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THE 3rd SCHIZOPHRENIA INTERNATIONAL RESEARCH SOCIETY CONFERENCE, 14-18 APRIL 2012, FLORENCE, ITALY: SUMMARIES OF ORAL SESSIONS

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Abstract

The 3rd Schizophrenia International Research Society Conference was held in Florence, Italy, April 14-18, 2012, and this year had as its emphasis, "The Globalization of Research". Student travel awardees served as rapporteurs for each oral session and focused their summaries on the most significant findings that emerged and the discussions that followed. The following report is a

composite of these summaries. We hope that it will provide an overview for those who were present, but could not participate in all sessions, and those who did not have the opportunity to attend, but who would be interested in an update on current investigations ongoing in the field of schizophrenia research.

Keywords

schizophrenia; genetics; gene-environment interaction; brain imaging; treatment; conference

INTRODUCTION

This was the 3rd international conference on schizophrenia research sponsored by the *Schizophrenia International Research Society*. The theme of this meeting was “The Globalization of Research”. Toward that theme a special emphasis was placed on contributions from a broad net of geographical locations and on providing announcements and travel awards to participants from almost all continents world-wide. Four full days were devoted to topics that ranged from basic science animal model studies to reviews of the latest ongoing new pharmaceutical trials. There were several sessions discussing the underlying brain changes and how they progress over time in people who develop schizophrenia and an equal number of sessions on new genetic approaches for facilitating the development of treatments, as well as the understanding of how environment interacts with the emerging risk genes. A special session was added on the last day to debate the necessity of including a prodromal diagnosis in the new DSM V criteria. Although the current report is organized by topic and thus cuts across multiple sessions in doing so, the highlight of the conference were the four unique plenary sessions that included updates on the latest advances in psychosocial and pharmacologic treatments, the genetics of schizophrenia, and the emerging information from psychoimmunology. Student travel awardees volunteered to serve as “rapporteurs” of oral sessions to summarize the major findings that were reported and the conclusions in discussions that followed. Similar reports from the 1st and 2nd international conferences have previously been published (Abubaker et al, 2008; Baharnoori et al., 2010).

I. EPIDEMIOLOGY (Reported by Charlotte Gayer-Anderson, Andrew Thompson, Antonella Trotta)

Advanced paternal age as a risk factor

Dbolores Malaspina (New York University, USA) introduced studies that suggest advanced paternal age (APA) contributes to a specific subtype of schizophrenia. Discussed were studies showing that APA is associated with greater autistic preoccupation, better responsiveness to treatment (Rosenfield et al, 2010), greater discrepancy between verbal and performance intelligence, and greater odor detection (Lee et al, 2011). *Christina Hultman* (Karolinska Institute, Sweden) presented evidence of a dose-response effect for APA in cases with bipolar disorder (Frans et al, 2008), and with increased *de novo* point mutations in autism (O’Roak et al, 2012). Frans et al (2011) found that increased maternal grandfather age also was associated with an increased risk of schizophrenia. APA is not specific to schizophrenia, but is associated with several other neurodevelopmental disorders as well. *John McGrath* (University of Queensland, Australia) discussed unpublished work using mice models; mice born from older sires were more anxious in a rat maze, had thicker cortices (similar to autism) and increased numbers of *de novo* CNVs, which included genes that have been previously associated with autism and schizophrenia. However, related mutations vary from offspring to offspring and the behavioral phenotype appeared

labile. *Anne Goriely* (University of Oxford, UK) discussed other relevant diseases as models for the biological and molecular basis of APA, including Apert syndrome (associated with FGFR2 mutations; Goriely et al, 2003). Apert mutations have been found to expand clonally in normal testes which leads to increased mutant sperm over time, thus causing the APA effect, and in rare cases lead to testicular tumors (Goriely et al, 2009). It was proposed that subtle alterations of the growth factor receptor-RAS pathway is linked to all neurodevelopmental disorders, including schizophrenia and autism (Goriely and Wilkie, 2012). However, the discussant (*Avi Reichenberg*, Institute of Psychiatry, UK) noted that the mechanisms of APA still remains unclear, and suggested that future research might focus on the role of epigenetic and environmental effects, and use stem-cell models to understand its basis.

Other environmental risk factors

Andreas Meyer-Lindenberg (University of Mannheim, Germany) discussed convergent evidence from imaging-genetic studies and epidemiological studies of the impact of social stress (urban birth, migration, and childhood adversity) on neural processes, and risk of psychosis. For example, Tyrka et al (2012) found hypermethylation of the gene, NR3C1, to be associated with a history of child adversity and attenuated cortisol responses to the Dex/CRH test. Given recent evidence of disturbances in the hypothalamic-pituitary-adrenal axis and stress-reactivity in psychosis, these results may be of particular importance in understanding how the environment impacts on the brain to increase risk of disorder. *Wim Velting* (Maastricht University, Netherlands) highlighted the benefits of using virtual reality paradigms to investigate social environments as a risk factor for psychosis, due to their replicable and controllable nature. Results from a pilot study of first-episode patients and controls showed greater severity of paranoid thoughts and increased physiological responses in patients as social environmental stress (population or ethnic density) increased. *Inez Myin-Germys* (Maastricht University, Netherlands) discussed the role of prefrontal dopamine in psychotic reactivity to daily life hassles. Lataster et al (in press) have compared prefrontal dopamine reactivity, using a PET paradigm and the Montreal Stress Imaging Stress task, in siblings of patients with psychosis and controls. Siblings had lower levels of dopamine reactivity to high stress in both the right and left ventromedial prefrontal cortex, and those siblings who had lower prefrontal dopamine reactivity were more likely to respond to daily life hassles (assessed with the Experience Sampling Method) with psychotic symptoms. *Bart Rutten* (Maastricht University, Netherlands) proposed that epigenetic variation in gene methylation (specifically MTHFR, DNMT1, DNMT3a, DNMT3b) may moderate susceptibility to psychosis following childhood trauma and social stress. In five separate cohorts, he found main effects of social stress (assessed with the Experience Sampling Methodology) on paranoia, and found that some of the gene SNPs were associated with paranoia and social stress in the normal population.

Homicide and schizophrenia

Olav Nielsen (Bispebjerg University Hospital, Copenhagen, Denmark) presented data from an Australian sample of homicides (Nielssen et al., 2007); 61% were first episode psychosis (FEP). Most homicides were in response to frightening delusions and command hallucinations were rare. A further meta-analysis of homicide studies and schizophrenia (Nielssen and Large, 2010) indicated that approximately 40% of homicides by patients with schizophrenia occurred in FEP cases, rates of homicide were much lower after treatment and DUP was significantly correlated with homicide (but dependent on the country of study). Other forms of violence were all elevated in FEP cases including major self-mutilation and violent suicides. Similarly, rates for any form of violence were high before treatment and lower after treatment. He concluded that earlier treatment for psychotic illness might reduce the incidence of homicide. *Matthew Large* (St. Vincent's Hospital, Sydney, Australia)

presented results from a number of studies (e.g. Large et al., 2009) and argued that there were high levels of heterogeneity in the rates of homicide among patients with schizophrenia and that results were generally based on data from developed countries. He concluded that from his data, the rates of homicide in the mentally ill vary and are determined by socio-economic factors. In the presentation about crimes in the Russian Republic, where there were a high number of repeat offences reported, repeat homicide was associated with a younger age, rural location, a psychopathic personality and a family history of alcoholism. Overall, however, recidivism is rare. *Seena Fazel* presented a case control study design using data from Sweden. There were some potentially modifiable risk factors, for example non-adherence to treatment, or chronicity of illness; other risk factors, however, were similar to those for violence in general. There was limited association between the presence of hallucinations and delusions and risk of homicide. He concluded that violence risk assessment was an “inexact science” and that clinicians are unlikely to identify patients on discharge that will kill other people. *Olav Nielsen* also presented data from a systematic review/meta-analysis on patients who are likely to kill. He concluded that stranger homicide was rare and less common among patients with schizophrenia than in the general population (Nielssen et al., 2011). Cases of stranger homicide were more likely to be male, have a history of conduct disorder, antisocial personality, homelessness, negative symptoms, and were more likely to be never treated. He concluded that risk assessment may not prevent the occurrence of stranger homicide but early treatment could possibly prevent such cases.

Excess of schizophrenia among immigrants to Europe

Increasing evidence suggests that the incidence of all psychoses is higher in first and second generation migrants and minority ethnic populations from non-Western countries to Western Europe (Morgan et al., 2010). However, the mechanisms underlying this association are still unclear and a wide range of explanations have been proposed, from genetic to neurodevelopmental to psychosocial. *Wim Veling* (*Parnassia Center for Early Psychosis, The Netherlands*) highlighted the role of timing of exposure to migration as a vulnerability factor to develop a psychotic disorder. He reported the results from two studies, a 7 year first-contact incidence study and a multi-ethnic cohort study, examining the prevalence, respectively, of psychotic disorders and psychosis-like experiences amongst immigrants, focusing on their age at the time of migration. Specifically, lower age at the time of migration was associated with a higher incidence of psychotic disorders and psychosis-like experiences among immigrants (Veling et al., 2011). Following a psychosocial model and the hypothesis of psychosis as continuum, *Craig Morgan* (*King's College, London, United Kingdom*) showed the results from a large population-based survey conducted in South-East London (SEL-CoH study). Compared to white British, black Caribbean and black African subjects were between two and three times more likely to report at least one psychotic-like experience. The higher prevalence in the two groups could be explained in part by the individual level factors of childhood and adult disadvantage measured in the study. From a biological perspective, *Marie-Jose Dealberto* (*Queen's College, Ontario, Canada*) supported the new hypothesis that a recently discovered vitamin D deficit could be responsible for the increased risk of psychosis in black first-generation immigrants and for the differences in clinical traits. *Carsten Pedersen* (*University of Aarhus, Aarhus, Denmark*) reported that being born in an urban area represents a selective mechanism that increased the risk for schizophrenia in Danish individuals who emigrated to a foreign country (Pedersen & Mortensen, 2006). *Jean-Paul Selten* (*Maastricht University, The Netherlands*), in line with his social defeat model (Selten & Cantor-Graae, 2005), suggested that chronic experience of social defeat, such as being a member of a sexual minority, may lead to sensitisation of the mesolimbic dopamine system and thereby increase the risk for schizophrenia. He also reported that a history of childhood trauma, bullying and discrimination may be mediating factors.

Sensitivity to the environment

There is evidence that genetic liability for psychotic syndrome is mediated in part by differential sensitivity to environments of victimization, experience of social exclusion and substances affecting brain functioning, having an impact during development (van Os et al., 2010). *Anthony Grace* (University of Pittsburgh) found that administration of the mitotoxin methylaxosymethanol acetate (MAM) to rats during prepubertal period led to adult rats that exhibited neuroanatomical, pharmacological, and behavioral characteristics consistent with schizophrenia. These rats also exhibited hippocampal hyperactivity that corresponds to a loss of interneurons. This hyperactivity caused an increase in the activity of DA neurons, thus increasing the responsivity of the DA system to stimuli (Lodge & Grace, 2008). Using an experimental social defeat model, *Jim van Os* (*Maastricht University, The Netherlands*), showed that early trauma, i.e. daily stress, and affect dysregulation may lead to sensitisation of the mesolimbic dopamine system and thereby increase the risk for schizophrenia. *Oliver D. Howes* (*King's College, London, United Kingdom*) also examined the key role of dopamine in psychotic disorders but in association with cannabis use. Unlike other drugs of abuse, a history of cannabis use is not associated with alterations in striatal dopamine D2/D3 receptor availability (Stokes et al., 2012). Conversely, his findings suggested that CB-1 receptor availability was associated with sensitivity to THC effects on emotional processing in the amygdala. *Andreas Meyer-Lindenberg* presented data about neural mechanisms of urbanicity and migration. Current city living is associated with increased amygdala activity while urban birth and migration status impact amygdala circuits, altering social stress processing in second generation immigrants (Lederbogen et al., 2011). It is clear that the debate about nature vs. nurture is still ongoing and the question remains how this disorder results from a dynamic interaction between neurochemical drive and a psychological and social process.

II. GENETICS (Reported by Savita Bhakta, Christina Castellani, Tze Jen Chow)

William Byerley (University of California at San Francisco, U.S.A.), discussed the genetic heterogeneity of schizophrenia and the complexity of some Mendelian traits. For example, non-syndromic auditory deafness (prevalence of 1/2400); has over 100 loci and several or more alleles per locus. Similarly, could there be as many as 2400 schizophrenia loci? He suggested that the families used for previous linkage analysis studies could now be re-examined by whole genome sequencing. *Maria Karayiorgou* (Columbia University, U.S.A.), spoke largely about CNVs and *de novo* mutations as contributors to schizophrenia. She believes that *de novo* mutations that occur in the germline of parents account for sporadic cases and may explain the evolutionary paradox of schizophrenia. Chromosome 22q11 microdeletions likely account for 1-2% of non-familial schizophrenia cases. In an experimental design with 150 sporadic schizophrenia triads (with no family history of disease) and 150 triad controls, the results showed that 10% of sporadic cases carried at least one *de novo* mutation, compared to 1% of controls. In conclusion, *de novo* mutations occur with considerable frequency and create a constant source of rare and highly penetrant variants to the pool of mutations implicated in schizophrenia. One questioner asked why people with schizophrenia are more likely to have *de novo* mutations, Dr. Karayiorgou responded that majority of these changes are happening in hotspots in the genome which affect the brain.

Dr. Robin Murray (Institute of Psychiatry, King's College, United Kingdom) talked about gene-environment interaction in psychosis. CNVs are rare and therefore probably only explain about 5% of schizophrenia. Common variants have very small effects, but they may explain around 30% of the overall risk. The rest may be gene-environment interaction and

the study of cannabis, genes and psychosis may be a good model for understanding the this interaction

Overlap between schizophrenia and bipolar disorder

Much attention has been given in recent years to the question of whether schizophrenia is a distinct illness or the most severe end of a spectrum of disorders. *Mark Weiser* (Tel-Aviv University, Israel); presented the hypothesis, that schizophrenia, like other mental illnesses, is not a distinct construct and presented data on psychotic symptoms in the general population. When subjects were asked if they had had psychotic symptoms in the past year, 14% of the general population responded with “often or very often”. In addition, if a sibling was hospitalized for schizophrenia there was an increased risk for the development of schizophrenia and also for bipolar disorders.

Rene Kahn (University Medical Center Utrecht, Netherlands), spoke about the brain changes seen in schizophrenia and bipolar disorder. There are brain abnormalities in bipolar disorder but they are not as extensive as those seen in schizophrenia. He found an overlap between the two disorders expressed as white matter abnormalities and this was associated with the underlying genetic vulnerability. In addition, a higher familial risk for both schizophrenia and bipolar Disorder was associated with decreased white matter volume.

Vahram Haroutunian (The Mount Sinai School of Medicine, U.S.A.), focused on gene expression studies in the brains of people with schizophrenia. Ankyrin-G (ANK3) which anchors several proteins involved in tight junctions in the brain, has been found to have decreased expression in the brains of individuals with schizophrenia. In addition he presented recent evidence which has linked ANK3 SNPs to bipolar disorder. Dr. Haroutunian argued for symptom-based neurobiological substrates rather than a “disease-based” approach.

Michael O'Donovan (Cardiff University, U.K.) focused on the overlap of risk factors for schizophrenia and bipolar disorder. He presented many genome regions that are thought to have risk factors for both bipolar disorder and schizophrenia and found that the overwhelming majority are common alleles. Although, specific rare alleles did not appear to be frequently present in both disorders, CNVs do occur in both disorders, just different ones.

Inez Myin-Germeys (Maastricht University, Netherlands) discussed reactivity phenotypes for genetic studies. Is there a reactive phenotype that comes about from an environmental incident merged with genetic architecture? She and colleagues used the experience sampling method (ESM), looking at people 10 times a day over 6 consecutive days at random moments and following people in their real life, which gives the opportunity to measure exposures as they occur in real time and then to investigate people's reactions to those exposures. Overall, they found that those patients who were homozygous for the Met allele of the COMT (Catechol-O-methyltransferase) gene reacted more negatively to stressful situations. They looked at the MTHFR gene and found that the interaction between COMT and MTHFR (Methylenetetrahydrofolate reductase) and stress resulted in a higher effect of stress on psychosis.

