself had not addressed in a prior meta-analysis. (Marshall et al. 2005). He also stressed that the findings by Dr. Melle were quite important since it has been one of the few studies able to demonstrate benefits on negative symptoms.