The 4th Schizophrenia International Research Society Conference, 5–9 April 2014, Florence, Italy: A summary of topics and trends

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The 4th Schizophrenia International Research Society Conference was held in Florence, Italy, April 5–9, 2014 and this year had as its emphasis, “Fostering Collaboration in Schizophrenia Research.” Student travel awardees served as rapporteurs for each oral session, summarized the important contributions of each session and then each report was integrated into a final summary of data discussed at the entire conference by topic. It is hoped that by combining data from different presentations, patterns of interest will emerge and thus lead to new progress for the future.
1. Introduction

Schizophrenia has been defined as a clinical entity for over a century, but despite decades of research, a definitive set of biological markers for the disorder are still not available, nor are treatments that prevent or cure it. The Schizophrenia International Research Society (SIRS) was formed in 2005 so that progress by communication and sharing of both similar and dissimilar findings between researchers could be facilitated world-wide. This report covers the 4th International Conference conducted by the society, this time with the theme of “Fostering Collaboration in Schizophrenia Research”. Toward that aim a special emphasis was placed on contributions from a geographically dispersed broad group of international investigators from over 40 countries and almost all continents worldwide. Four full days were devoted to topics that ranged from the underlying biology to reviews of the latest ongoing new pharmaceutical trials. Although the current report is organized by topic and thus cuts across multiple sessions in doing so, the highlights of the conference were the four unique plenary sessions that included an update on therapeutics, the impact of genomics and connectomics approaches on schizophrenia research, behavioral and imaging translational paradigms in drug development, and the clinical challenges of comorbidity with addiction and somatic disease. The plenaries were designed to air controversial and major issues in schizophrenia research and to have audience discussion with input from a range of diverse investigators who don't often have the opportunity to think about the topic at hand. 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. These were then synthesized into the following report that integrates information from separate sessions into a review of the major current trends in research topics pursued. In this way, isolated findings reported in different sessions are merged in an attempt to see patterns in the results that could pave the way to future progress. Reports from the 1st, 2nd and 3rd international conferences were previously published (Abubaker et al., 2009; Baharnoori et al., 2010; Abb et al., 2012). Thus, the following summarizes the 2014 conference.

2. Inflammation in schizophrenia

Although inflammatory and immunological measures have long been studied in schizophrenia, this field has recently been revived with the presence of new exciting findings. Dr. Mary Clarke (RCSI Psychology & Psychiatry, Dublin, Ireland) proposed that inflammation was the common underlying process produced by adverse environmental stress and thus measurements of inflammation might potentially be useful as state and trait markers. She based this on studies of fetal stress associated with developmental delay, increasing the risk for schizophrenia and that fetal distress during delivery further increased this risk. Postnatal stress was found to be an even greater risk factor compared to pre-natal stress. In support of this notion, Dr. Urs Meyer (ETH Zurich, Switzerland), showed in mice that prenatal immune activation and pubertal stress synergistically interact to disrupt long term behaviors. He hypothesized that prenatal immune stress acts as a "disease primer" which potentiates the detrimental neuronal effects of postnatal stressors and increases the vulnerability to neuro-inflammatory changes in response to stress. Thus, it was suggested that prevention of transient neuroinflammatory changes in response to pubertal stress could potentially prevent later behavioral abnormalities. The timing of the administration of anti-inflammatory agents would be crucial for maximal effectiveness. In another animal model, Dr. Marco Riva (University of Milan, Italy) reported sex specific methylation of gene promoters in the prefrontal cortex and hippocampus of prenatally stressed rats. Methyline analyses from DNA from humans and animals, all of whom experienced early life stress, identified a common methylation pattern for the Ank3 gene. He concluded that prenatal exposure to stress produces long lasting epigenetic changes that affect brain by altering brain development and maturation. In another study, Dr. Akira Sawa (Johns Hopkins Schizophrenia Centre, Baltimore, USA) showed altered tyrosine hydroxylase (TH) expression, methylation of TH promoters, selective increase of DNA methylation in the mesocortical dopamine projection, methylation of BDNF and methylation of glucocorticoid receptors in DISC-1-DN-Tg-PrP stressed mice with reduced locomotor activity. He also showed evidence that administration of the glucocorticoid receptor antagonist, mifepristone, normalized DNA methylation in the dopamine projection, BDNF methylation and behavior deficits. Similarly, in a human trial, mifepristone has been shown to be effective in the treatment of psychotic depression by possibly re-regulation of the HPA axis (Flores et al., 2006). He further suggested that a subpopulation of patients or those at high risk for schizophrenia with an elevation in HPA axis expression could be targeted for treatment with mifepristone.

Dr. Golam Khandaker (Cambridge University, UK) discussed the role of early-life infection and inflammation in schizophrenia and depression in young adults. He presented data from the population-based Avon birth cohort in which Interleukin-6 (IL-6) and C-reactive protein were measured in non-fasting serum samples obtained at age 9 years. Psychotic experiences, psychosis and depression were measured at age 18. At follow-up, about 4% of the participants reported psychotic experiences (1.5% met the criteria for psychotic disorder, and 17% met the criteria for depression). Participants in the top third of IL-6 values, compared with the bottom third at age 9 years were about twice as likely to develop psychotic experiences at age 18 years. The risks of psychotic disorder and of depression at age 18 were also increased with higher IL-6 at baseline in a dose–response relationship. These findings suggest that high levels of the inflammatory marker IL-6 in childhood are associated with the risk of subsequent psychosis and depression in young adulthood. He also presented work on early-life exposure to Epstein Barr Virus, childhood IQ, and the risk of psychotic experiences in the ALSPAC birth cohort. IQ did not explain EBV–PE association, but serologically confirmed that EBV exposure at 4 years was associated with a five-fold risk of definite psychotic experiences at age 13.