The D2 receptor in schizophrenia

Anissa Abi-Dargham focused on striatal DA alteration in schizophrenia. In schizophrenia, DA release is positively correlated with the severity of psychosis (Laruelle et al, 1996) with an increase in the rostral caudate of the striatum (Kegeles LS et al, 2010). In contrast, cocaine addicts and alcoholics show decrease D2 receptor density and decrease DA release in ventral striatum (Martinez D et al 2004 and 2005). She studied the pattern in dual

diagnosis schizophrenia patients with alcohol dependence and found DA release to be similar to that in alcohol dependence alone, except within the striatal region. These findings could be due to abnormal D2 signaling, D2 receptor internalization or from effects on other components of the neural circuitry.

Christoph Kellendonck presented animal data further examining the role of striatal D2 receptors (D2R). He discussed the effect on striatal dendritic morphology and the role of inward rectifying potassium (Kir) channels. D2 transgenic mice exhibit selective cognitive impairments in working memory tasks that persist even after the transgene has been switched off (Kellendonck C et al, 2006). Deficits in incentive motivation are reversible and are likely due to increased excitability of medium spiny neurons (MSN) mediated by Kir channels. D2R upregulation reversibly decreases dendritic morphology of striatal MSN, reducing Kir channels in striatum leads to increased MSN excitability and morphology. Thus, for treatment of motivational deficits future drug development may be successful by targeting Kir channels.

Alessandro Bertolino discussed the effects of isoforms of D2R- D2S (presynaptic), D2L(postsynaptic) and D2 cAMP (independent) pathways on the brain. The intronic SNP (rs1076560) of the DRD2 gene on chromosome 11 showed increased D2S receptor density in GG homozygotes resulting in decrease DA stimulation with a bromocriptine challenge. The A allele of SNP (rs1130233) of the AKT1 gene along with the DRD2 gene modulates anterior cingulate activity during the performance of an N-back task. TT homozygote of the SNP (rs12630592) of the GSK3 β gene showed decreases in PFC activity and cortical thickness in Brodmann area 10. Thus, genetic effects are also important and the role of epistasis should be considered.

Anil Malhotra discussed the effect of genetic variation in D2R on antipsychotic drug efficacy and side effects. Treatment resistant patients with the deleted allele of the -141C Ins/Del SNP of DRD2 gene failed to respond to clozapine (Malhotra et al, 1999), while first episode drug naive patients without the Del allele were significant responders (Lencz et al, 2006). In a recent meta-analysis, the Del allele was associated with weight gain in patients treated with antipsychotics (Zhang JP et al 2010). Thus, the DRD2 gene polymorphism is important in antipsychotic efficacy and is related weight gain.

Sir Robin Murray led the discussion pointing out the limitation of having a small power with heterogeneity of drugs of dependence in the dual diagnosis study. He also suggested consideration of environmental factors and the effect of antipsychotic treatment on drug dependence in dual diagnosis patients. He stressed the importance of looking at gene $\times$ gene interaction and that antipsychotic drug response or related side effects can be guided by more than one gene.

Candidate genes

David Porteous reported on next generation sequencing of the DISC1 locus. He emphasized that DISC1 has both rare and common variants that contribute to altered biological functions. However, he commented that there is no GWAS result that shows linkage for DISC1 in schizophrenia, although strong association was found in recurrent major depressive disorder. He emphasized the importance of searching for biological significance, not only statistical significance.

Dan Rujescu gave a summary of genome-wide studies of CNVs in schizophrenia and questioned whether they are schizophrenia-specific or phenotypic-specific. Some de novo CNVs such as a deletion at 1q21.1 and 15q11.2 fail to replicate on a larger scale, while a maternally derived microduplications of 15q11-q13 has been.

Sequencing

Dick McCombie spoke on family studies of cognitive disorders. He shared an on-going study of synaptome and exome sequencing in bipolar disease using a very large data set. However, a lot of noise was generated and he explained a simulation test that was used to control the noise. He concluded by encouraging future studies on the genetic variations that may influence gene functions, and how to group and weigh variants to improve statistical analysis. *Shaun Purcell* continued the discussion on exome sequencing in schizophrenia. He spoke on his on-going studies using familial transmission to prioritize rare variants in Bulgarian and Swedish datasets. Two approaches were suggested to assess roles of variations: (1) to reduce the search by studying, for example de novo variants and large genic deletions; and (2) to cast a wider net, looking at large sets of genes and aggregated effects. *Shane McCarthy* spoke on Family Based Sequencing of Extended Pedigrees and Trios with schizophrenia and presented a few gene he thought were of interest in schizophrenia, such as the PER1 mutation, the highly conserved TRAPPC9, and MECP2 gene found on the X-chromosome. *Christina Castellani* presented data from an ongoing study examining the complete genome sequence of monozygotic twins discordant for schizophrenia. Two unique families each with a pair of monozygotic twin pairs discordant for schizophrenia were found to have CNVs some of which were de novo.

Risk expression

Afke Terwisscha van Scheltinga, presented findings from her study examining the association of common polygenic variation and total brain volume in schizophrenia, showing significant variation in total brain volume and white matter (WM) volume with maximum variation explained by a smaller set of SNPs. The SNPs associated with schizophrenia accounted for 5.1% of variance in the WM volume.

Johanna T.W. Wigman shared her findings examining the link between vulnerability and clinical need in young individuals with persistence of an extended psychosis phenotype. In a longitudinal study young individuals ages 10-18yrs were followed and those with persistence of subclinical psychotic symptoms were identified. These individuals were found to have higher levels of secondary distress, depression, social and attention problems and likely to seek clinical help.

Vera Morgan presented novel data from a large population prevalence survey with special focus on utilizing the data to guide psychosis research and mental health reform, details of which can be found on the website, <http://www.health.gov.au/internet/main/publishing.nsf/Content/mental-pubs-p-psych10>.

Merete Nordentoft shared her research on risk for suicide after a first hospitalization. Her team concluded that men have higher cumulative absolute risk compared to women for all of the diseases tested. Co-morbid substance abuse and deliberate self-harm increased the risk. The one-week critical period after the patient was discharged marked the highest risk for suicide.

Åsa Blomström focused on fetal exposure to maternal antibodies such as T.gondii and CMV. Archived maternal sera or fetal blood was used, Maternal exposure to T. gondii was associated with schizophrenia risk in offspring.

Nicholas J. Bradshaw presented his latest research on structural elucidation of DISC1 Pathway Proteins. He focused on DISC1 interacting genes: NDE1 and NDEL1, both known for their association with schizophrenia, and described the C-terminus fold-back mechanism of the NDE1/NDEL1 which confers protein stability and facilitates protein-protein interaction.

Sherry Leonard introduced a new gene, *CHRFAM7A*, almost identical to *CHRNA7* gene, but with copy number differences. She spoke on the expression and function of both *CHRNA7* and *CHRFAM7A*. The *CHRNA7* gene codes for $\alpha 7$ receptor, a nicotine receptor that also provides protection against inflammation. Patients with schizophrenia have less $\alpha 7$ receptor and thus have less immune protection. Smoking increases *CHRNA7* mRNA and protein in brain. Thus Dr. Leonard suggested that smoking might be a form of self-medication by patients with schizophrenia.

III. THE PRODROMAL STATE HIGH RISK AND EARLY PSYCHOSIS

(Reported by Ricardo E. Carrión, Kristen Haut, Laura M. Tully, MS Byun, Ashleigh Lin)

The Italian research experience with first episode psychotic patients

This special session focused on studies of first episode psychosis (FEP) across research centers in Italy. Collectively, the studies highlight the importance of clarifying the gene-environment interaction in schizophrenia. *Ilaria Tarricone* (Bologna University, Italy) discussed the 8-year, prospective FEP study that aimed to assess the incidence rate (IR) of FEP in Bologna, a large urban city in Northern Italy. Dr. Tarricone reported that while the overall IR of psychosis in Bologna is 16.4 per 100,000 inhabitants per year, the IR was doubled for migrants at 3.9% (38.8 per 100,000). These results suggest that overall IR is masking a growing problem of instability and lower social cohesion among the increasing immigrants. *Sarah Tosato* (University of Verona, Italy) highlighted the findings of the Psychosis Incident Cohort Outcome Study (PICOS), a large multisite (currently 28 sites) research study located in the Veneto Region of northern-east Italy (Bertani et al., 2012). Dr. Tosato emphasized that sociocultural and contextual factors, such as tolerance and family support, mediate the impact of symptoms and disability. *Alice Mulè* (University of Palermo, Italy) presented data on the incidence of psychotic disorders in Palermo, the capital of Sicily located in southern Italy. Prevalence rates of psychosis in Palermo were similar to those observed in Bologna and far lower than the typical IR of 3.17% found in England (Kirkbride et al., 2012). Dr. Mulè hypothesized that social network structures and cohesion might have the potential to mitigate the risk factors of psychosis in their region. Finally, *Marta Di Forti* (Kings College, UK) and *Valentina Rumeo* (University of Palermo, Italy) presented and compared data on FEP from Palermo and South-East London in relation to cannabis use. Palermo FEP with cannabis use had a lower mean age of onset (23 years-old) and were more likely to live at home with parents when compared to patients in London. Dr. Di Forti attributed the earlier age of onset in Palermo with the high proportion of males in the sample (83%), which is consistent with previous reports (Hafner et al., 1998; Larsen et al., 1996). Regional differences, rather than cannabis use, accounted for the large variation in social and role functioning.

Intervening in people at-risk for psychosis

This session addressed the outcome of recent attempts to develop interventions to prevent transition to psychosis or minimize illness severity in ultra-high risk (UHR) patients. *Anthony Morrison* (University of Manchester, UK) discussed a randomized-controlled trial (RCT) of Cognitive Therapy (CT) in UHR individuals demonstrating greater reduction in symptom severity with CT. Contrary to previous results (Morrison et al., 2004), no significant difference in transition to psychosis was found with low rates in both the CT (6.9%) and control groups (9%). On the other hand, *Mark Van der Gaag* (VU University and EMGO Institute) reported on a CBT trial in UHR patients with recent social decline, finding reduced transition to psychosis in CBT patients with many in both groups showing symptom remission. *Patrick McGorry* discussed a RCT investigating CBT with and without

antipsychotic medication in UHR patients. Both treatment groups as well as placebo-controlled supportive therapy improved significantly with no group differences at follow-up. *Andreas Bechdolf* (University of Cologne, Germany) discussed the design and sample of a RCT to address differential efficacy between CBT, antipsychotic medications and nonspecific treatment. A majority of patients reported Axis I psychopathology and psychosocial treatments were generally preferred to medication. *Dr. Paul Amminger* (University of Melbourne, Australia) reported that while Omega-3 fatty acid supplementation has been shown to reduce risk of transition to psychosis (Amminger et al., 2010), baseline levels of these fatty acids did not predict subsequent transition after controlling for clinical factors, although baseline levels of nervonic acid may be predictive (Amminger and McGorry, 2012). However, it is noted that transition to psychosis as a primary outcome measure may be problematic in light of the prevalence of APS in the general population. Instead, a broader understanding of a fluctuating “psychosis dimension” (van Os and Linscott, 2012) may impact the prognosis and course of individuals reporting these symptoms.

Multimodal neuroimaging of prodromal psychosis

This symposium had a particular focus on the use of multimodal neuroimaging techniques to understand the transition to psychosis and to identify reliable predictors of disease onset. *Paolo Fusar-Poli* (University of Pavia, Italy) presented research showing increases in striatal dopamine (DA) in CHR subjects associated with transition to psychosis (van Os et al., 2009), and hyperactivity in prefrontal regions during an fMRI verbal fluency task (Linscott and van Os, 2010). *Fusar-Poli et al.*, (2012) also showed gray matter (GM) loss in the inferior frontal gyrus (IFG) significantly associated with conversion to psychosis, indicating that this region is crucial in the transition phase. *Chris Chaddock* (Institute of Psychiatry, UK) presented research showing increased DA synthesis is associated with decreased neural activation in striatal, insula, cingulate and orbitofrontal cortices during reward processing, with greater abnormalities associated with increased symptom severity. *Stefan Borgwardt* (University of Basel, Germany) presented research demonstrating neural abnormalities in working memory processing in CHR subjects related to duration of the prodromal period; longer durations associated with functional hypoactivation and reduced GM in prefrontal and limbic regions (Amminger and McGorry, 2012). *Nikos Koutsouleris* (Ludwig-Maximilian-University, Germany) presented data demonstrating pattern classification analysis on neuroanatomical MRI in CHR subjects, resulting in approximately 80% prediction accuracy for the transition to psychosis compared with an approximate 10-40% using current methods. This study suggests that diagnostic accuracy could be improved through the use of neuroimaging (Koutsouleris et al., in press; Koutsouleris et al., 2009). *Stephen Lawrie* (University of Edinburgh, UK) presented new data from the Edinburgh High Risk Study demonstrating that genetic high risk subjects show reduced functional connectivity between the thalamus and the IFG compared to healthy individuals; this reduced connectivity correlates with increased delusions and reduced cortical surface area (Dauvermann et al., 2012). Collectively, these presentations suggest there are reliable neural predictors of psychosis onset that could be used to improve diagnostic prediction and develop preventative interventions.

Risk factors and prevention of psychosis: New NAPLS 2 Data

The North American Prodrome Longitudinal Study (NAPLS 2), an 8-site consortium (Addington et al., 2007), was designed to track the pathophysiological processes leading to psychosis by prospectively following a large sample of individuals at CHR. Five investigators from the consortium discussed findings from the ongoing project. *Tyrone Cannon* (University of California, Los Angeles, USA) demonstrated a greater rate of decrease in gray matter (GM) density and disrupted white matter (WM) integrity for CHR

converters over 12-months. These results implicate a possible path to schizophrenia via the disruption of normal cellular maturational events, such as synaptic pruning and increased myelination, in high risk individuals. *Daniel Mathalon* (University of California, San Francisco, USA) discussed enhancing diagnostic prediction with event-related potential (ERP) measures, presenting data demonstrating the Mismatch Negativity (MMN) amplitude reduction is associated with an increased likelihood of developing psychosis. *Larry Seidman* (Harvard Medical School, USA) used exploratory factor analysis to reduce the initial large set of neurocognitive variables to five domains: visuospatial abilities, attention/working memory, verbal abilities, and declarative memory. Deficits in declarative memory emerged as a key factor in conversion. *Jean Addington* (University of Calgary, Canada) highlighted the high reported baseline rates of childhood trauma and discrimination in CHR patients. Bullying-victimization, in particular, was associated with a higher rate of conversion to psychosis. *Barbara Cornblatt* (Zucker Hillside Hospital, USA) emphasized the persistent deficits in social functioning in converters over 12-months. These data showed that pre-morbid deficits in social functioning are long standing vulnerability traits, and can potentially contribute to accurate prediction of transition; therefore they are important in the treatment of disability.

Clinical and social characteristics of people at-risk for psychosis

Lucia Valmaggia (Institute of Psychiatry, UK) presented data that showed both help-seeking and non-help-seeking UHR individuals experience greater levels of psychosocial stress compared with healthy controls (HC) and current stress is associated with psychotic symptomatology. *Barnaby Nelson* (University of Melbourne, Australia) demonstrated that the disturbance of the basic self in UHR population is higher than HC and it might be related to the core phenotypic features of schizophrenia spectrum pathology and may provide a useful strategy to reduce 'false positive' cases (Nelson et al., in press). He also found that just over 50% of the UHR group with a poor outcome could be identified through their transition status, suggesting that not all transitions have poor functional outcome. He discussed that poor functional outcome itself might be closer to an underlying neurodevelopmental basis of schizophrenia than transition to psychosis per se.

On axis I and II comorbidity, *Andreas Bechdolf* (University of Cologne, Germany) found that help-seeking outpatients in the early initial prodromal state of psychosis (EIPS) showed more than 60% axis I and approximately 50% axis II comorbidity, suggesting that EIPS represents a clinical population.

Marco Armando (Sapienza University, Italy) demonstrated that early/very early-onset schizophrenia (EOS/VEOS) showed a different prodromal and psychotic profile compared to adult-onset schizophrenia (AOS), such as higher rate of developmental disabilities and positive/negative symptoms. This finding indicates that early detection and treatment may face different or additional challenges in EOS/VEOS compared to AOS. *Mark Weiser* (Sheba Medical Center, Israel) as a discussant emphasized the importance of providing interventions to the majority of UHR individuals who do not convert to psychosis but still have poor functioning.

Neuropsychology and neurodevelopment

Ian Kelleher (Royal College of Surgeons in Ireland) began with data showing that psychotic symptoms are relatively common in adolescence and indicate risk for later psychiatric morbidity (Kelleher et al., 2012). He presented data on children (ages 11-13) in the general population who were assessed for psychotic symptoms and neurocognitive ability. 22.6% reported psychotic symptoms and the presence of any psychotic symptom was associated with lowered processing speed and spatial working memory, suggesting that children and

adolescents with psychotic symptoms may show deviations from normal cognitive development.

Juliet Richetto (University of Milan, Italy) presented a study in which pregnant mice were treated with synthetic viral mimetic poly(I:C) or control solution, and then reared by poly(I:C)-treated or vehicle-treated surrogate mothers. Results showed that working memory and spatial recognition memory were impaired only in offspring of poly(I:C)-treated mothers, regardless of rearing. Alternatively, amphetamine sensitivity was evident in mice reared by poly(I:C)-treated surrogates, regardless of the viral infection of their mothers. This demonstrated both that prenatal inflammatory processes disrupt cognition and that postnatal maternal factors are sufficient to change offspring responsiveness to dopaminergic psychotomimetic drugs.

Monica Aas (University of Oslo, Norway) discussed the relationship between childhood trauma, cognitive function and the BDNF Val66Met (rs6265) genotype. Using data from 249 young people with schizophrenia and bipolar disorder, she demonstrated that Met carriers (Val/Met or Met/Met) showed lower perception and visual ability, and executive function than Val/Val carriers. However, within the group of Met carriers, poorer cognitive performance was only evident in those individuals who had experienced physical abuse. This highlights the need to focus concurrently on genetic and environmental risk factors together.

Larry Seidman (Harvard Medical School, USA) presented recent meta-analyses of neurocognition in the psychosis risk syndrome (PRS) and in youth at familial high risk (FHR) for schizophrenia under age 30. The results demonstrated that not only PRS but also FHR individuals showed moderate neuropsychological impairments, but subjects who developed psychosis showed more severe deficits than those who did not in both groups. He also noted that future work should assess genetic and environmental factors that explain the effect of familial history (Agnew-Blais and Seidman, in press; Giuliano et al., 2012).

Kristin Laurens (Institute of Psychiatry, UK) presented data on psychotic-like experiences (PLEs), demonstrating high rates of PLEs in children aged 9-11 (Laurens et al., 2007). She showed that, in these children, a psychotic-like construct was dissociable from, but correlated with, constructs representing internalizing and externalizing psychopathology. Regarding the trajectory of PLEs, Dr. Laurens found that PLEs were transitory for most children, but that their persistence was associated with increased risk for both internalising and externalising behaviors (Laurens et al., in press).

Helen L. Fisher (Institute of Psychiatry, UK) introduced a prospective study from a UK cohort that found that bullying and exposure to domestic violence in early childhood were associated with the presence of psychosis-like symptoms at the beginning of adolescence and were partially accounted for by indirect pathways via depressive symptoms, external locus of control and low self-esteem, which might be potential targets for preventative interventions. Another prospective study from the Northern Finland 1986 Birth Cohort was described *Pirjo H. Mäki* (University of Oulu, Finland). The results showed that antisocial and neurotic symptoms in childhood did not predict psychosis while both the positive and negative features, common in adolescents, were predictive. *Annica Fors* (Karolinska Institute, Sweden) presented a case-control designed study which showed an association between the presence of hearing/speech impairment at age 4 and adult risk of non-affective psychosis. This finding suggests that hearing/speech impairment, which can be detectable with inexpensive screening, might represent a potentially modifiable risk factor for non-affective psychoses.

Subclinical psychotic experiences: Associated psychopathology and outcomes

This session addressed factors impacting the clinical relevance of subclinical psychotic experiences (SPE). *Mark Weiser* (Sheba Medical Center, Israel) reported on the association between APS (Attenuated Psychotic Symptoms) and suicidal ideation in a psychiatric epidemiological study. APS demonstrated a dose-response association with suicidal ideation (odds ratio (OR) of 7.58 for 'strong' APS) though not completed suicide. *Ian Kelleher* (Royal College of Surgeons in Ireland) also reported on suicidal behavior in adolescents reporting SPE, finding that these symptoms increased risk for self harm, suicidal behavior, and suicidal plans/acts. *Richard Linscott* (University of Otago, New Zealand) followed-up on previous meta-analyses of SPE (Linscott and van Os, 2010; van Os et al., 2009), finding a 2.5% incidence and 7.2% prevalence of SPE. He demonstrated a probabilistic relationship between SPE and psychotic disorders with 7.4% developing a psychotic disorder but approximately 80% remitting over time. *James Scott* (University of Queensland, Australia) demonstrated increased rates (OR=1.61) of hallucinations in 14-year olds with a substantiated history of maltreatment, especially emotional abuse or neglect. *Cherrie Galletly* (University of Adelaide, Australia) discussed developmental factors influencing SPE. In addition to parenting, emotional disturbance and alcohol use, higher lifetime trauma was associated with SPE, though exposure to a single large trauma did not appear to increase risk. Females also show increased SPE with increased lead exposure in childhood. Thus, taken together, these studies demonstrate the clinical relevance of SPE, including their relationship with suicidality and the comorbidity with other psychiatric symptoms, suggesting the need to reconsider psychotic symptoms as relatively common mental symptoms that are part of a non-linear continuum from SPE to schizophrenia.

Affective dysfunction and associated developmental vulnerabilities across the continuum

Ashleigh Lin (University of Birmingham, UK) reported a study showing that within a non-psychotic help-seeking cohort, depressive symptoms and subclinical psychotic experiences co-occurred in time but never predicted each other over time (Wigman et al., 2011). In a general population study, the persistence of subclinical psychotic experiences was associated with higher depression, greater use of emotion-oriented coping, and lesser use of task-oriented coping (Lin et al., 2011). *Marco Armando* (Sapienza University, Italy) described a cohort with social anxiety disorder, comparing patients with and without clinically-relevant psychotic experiences (Armando et al., in submission). Patients with social anxiety disorder plus psychotic symptoms had higher levels of depression, negative symptoms and intolerance of uncertainty than patients with social anxiety disorder but no psychotic symptoms, indicating the pathological nature of psychotic symptoms. *Maria Michail* (University of Nottingham, UK) presented her findings from UHR and first-episode psychosis (FEP). She showed high levels of clinically-relevant social anxiety symptoms in both patient groups, which were associated with a greater likelihood of comorbid moderate/severe depression. Moreover, social anxiety symptoms were not related to the level of positive psychotic symptoms or the perception of threat in the FEP group. Dr. Michail presented a model for the link between social anxiety and psychosis, suggesting that shame proneness and shame perception regarding mental illness could feed social anxiety (Michail and Birchwood, 2009). *Ruchika Gajwani* (Birmingham and Solihull Mental Health Foundation Trust) presented data on the links between childhood trauma, attachment style and affective dysregulation in UHR and FEP. Affective dysregulation was high in both samples, indicated by elevated social phobia, depression and suicidal ideation. The proportion of participants with fearful attachment style was also high. Many had experienced childhood trauma, which in turn was related to insecure attachment (Gajwani et al., submitted). Overall, these studies demonstrated that affective dysregulation and psychotic experiences are closely intertwined at all stages of the psychosis continuum.

Distinguishing non clinical PLEs from clinical psychotic symptoms

Emmanuelle Peters (Institute of Psychiatry, UK) demonstrated that the key difference between non-clinical and clinical individuals with PLEs is not the experience itself, but how the individual appraises the experience, providing support for a cognitive model of psychosis (Peters et al., 2011). *Kristin Daalman* (University Medical Center, Netherlands) presented research examining the relationship between trauma and auditory verbal hallucinations (AVHs) in healthy and psychotic individuals. The data did not support traumogenic models of AVHs; there were no differences in the occurrence of trauma between the healthy AVH and patient AVH groups, nor was there a relationship between trauma and characteristics of AVHs (Daalman et al., in press). *Mike Jackson* (Bangor University, Wales UK) presented data comparing non-psychiatric voice hearers (NPVH) and psychiatric voice hearers (PVH). NPVH report less negative content, less negative appraisals, and a reduced need for control over their experiences, suggesting that metacognitive beliefs about psychotic experiences could contribute to the varying levels of distress and need for care in voice hearers. *Iris Sommer* (University Medical Center, Netherlands) presented fMRI and PET data comparing the neural correlates of AVHs in non-psychotic and psychotic individuals. Results showed no group differences in neural activation or dopamine synthesis during AVHs, indicating that it is not the physical nature of the experience of AVHs that distinguishes psychotic and non-psychotic voice hearers (Diederer et al., in press; Howes et al., in press).

IV. CANNABIS (Reported by Sahoo Saddichha, Felipe V Gomes)

Cannabis and psychosis: Is there a relation?

The association of cannabis with psychosis remains controversial. In this session environmental modifiers that influence the role of cannabis in psychosis were examined, *Antonella Trotta* evaluated the interactions between bullying during childhood and later psychosis and the influence of cannabis in the Genetics and Psychosis (GAP) study. Although there was a definite interaction with bullying, cannabis played no role among these individuals in developing psychosis in later life. Victims of bullying also did not indulge in any increased cannabis use when compared to controls. *Laura Ferraro* also analyzed the same sample from the GAP study to evaluate whether premorbid IQ, cannabis use and current IQ were related in patients with psychosis. She observed that patients who used cannabis had better premorbid IQ with a difference of 11.3 points in IQ than the non users. However, there was no evidence that cannabis had any protective role in cognitive functions, thereby concluding that cannabis use may provoke psychosis in individuals with abnormal neurodevelopment. *Fabio Allegri* evaluated whether cannabis has any role in the age of onset of psychosis, and whether sex has a moderating influence. Using survival analysis, he observed that males with cannabis use had the highest risk, followed by men using cannabis and other drugs combined. Women with cannabis and other drugs and women using only cannabis had a lesser risk, thereby concluding that being female may moderate the influence of cannabis on the risk for psychosis.

Paul Morrison attempted to explain the underlying mechanisms linking Δ^9 -tetrahydrocannabinol (THC), the main compound from cannabis, and the development of psychotic symptoms. One possible hypothesis was the release of dopamine from the striatum (Bossong et al., 2009; Cheer et al., 2004), although some studies do not show this (Barkus et al., 2011; Stokes et al., 2009). It may also be possible that THC can disrupt neuronal oscillations that seem to depend on reciprocal glutamatergic and GABAergic connections (Morrison et al., 2011; Uhlhaas and Singer, 2010). A further complication was the finding that pre-treatment with cannabidiol (CBD), a major cannabis constituent which is devoid of the typical effects of the plant, was able to decrease the THC-elicited positive psychotic

symptoms in healthy volunteers. *Philip McGuire* then presented data on the effects of THC on cognitive and emotional processing and provocation of psychotic and anxiety symptoms with an attempt to differentiate the effects of THC from those of CBD. He showed that THC and CBD had opposite effects on the neuronal and symptomatic response to fearful faces. CBD reduced the subjective anxiety, an effect related to activation in the amygdala and the anterior cingulate cortex, whereas the anxiogenic effects of THC were related to effects in frontal and parietal areas (Fusar-Poli et al., 2009). Additionally, *Bhattacharyya et al. (2012)* investigating the effects of THC and CBD during attentional salience processing showed that THC and CBD differentially modulate prefrontal, striatal and hippocampal function. These effects may contribute to the effects of cannabis on the risk of psychotic disorders and explain the therapeutic potential of CBD as an antipsychotic. *Jose A. Crippa* focused on the antipsychotic properties of CBD, which have been demonstrated in several studies (Zuardi, 2008; Zuardi et al., 2009). Dr. Crippa demonstrated that CBD can produce multiple pharmacological effects, such as anxiolytic, anticonvulsant, antidepressant, antioxidant, anti-inflammatory, by different mechanisms (for review see Izzo et al., 2009). However, CBD may not be effective for treatment-resistant schizophrenia. *Markus Leweke* presented evidence from a double-blind, randomized clinical trial in acute schizophrenia that CBD treatment was accompanied by a significant increase in serum endocannabinoid anandamide (AEA) levels, which was significantly associated with clinical improvement, suggesting that inhibition of AEA deactivation may contribute to the antipsychotic effects of CBD (Leweke et al., 2012). In addition, significantly higher levels of serum AEA and palmitoylethanolamide were observed in twin pairs discordant for schizophrenia and bipolar disorder when compared to healthy twins, suggesting a protective role of AEA in schizophrenia.

However, in addition to the above, there are other environmental factors that may play a role in developing psychosis. *Rebecca Kuepper*, in her earlier studies, had observed that cannabis use is definitely one of the factors which increase the risk to develop psychosis. In her latest findings, she presented data which showed that in such individuals who smoke cannabis and later develop psychosis, trauma increases the risk by nearly 1.5 times (Konings et al., 2012), and only in urban areas (but not rural), cannabis may increase the risk of developing psychosis (Kuepper et al., 2011).

Migration with increasing number of moves also increased the risk (Kuepper et al., 2011). She hypothesized that dopamine reactivity is higher in such individuals and their relatives, when exposed to THC, but not in controls, leading to a common molecular mechanism.

Genetic factors are one of the strongest mediators of this tenuous link between cannabis and psychosis. *Deepak Cyril D' Souza* evaluated the role of several genes including the CNR1 gene on Chromosome 6q14 which coded for the CB1 receptor, GABRA 2 SNP on Chromosome 4 which coded for GABA receptor, Dopamine β hydroxylase gene and the COMT Val158Met gene. Administering THC in healthy individuals, he found no interaction effects for the CNR1 gene, GABRA2 SNP and Dopamine β hydroxylase; however COMT was moderately influential. *Marta di Forti* evaluated the gene environment interaction on cannabis and psychosis using the AKT1 gene, which is phosphorylated by THC. She used the SNP rs2494732 which has two allelic forms- CC and TT. Using a cohort from the GAP study, she observed that the AKT1 genotype by itself did not predict psychosis. However, gene-environment interaction was significant with individuals with the CC alleles having increased risk to develop psychosis after cannabis use than the TT alleles. In addition, CC allelic individuals who used cannabis daily had a 7 times greater risk developing psychosis. She then went on to evaluate the roles of the other genes such as COMT and DAT1 on psychosis, which was not significant. But when all three risk genes were combined, the risk of psychosis increased exponentially. What this meant was that individuals having all three

risk genes and consuming cannabis daily had the greatest risk for psychosis. *Ruud van Winkel* confirmed the gene-environment interaction comparing the COMT and the AKT1 genes. He observed that AKT1 gene alleles were associated with schizotypy. However, whether an individual had 1, 2, 3 or all 4 risk alleles, the risk of developing psychosis remained nearly the same, which was definitely higher than having no risk alleles.

In summary, cannabis and psychosis are definitely linked, but there are moderating influences of both genes and environment. Most importantly, it is the gene-environment interaction that plays a major role in determining who develops psychosis among all those who are exposed to cannabis use.

V. COGNITION (Reported by Jared W Young)

Intelligence and both schizophrenia and bipolar disorder

Avi. Reichenberg examined whether premorbid cognitive function was distinguishable in patients with schizophrenia (SZ) compared to Bipolar Disorder (BD). A population study was conducted identifying subjects developing SZ patients without affective symptoms, SZ with co-morbid affective symptoms, bipolar psychotic patients, and nonpsychotic patients with BD. Those that developed SZ exhibited poorer cognition (social work, physical activity, and school adjustment) than healthy subjects, those with BD comorbidity exhibited normal social functioning. Male nonpsychotic patients with BD exhibited better cognitive performance than controls (verbal analysis, math, and non-verbal analogies), while females did not. IQ scores <85 meant a 2-fold increase risk of SZ in male, but a 4-fold increase in females. Individual differences occur within cognitive domains and modularity within SZ and BD can be identified (Newman, 2006). When grouped, SZ and BD subjects appeared in groups separated by severity of dysfunction, but the ratio of SZ to BD was greatest in most severely impaired and lowest in the least severely impaired group.