Dr. Iris Sommer (University Medical Center Utrecht, The Netherlands) reviewed double blind placebo-controlled randomized trials of anti-inflammatory agents on symptom severity in schizophrenia patients. Aspirin, N-acetylcysteine, and estrogens showed promise, but EPA fatty acids, celecoxib, davunetide and minocycline showed no effects. Negative results may be due to either too short a treatment trial or not targeting the stage of illness when inflammation is at its peak.

Dr. Robert Volk (Johns Hopkins School of Medicine, Baltimore, USA) presented evidence that schizophrenia patients have a different oro-pharyngeal microbiome than healthy subjects. Schizophrenia patients have higher levels of streptococcus and inflammatory markers,
but lower levels of haemophilus. Different frequencies of retroviruses (Hers) were also found.

Dr. Faith Dickerson (Johns Hopkins University, Baltimore, USA) presented differences in inflammatory markers between recent onset psychosis and established multi-episode schizophrenia. Patients with established schizophrenia had an elevation in a general inflammatory marker (C-reactive protein) and intestinal inflammatory marker, while those with a recent onset of psychosis showed decreased levels of some markers.

Dr. Thalia van der Doef (VU University Medical Center, Amsterdam, The Netherlands) examined regional microglial activation in patients with schizophrenia in early stages of the disease using a PET ligand [11C]PK11195. Previous findings of widespread microglial activation in patients were not confirmed, although increased [11C]PK11195 binding was found in the temporal cortex, highlighting this region for future studies.

Dr. Alan Brown (Columbia University, New York, USA) discussed serologically documented maternal influenza and bipolar disorder with psychotic features in adulthood, with the aim of determining whether serologically documented gestational exposure to influenza relates to risk of bipolar disorder in adults. A fivefold increased risk of bipolar disorder with psychotic features was shown, validating prior findings of clinical influenza and bipolar disorders with psychotic features in the same birth cohort, and supporting the hypothesis that prenatal influenza may increase the risk for psychosis.

Dr. Asa Blomstrom (Karolinska Institutet, Solna, Sweden) presented work on childhood infection and risk of psychotic disorder. Strengths of her study were a large, population based birth cohort that included the entire Swedish population, considered multiple confounders, and obtained reliable diagnoses. Limitations included crude exposure, follow-up time until the age of 38, and multiple testing. Overall, weak associations were found. Both social and genetic factors have shown to be related to infections. Dr. Hakan Karlsson (Karolinska Institutet, Solna, Sweden) gave an overview of early infection/inflammation and the later development of psychoses, concluding that maternal infections during pregnancy confer increased psychosis-risk to offspring. Healthy neonates appear to have an innate immune response against maternal infection with T gondii or CMV, but not with HSV-1/-2; neonates who will develop psychosis or not. This is attributed to maternal factors, genes, and signals. Dr. Urs Meyer (Swiss Federal Institute of Technology, Zürich, Switzerland) discussed developmental immune activation models in rodents, showing that prenatal exposure to infectious and inflammatory stimuli induces a wide spectrum of brain and peripheral abnormalities in numerous species. Experimental support for human epidemiological findings suggests an association between early-life infections and later development of brain disorders. Prenatal immune activation models, or “neurodevelopmental disruption models” are etiopathologically highly relevant for neuropsychiatric disorders with developmental components. They do not rely on a presumption of the neural substrates of a disorder, and are therefore open to multiple hypotheses testing as well as longitudinal investigations. These models are excellent experimental tools to study gene–environment and environment–environment interactions. Such approaches have both etiological and mechanistic relevance to multi–factorial and multi–symptomatic disorders, including schizophrenia, autism, and bipolar disorder.

Dr. Johann Steiner (University of Magdeburg, Germany) presented the prevalence of NMDA-receptor antibodies in an unmedicated, acutely ill population diagnosed with schizophrenia (SZ). Major depression (MD), and borderline personality disorder (BPD), as well as controls. NMDA receptor antibodies were present in 10% in SZ, 3% in MD, 0% in BPD, and 0.5% in healthy controls (Steiner et al., 2013). Retesting with recent commercial assays increased the prevalence of antibody-positive controls to 4%. It is unclear if the presence of NMDA-receptor antibodies in healthy controls increases the risk for developing neuropsychiatric disorders. The blood–brain barrier integrity seems to play an important role (Hammer et al., 2013). Dr. Belinda Lennox (University of Oxford, UK) discussed the prevalence of receptor antibodies in patients with schizophrenia and their clinical characteristics. An estimated 6–7% of subjects during the first episode of psychosis have receptor antibody biomarkers (Zandi et al., 2011); they may be more resistant to conventional treatments and may have increased cognitive impairments and movement disorders. These patients may respond better to immunotherapy than anti–psychotics. Dr. Takashi Kanbayashi (Akit University, Japan) presented a series of case treatments with a positive NMDA-receptor antibody in three groups of patients: those with limbic encephalitis, schizophrenia and narcolepsy. In the schizophrenia/schizoaffective disorder group, 8/120 were positive to NMDA-receptor antibodies; 7/15 encephalitis cases had catatonic symptoms. NMDA-receptor encephalitis could be included for differential diagnosis in catatonia. ECT might be a treatment option in patients with NMDA-receptor encephalitis and psychotic symptoms.