Neurocognitive Functioning in Twins Discordant for Schizophrenia and Bipolar Disorder—*Rachel Higier* studied twins discordant for schizophrenia and for bipolar disorder. SZ patients performed worst at verbal fluency, while SZ cotwins were normal. BD patients did not differ from controls, while their unaffected cotwins performed better than controls in verbal fluency and had higher positive temperament traits. Patients with SZ exhibited the lowest positive temperament ratings.

Intelligence in Bipolar Disorder: Normal, Impaired or Enhanced?—*James H. MacCabe* examined the cognitive performance of 13 and 18 year olds whom went on to develop SZ or BD. Cognitive data was normalized to unaffected control data. All but spatial memory was normal in 13 yr olds that developed SZ, while by 18 years of age, all cognitive measures were poor, even though SZ onset was not until about age 25. Subjects that developed BD outperformed controls on every task at both time points (although reasoning was normal at 13 years of age). Dr. MacCabe proposed a 3 Hit model: 1) SZ have premorbid IQ deficits, premorbid BD subjects may even be above controls; 2) Both groups get worse during adolescence; and 3) patients decline further after illness onset (although this could be affected by medication, or distraction due to the illness). The decline in performance from 13 to 18 year old was only relative to the normal population. Thus, it is also feasible that premorbid SZ subjects simply did not learn as readily as controls over this timeframe.

Simon Kyaga studied the link between genius and insanity, something recognized since the time of Aristotle. Interestingly, creativity has been associated with the neuregulin 1 gene and with increased psychosis risk (Keri et al., 2009). SZ, BD patients and their relatives had a significant increase in the likelihood of holding a position of artistic creativity, but significance was lost when problem solving was included. BD and Autism patients were

more likely to be scientific, while patients with SZ were as likely to be employed in scientific as artistic careers. The presence or absence of psychosis in BD did not affect profession.

VI. PSYCHOSOCIAL STUDIES (reported by Eva Velthorst, Adelufosi Adegoke, Gregory Strauss, Ahmet Yiğit Aktener)

Understanding the path to better functioning

Elyn Saks (University of Southern California) examined high achieving (occupational status) patients diagnosed with schizophrenia and how they manage their symptoms (Cohen et al., 2011). She used a qualitative method to obtain in-depth information about the patients' family history, social and daily functioning and living situation. Amongst others, taking medication as prescribed, utilizing social supports and controlling the environment were used as compensatory mechanisms. Common reported avoidances were the use of illicit drugs and alcohol, crowded social situations, and isolation. She emphasized the importance of examining strategies used by high achieving individuals, as these may be of use by patients who are less successful in managing their symptoms.

James MacKabe presented data on schizophrenia patients with superior intellectual functioning. He linked hospitalization records of individuals in Sweden to their school grades at age 16. Consistent with the literature (Khandaker et al., 2011), he found that having high school grades is in fact associated with a lower risk of developing schizophrenia compared to having average or low grades. First attempts to study the association between creativity and schizophrenia do suggest that there may be an association, particularly with a higher amount of creative professions in relatives (e.g. Kyaga et al., 2011). Dr. MacCabe subsequently examined whether the high intellectual functioning group does have subtle cognitive deficits. His data suggest that there is a group of high cognitively intact patients who are statistically indistinguishable from controls. However, when examining their results in more detail, their cognitive profile may show some minor cognitive deficits. The high intact groups were found to present with less negative symptoms and a better level of overall functioning.

Contrary to the first two presentations, *Keith Neuchterlein* focused on the *typical* person with an initial episode of psychosis. First, he examined a combination of Individual Placement and Support (IPS) and social skills training as a way to help first episode patients to return to competitive work as soon as possible. In his 18-month RCT, he compared this combination to a comparison group with standard approach and found that IPS essentially doubled the amount of people going back to work or school within 6 months, and IPS seemed to lead to persistent improvements in their return to work or school. Second, in a 12-month RCT he looked at the additive role of long-term injectible risperidone in a similar group. He found that (in addition to IPS) consistent use of anti psychotic medication in the period after an initial episode reduces relapse risk but also further improves cognition and work functioning. The findings suggest that medication adherence was driving these advantages.

Jean Addington aimed to determine predictors of good functional outcome, both in a first episode sample (FEP) and in a group at Clinical High Risk (CHR) for developing a first psychosis. She found the percentage of patients with a good level of functioning to decline with the severity of the illness. In those who met the CHR criteria, 60% did have good functional outcome, among those at CHR who actually developed a psychotic illness, 30% had good outcome. In the FEP group with a clear diagnosis of a psychotic illness, good outcome was even less. For both FEP and CHR it was early functioning and particularly the

level of negative symptoms, which differentiated good and poor functioning individuals. Dr. Addington suggested that understanding the beginning and course of poor social and role functioning may be very crucial in our understanding of schizophrenia, even more so since poor functioning can be present in those who do not go on to develop a psychotic illness as well. *In summary*, recovery to a high level of functioning from schizophrenia is possible.

Integrating social and biological factors to predict the course and outcome of psychosis

Evidence from two large epidemiological first episode psychosis cohorts were presented (PICOS: the Psychosis Incident Cohort Outcome Study (PICOS) conducted in Italy and the Aetiology and Ethnicity in Schizophrenia and Other Psychosis (AESOP) in the United Kingdom. *Sarah Tosato* (University of Verona, Italy) presented baseline findings about the impact of cannabis use on the age of onset of psychosis among FEP patients in the PICOS study. The study reported that 20% of FEP patients were cannabis users, the prevalence being higher than that found in the general population. A strong correlation was found between male sex, younger age and cannabis use among this cohort. Also, cannabis users in Italy have an earlier age of onset of FEP after controlling for sex and diagnosis, at least in vulnerable subjects. She concluded that the window before the development of frank psychosis among young people taking cannabis in Italy is a time for intervention in order to prevent long-lasting disability and improve functioning.

Antonello Lasalvia (University of Verona, Italy) reported other findings from the PICOS study, focusing on the predictors of two-year outcomes among FEP patients in Italy. Previous studies have reported an association between long Duration of Untreated Psychosis (DUP), poor Premorbid Functioning (PF) and poor clinical as well as social outcomes (Silverstein et al., 2002). In the PICOS study, premorbid functioning was moderately impaired in 40% of subjects, being worse in patients with schizophrenia than other diagnostic groups. At two years follow-up, 82% of patients were still in contact with services, schizophrenia diagnostic groups (especially those with continuous symptoms) being more engaged while the affective psychosis group were less engaged. Also poor PF, especially in adolescents, predicted worse clinical outcome (negative and disorganised symptoms). He concluded that the low predictive power of PF and DUP shows that other significant variables may be involved in predicting 2 year outcomes among FEP patients.

Craig Morgan (Institute of Psychiatry, King's College, London) presented initial findings from the AESOP-10 study regarding ethnicity and the long-term course and outcome of psychosis. Previous studies have reported that the incidence rate for all psychoses is higher among black Caribbeans and black Africans in the UK (Fearon et al, 2006). In the AESOP-10 study, data from 365 patients of 437 (out of the initial 551 patients) that could be traced at 10years was examined to obtain information on the outcome. The result revealed that 22.7% of patients had continuous symptoms with no remission, 38.6% had episodic symptoms while 38.6% had neither episodic nor continuous symptoms. Black Caribbeans were more likely to experience a continuous episode of illness and more negative symptoms but less likely to harm themselves compared to Black Africans. Black Caribbeans and Black Africans are more likely to be re-hospitalised compared to white British. Black Caribbeans and Black Africans had higher odds (2.7 and 3.38 respectively) of being coerced into admission compared to British whites and are more likely to be unemployed, single and more likely to have poor housing.

Paola Dazzan (Institute of Psychiatry, King's College, London) focused on the clinical and biological predictors of outcome in the AESOP study at 10years follow up. Risk factors predicting outcome that were evaluated include diagnosis at onset, mode of onset, duration of untreated psychosis, neurological and neuropsychological functions. Up to 80% of patients with schizophrenia and bipolar affective disorder maintained the same diagnosis at

10 years follow up. Patients with schizophrenia at baseline were more likely at follow up to have negative symptoms, more likely to be still psychotic and more likely to have non-episodic course of illness. Also, patients with long duration of untreated psychosis (DUP) were more likely to have negative symptoms and more likely to have a continuous illness course type. Patients with insidious mode of illness onset at baseline were also more likely to develop the poor outcome indicators. There is also an increased likelihood for those with poor insight to have more negative symptoms at follow up. In the future, investigators in the AESOP-10 study aim to explore the weight of each risk factor in contributing to poor outcome and to evaluate how they interplay to predict clinical and social outcomes in individual patients.

Dual process theory: Automatic and controlled processes and their implications for psychosocial treatment

David Roberts (UCLA, Los Angeles, CA) introduced the concepts of automatic and controlled cognitive processes, and how schizophrenia patients demonstrate more impairment on tasks tapping into controlled than automatic processing (Gold et al., 2009). Deficits in controlled processing may predict deficits in the processing of social information and contribute to symptoms and functional impairments. By improving impairments in social cognition, one may be able to improve social functioning and symptoms of schizophrenia. However, current treatments do not always take these processes into account. New treatment programs that utilize strategies capable of augmenting automatic and controlled social cognitive processes are being developed, and there is some evidence that such psychosocial interventions improve social functioning in schizophrenia. For example, Dr. Roberts utilized a modified alternative explanation strategy, which he and colleagues termed the “Mary, Eddie, Bill technique”, that aims to change a patient’s attributional style and tendency to jump to conclusion by reducing effortful processes and facilitating more adaptive automatic thoughts. Mueller and colleagues have used “Integrative Neurocognitive Therapy”, a group psychosocial treatment that uses an integrated controlled and automatic processing approach to target cognitive functioning and improve social functioning. Douglas Turkington and colleagues (2008) have developed a Cognitive Behavioral Therapy (CBT) intervention for psychosis, which has shown consistent evidence of improving psychosis using techniques targeting automatic thoughts, core schemas, and cognitive distortions. Velligan and colleagues have developed a Cognitive Adaptation Training (CAT) intervention designed to account for deficits in controlled and automatic cognitive processes, which may achieve its effects on outcome by reducing controlled processing load while utilizing strategies that make cues easier to follow, increasing fluency experiences and making behavior less effortful, repeating actions until they are automatic and behavioral changes become habitual. In summary, changes in outcome may occur when techniques are used that target both controlled and automatic processes concurrently, potentially allowing patients to “reconstruct a narrative of themselves”. When repeated persistently, one’s self perception and response to others may change, which can allow for new automatic thoughts and the development of new, more functional behaviors.

Personalizing social and cognitive remediation

Kelly Allott (University of Melbourne, Australia) reviewed the literature indicating that social cognition may be a better predictor of real-world functional outcome than neurocognition, and suggested that despite developments in utilizing cognitive remediation programs to enhance neurocognitive ability and outcome, few interventions have been developed for social cognition. *Pamela Marsh and William Horan* presented evidence for two new social cognition training programs, which utilize manualized training to influence specific social cognitive processes, such as social perception, theory of mind, attributional style, and emotion perception. Both studies showed some improvement in specific social

cognitive domains, but there was little evidence for social cognitive enhancements being due to concurrent general neurocognitive training (Horan et al., 2011). *Alice Medalia and Francis Dark* discussed the utility and feasibility of personalized skills training and cognitive remediation interventions, and indicated that these procedures are well accepted by consumers, therapists, and trainers; however, organizational structure is crucial to maintain gains achieved. Thus, social cognitive training appears to be a promising new direction; however, appropriate assessment may be crucial for developing individualized treatment and successfully moving gains from the clinic to the community.

The use of neuroimaging in cognitive rehabilitation

Christos Pantelis (University of Melbourne, Australia) stated while it is suggested that cognitive deficits in schizophrenia are enduring and stable, there is emerging neuroimaging findings indicating a deteriorative process. Spatial working memory (SWM) is impaired before the illness onset but attention set shifting ability is progressively impaired as the illness advances. Wykes et al. in 2002 showed that cognitive remediation therapy (CRT) increased brain activity in areas associated with working memory. Cognitive enhancement therapy (CET) and cognitive adaptation therapy (CAT) are other significant cognitive rehabilitation approaches. SWM impairment at the onset suggests a neurodevelopmental arrest associated with dorsolateral prefrontal cortex (DLPFC) dysfunction. However, CAT for SWM is shown to be beneficial. Neurodegeneration is implied in findings such as attention set shifting deficits where orbitofrontal cortex impairment is prominent. CRT is also beneficial in such deficits.

Other studies of cognitive rehabilitation

Steffen Moritz (Hamburg-Eppendorf University, Clinic for Psychiatry and Psychotherapy) presented data on metacognitive training (MCT) in schizophrenia (i.e. thinking about ones' thinking). MCT enhances metacognitive abilities in patients with psychosis and also ameliorates cognitive biases subserving delusions. It consists of 8 modules administered twice weekly to groups of 4 – 8 patients. 8 modules consist of; Attributional Style (self-serving bias), Jumping to Conclusions (data-gathering, liberal acceptance, 2 modules), Changing Beliefs (in corrigibility), Empathy (theory of mind, Order, 2 modules), Memory (avoidance of intrusions), Self-esteem (depressive thinking styles). MCT reduced delusional belief and jumping to conclusions in patients with schizophrenia.

Douglas Turkington (University of New Castle, United Kingdom) described CBT for positive and negative symptoms. He stated that although a Cochrane review in 2012 showed CBT did not have a significant difference over other therapies, different groups of patients can have different amount of benefits. While one fMRI study with CBT found that 31.8% of patients with persistent auditory hallucinations had CBT related reduced activity in limbic and cortical regions, another similar study showed improvement in only 4.81% of patients. He summarized that CBT can be applied by case managers, is modestly superior to other talking therapies, is less effective on negative symptoms and can be tried in patients that do not accept medication.

Michael Green (University of California, Los Angeles, Semel Institute for Neuroscience and Human Behavior) described how social cognition is directly associated with community functioning. It encompasses emotional processes, social processes, attributional styles, theory of mind and empathy. It also seems to mediate the relation between neurocognition and functional outcome. Empathic accuracy, an important part of social cognition, is reduced in both positive and negative symptom patients according to fMRI studies. A 2 year pilot study showed beneficial results of social skills training in social cognition but not in social functional capacity. Dr. Green suggested future community training, possibly with

oxytocin augmentation prior to training, and the notion of adding social cognitive training to supported employment programs.

VII. SEX DIFFERENCES (Reported by Brandon Abbs)

Bruno Averbeck (the National Institute of Mental Health, USA, Laboratory of Neuropsychology) presented data on oxytocin administration in patients with schizophrenia and Rhesus macaque monkeys. Dr. Averbeck presented stereotyped and morphed facial expressions to patients with schizophrenia and control subjects, demonstrating that patients were less accurate than controls at naming the emotion the face expressed. When oxytocin and placebo were administered intranasally (otherwise, oxytocin does not cross the blood-brain barrier) to male patients in a separate double-blind cross-over study, emotion perception improved overall, explaining 22% of the patient/control difference seen in Experiment 1. Work elsewhere shows that looking at the face's eyes is related to better perception and oxytocin can increase looking into the eyes in patients with autism spectrum disorder. Dr. Averbeck has seen a similar effect in Rhesus monkeys, using this animal model to study the effect's underlying neural circuitry.

Leah Rubin (U. of Illinois, Chicago) showed that oxytocin may supersede fluctuating hormone effects. Dr. Rubin studied patients with schizophrenia compared with controls. All participants completed 2 study visits approximately 42 days apart, which meant that women were tested during different phases of 2 different menstrual cycles. Women showed typical hormonal variation in estradiol and progesterone irrespective of psychiatric diagnosis (follicular: low estradiol/progesterone; mid-luteal: high estradiol/progesterone). Women with schizophrenia had less progesterone and men had less free testosterone. Female symptoms varied with menstrual cycle (PANSS Total, positive, and general score lower in mid-luteal), but this change was explained by baseline oxytocin (greater oxytocin = fewer symptoms) not fluctuating hormones. In men, more oxytocin predicted fewer prosocial symptoms. Women recognized faces better during the early follicular phase with oxytocin showing positive-emotion attribution bias.