Hannelore Ehrenreich (Max Planck Institute of Experimental Medicine, Göttingen, Germany) presented results from a study with over 4200 subjects (Hammer et al., 2013). Unexpectedly, 10% of all individuals carry the NMDA-receptor1 antibody. The antibody functionality in vitro was comparable across groups. In an animal model with a deficient blood–brain barrier, antibodies have effects in behavioral tests. Patients with antibodies to the NMDA-receptor and a history of neurotrauma or birth complications had more neurological abnormalities when compared to other groups, suggesting that antibodies gain relevance upon blood–brain barrier disturbance.

Dr. Souheil Najjar (New York University, New York, USA) discussed the differences between NMDA-receptor encephalitis and other types of encephalitis and highlighted the importance of finding biomarkers to study the blood–brain barrier integrity and NMDA-receptor antibodies.

Dr. Thomas Weickert (University of New South Wales, Kensington, Australia) presented data from a study of adults with schizophrenia and healthy controls. Using mRNA cytokine levels as a marker of inflammation, it was found that individuals with schizophrenia were significantly more likely to be characterized by high inflammation than controls. Furthermore, among individuals with schizophrenia, higher IL1β mRNA levels were associated poorer verbal fluency performance and reduced Broca’s area volume. He and colleagues have shown that white matter interneurons are increased in schizophrenia (Joshi et al., 2012), whereas other studies showed that cortical interneurons are reduced (Fung et al., 2010). More recently, white matter interneurons were only increased in a subset of patients with high expression of inflammatory markers.

Dr. Patricio O’Donnell (Pfizer, Cambridge, USA) investigated the role of oxidative stress in dysfunction of fast-spiking parvalbumin positive interneurons, using the neonatal ventral hippocampus lesion (NVHL) animal model. Daily treatment with the antioxidant N-acetyl cysteine (NAC) beginning prior to the neonatal lesion prevented oxidative stress, neurodegeneration of fast-spiking parvalbumin positive interneurons, using the neonatal ventral hippocampus lesion (NVHL) animal model. Daily treatment with the antioxidant N-acetyl cysteine (NAC) beginning prior to the neonatal lesion prevented oxidative stress, along with electrophysiological and behavioral changes that have previously been described in the model. Preliminary findings suggest that NAC treatment later, in the NVHL model, during adolescence, may also be beneficial, supporting the utility of this therapy in early intervention paradigms.

Dr. Jaana Suvisaari (National Institute of Health and Welfare, Helsinki, Finland) reported findings from a longitudinal study of 37 patients investigating changes in inflammatory markers in patients who presented with first episode psychosis. When compared with age and sex matched controls significant differences were found in CCL2-macrophage derived chemokine. This effect was decreased on follow-up but it is still higher than control. It did not correlate with MRI gray matter changes but was associated with changes in white matter volume.

Dr. Sonal Shah (University of Western Australia, Crawley, Australia) presented an epidemiological analysis of a Western Australian cohort study showing increased risk of mortality in offspring of mothers with schizophrenia. The prevalence of general socio-demographic risk factors
is related to increased mortality, such as poor physical health and poor obstetric outcomes.

3. Genetic studies

Dr. Patrick Sullivan (University of North Carolina, Chapel Hill, USA), gave a review of current genome-wide association studies (GWAS) undertaken within the large international collaboration network, The Psychiatric Genomics Consortium (PGC). The PGC currently has data from 376 investigators with over 36,000 schizophrenia cases and over 40,000 controls. They succeeded in identifying 128 genome-wide significant loci, and re-confirmed the involvement of DRD2 and NMDA receptor genes including GRIN2A and GRM7, calcium biology (CACNA1C, CACNB2) genes, and microRNA-137 (Purcell et al., 2014; Ripke et al., 2013, 2011).

Dr. Jonathan Sebat (University of California, San Diego, USA) presented studies that confirm the role of rare gene sequence deletions or insertions, copy number variants (CNVs) as risk factors for schizophrenia, autism and bipolar disorder. He mentioned that mutations have been reported by clinical genetic labs for pediatricians for years. As an example, he referred to the 22q11.2 deletion syndrome and A2BP1 deletion, which are well-known risk factors for schizophrenia, autism and some other mental and cognitive disorders. Newly found CNV’s associated with schizophrenia now include duplications within the neureptopeptide receptor gene VIPR2 (Vacic et al., 2011) and CNVs of the 16p11.2 region (Guha et al., 2011), which involve the development/regulation of synaptic networks and which has been shown to be regulated by disrupted-in-schizophrenia-1 (DISC1), a proposed risk gene for schizophrenia.

Dr. James Walters (Cardiff University, UK) focused on genetic studies of treatment resistant schizophrenia (TRS) with a particular emphasis on the dopamine and glutamate based pathophysiology of the illness. TRS cases from the CLOZUK sample (Novartis) displayed an association with N-methyl-D-aspartate receptor gene sets, but not genes from dopamine-based pathways. This was in contrast to those with schizophrenia who were not selected for treatment-resistance. These findings suggest that treatment resistance may be useful in defining those with distinct pathophysiology.

Dr. Sharon Hollins (University of Newcastle, Callaghan, Australia) spoke on the role of microRNA (miRNA) in the brains’ response to maternal immune activation and adolescent cannabis exposure, alone and in combination as environmental risk factors for schizophrenia. Male Wistar rats exposed to immune activation in utero with polyinosinic-polycytidilic acid and subsequently treated with the synthetic cannabinoid HU210 identified genes regulated by the differential expression of miRNA’s linked to synaptic transmission, transmission of nerve impulses and cell–cell signaling in the left entorhinal cortex. Thus the interaction of both an early and late environmental insult can enhance changes in offspring miRNA expression in the entorhinal cortex with possible outcomes relevant to schizophrenia in adulthood.