Cort Pederson (University of North Carolina, NC) presented data from clinical trials performed with David Feifel. A double-blind cross-over, proof-of-concept clinical trial was completed where patients were given oxytocin (40 IU) or placebo twice daily for 3 weeks then switched after a 1-week washout period. A 14-day parallel arm study with patients was also completed. The first group showed decreased positive and negative symptoms, including PANSS total score with treatment. In the 14 day study, significant improvement in the Brune Theory of Mind Test of 2nd & 3rd order false belief and deception, and PANSS social items was found. Patients administered oxytocin rated faces as being more trustworthy than when they were on placebo. In a second study, improvement on the California Verbal Learning Test's Total Recall and Short Delay Free & Cued Recall was found, suggesting that oxytocin may also improve cognition.

Heidi Wehring (University of Maryland, MD), presented data on patients who completed an ongoing adjunctive-therapy 3-week double-blind placebo trial. Symptoms on the Brief Psychiatric Rating Scale (BPRS) improved with oxytocin, especially negative symptoms, and the University of Pennsylvania Smell Identification Test showed better identification of pleasant smells. Oxytocin interacted with Diabetes Mellitus status with an effect on serum glucose level, suggesting a hypothalamic effect that interacts with baseline metabolic function.

Anita Riecher-Rössler, (University of Basel, Switzerland) reviewed sex differences in schizophrenia and the impact of estrogens and progesterins on clinical course and outcome.

She differentiated between the organizational effects of gonadal steroids acting through effects on brain morphology and synaptic connectivity and activation effects that act through effects on brain function (e.g., as a function of menstrual cycle, pregnancy, birth control, hormone therapy, etc.). In general, women with schizophrenia experience a later onset (including a late-life incidence increase around the age of menopause) and need less neuroleptic medication. Further, during the perimenstrual period where women experience low estradiol and low progesterone, there is an excess of onset/relapse and symptoms are typically worse compared with time periods when progesterone is higher. In the perimenopausal period, estrogen therapy can limit the need for antipsychotics and prevents relapse.

Cynthia Shannon-Weickert (University of New South Wales, Australia) investigated why a testosterone spike in adolescence does not protect males from schizophrenia onset. Male macaque monkeys leave their families during adolescence and assimilate with another social group, providing a natural study of testosterone's effects on social standing during adolescence. Dr. Weickert observed castrated male macaque monkeys and surgery-controlled monkeys during this transition. Castrated males did not rise in social status in the new group, but showed cognitive flexibility, while intact animals rose in status but showed less flexibility. In humans, testosterone improves negative symptoms and cognition, including inhibition in dorsal lateral prefrontal cortex (DLPFC). Androgen increases may not be as pronounced or have the same effect in males who develop schizophrenia, perhaps because of effects on androgen receptors in the DLPFC. These effects, in interaction with sex-steroid genes, could affect brain plasticity/adaptation to fluctuating hormone levels during adolescence and attenuate testosterone's effects in schizophrenia.

Martin van den Buuse (University of Melbourne, Victoria, Australia), presented on the interaction estrogen and dopamine receptors using prepulse inhibition (PPI; sensory gating) in humans and rats. He first showed that acute estrogen treatment in 15 healthy human females prevents PPI disruption caused by serotonin agonist treatment. In rats, estrogen was then shown to block PPI effects caused by disrupting NMDA and dopamine pathways. In nucleus accumbens, estrogen attenuated drug effects on D2 transporter and receptor density (receptor effects were also in caudate nucleus). In males, testosterone's PPI effect is less clear, but mouse models of spatial memory suggest testosterone interacts with genotype (in this case, BDNF and Reelin) to act on NMDA pathways (specifically, NR2B receptors). Together, data suggest diverse effects for gonadal hormones on a variety of neurotransmitter systems implicated in schizophrenia.

Andreas Meyer-Lindenberg (University of Mannheim, Germany) spoke on prosocial neuropeptides, which mediate social bonding and buffer against stress effects. Allelic variation in the oxytocin receptor OXTR (SNPs rs53576 and rs2254298; an autism risk gene) was shown to relate to amygdala volume sex differences (increase in males, decrease in females; measured through in vivo human structural MRI) and decreased hypothalamic volume (more so in males), as well as increased amygdala reactivity (in fMRI) in both sexes hypothalamus-anterior cingulate (ACC) coupling in males. Oxytocin administration reduced absolute amygdala reactivity and connectivity with brainstem regions, and vasopressin (found to affect social behavior in prairie voles) reduces ACC regulation and modulates temporoparietal junction activity during social recognition. These results have implications for possible new treatments that, concurrent with psychotherapy, may promote prosocial behavior and reduce social anxiety and stress reactivity.

VIII. BASIC SCIENCE SESSIONS (Reported by Maria D Rubio, Rachael Blackman, Natalie Beveridge, Frankie HF Lee)

Cellular trafficking in schizophrenia

Several cellular trafficking abnormalities are starting to emerge as candidate mechanisms underlying synaptic transmission dysfunction in schizophrenia. *Volker Haucke* (Freie Universitat Berlin, Germany) presented data supporting a pivotal role of Stonin 2, an endocytosis adaptor protein, in synaptic vesicle endocytosis rate, surface synaptotagmin distribution, synaptic vesicle number and seeking and impulsive behavior seen in illnesses such as Tourette's and schizophrenia. *David Cotter* (Beaumont Hospital, Ireland) presented a proteomic and genomic approach to the clathrin interactome in the pathophysiology of psychosis. *Chang-Gyu Hahn* (University of Pennsylvania, USA) discussed the selective increase in NR1 (NMDA receptor subunit 1) subunit expression in a PSD (post-synaptic density) subcellular fraction in schizophrenia and its implication in NMDA receptor functionality. Interestingly, this distinct increase is due to an increase in the NR1C2' subform and its interaction with the PSD. *James Meador-Woodruff* (University of Alabama at Birmingham, USA) examined the S-palmitoylation of proteins, showing an overall decrease in this post-translational modification in schizophrenia.

Animal models

Anthony Hannan (University of Melbourne, Australia) discussed how gene-environment interactions produce and modulate endophenotypes. Even in the genetic disorder Huntington's disease (HD), environment can change the course of the illness. When exposed to an enriched environment, R6/1 transgenic mice (HD model) showed delayed onset of motor dysfunction (van Dellen et al., 2000) as well as a correction of a depression-like endophenotype (Pang et al., 2009). Environmental enrichment also positively impacts schizophrenia models as evidenced by amelioration of prepulse inhibition deficits in Phospholipase C-beta 1 knockout mice (McOmish et al., 2008). *Urs Meyer* (Swiss Federal Institute of Technology (ETH) Zurich, Switzerland) presented a rodent model, inspired by human epidemiological studies, and focused on the role of prenatal infection and inflammation in schizophrenia. In a two-hit schizophrenia model, low dose poly (I:C) and peripubertal stress, prepulse inhibition deficits were only seen when both stressors were present. *Grainne McAlonan* (King's College London, United Kingdom) gave an overview of the use of MRI as a translational tool to study neurodevelopmental disorders such as schizophrenia and autism in mouse models. Dr. McAlonan showed how MRI can be used as a sensitive measure to study acute structural changes in disease. *Jared Young* (University of California at San Diego, USA) discussed the challenge of modeling negative schizophrenia symptoms in animals. Observing an animal's willingness to work for reward may be one way. This approach with schizophrenia models has yielded contradictory results, with D₁ receptor knockout mice showing less willingness to work (similar to patients) and phencyclidine-treated mice showing the opposite. Dr. Young explained these results by positing that PCP may lead to perseveration or have some stimulant effects.

Systems neuroscience underlying schizophrenia models

This symposium focused on a more comprehensive approach to the understanding of schizophrenia, targeting overall brain systems modifications in the illness. *Anthony Grace* (University of Pittsburgh, USA) discussed the MAM (methylazoxymethanol acetate) developmental disruption model of schizophrenia. He reported that hippocampal hyperactivity represents increased DA neuronal firing due to a decrease in GABAergic interneurons in this brain area. He found that pre-pubertal administration of diazepam prevented DA hyperfiring in animals. *Philip McGuire* (King's College London, UK) studied

the structure (parahippocampal volume), function (PF/midbrain connectivity) and neurochemistry (glutamate, DA levels) of this brain region in people with ultra high risk (UHR) of developing schizophrenia. He reported that baseline subcortical dopaminergic and glutamatergic function as well as functional and structural function in cingulate, prefrontal and medial temporal cortex at presentation are associated with later transition to the illness. He reported that the findings at presentation are associated with later transition to the illness. *Michael O'Donovan* (Cardiff University, UK) discussed the analysis of de novo rare genomic copy number variants that yielded evidence of mutations in synaptic function and in particular aspects relevant to cognition. *Carol Tamminga* reported on a study that showed a possible cause of hyperactivity in the hippocampus and its effect on brain anatomy. An increase in GluN2B/1 protein levels in CA1, GluN1 decrease in DG and BDNF mRNA increase in CA3, in addition to a possible increase in spine density in CA3, suggest a mechanism for the increase in synaptic strength in this area of the brain.

Oxidative stress, inflammation, and misfolded proteins

Accumulating evidence has suggested that oxidative stress, inflammation processes and misfolded proteins may be implicated in the pathology of schizophrenia. *Akira Sawa* (Johns Hopkins School of Medicine, Baltimore, USA) presented new data which supports the increased susceptibility to oxidative stress in patients with schizophrenia, specifically reporting decreased levels of glutathione (GSH) in the anterior cingulate cortex of schizophrenia patients as measured by magnetic resonance spectroscopy (MRS). *Jennifer Coughlin* (Johns Hopkins School of Medicine, Baltimore, USA) examined the cerebrospinal fluid (CSF) from patients with recent-onset schizophrenia (within the first five years of disease) and reported the novel finding of a dramatically reduced level of soluble superoxide dismutase-1 (SOD1), perhaps due to increased levels of insoluble and misfolded SOD1. *Kim Do* discussed work with Dr. Anita Kulak (Lausanne University Hospital, Switzerland) that discussed how deficits in GSH synthesis and regulation are vulnerability factors for schizophrenia. Notably, in a mouse model of redox dysregulation, treatment with the antioxidant N-acetylcysteine from gestation normalized many neurochemical alterations to wild-type levels. *Carsten Korth* (University of Dusseldorf Medical School, Germany) discussed the presence of misfolded proteins in the schizophrenia brain. Particularly, the misfolding of high molecular weight DISC1 was shown to be linked to specific conditions of oxidative stress. *Motomasa Tanaka* (Riken Brain Science Institute, Tokyo, Japan) also discussed protein misfolding and aggregation (notably, DISC1 co-aggregating with TDP43) in frontotemporal lobar degeneration (FTLD), a neurodegenerative disorder often misdiagnosed as schizophrenia in its early stages.

Neuropathology and electrophysiology

Christopher Chaddock (King's College London, United Kingdom) discussed how a neural abnormality in prediction error signals in a reward learning task exists prior to the onset of schizophrenia. Vibeke Catts (Schizophrenia Research Institute, Australia) reported that NMDA NR1 protein and mRNA levels were reduced in the dorsolateral prefrontal cortex in schizophrenia patients.

Darryl Eyles (Queensland Brain Institute, Australia) proposed a re-thinking of the dopamine (DA) hypothesis of schizophrenia. The most recent version of this hypothesis posits DA as the "Final Common Pathway" (Howes and Kapur, 2009). Based on evidence from epidemiologically driven animal models, Dr. Eyles suggested DA may represent the "start of the journey" toward schizophrenia rather than its endpoint.

Verian Bader (Heinrich-Heine University Dusseldorf, Germany) reported that DISC1 (disrupted-in-schizophrenia 1) protein and aggregates were capable of invading cells. Lisa-

Marie Greenwood (University of Wollongong, Australia) presented evidence that auditory mismatch negativity was decreased in chronic cannabis users and was correlated with psychosis-like symptoms. Margaret Niznikiewicz (Harvard Medical School, USA) reported no difference between schizophrenia patients and controls in EEG signal for neutral voice processing, while nearly all stages of neutral face processing were impacted in patients. Audiovisual processing in patients was less impacted than face alone. Mariken de Koning (Academic Medical Centre, Amsterdam) discussed how changes in non-displaceable binding potential (an indication of $D_{2/3}$ receptors' occupancy by endogenous DA) were not correlated with changes in prepulse inhibition. Dr. de Koning suggested these results were due to the markers measuring different things. Francois Gastambide (Eli Lilly, United Kingdom) discussed the viability of the mGluR5 positive allosteric modulator, LSN2463359, to reverse dysfunction in schizophrenia models. LSN2463359 attenuated deficits on an attentional set shifting and reversal learning paradigm in methylazoxymethanol acetate (MAM) but not phencyclidine (PCP) treated rats, a result that seems to be due to the non-competitive nature of PCP.

NMDA -deficiency hypothesis of schizophrenia

The exact mechanism by which disturbances in the glutamate system can lead to schizophrenia (SZ) remains unknown. This symposium focused on providing experimental and clinical data to relate the importance of NMDA receptor dysfunction in SZ. *Patricio O'Donnell (University of Maryland, MD)* stressed the importance of dopamine-NMDA maturational changes on GABA interneurons and their effect in maintaining a balanced excitation-inhibition cortical circuit. *Guillermo Gonzalez-Burgos (University of Pittsburgh School of Medicine, Pittsburgh, PA)* presented electrophysiological and computer-network model data that suggest activation of parvalbumin-positive GABA interneurons and generation of gamma oscillations are largely dependent on AMPA receptor-mediated excitation, but not NMDA. *Peter J. Uhlhaas (Max-Planck Institute for Brain Research, Frankfurt am Main, Germany)* highlighted the role of neural oscillation and synchrony in SZ using magnetoencephalography. SZ patients displayed a reduced high-frequency gamma-band activity (60-120Hz) and upregulated resting-state gamma activity. Dr. Uhlhaas also noted pronounced changes in high-frequency oscillations during maturation. *Daniela Alberati (F. Hoffmann-La Roche Ltd., Basel, Switzerland)* presented new preclinical and clinical data on RG1678 (bitopertin), a glycine reuptake inhibitor that enhances NMDA receptor function. RG1678 showed improvement in aspects of behavioral abnormalities in rodent models and it further increased the efficacy of risperidone and olanzapine but not clozapine. It represents a promising new treatment for schizophrenia as RG1678 is showing beneficial effects towards negative symptoms. *Marc Laruelle (Yale School of Medicine, CT)* reported an increase in dopamine transmission at D_2 receptors in the associative striatum in schizophrenia and that upregulation of dorsal lateral prefrontal cortex D_1 receptors correlated with poor working memory performance. He proposed that a deficit in NMDA receptor function in schizophrenia might contribute to the disturbances of dopamine transmission observed.

Blood biomarkers

The identification and characterization of putative biomarkers as objective indicators of illness cause, course, and/or treatment response represents a major challenge for schizophrenia research. Drawing from literature and his own studies. *Peter Buckley (Georgia Health Sciences University, Augusta, USA)* highlighted how BDNF might serve as a novel and heuristic potential biomarker of both molecular neurobiology and disease trajectory. *Sabine Bahn (University of Cambridge, UK)* discussed her development of a candidate biomarker panel in patient serum in drug naive, first onset schizophrenia patients. Using high throughput proteomic profiling a test has been developed that can be used to help

confirm the diagnosis of schizophrenia. *Marquis Vawter* (University of California, Irvine, USA) compared gene expression patterns in the brain and the periphery that enabled only co-expressed genes to be analysed. A panel of 22 mRNA transcripts associated with antipsychotic drug treatment response was identified. *Murray Cairns* (Schizophrenia Research Institute, Sydney, Australia) discussed findings of reduced microRNA expression in the peripheral cells of schizophrenia subjects. An 11-miRNA signature was identified that predicted membership into cognitive-deficit and cognitively spared subgroups of schizophrenia.