Dr. Sarah Bergen (Karolinska Institute, Stockholm, Sweden) discussed polygenic risk score differences within and between case and control groups by rare CNV carrier status using the Swedish Schizophrenia Consortium as the discovery sample as a means to score the International Schizophrenia Consortium subjects. It was found that within schizophrenia cases, CNV carriers did not demonstrate significantly lower risk scores than non-carriers. Cases with either class of CNV membership had higher polygenic scores compared to control subjects carrying CNVs. Notably, control subjects with specific associated CNVs had lower polygenic scores than other control subjects, but controls with and without large deletions had similar scores. These preliminary results are partly inconsistent with an additive model of CNV and polygenic risk. It was concluded that the presence of an associated CNV alone is not sufficient to result in schizophrenia phenotype, but also requires an increased risk from common variants.

Dr. Anne Bassett (University of Toronto, Canada) reported on the 22q11.2 deletion (22qDS), one of the most widely known associated CNVs, and described it as a unique opportunity to understand mental illnesses. Most cases of 22qDS are heterozygous and most are de novo cases (only 5–10% are inherited). However, if one parent has a deletion, the chances of having an affected offspring is about 50%. 22qDS carriers have a significant risk of developing psychiatric illness (attention deficit hyperactivity disorder, schizophrenia, and affective disorders; Schneider et al., 2014), and have a 10-fold increased risk of Parkinsonism, and increased risks of seizures and intellectual disability. Dr. Bassett indicated that impaired expression of DGCGR8 (DiGeorge syndrome critical region gene 8, regulating miRNA biogenesis) and miR185 (gene, encoding microRNA-185) within the deletion region may lead to a down-regulation of specific miRNA subsets in the prefrontal cortex and hippocampus.

Dr. Clodagh Murphy (King’s College London, UK) presented high co-morbidity rates among 22qDS patients with ADHD (35–45%), autism spectrum disorders (19–50%) and obsessive–compulsive disorder (>33%). More than 40% of 22qDS patients develop psychosis (about 20% of these patients may develop schizophrenia with a mean onset age of about 19 years).

Dr. Jacob Vorstman (University Medical Center Utrecht, The Netherlands) focused on the significance of childhood phenotypes to risk of psychosis, and presented data from longitudinal cognitive and behavioral assessments of patients with 22q11DS. In a study of adults with 22q11DS, carried out in collaboration with Anne Bassett from University of Toronto, he reported that autistic features in
childhood are not associated with an increased prevalence of schizophrenia in adulthood. With Sasja Duijff from the Utrecht group he also reported that a subgroup of children with 22q11DS show a decline in cognitive abilities as they age.

The field has currently moved beyond GWAS to gene sequencing studies for identifying common variants conferring risk for psychiatric illness. Dr. Shaun Purcell (Mount Sinai Hospital, New York, USA) discussed the utility of multi-gene analyses and exome sequencing as key tools for identifying de novo single nucleotide variants (Froemer et al., 2014) as well as CNVs (Kirov et al., 2012). The importance of cross-disease effects was emphasized between schizophrenia and other neuropsychiatric conditions when applying such tools (Froemer et al., 2014). Notably, exome sequencing was found to establish a polygenic basis for schizophrenia that includes ultra-rare and de-novo coding mutations.

Dr. Maree Webster (Stanley Medical Research Institute, Chevy Chase, USA) reported on the RNA sequencing of the choroid plexus of 34 patients with schizophrenia and 34 controls. 53 differentially expressed genes many of which are associated with immune and inflammatory response. Interestingly, there were significant differences between Pentraxin (PTX3), CCL20, and CCL2 in the choroid plexus but they were not differentially expressed in serum measurements.

Dr. Pippa Thomson (University of Edinburgh, UK) spoke about the complexity of common and rare variation using as an example next generation sequencing of the Disrupted-in-schizophrenia-1 (DISC1) locus. Data from a study conducted in 1542 individuals including 653 individuals with psychiatric illness (i.e. schizophrenia, bipolar disorder and recurrent major depressive disorder) and 889 controls from the Lothian Birth Cohort 1932, found rare DISC1 coding variants with functional effects on key biological functions. Burden analyses implicated DISC1 variants in recurrent major depression, age of onset and cognition (Thomson et al., 2014). No association was identified with schizophrenia or bipolar disorder. The results suggest that variants that alter gene expression are just as important as those that alter protein sequence in the disease pathophysiology of major mental illness. This project is being expanded to examine the complexity of the DISC1 interactome involving over 260 genes which are implicated in downstream signaling of the DISC1 pathway (Camargo et al., 2007; Henannah and Porteous, 2009).

Dr. Jesse Gillis (Cold Spring Harbor Laboratory, USA) discussed the importance of considering gene networks as a means for integrating potentially diffuse functional effects of genes into a single common framework. It was emphasized that because of the complex biology of the brain, interpreting systemic properties of the brain especially in the context of psychiatric illness is more likely to benefit from computational means. In this regard, the central top-down principle in the interpretation of gene networks is “Guilt by Association” which states that genes which share functions are more likely to be associated (Gillis and Pavlidis, 2011, 2012). This principle generally finds application in two uses within networks: first, in attempting to learn gene properties; and, second, in validating the network as a whole. Data generated from separate co-expression networks from control and schizophrenia prefrontal cortex found that differences in global network properties were small (Mistry et al., 2013). Characterization of functional clusters in each network with cell-type marker genes displayed differences that link together disease-related processes. Notably, differentially expressed genes in schizophrenia also associate with biologically relevant clusters providing evidence for systems level dysfunction (Mistry et al., 2013). Multi-functionality of genes may represent a confounding interpretation of many biological experiments and has a particularly confounding effect on computational attempts to exploit known information and in the examination of gene networks.