Role of glia in schizophrenia

Daniel Martins-de-Souza (Max Planck Institute of Psychiatry-Proteomics and Biomarkers, Munich, Germany) compared the protein expression profiles and reported differential expression of oligodendrocyte- and myelin-related proteins in post-mortem schizophrenia brains vs. controls. *Natalya A. Uranova* (Laboratory of Clinical Neuropathology, Mental Health Research Center, Moscow, Russia) found significant reduction of oligodendrocyte densities in BA39 of patients with schizophrenia, particularly within the poor/fair insight group. *Johann Steiner Steiner* (University of Magdeburg, Magdeburg, Germany) highlighted the protective effects of haloperidol and clozapine in enhancing the viability of OLN-93 oligodendrocytes under the serum and glucose deprivation model. These findings suggest novel mechanistic actions of antipsychotics and may help future development of treatments targeting against oligodendrocytes. *Mikhail V. Pletnikov* concluded the symposium by discussing the role of Disrupted-in-Schizophrenia 1 (DISC1) in astrocytes. Using an inducible astrocyte-specific mutant DISC1 mouse model, he found significantly lower levels of serine racemase and D-serine but no significant effects on glutamate uptake or any major behavioral abnormalities.

IX. BRIAN IMAGING (Reported by: Emre Bora, Maurice Cabanis, Meina Quan)

Progressive change in brain structure and function in psychosis

Matthew Kempton (Institute of Psychiatry, United Kingdom) reported his findings of a region of interest meta-analysis of medication naive schizophrenia patients. This meta-analysis found that medication naive patients had increased ventricular volume and also volume reductions in total brain gray and white matter, thalamus, caudate and hippocampus. He also compared his findings with first-episode (Steen et al 2006; Vita et al., 2006) and chronic schizophrenia (Wright et al 2000) metaanalyses. The only significant difference was that caudate volumes were smaller in medication naive patients compared with the other 2 groups of largely medicated patients. Dr. Kempton also emphasized the importance of conducting large-scale follow-up studies to investigate brain imaging abnormalities before the onset of psychosis and their change at multiple time points. He gave information about EU-GEI, a multi-center study, which will collect MRI data at multiple time points, including fMRI (hippocampus-striatum connectivity), cortical thickness, and prediction, using machine learning.

Oliver Howes (Kings College, London, United Kingdom) presented data from a meta-analysis showing that there is no consistent evidence for change in receptor, transporters and postsynaptic abnormalities of the dopamine system in schizophrenia (Chen et al 2011), however evidence is strong for increased presynaptic dopamine. Effect size of this abnormality is rather large in dorsal striatum (Cohen D=0.8) and this abnormality is specific to schizophrenia as it was not observed in bipolar and anxiety disorders and community subjects who reports hallucinations (Howes et al 2012). Dr. Howes and his group also found a similar increase in UHR subjects and this abnormality is related to outcome (Howes et al

AJPsych 2011). His longitudinal data also suggest that presynaptic dopamine further increase as psychosis develops (Howes et al., Mol Psych 2011). Moreover, presynaptic dopamine levels in striatum were found to be negatively related to glutamate levels in hippocampus in schizophrenia patients (Stone et al., 2010).

Stefan Borgwardt summarized evidence suggesting that gray matter volume abnormalities already exist in UHR (Fusar-Poli et al., 2011) and these abnormalities are progressive, even beyond 5 years. Unlike volume abnormalities, cortical surface abnormalities might be more static. In both genetic and clinical high risk studies converters have more severe progressive changes (Sun et al., 2009; Takahashi et al 2009). However, there are limited findings for white matter, *Rene Kahn* (University Medical Center Utrecht, Utrecht, Netherlands) reported similar progressive structural changes and also provided evidence suggesting that genetics, illness related factors and cannabis use have effects on progressive changes. This session emphasized the need for further multimodal, multi-center studies.

Neural network changes and dysconnectivity

Olaf Sporns (Indiana University, Bloomington, Indiana, United States) reviewed different approaches for clarifying the structure and function of various network systems. He described brain networks and their particular topological characteristics (e.g. small-world attributes, modularity, hubs) and emphasized the relevance of connectomics for understanding the development of dysfunction.

Edward Bullmore (University of Cambridge, Cambridge, Cambridgeshire, United Kingdom) discussed the evolutionary and developmental implications of economical network models of the connectome. Economical models, which try to explain the formation of different networks, look at connections between various positions in terms of a trade-off between cost and value. These theories can be applied to connections between different brain regions. Current studies using graph theory have shown that in comparison to healthy controls brain networks in schizophrenia patients are slightly more efficient and robust (higher topological values), but less parsimoniously connected (higher cost). These findings suggest that the so-called schizophrenia connectome may emerge due to a developmentally biased economical trade-off in the network formation. Overall, Dr. Bullmore concluded that schizophrenia is a disorder of large scale brain network organization and the new network science has much to offer in elucidating the phenotype and its pathogenesis from neuroimaging data. *Martijn Van den Heuvel* (University of Utrecht, Utrecht, Netherlands) also presented new data showing the importance of brain hubs in terms of efficiency and of hub dysconnectivity for understanding schizophrenia pathology.

Alex Fornito (NICTA Victorian Research Laboratory, The University of Melbourne, Victoria, Australia) presented evidence from several structural and functional neuroimaging studies of brain connectivity disturbances in people with schizophrenia. His findings suggest that patients show generalized deficits in functional connectivity that particularly affect links between frontal and posterior areas, and which also appear to have an anatomical basis. In some, but not all cases, these network changes were correlated with measures of intra-regional dysfunction. Furthermore, Fornito presented data indicating that disturbances in brain network topology play a role in patients' cognitive deficits, and that these topological properties are under genetic control, leading to the idea of connectivity-based disease endophenotypes. In summary, connectomics may be important not only in the context of understanding the genesis of schizophrenia but for developing treatments including psychotherapeutic approaches.

The effects of psychopharmacologic treatment on the brain

Markus Leweke presented the effects of antipsychotics on functional and structural plasticity in the human brain. He summarized the action of dopamine on prefrontal cortex (PFC), as well as PFC function coupled to subcortical dopamine activity (Meyer-Linderberg et al., 2002). In addition he discussed genotype-directed neurocognitive pharmacotherapy of schizophrenia, such as with COMT polymorphisms, D2 modulation, as well as potential new targets beyond dopamine (Yücel et al., 2008).

Nancy C. Andreasen (University of Iowa, Iowa City, USA) discussed the lifetime trajectory of brain tissue change in schizophrenia, showing that tissue loss is already present in neuroleptic naïve patients at onset, which indicates the occurrence of an intrinsic disease process. She then presented data on the relative contributions of three factors that could affect tissue loss after onset: substance abuse, relapse duration, and medication; she used a statistical model that permitted examination of their effects independently. Substance abuse had essentially no effect, but both treatment intensity (measured in dose years) and relapse duration were related to both generalized and specific tissue loss in multiple brain regions. She emphasized that these results were averages, and would not apply to all patients. In the context of the relapse effects, she emphasized that treatment is beneficial; in the context of the dose year effects, but she emphasized the importance of using the lowest possible dose to control symptoms.

Rene S. Kahn (University Medical Center Utrecht, Utrecht, Netherlands) presented the reasons why antipsychotics are good for the brain. He talked about progressive brain change and outcome, and mentioned the relation between total duration psychosis/remission and brain changes including gray matter (GM) loss and lateral ventricle (LV) volume increase. He mentioned that big change happens early on in the disease and the more brain change in the first year, the poorer outcome later in 2 years or 5 years. Then he gave examples of antipsychotics effects on cerebral, LV, hippocampus, and frontal GM volume, and cortical thickness (e.g. van Haren et al., 2011). He discussed that in schizophrenia, the excessive thinning of cortex is most pronounced in the frontal and temporal areas, and progresses across the entire course of the illness, and appears related to outcome while medication intake appears to attenuate these changes.

Eva M. Meisenzahl (Ludwig-Maximilians-University, Munich, Germany) presented differential effects of neuroleptic treatment on clinical improvement in first-episode schizophrenia. She described the causes of brain pathology in schizophrenia, including unknown genetically driven, altered neuroplasticity, and possibly medication effects. She reported results from MRI scans of medication naïve patients (Meisenzahl et al., 2012, unpublished) and clinical course under medication during the first year of illness, using new multivariate methodology. In her study, the progressive morphometric alterations underlying schizophrenia appear to be independent of treatment- and course-induced neuroplasticity. This may support a plastic and dynamic CNS rebalance rather than predominantly toxic effects in schizophrenia patients, while the actual pathophysiological disease-dependent process seems to be progressive.

Neuroimaging

Lena Palaniyappan (University of Nottingham, Nottingham, United Kingdom) reported findings from 4 independent cohort examining cortical gyrification, surface area and thickness using the Freesurfer software program. Three of these were cross-sectional analyses in adult patients and one was a longitudinal sample of early onset psychosis. In cross-section, the most common finding was reduction in gyrification of the fronto-insular cortex. Early onset patients had increased gyrification in the same region however

gyrification was decreased on follow-up and this reduction was related to poorer semantic fluency. Also, decreased gyrification in the right fronto-insular cortex and left dorsolateral prefrontal cortex was related to more severe disorganization symptoms.

Machteld Marcelis (Maastricht University, The Netherlands) presented findings of a study examining the effect of trauma on white matter integrity in schizophrenia, in their relatives and controls using diffusion tensor imaging (DTI). DTI data was analysed using TBSS (Tract Based Spatial Statistics). Patients had decreased fractional anisotropy (FA) and their relatives had intermediate findings between patients and controls. Past trauma had some effect on FA findings in patients however this did not explain all findings.

Vina Goghari (University of Calgary, Canada) presented a study examining effects of 8 weeks of atypical antipsychotic treatment on middle frontal gyrus thickness in first-episode psychosis. All of the patients were medication naive. There were no baseline abnormalities in the patients however the thickness in middle frontal regions was increased especially in rostral part over time. It was speculated that changes in glial cells might play a role in these findings.

Ofer Pasternak (Brigham and Women's Hospital, Boston, MA) reported that free-water imaging revealed a global inflammatory effect and local axonal degeneration in first episode schizophrenia. He explained the abnormalities by two microstructurally separate components, the extracellular volume and the tissue anisotropy. He found a global increase in free-water, while tissue-FA was limited to frontal lobe.

Mette Nielsen (Center for Neuropsychiatric Schizophrenia Research, Copenhagen University Hospital, Glostrup, Denmark) used fMRI MID (monetary incentive delay) task (Cooper and Knutson, 2008) to examine reward anticipation before and after neuroleptic treatment. She found that at baseline, antipsychotic naive patients had reward disturbances in ventral striatum that were related to positive symptoms, and dopamine D2 blockade improved the disturbances as well as positive symptoms.

Nora Vyas (Child Psychiatry Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, United States) presented data on alterations in magnetoencephalographic (MEG) gamma oscillatory patterns during resting-state in patients with childhood-onset schizophrenia (COS), non-psychotic siblings and healthy controls. A recent MEG resting-state study on adult-onset schizophrenia (AOS) patients showed reduced gamma power in the posterior regions of the medial parietal cortex. The presented study aimed to investigate oscillatory patterns during resting-state in COS patients. Reduced activity in the alpha frequency band in the fronto-parietal network, and in the gamma frequency bands in the occipital lobe in COS was 'shared' in healthy sibling, suggesting that some of these circuit abnormalities could be trait markers for schizophrenia. The abnormalities in COS appeared to be stronger than those reported in AOS.

Peter Woodruff (Sheffield Cognition and Neuroimaging Laboratory [SCANLab], Academic Clinical Psychiatry, Dept. Neuroscience, Faculty of Medicine, University of Sheffield, The Longley Centre, Norwood Grange Drive, Sheffield, S5 7JT, United Kingdom) proposed a model for the genesis of auditory hallucinations and introduced the "saturation hypothesis", according to which auditory hallucinations compete with external speech for the same neurophysiological resources. He suggested that an "expectation/prediction error" influences the system, which alters the threshold activating the temporal lobe in response to signals of spontaneous activity in the auditory cortex interacting with external speech. This implicates a top-down modulation of the auditory cortical response and could explain the sensation of auditor hallucinations.

X. IMMUNOLOGIC STUDIES (Reported by M Dmítrzak-Węglarz, Aleksandra Szczepankiewicz)

Immune response in schizophrenia: Host-environment interactions

Alan Brown (Columbia University, NY, USA) gave an overview of studies suggesting a link between exposure to the influenza virus during pregnancy and the development of bipolar disorder (BD) and schizophrenia (SZ) in adult children (Brown and Derkits, 2010; Mortensen et al., 2011). He pointed to a number of limitations of these studies, in particular the difficulty in separating the impact of infection from other early risk factors, such as parental age, obstetric complications or hypoxia as well as misclassification of diagnosis and infection exposures. Therefore, serological biomarkers were used as markers in a prospective cohort study (Brown, 2012; Brown et al., 2004). The implications of the associations found are relevant for preventive immunization before pregnancy and improvements in hygiene.

Faith Dickerson (The Stanley Research Program at Sheppard Pratt, Baltimore, USA) focused on endogenous retroviruses (HERVs; elements of the human genome arisen from the insertion of retroviruses during cellular infection). A study of individuals with schizophrenia showed an increased rate of transcription of (HERVs) as well as antibodies to these agents in the cerebrospinal fluid (CSF) and blood (Perron et al., 2008; Yolken, 2004). Further work was directed at characterizing the specific antibodies, existing transcripts and homologue sequences of three retroviruses (MuLV, FIV and MPMV) and defining the role of these agents in recent onset psychosis, multi-episode schizophrenia and non-psychiatric controls. Elevated levels of MuLV and MPMV antibodies in patients with recent onset psychosis and MuLV and FIV in patients with acute mania were found. However, it was concluded that the elevated level of specific antibodies may be linked to infections as well as to abnormalities in immune system (Dickerson et al., 2012).

Michael Plentnik (Johns Hopkins University School of Medicine, Baltimore, USA) presented data from a study that evaluated the interaction between mutant human DISC1 (mhDISC1) and maternal immune activation implicated in schizophrenia (Abazyan et al., 2010). In this model the polyI:C was used to induce a strong innate immune response as it mimics prenatal exposure to infectious factors. It was found that in mutant mice prenatal interaction modulated secretion of inflammatory cytokines in fetal brains and levels of mhDISC1, endogenous mouse DISC1, and GSK-3 β . Possible DISC1 and neuroimmune/inflammatory pathway was discussed by Kamiya A et al. (Kamiya et al., 2012). These results confirmed that polyI:C-treated mhDISC1 mice are a valid animal model for schizophrenia with GxE interactions. Dr. Plentnik also focused on evidence linking *Toxoplasma gondii* infections to schizophrenia possibly by affecting neurotransmitters, in particular dopamine, glutamate and GABA which are upregulated by DISC1 and thus may affect cognition and behavior (Yolken et al., 2009).

Dorothy Schaffer (Stanford University School of Medicine, Stanford, USA) showed that microglia are active phagocytes of unstable synapses and play a major role in synaptic pruning during postnatal development in mice (Stevens et al., 2007). Examining gene activity in neurons confirmed that synapses showed increased activity of the immune C1q gene. C1q is a classic innate immune molecule which initiates the molecular pathway for tagging cells for elimination. Experiments in retinal neurons suggested that C1q, C3 and other members of the complement cascade mark certain synapses for elimination. These ligands are recognized via CR3 receptors on the microglia cell surface. Further studies will be carried out to clarify the mechanism of recognition and identification of unstable synapses and whether this mechanism is disturbed in schizophrenia.

Nicola Cascella (Meryland University School of Medicine, Baltimore, USA) reported results of an investigation of the prevalence of Celiac disease (CD) and gluten sensitivity (GS) in schizophrenia from the original CATIE cohort (Cascella et al., 2011). The analysis was focused on tTG6 antibodies and their relationship to anti-tissue transglutaminase 2 (tTG2) and to antigliadin antibodies. Results indicated a higher prevalence of tTG6 antibodies in schizophrenia and confirmed that it may be a useful biomarker to identify patients whose gluten-free diet can potentially contribute to the improvement of symptoms (Cascella et al., 2012).