Other miscellaneous presented genetic studies included: Dr. Vaidy Swaminathan (University of Melbourne, Melbourne, Australia) presenting that single nucleotide polymorphisms for the EGF gene are associated with cognitive impairment in schizophrenia and Dr. Ary Gadelha (Federal University of São Paulo, São Paulo, Brazil) describing a series of experiments to elucidate the relationship between angiotensin converting enzyme (ACE) and schizophrenia. His group found that blood enzyme activity was higher in patients than in control. When comparing those with high ACE to low ACE, subjects with high ACE had worse performance on Hopkins Verbal Learning test. In a mouse model comparing mice with 1, 2 or 3 copies of ACE genes, mice with 3 copies showed lack of preferential exploration of new objects.

4. Studies of the prodromal state, high risk and early psychosis

Whether an attenuated psychosis syndrome (APS) should be its own entity was discussed and different viewpoints represented: Dr. Paolo Fusar-Poli (Institute of Psychiatry, London, UK) presented results on the reliability and validity of APS arguing that it is a much needed diagnostic category. Although the results were quite limited and inconclusive, there was a study showing that test–retest reliability of APS in DSM-5 field trials was good (intraclass kappa = 0.46; Regier et al., 2013). The prognostic validity of the psychosis high-risk state has been supported by several studies. For example, Fusar-Poli et al. (2012a) found in a meta-analysis that the risk of transition to psychotic disorders at two years is about 30%, and that the transition rate could be improved by recruitment strategies (Fusar-Poli et al., 2014). On the other hand, Dr. Jim van Os (Maastricht University, The Netherlands) argued that an APS diagnostic category is not needed, and ultra high risk (UHR) states more likely represent the common mental disorders plus subthreshold psychotic experiences. According to DSM-5 criteria for APS, people with high risk states may already be diagnosed with mental disorders, such as anxiety or depression. Hence, the so-called ‘transition’ probably refers to transition from a common mental disorder with a certain degree of psychosis to one with a greater degree (van Os and Murray, 2013). Nevertheless, evidence was presented by Dr. William Carpenter (University of Maryland, College Park, USA) from studies of brain imaging, cognition, negative symptoms, course, and treatment to support the established validity for a new diagnosis of APS. It was also suggested that having an APS will lead to better early detection and intervention. Dr Castle (The University of Melbourne and St. Vincent’s Hospital, Australia) suggested that even if we were able to predict which individuals might ‘transition’ to psychosis, there is little consistent evidence to support an effective intervention strategy. Anti-psychotic medications and psychological treatments have been trialed but with rather unpromising outcomes in terms of diverting people from transitioning. One positive study of omega-3 fatty acids remains unreplicated.

Dr. Kelly Anderson (CAMH, Toronto, Canada) shared findings from her recent systematic review and comparative study of pathways to care in first episode psychosis (FEP) across different ethnic groups. She found that patients of African descent had an increased likelihood of having police involvement and involuntary admissions, and thus shorter duration of untreated psychosis (DUP) compared with Caucasian patients. Asian patients were less likely to have involuntary admissions, but did not differ in DUP (Anderson et al., 2014). Thus, different pathways to care were observed across ethnic groups.

Dr. Michael Birnbaum (Zucker Hillside Hospital, Glen Oaks, USA) spoke on use of social media in early psychosis. He highlighted its potential as a useful platform for early intervention in first episode psychosis. Based on an online search on Google, Facebook and Twitter, he found that only a few of the online resources provided appropriate information that promote help seeking behavior and access to appropriate treatment. Furthermore, he identified the internet as the primary source for obtaining information for youth with early phase psychosis. However, insufficient information on the internet often leads to treatment delays. Future collaboration with business partners might enhance the information provided by search engines in order to...
facilitate the obtainment of accurate information about symptoms, and obtaining treatment.

Dr. Max Birchwood (University of Birmingham, West Midlands, UK) presented data on the efforts to reduce DUP through modification of care pathways in psychosis services in the UK. He discussed the result of a review, which suggested a significant association of DUP with treatment outcome (Marshall et al., 2005) and proposed a critical DUP of a maximum of 8 weeks. Increasing access through an early intervention campaign that provided increased availability of information was shown to reduce the existing treatment delays in the UK. Dr. Anita Riecher-Rossler (University of Basel, Switzerland) reported data from the Basel early detection of psychosis (FePsy) clinic. Out of 462 individuals screened, 29 developed a psychosis and delays in treatment were worse in male than in female patients. The females sought help earlier and more frequently than males. Family and friends were reported to be the primary source of help.

Dr. Nomi Werbeloff (Sheba Medical Center, Ramat Gan, Israel) noted that psychotic experiences in the general population are far more prevalent than psychotic disorders themselves, but have been associated with risk for psychotic disorders later in life. Utilizing data from a two-stage epidemiological study among young adults aged between 25 and 34 in a population based 10-year birth cohort (1949–1958) conducted in Israel in the 1980s, it included initial assessments of psychotic experiences with data collected twenty five years later. The results showed that people with psychotic disorders, but not those with only psychotic experiences, were at increased risk of premature death. Although persons with psychotic experiences share some demographic and clinical characteristics with those who had psychotic disorders, premature death appears to be unique to patients with clinically diagnosed disorders. Possible mechanisms that may explain the high mortality rates in people with psychotic disorders include unhealthy lifestyles, under-utilization of general medical services, lower quality of medical care and long-term use of anti-psychotic medication, and suicide.

Dr. Ian Kelleher (Royal College of Surgeons, Ireland) reported that psychotic experiences are associated with an increased likelihood of suicidal ideation, behavior in adolescents from the general population (Kelleher et al., 2012) and suicide plans/attempts in adolescents with affective, anxiety, or behavioral disorders (Kelleher et al., 2013b). He also presented longitudinal studies indicating that psychotic experiences at ages 16 to 17 years predicted increased likelihood of persistence of suicidal ideation at 19 to 20 years (Kelleher et al., 2014) and that adolescents with psychopathology who endorsed psychotic experiences had an increased risk of suicide attempts in the following 12 months (Kelleher et al., 2013a). Finally, he presented data showing an association between childhood trauma (physical assault and bullying) and psychotic experiences and that childhood trauma strongly predicted psychotic experiences in a dose–response manner (Kelleher et al., 2013c).

Dr. Rachel Upthegrove (University of Birmingham, UK) focused on suicidality and the depressive dimension of psychotic phenomenology in first-episode psychosis (FEP). She showed that prodromal depression predicts the presence of future depression and acts of self-harm (Upthegrove et al., 2010) and that illness and symptom appraisals play a role in depression and suicidal behavior in the early phases of psychosis (Upthegrove et al., 2014). She also discussed a qualitative study in which the experience of depression following FEP was found to encompass themes such as loss, social isolation, shame, and embarrassment (Sandhu et al., 2013).

Dr. Rina Dutta (Institute of Psychiatry, London, UK) spoke about the epidemiology of and early risk factors for suicide in a clinically representative cohort of FEP patients. Her results showed that the risk of suicide was approximately 12 times greater than in the general population and that the risk persisted over time, being approximately 4 times greater than in the general population 10 years after first onset (Dutta et al., 2010). She also discussed her risk factor study indicating that both cumulative threshold number of symptoms (as an index of illness severity) and manic symptoms were associated with completed suicide (Dutta et al., 2011). Thus, psychotic and depressive symptoms should be asked about in mental health services and the monitoring of risk for suicide should be an ongoing process not limited to the early phases of psychosis.

Dr. Barnaby Nelson (University of Melbourne, Australia) highlighted the relevance of childhood trauma (CT) to the UHR population. He presented results from a number of studies carried out at the PACE clinic showing a high prevalence of traumatic events in UHR individuals (Bechdolf et al., 2010), that sexual CT predicts transition to psychosis (Thompson et al., 2014), and that different forms of CT seem to be differentially associated with the nature of attenuated psychotic symptoms (Velthorst et al., 2013).

Dr. Bruno Etain (INSERM, France) focused on how CT affects the clinical expression of bipolar disorder. He introduced studies indicating that, among subtypes of CT, emotional abuse shows a preferential association with bipolar disorder (Etain et al., 2010) and that emotional and sexual forms of abuse are associated with a severe clinical manifestation (Etain et al., 2013). He suggested that different trajectories might result from different CT exposures and presented work looking at intermediate psychological dimensions that may mediate between CT and the expression of the disorder. As one example, emotional abuse was found to be associated with higher levels of affective lability and affect intensity in bipolar patients.

Dr. Valeria Mondelli (Institute of Psychiatry, London, UK) presented data indicating that CT contributes to the abnormal biological stress response that characterizes the onset of psychosis. She reported a study showing that exposure to sexual abuse was associated with different HPA axis functioning in FEP patients and healthy controls: patients with exposure had a lower cortisol awakening response than patients without exposure, whereas controls with exposure had higher cortisol awakening response than controls without exposure. She also presented findings related to neurotrophic factors and pro-inflammatory cytokines; specifically, it was found that higher CT was associated with lower levels of Brain Derived Neurotropic Factor (BDNF) and increased levels of Tumor Necrosis factor (TNF)-alpha in FEP patients.

Dr. Martine van Nierop (Maastricht University, The Netherlands) and co-authors conducted two population-based studies to assess childhood trauma and related psychotic symptoms. They saw a significant association between childhood trauma and psychotic experiences. Intention-to-harm experiences were more strongly associated with psychotic experiences than childhood trauma without intent (van et al., 2014).

Dr. Charlotte Gayer-Anderson (King’s College, London, UK) discussed the association between childhood adversity and later risk of psychosis. Her group has conducted a case–control study of first-episode psychosis patients, which showed that severe sexual and physical abuse was associated with increased risk of psychosis. The risk was reduced in cases with perceived high level of support from peers; cases with perceived low support in childhood were seen to have increased risk of psychosis.

Dr. Alessandra Raudino (University of New South Wales, Kensington, Australia) presented data from a longitudinal study of 561 children investigating the relationship of internalizing and externalizing problems and the occurrence of psychotic like experiences (PLE). There was a stronger association between internalizing problems and PLEs. However, both persistence and incidence of internalizing and externalizing problems are associated with increased incidence of PLEs in middle childhood.

Dr. Andrew Thompson (University of Warwick, Coventry, UK) presented data from the Avon Longitudinal Study of Parents and Children (ALSPAC) showing that frequent nightmares and night terrors experienced in early childhood (2.5 to 9 years), but not difficulty getting to sleep and night waking, were significantly associated with psychotic symptoms at age 12. Furthermore, those reporting nightmares at age 12 were twice as likely to experience psychotic symptoms at age 18 than those who did not.
Dr. Juha Veijola (University of Oulu, Oulu, Finland) reported that difficulty or uncertainty in making contact with others in adolescence was significantly more common among members of the Northern Finland Birth cohort who were later hospitalized with psychosis, compared to those hospitalized for non-psychotic disorders, and non-hospitalized controls. These results indicate that social problems may be specifically associated with risk of developing psychotic disorders.