Models from immunology and experimental medicine

Preben BoMortensen (University of Aarhus, Aarhus, Denmark) stressed the important role of epidemiological studies in generating hypotheses regarding an immunological component to schizophrenia as well as testing it. In previous studies it was reported that some infections may increase the risk for schizophrenia, in particular when genetic polymorphisms are also taken into account (i.e. NMDA receptor polymorphism and HSV2 infection; Demontis et al., 2011). Future direction will be focused on monitoring familial/genetic susceptibility to infections as important risk factors in schizophrenia. It was emphasized that autoimmune diseases predicted increased risk of schizophrenia in individuals with past history of autoimmune diseases (Eaton et al., 2010). In studies analyzing the synergistic effect between schizophrenia risk and presence of infections and autoimmune diseases, a higher odds ratio was observed in comparison to small effects of each risk factor separately.

Alan Brown (Columbia University, NY, USA) focused on the analysis of prenatal exposure to infections and the risk of schizophrenia. The main observation was that influenza infection during the first half of pregnancy was significantly associated with schizophrenia and that maternal seropositivity to *Toxoplasma gondii* showed correlation with schizophrenia with OR of 2.6 (Brown, 2006). See above. The most important infections accounting for schizophrenia development were respiratory and genital/reproductive infections (with the ORs of 2.06 and 5.03, respectively) after adjusting for maternal age, race and mental illness. In the DIBS (Developmental Insult and Brain Anomaly in Schizophrenia) study schizophrenia was analyzed as an outcome in the CHDS (Child Health and Development Study) cohort and significant relationship between prenatal serologically confirmed infection (influenza, *T. gondii*) and executive functions in schizophrenia was found, as well as the observation that increased level of IL-8 in mothers correlated with brain abnormalities in schizophrenia cases, however, the study included a limited number of subjects (Ellman et al., 2010).

Peter McGuffin (King's College, London, UK) summarized the long history of studies finding associations of the HLA antigens with schizophrenia and more recently results of GWA studies implicating the MHC genes as candidates (Ripke et al., 2011). The best SNP that showed genome wide significance for schizophrenia was rs6932590 within the MHC gene, although genome wide significance was observed across the huge genomic region (5.5 Mb) with independent signals in histone cluster, NOTCH4 and HLA DRB1* genes (Williams et al., 2011). However, allelic association could be due to factors other than causative, such as population stratification or just multiple testing.

Barbara Sperner-Unterweger (Innsbruck Medical University, Innsbruck, Austria) addressed neuroinflammation differences between schizophrenia and MDD. Schizophrenia was characterized by an increase in the IL-2 activation system, high Tregs activity and Th1/Th2 imbalance, whereas depression was characterized by decreased Tregs level and increased Th1/Th2 ratio in peripheral blood (Drexhage et al., 2010). Moreover, inflammation may induce changes in metabolic pathways by altering neurotransmitter metabolism such as

tryptophan or kynurenic acid. Among other risk factors related to inflammation, psychosocial stress is one of the key players (Miller et al., 2009).

XI. PHARMACOLOGIC TREATMENT (Reported by Rashmin Achaliya, Joshua Kantrowitz, Lena Palaniyappan, Hirouki Uchida)

Long acting injectable antipsychotic medications

This symposium discussed the utility of long acting depot medications. *Taishiro Kishimoto* (*Zucker Hillside Hospital, Glen Oaks, New York*) reported a meta analysis comparing studies Long-Acting Injectables (LAIs) vs. Oral Antipsychotics (OAPs) in Schizophrenia. 21 RCTs (n=5,130) were included where medications were given lasting >6 months. This analysis showed only fluphenazine LAIs showed significant superiority over OAPs with regard to relapse, drug inefficacy and hospitalization. When pooled, LAIs were similar to OAPs for relapse prevention. First-generation antipsychotics (FGA)-LAIs studies (or older studies) showed superiority of LAIs over OAPs while second-generation antipsychotics-LAIs did not. In conclusion, RCTs pooled LAIs did not reduce relapse compared to OAPs.

Three open label, randomized effectiveness studies of long acting Risperidone were then presented. *Nicholas Keks* (*Mental Health Research Institute of Victoria, Melbourne, Victoria, Australia*) discussed efficacy and tolerability of LAI Risperidone vs. Oral Olanzapine in Schizophrenia and Schizoaffective Disorder (Keks et al., 2007). Patients were randomized to receive risperidone injections or olanzapine for 52 weeks, the two groups being comparable on demographics. Few clinical differences were seen, and LAI was statistically non-inferior to oral olanzapine. Weight gain was greater in the olanzapine group (4.0kg vs 1.7kg, $p<0.05$). In contrast, benefits were seen over oral quetiapine in a study (Gaebel et al., 2010) presented by *Wolfgang Gaebel* (*Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany*). He reported open label RCT assessing Relapse with Risperidone LAI vs. Oral Quetiapine. Patients with schizophrenia or schizoaffective disorders were randomly assigned to open treatment with LAI or oral quetiapine. The study showed that RLAI has significant advantages in time to relapse ($p<0.001$) as well as in relapse rates (RLAI: 16.5%; quetiapine: 31.3%; $p<0.001$) and symptom improvement according to PANSS-total-score ($p<0.001$). Prevalence of side effects was low.

Nina R. Schooler (*State University of New York Downstate Medical Center*) presented the PROACTIVE trial. Patients with schizophrenia or schizo-affective disorder were randomly assigned to either LAI risperidone microspheres or any oral 2nd generation oral antipsychotic for up to 30 months. Relapse was determined by an independent committee blinded to treatment. There were no significant differences in time to 1st relapse between treatment groups, with the overall rate less than 40%, although LAI was superior in BPRS Psychosis cluster ratings.

Treatment of early onset psychosis

Celso Arango (*Hospital General Universitario Gregorio Marañón, Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Madrid, Spain*) presented an interim analysis of a one-year follow-up longitudinal study of a large sample of antipsychotic naïve children and adolescents (ages 4-17, mean 14 years) exposed to antipsychotics. Six month data was presented for metabolic/weight outcomes and one year data was presented for one year). Most patients were started on risperidone, with quetiapine and olanzapine also common. Olanzapine led to the largest increases in weight, and risperidone the most EPS. Most of the weight was gained within the first month, but continued to increase over the at least the first six months.

Christoph Correll (The Zucker Hillside Hospital, Glen Oaks, New York, USA) followed with a Meta-analysis of the safety and efficacy of antipsychotics in early onset schizophrenia including 15 randomized controlled trials. Few differences between agents were seen, with a mean effect size vs. placebo of 0.41 sd. Only clozapine separated from the others, with a NNT of 3 compared to olanzapine in one study. All included antipsychotic separated from placebo except for ziprasidone (Findling et al., 2010) and paliperidone (Singh et al., 2011), which were flexibly dosed based on weight, leading to overall low doses, thus dosing by weight was not recommended.

Sanjiv Kumra (University of Minnesota, Department of Psychiatry, Minneapolis, MN) presented data on the use of clozapine in this population. Clozapine is clearly effective in treatment resistant populations, even compared to high dose olanzapine (Kumra et al., 2008). Negative symptoms were more improved with clozapine. He explored potential reasons for clozapine's superiority. Clozapine did not appear to slow the loss of gray matter in patients with child-onset schizophrenia (Mattai et al., 2010), although potential differences in white matter was not studied.

Sophia Vinogradov (San Francisco Department of Veterans Affairs Medical Center and Department of Psychiatry, University of California, San Francisco, San Francisco, CA) described a potential cognitive remediation intervention for early psychosis based on enhancing neuroplasticity based through highly intensive, repetitive training of the early sensory system (Adcock et al., 2009), which demonstrated significant cognitive improvement after 50 hours of auditory training. A newer study also suggested that these techniques may be effective in younger patients.

Other treatment studies

Stefan Lecht (Technische Universität München, Germany) presented a meta-analysis of marketed antipsychotics. They included 203 blinded RCTs with 40241 participants (Leucht et al., 2009). Clozapine, amisulpride and olanzapine were the three most efficacious and acceptable antipsychotics. Clozapine, quetiapine and sertindole produced the fewest extrapyramidal side-effects and ziprasidone, haloperidol and lurasidone the least weight gain generation antipsychotics. These findings should be considered for treatment guidelines.

Rafael Penadés (*Servicio de Psicología Clínica, Hospital Clínic de Barcelona, Spain*) presented evidence suggesting that cognitive remediation therapy (CRT) leads to reduction of the non-specific activation of the working memory network and the improvement of the deactivation of the default mode network, indicating enhancement in activation of the working memory network (Penadés et al., 2010). Additionally, a significant increment in white matter integrity as evidenced by Fractional Anisotropy in the Corpus Callosum (CC) was found.

Matthew Kurtz (*Department of Psychology, Wesleyan University, Middletown, CT*) presented data on the role of cognitive remediation in enhancing response to social skills training. Cognitive remediation produced a trend towards improvement in elementary measures of working memory. More distal measures (community functioning) of psychosocial functioning showed more improvement (Kurtz and Mueser, 2008).

Antonio Vita (University of Brescia, School of Medicine, Brescia, Italy) found that baseline clinical predictors of cognitive improvement were higher psychosocial functioning and lower antipsychotic mean dosage. Moreover, a younger age, a shorter duration of illness and a lower antipsychotic dose intake significantly predicted cognitive normalization.

Iris Sommer (University Medical Center, Utrecht, Netherlands) presented a meta analysis on role of Non-steroidal Anti-inflammatory Drugs in Schizophrenia, including 5 double-blind randomized placebo-controlled trials. A mean effect size of 0.43, significant at $p=0.02$ in favour of NSAIDs on total symptom severity was seen (Sommer et al., 2011).

Marieke Pijnenborg (University of Groningen, Groningen, Netherlands) conducted a meta-analysis on the effectiveness of psychological and pharmacological treatment options to enhance insight. A total of 18 RCT's were included. Overall, the interventions had a medium effect size.

Jing-Ping Zhao and Ren-Rong Wu (Institute of Mental Health of the Second Xiangya Hospital, Central South University, Chang Sha, Hunan, China) reported results from two placebo-controlled trials to investigate the efficacy and safety of using metformin in treatment of antipsychotic-induced weight gain and amenorrhea in patients with first-episode schizophrenia. In the first trial, the lifestyle-plus-metformin treatment was significantly superior to metformin alone and to lifestyle-plus-placebo for weight, body mass index, and waist circumference reduction. In the second trial, metformin-treated patients were more likely to resume their menstruation than placebo-treated patients.

Jonathan Rabinowitz (Barllan University, Ramat Gan, Israel) presented post hoc analysis from several studies suggesting that benzodiazepine use in clinical trials did not appear to have negatively impacted the study results and, in the case of males, resulted in finding greater differences.

Relapse prevention in schizophrenia

Shitij Kapur (King's College London, United Kingdom) presented pre-clinical animal experiments on effects of antipsychotic exposure on brain volume (Vernon et al., 2011) and on supersensitivity psychosis. The findings suggested that exposure to antipsychotics had longer-lasting and compensatory effects on the brain; while the animal findings are not direct models of the human condition, they identify the neurobiological considerations that should inform human investigations.

Christoph Corell (The Zucker Hillside Hospital, Glen Oaks, NY, USA) presented an up-to-date meta-analysis on the benefits of second versus first generation antipsychotic drugs for relapse prevention of schizophrenia (Kishimoto et al., 2011). Second generation antipsychotics were significantly superior to first generation antipsychotics in preventing relapse. Superiority of second generation antipsychotics was confirmed in double-blind trials, first- and multi- episode patients. No evidence of significant heterogeneity or publication bias was found.

Elizabeth Kuipers (Institute of Psychiatry, London, United Kingdom) presented recent data on the effectiveness of cognitive behavioral therapy (CBT) for relapse prevention of schizophrenia, a randomized trial compared effectiveness of cognitive behavioral therapy with treatment as usual in a recently relapsed sample (Garety et al., 2008). The results suggested that there was a subgroup of patients with psychosis who responded well to CBT.

Cardiovascular risk in schizophrenia

This symposium highlighted the importance of monitoring to reduce cardiac mortality in schizophrenia. *Marc De Hert* (Psychiatric Centre Katholieke Universiteit Leuven campus Kortenberg, Belgium) presented a systematic evaluation of guidelines for monitoring cardio-metabolic risk in schizophrenia (AGREE collaboration, 2003). There were wide variations in the recommendations, highlighting the lack of agreement among the consensus groups even for well known risk factors such as a family history of cardiovascular and metabolic

diseases, smoking and the need for a general physical examination. He described the usefulness of a relative risk chart in quantifying the cardiovascular risk on the basis of smoking status, systolic blood pressure and cholesterol levels (De Hert et al., 2009). He concluded by stating that FDA warnings with respect to the adverse risk profiles of antipsychotic drugs have influenced clinician prescribing patterns, but unfortunately not their monitoring efforts (Morrato et al., 2010).

Shubulade Smith and Fiona Gaughran (Kings College, London United Kingdom) described the program, IMPACT (Improving physical health and reducing substance use in severe mental illness (IMPACT)) that is currently active in South London. IMPACT targets the poor physical health and excessive substance use through an evidence-based, culturally appropriate and innovative health promotion program. It includes 3 overlapping projects: a) A cohort study of physical health and substance use for a year in first episode psychosis, b) the development of the IMPACT interventions and c) An RCT evaluation of the effectiveness of IMPACT. Observations from the cohort study suggest that more than half of the patients with psychosis in the sample were obese, with females being disproportionately more affected. The IMPACT intervention is provided by community mental health practitioners over a 6-9 month period and combines the principles of Cognitive Behavioral Therapy (CBT) with Motivational Interviewing (MI). This project is in progress and results will be forthcoming.

Urban Osby (Karolinska Institutet, Stockholm) addressed issues related to shared genetic risks for schizophrenia and cardiovascular disease. Studies have shown that glucose regulation dysfunction is evident even in drug naive schizophrenia patients pointing towards shared genetic risk burden in schizophrenia and diabetes. Preliminary data on genetic associations in a cohort of patients from Sweden revealed that other than the MTNR1B polymorphism, the genetic determinants of metabolic syndrome in patients with schizophrenia may be distinct from those in the general population.

Azizah Attard (South London and Maudsley NHS Foundation Trust, Denmark Hill, London, United Kingdom) discussed the Maudsley Prescribing Guidelines for the QTc changes in patients treated with antipsychotics. She stressed that there is no accepted range of safe QTc values due to the variations in various physiological and environmental factors among individuals, and different views among cardiologists (Murray et al., 1994). Nevertheless it is an important predictor of adverse cardiovascular outcome in patients with schizophrenia. Recommendations to reduce risk included prescribing the lowest possible dose, avoiding polypharmacy, and performing a baseline/yearly ECG.

New pharmacologic treatments

This session included 7 brief presentations on several promising new compounds in development for treating schizophrenia. The importance of using pharmacogenetics was noted by the example of the selective therapeutic effect of folate on negative symptoms seen in T allele carriers of methylenetetrahydrofolate reductase C677T gene (Hill et al., 2011.). Also, the importance of targeting neuroplasticity was also discussed in the wake of the posited role of ventromedial prefrontal cortex in the impaired fear extinction memory, especially in patients with active delusions (Holt et al., 2009).

John Kane drew attention to the declining effect sizes in recent clinical trials compared to earlier ones. In schizophrenia clinical trials, placebo response rates have dramatically risen since 1993 (Kemp et al., 2010). It is unclear whether trial participants in recent studies truly represent the acutely unwell patients with an exacerbation of schizophrenia. In this context, establishing a stable baseline and minimising placebo response is crucial to achieve a higher success rate. *Shatij Kapur* discussed the difficulties in recruiting clinicians and trial

participants. They cannot present novel agents as hopeful new alternatives, in striking contrast to the trials that took place in the 1950s and 60s. It has also become increasingly difficult to find trial participants and financial pressure is a collective problem in designing successful trials. A greater understanding of these issues across the globe is leading to a rethink of clinical trial strategies.

Anjana Bose (Forest Pharmaceutical) presented the safety and efficacy data on cariprazine, an antagonist-partial agonist at D2/D3 receptors with a preferential D3 affinity. A double blind fixed-dose RCT with cariprazine administered at either 1.5mg, 3mg or 4.5mg doses, compared with placebo for 6 weeks followed by 2 weeks safety follow-up showed significant superiority for cariprazine at all doses compared with placebo in acute exacerbation of schizophrenia with good tolerability.