Dr. Monica Aas (University of Oslo, Oslo, Norway) presented data that support gene × environment interactions as mechanisms behind brain abnormalities, CT and cognitive impairments in psychoses. In a sample of schizophrenia spectrum and bipolar disorder patients, it was found that Methionine (met) allele carriers of the BDNF Val66Met polymorphism with exposure to high CT had worse cognitive performance and more brain abnormalities (i.e., smaller right side hippocampal volume and larger lateral ventricles) than all other groups (Aas et al., 2013). She also reported a study showing that met carriers of the BDNF Val66Met with high CT had the lowest BDNF RNA levels. In conclusion, Dr. Paola Dazzan (Institute of Psychiatry, London, UK), highlighted relevant points on CT in general, including the issue of specificity/non-specificity of the effects of CT, as well as the need to elucidate factors that may confer resilience to the development of psychotic illness following CT.

With regard to the underlying anatomy and biochemistry, one possibility is that the associative striatum is a locus of vulnerability for transition to psychosis and that the dysregulation of dopamine transmission underlying symptoms of schizophrenia is rooted in the ventral striatum. Based on animal studies, Dr. Bita Moghaddam (University of Pittsburgh, Pittsburgh, USA) posited that dopamine hypo-activity in the dorsal striatum in adolescents may represent a disruption in normal development that puts people at risk for schizophrenia. She presented data from adolescent rats that evidenced disruption of dopamine synthesis by omega-3 fatty acids. This finding is noteworthy, as omega-3 fatty acids have been found to negatively influence the transition to psychosis in high risk individuals.

Interneuron pathology has been identified as a hallmark feature of schizophrenia in postmortem studies. There is a widespread migration of interneurons that are born postnatally in the subventricular zone away from the rostral migratory stream into various cortical and subcortical regions (Inta et al., 2011). One of these populations of adult-born interneurons, which are dopamine D3 receptor expressing neurons of the Islands of Calleja, may be important in the pathophysiology of schizophrenia. Dr. Bita Moghaddam (University of Pittsburgh, Pittsburgh, USA) spoke on the role of cortical interneuron to modulate cortical circuit activity, disruption of which is thought to contribute to cognitive deficits in schizophrenia. GABAA receptors are thought to play a role in dis-inhibiting pyramidal neurons, however using an inverse agonist against this receptor in freely moving rats using in vivo electrophysiology, showed unexpected effects of this drug to reduce pyramidal neuron firing and increase gamma power. Dr. Tiziano Colibazzi (Columbia University, New York, USA) presented data that collectively demonstrated disruptions of connectivity between the DLPFC and dorsal striatum. Longitudinal imaging data was collected in multiple modalities from a cohort of control subjects and patients at UHR for developing psychosis. During performance of a task-based fMRI paradigm (Simon task) assessing cognitive control, decreased activation was evidenced in the DLPFC and caudate in UHR subjects versus controls. This finding was corroborated by abnormal functional and structural connectivity between the caudate and frontal cortex, evidenced by resting state fMRI and diffusion tensor imaging respectively.

Using data from proton magnetic resonance spectroscopy studies, Dr. Camilo de la Fuente-Sandoval (National Institute of Neurology and Neurosurgery, Mexico City, Mexico) proposed that glutamate levels are increased in the dorsal caudate in UHR and anti-psychotic naïve FEP patients. UHR subjects showing eventual conversion to psychosis evidenced increased glutamate levels at baseline as compared to control and non-converting UHR subjects. Additionally, increased GABA levels were evidenced in the striatum of UHR subjects.

Dr. Paul Allen (King’s College, London, UK) focused on the neurobiological basis of functional outcome in UHR patients of psychosis. Cortical responses during a verbal fluency task were measured using functional magnetic resonance imaging and proton magnetic resonance spectroscopy (1H-MRS) was used to measure thalamic glutamate levels. UHR subjects with poor functional outcome at 18 months follow-up showed greater activation in the left inferior frontal, superior temporal gyri, the insula bilaterally and the right parahippocampal gyrus relative to UHR with a good outcome and to the control group. In addition, the poor functional outcome group also had lower levels of thalamic glutamate relative to the good functional outcome group.

Dr. Oliver Howes (King’s College, London, UK) investigated the relationship between presynaptic dopamine function and clinical outcomes in people who met UHR criteria, in people who experienced long term sub-clinical symptoms and in patients with schizophrenia (Demjaha et al., 2012; Howes et al., 2013; Egerton et al., 2013; Howes et al., 2009). All participants underwent DOPA PET imaging to index dopamine synthesis capacity in the associative striatum, known to be altered in schizophrenia. Presynaptic dopaminergic function was elevated in the UHR who subsequently developed psychosis compared to the ones that did not develop psychosis. There were no differences in dopamine release at follow-up between UHR and the ones that did not meet UHR criteria, and also the population with psychotic symptoms. Thus, elevated dopamine synthesis capacity seems to be specifically linked to people in the prodromal phase of psychosis (Howes et al., 2011).