Rob Conley (Eli Lilly) presented safety and efficacy data on LY404039, a selective mGlu2/3 receptor agonist. Phase 2 clinical studies show mixed results with one study showing no difference between placebo and LY404039 in various fixed doses (5, 20, 40 and 80mgs) (Kinon et al., 2011) while the other showing a significant effect observable even at the first week of treatment (Patil et al., 2007). Interestingly, the major difference between the two trials was the overall placebo response, which for some unexplained reason, was much more pronounced than expected in the trial with negative results. Unpublished observations from a 6 months follow-up analysis suggest that significantly fewer patients on LY404039 show a categorical 7% weight, as compared to atypical antipsychotics.

Gerhard Gross (Abbott, Germany) highlighted several pre-clinical studies of ABT-925, a potent and selective D3 antagonist with minimal D2 effects. ABT-925 counteracted the social discrimination deficit in rats produced by neonatal phencyclidine and significantly improved performance in an extra-dimensional shifting paradigm. A double blind trial in acutely exacerbated patients however had negative results, although a trend towards improved negative symptoms/cognitive dysfunction was seen. Given that 150mg ABT-925 produces only 40% occupancy of D3 receptors in vivo (Graff-Guerrero et al., 2010), higher occupancies may be required for more robust therapeutic effects.

David Hosford (Targacept) presented the results of the alpha-7 nicotinic modulator TC-5619, which has shown a high selectivity towards the alpha-7 subunit of the nicotinic receptor with beneficial effects in preclinical models of schizophrenia. The phase 2 study aimed at assessing the efficacy, safety and tolerability of fixed dose titrations (1mg, 5mg and 25mg) of TC-5619 as augmentation therapy to quetiapine or risperidone to improve executive function in stable outpatients (in India and the US) with schizophrenia. No clinically meaningful differences were noted in the safety and tolerability profile between the placebo group and the TC-5619 group. Significant improvement in executive functioning was seen in weeks 4 and 12, with more marked improvement in patients who were tobacco users (46% of the total sample). By week 12, significant improvements in SANS scores were also noted.

Ronald Marcus (Bristol Myers Squibb) presented the principles behind a proof-of-concept study of alpha-7 nicotinic partial agonist agents in cognitive impairment associated with schizophrenia. Receptor desensitization and inverted U shaped dose response relationship along with the interference caused by the high prevalence of smoking in patients are some of the challenges that challenge the translation of agents from proof-of-mechanism trials to full development.

Daniel Umbricht (Hoffmann-La Roche) presented the results of a Phase II glycine reuptake inhibitor bitopertin for predominant negative symptoms. Patients were randomised for 8

weeks in addition to their second generation antipsychotic therapy. By week 8, the 10mg and 30mg bitopertin add-on groups showed significant statistical difference in PANSS negative symptom factor from the placebo add-on group. A post-hoc analysis revealed that the greatest effect of bitopertin was on the domain of avolition (apathy and social withdrawal). Phase III studies are ongoing.

Kimberly Vanover (Intra-Cellular Therapies Inc.,) gave an overview of the diverse mechanisms of action of the agent ITI-007 that includes 5-HT_{2A} antagonism, dopamine and glutamatergic phosphoprotein modulation, and 5-HT reuptake inhibition. This drug improved sleep in patients with primary insomnia, and has shown early signals for both antipsychotic and antidepressant response. Methods used in a phase II double blind placebo controlled trial on patients with acute exacerbation of psychotic episode wherein either 60mg or 120mg of ITI-007, or risperidone or placebo was administered for 4 weeks were presented.

XII. NON-PHARMACOLOGIC TREATMENT (Reported by Hiroaki Hori and Sonia Ruiz de Azua)

Treatment options for refractory positive and negative symptoms

Stefan Lecht (*Technische Universität München, Germany*), reviewed the pharmacological augmentation strategies for schizophrenic patients with insufficient response to clozapine. He conducted a meta-analysis (Sommer et al., in press) which included only double-blind randomized controlled trials (RCTs) of at least 2-week duration of clozapine augmentation by a second drug. There were 29 RCTs reporting information about 15 different drugs augmentation: antiepileptics, antidepressants, antipsychotics and glutamatergics. For antiepileptics, lamotrigine and topiramate showed superior efficacy to placebo in total symptoms and positive symptoms, respectively. Regarding antidepressants, citalopram improved total and negative symptoms compared with placebo. The only antipsychotic agent that was superior to placebo in reducing positive, negative and global symptoms was sulpiride. For glutamatergic drugs, CX516 was superior to placebo in ameliorating negative as well as total symptoms.

Iris Sommer (*University Medical Center, Utrecht, Netherlands*), described transcranial magnetic stimulation (TMS) for the treatment of hallucinations. This treatment can influence focal brain activity without serious side effects, although it cannot reach deep areas of the brain and its effect is relatively short-lived. There is evidence indicating that TMS alleviates medication-resistant auditory verbal hallucinations (AVH) (Hoffman et al., 2003). Some studies have found a correlation between hallucinations and the activation of the temporoparietal cortex (TP) and thus have applied low frequency TMS to the TP for the treatment of AVH. Her research group conducted an RCT (Slotema et al., 2011), where patients with medication-resistant AVH were assigned to fMRI-guided TMS, TMS at the left TP (no-guided), or to sham treatment. No significant differences in severity of general psychotic symptoms were found among the three treatment conditions. However, future studies that employ more effective TMS stimulation paradigms, more effective TMS coils, and direct cortical stimulation are warranted.

Donald Goff (Nathan S. Kline Institute, NY, USA) spoke on: folate and d-cycloserine (a glutamatergic agent) in treatment-resistant schizophrenia. Methylenetetrahydrofolate reductase (MTHFR) plays a critical role in folate metabolism. His group has focused on the 677C>T polymorphism of the MTHFR gene and found that this hypofunctional variant is associated with negative symptom severity in schizophrenia (Roffman et al., 2008). This variant, when coupled with other 3 missense polymorphisms in folate-regulating enzymes,

accounted for even greater variance in negative symptoms (Roffman et al., in press). Furthermore, in a folate supplementation trial, the MTHFR genotype influenced change in negative symptoms (Hill et al., 2011). He also mentioned the importance of NMDA receptors in memory consolidation. D-cycloserine administration was found to improve negative symptoms and, after the single-dose administration, improved delayed thematic recall in schizophrenia patients (Goff et al., 2008). He also suggested that d-cycloserine could facilitate an effect of cognitive behavioral therapy to reduce delusions in schizophrenia (Gottlieb et al., 2011). However, when serum homocysteine was measured in the folate supplementation trial, it was not predictive of response.

Elizabeth Kuipers (Institute of Psychiatry, London, United Kingdom), presented data on cognitive behavioral therapy for psychosis (CBTp). She noted that there are some models for CBT in psychosis (Garety et al., 2007; Garety et al., 2001; Kuipers et al., 2006) and that the efficacy of this therapy has been demonstrated by a number of systematic reviews. NICE guidelines recommend the use of CBT in the treatment of schizophrenia patients, even in medication-resistant patients. Their group has been working on developing new CBTp treatments with the focus on reasoning biases. They have been working with intervention for anxiety, specific interventions for poor family relationships or patients in an adverse environment, and new brief interventions for intrusive imagery associated with distressing hallucinations and paranoia and for the cognitive reappraisal of critical comments. The dorsolateral prefrontal cortex activity was found to predict responsiveness to CBTp (Kumari et al., 2009).

Georgios Petrides (The Zucker Hillside Hospital, NY, USA) spoke on the effectiveness of electroconvulsive therapy (ECT) for clozapine-resistant schizophrenia. He first stated that 30 to 60 percent of schizophrenia patients fail to respond to clozapine and thus clozapine-resistant schizophrenia represents a significant clinical problem. Despite its disadvantages (e.g., relatively short term effect, less practicability/availability and stigma) as well as clinical concerns (e.g., prolonged seizures and cognitive deficits), ECT would be one of the promising clozapine augmentation strategies. Several case reports suggest this. Synergism can occur between neuroleptics and ECT, and ECT and clozapine are shown to have similar electrophysiological effects. In a randomized trial, 10 of 20 clozapine-resistant patients with schizophrenia responded to ECT. Specifically, disorganization, hostility and aggression responded very quickly, followed by delusions and hallucinations.

Physical exercise

Tomas Scheewe (Rudolf Magnus Institute for Neuroscience Utrecht, Utrecht, Netherlands), presented the TOPFIT (The Outcome of Psychosis and Fitness Therapy) program. The aim of this program is to investigate if exercise therapy improves physical health in patients with schizophrenia. For this purpose, they performed a single-blind multicenter randomized controlled trial. The treatment consisted of cardiovascular exercise and muscle strength while the control group received occupational therapy. At baseline schizophrenic patients had poorer physical and reduced cardiorespiratory fitness compared with controls, and exercise therapy improved cardiorespiratory fitness in both groups. Also, there was a trend for improvement of psychotic symptoms in patients who received the exercise.

Davy Vancampfort (University Psychiatric Centre, Catholic University Leuven, Kortenberg, Belgium), summarized an evidence-based physical activity guideline for people with schizophrenia. First, he introduced the International Organization of Physical Therapists in Mental Health (IOPTMH), which works in the field of psychiatry and mental health to minimize cardio-metabolic risks in patients with schizophrenia. It is well established that schizophrenia patients have a significant excess of premature mortality compared to the general population; its major natural cause is cardiovascular diseases. Only about 30% of

these patients can be classified as being regularly active, in contrast to about 60% in a non-psychiatric comparison group. In addition, overall sitting time is associated with a greater risk of metabolic syndrome in schizophrenia (Vancampfort et al., in press). Although improving physical activity levels in schizophrenia represents a clinical challenge, it is useful for those physicians who prescribe exercise to take into account the following 4 factors collectively named “FITT”: frequency (5 or more days/week), intensity (at least moderate intensity as indexed by 50-70% of his/her maximum heart rate), type of exercise (patients can engage in any activity they like) and time (the goal for time of exercise can be set at 30 min/day).

Susanne Wolf, (Max-Delbrück-Center Berlin, Berlin, Germany) addressed the topic of neurogenesis. Neurogenesis occurs in the subventricular zone of the lateral ventricles and in the subgranular zone of the hippocampal dentate gyrus. Importantly, neurogenesis in hippocampus (type 2 cells) is shown to be facilitated by running. In their recent study (Wolf et al., 2011) double-stranded RNA (polyribonucleosinepolyribocytidylic acid, or PolyI:C) was injected in pregnant mice to induce a maternal viral-like infection, a mouse model for schizophrenia. The progeny exhibited impairments in the open field test and in sensorimotor gating as measured by prepulse inhibition of the startle response, which were accompanied by reduced baseline hippocampal neurogenesis. Telomerase activity in neural precursor cells was reduced from birth on and telomere shortening was found in the same cell type in adult life. After 10-day voluntary wheel running, the behavioral deficits, reduced adult neurogenesis, and cellular senescence were rescued, while the telomere shortening was not.

Frank Pajonk, (*University of Göttingen, Göttingen, Germany*) spoke on the link between schizophrenia, hippocampus, neurogenesis, cognition and physical activity. Some studies have found that exercise could increase the levels of brain-derived neurotrophic factor and mobilize gene expression profiles in mice (Cotman and Berchtold, 2002). Physical activity has been associated with improvement in cognitive functioning and with increment in gray and white matter (Smith et al., 2010). The aim of the present study was to determine whether aerobic fitness could increase hippocampal volume in patients with schizophrenia (Pajonk et al., 2010). Male patients with schizophrenia were randomized to aerobic exercise or non-exercise groups. Healthy controls also completed the exercise. Exercise increased the hippocampal volume in both groups. In the schizophrenia exercise group (but not the controls), change in hippocampal volume was associated with an increase in the N-acetylaspartate/creatine ratio in the hippocampus. In addition, improvement in short-term memory performance in the combined exercise and non-exercise schizophrenia group was correlated with change in hippocampal volume. Schizophrenic symptoms improved in the exercise group and worsened in the non-exercise group, although there was no relationship between changes in symptoms and hippocampal volumes.

Douglas Noordsy (Dartmouth Medical School, NH, USA) discussed integrated treatment in schizophrenic patients and possibilities to include exercise to improve physical health. He also noted that motivating patients to do exercise is difficult and thus dropout rates are high in all studies.

Peter Falkai (*University of Göttingen, Göttingen, Germany*) described the influence of exercise on the hippocampus and cognition. Schizophrenic patients were recruited and randomized to two treatment conditions: cycling plus cognitive intervention or table soccer plus cognitive intervention, both for 3 months. Matched healthy controls were also recruited and assigned to cycling plus cognitive intervention. No significant volume changes were detected using an automated analysis system (FreeSurfer), but using manual tracing they found significant increases in left and right hippocampus. Aerobic exercise had beneficial

effects on symptomatology, everyday functioning and cognitive functioning as assessed with a verbal memory test.

Jingxia Lin, (University of Hong Kong, Hong Kong) spoke on the effects of yoga and aerobic exercise on neurocognition and brain structure in early psychosis. She started by briefly describing yoga, a specific type of exercise that includes breathing practice, body postures and relaxation/meditation. In an ongoing trial, patients with recent-onset psychosis are assigned either to a 12-week yoga intervention group, 12-week aerobic exercise intervention group or control group (i.e., patients in a waiting list). Depressive symptoms were reduced both in the yoga and aerobic exercise groups. Recognition memory improved only in the aerobic exercise group while working memory markedly improved in both intervention groups. The volume of the mid-anterior cingulate cortex increased only in the yoga group.

René Kahn (University Medical Center Utrecht, Utrecht, Netherlands), presented the results of a randomized clinical trial conducted in Netherlands (Scheewe et al., in press). In this study schizophrenic patients and sedentary controls were recruited and evaluated at baseline and after 6-month treatment. Patients were randomized to cardiovascular exercise or occupational therapy (creative and recreational with no physical activities) and controls were randomized to cardiovascular exercise or normal life. Regarding the physical health, the exercise group had an increase in cardiorespiratory fitness and a trend-level reduction in triglyceride levels. At a clinical level, reduced psychotic and depressive symptoms and lower need for care were found in the exercise group as compared with the non-exercise group. Exercise therapy had a significant effect on global brain volumes in patients and controls. He concluded that increased fitness levels were associated with attenuated brain volume loss in patients and with cortical thickness increase in patients and controls, especially in the left hemisphere.

Alasdair Barr (University of British Columbia, Vancouver, Canada) noted that second generation antipsychotic drugs, despite their advantages, are associated with serious metabolic side effects, which can be caused at least partly by acute physiological effects of antipsychotics themselves that are independent of their influence on appetite and food consumption. He and colleagues studied whether chronic exercise can reverse the unfavorable metabolic effects of olanzapine in adult female rats. By the 5th week of treatment, rats that were given access to exercise wheels showed a partial reversal of glucose intolerance caused by olanzapine.

XIII. SUMMARY (Reported by Taishiro Kishimoto)

This congress emphasized the world-wide need for further focus on various non-pharmacologic treatment modalities, and more integration and crosstalk between different perspectives (i.e. epidemiology and neuroimaging, gene expression studies and treatment research). It will be increasingly important for future meetings to even better integrate findings on a systems level and thus combine molecular level data with neural networks as well as environmental factors. Sir Robin Murray raised the question of whether the dopamine system(s) can still be thought of as a final common pathway to schizophrenia. To what extent can the dopamine hypothesis accommodate the emerging findings relating cannabis as a risk factor? He noted that, in fact, drugs of abuse have played an important role in developing hypotheses for schizophrenia pathophysiology (i.e. amphetamine, LSD, and ketamine). He then suggested the need for a new hypothesis to accommodate the effect of cannabis and the need to explore further the interactions between the endocannabinoid and dopamine systems. He commented that dopamine might account to some extent for positive symptoms associated with schizophrenia and that D2 gene expression in the

striatum may produce cognitive abnormalities in the frontal cortex, but it is unclear whether they can account for the developmental abnormalities also seen. He expressed satisfaction in witnessing considerable progress on multiple fronts. At the same time he highlighted the importance of substantially increasing available sample sizes when exploring gene-environment interactions and challenged the field to consider conducting large enough studies by world-wide collaborations, consistent with this year's congress theme: *The Globalization of Schizophrenia Research*.

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