Dr. Max de Leeuw (University Medical Centre Utrecht, Utrecht, Netherlands) presented data from an fMRI study examining reward processing among healthy siblings of individuals with schizophrenia. Using a Monetary Delayed Incentive Task, it was found that relative to healthy controls, siblings demonstrated hypoactivation in the ventral striatum during reward anticipation and hyperactivation in the ventral striatum and orbital frontal cortex during receipt of reward. These abnormalities, which have been similarly observed among patients with schizophrenia, may be due to impairments in dopamine transmission and might possibly reflect genetic vulnerability for psychosis.

Dr. Paul Allen (Institute of Psychiatry, London, UK) described an MRI and 18 F-DOPA PET study examining individuals at UHR for psychosis and controls. A dissociation in the relationship between resting cerebral blood flow in the hippocampus and presynaptic striatal dopamine function was observed with a negative association found among UHR youth and a positive association observed in the controls.

Dr. Lawrence Kegeles (Columbia University, New York, USA) discussed the data from his three studies conducted on the effects of anti-psychotic medication on GABA and glutamate (Glu) abnormalities. The results revealed that GABA and glutamate levels were abnormally elevated in FE-patients, but medicated patients did not show these elevations, suggesting that anti-psychotic medication may lower these levels. Elevations in both GABA and glutamate in schizophrenia suggest that glutamate elevation may be more primary in the pathophysiology of the illness.

Dr. Alice Egerton (King’s College, London, UK) focused on glutamate brain levels as a predictor of functional outcome. Using magnetic resonance spectroscopy (1H-MRS), she showed that lower levels of thalamic glutamate at presentation were associated with subsequent functional decline in individuals at UHR of psychosis. Conversely, higher anterior cingulate cortex glutamate levels were present in those UHR individuals whose functioning has deteriorated.

Dr. Kristin Laurens (University of New South Wales, Australia; Institute of Psychiatry, London, UK) reported the results of an event-related potential (ERP) study examining P3 component amplitude in children at-risk for schizophrenia because they have a family history of the disorder (FHx) or present multiple antecedents of schizophrenia (A5z). Both at-risk groups (FHx and A5z) showed...
reduced P3a amplitude (indexing an involuntary response to novel stimuli) relative to typically-developing children, but no differences in P3b amplitude (indexing conscious processing) were observed. In addition, it was found that among FHx and ASz children, but not typically-developing children, P3a amplitude was negatively associated with the cortisol awakening response.

In another attempt to predict conversion, Dr. Dorien Nieman (VU University Amsterdam, Netherlands) presented data showing that an integrative model with measurements of both premorbid adjustment and parietal P300 amplitudes could improve the prediction of conversion to psychosis in a clinical high-risk population. The prognostic score generated by the model showed both good sensitivity and specificity (Nieman et al., 2013).

Dr. Marco Hirstein (University of Bergen, Norway) presented the results of a meta-analysis indicating that non-right-handedness is significantly more common among individuals with schizophrenia than healthy controls. This result was consistent across males and females, and a slightly larger effect was observed when only studies using behavioral measures (rather than self-report) to assess handedness were considered. Interestingly, the findings appeared to be largely accounted for by higher rates of mixed handedness, as opposed to left hand preference, among individuals with schizophrenia.

Dr. Tyrone Cannon (Yale University, New Haven, USA) updated on multivariate predictor algorithms of high risk psychosis to capture population at risk of imminent onset. He showed that elevated cortisol and electrophysiological measures as lower mismatch negativity, lower p300 amplitude were considered stable biomarkers especially useful for prediction of diagnosis whereas lower cortical GM density was present in the patients that converted to psychosis. This work suggests that the emergence of psychosis is marked by a dynamic and potentially reversible process that results in a reduced structural and functional connectivity. He stressed the need of segregation between biomarkers in stable and progressive but also the importance on trying to define better the high risk populations by assessing them more frequently. He suggested the abnormality in neurodevelopmental processes as the primary hypothesis and the abnormalities in NMDA as a key mechanism that may result in excessive DA release.

Dr. Stephen Lawrie (University of Edinburgh, Edinburgh, UK) updated his and his colleagues’ work on clinical and imaging prediction of schizophrenia in people at high familial risk who were followed over 10 years. They extracted structural brain data and combined the brain maps with clinical, cognitive and genetic variables for support vector machine analysis. In this model, they identified baseline prefrontal cortical folding, schizotypy, COMT Val/Met status and psychotic symptoms as the strongest positive predictors of schizophrenia. He pointed out that only neuroimaging structural data as gyrification index and global cortical thickness measures had strong predictive value as a marker of illness as Sprooten et al. (2013) has recently shown. Thus, there are glutamate release alterations, and dopamine release and cortical thickness loss in the prodrome. It is important to disentangle what comes first and how these are related to the role of stress and inflammation in the conversion to psychosis.

Treatment of people at clinical high risk was also reviewed in several presentations. Dr. Patrick McGorry (Orygen Youth Health Research Centre, Parkville, Australia) presented findings on the effects of randomized controlled trials (RCT) in UHR individuals and gave an update of their ongoing multi-site projects. At the 12 month follow-up, three RCT trials (cognitive therapy + risperidone; cognitive therapy + placebo; and supportive therapy + placebo) showed improvement in negative symptoms and overall functioning. However, there were no significant group differences on the transition rates (McGorry et al., 2013). New directions for future clinical trials were suggested, such as adopting sequential screening to increase efficiency (Rietdijk et al., 2012) and broadening input and outcome targets (van Os and Linscott, 2012).

Dr. Anthony Morrison (University of Manchester, Manchester, UK) presented data demonstrating that cognitive behavioral therapy (CBT) for internalized stigma in people with at-risk mental states is effective. Instead of increasing internalized stigma, cognitive therapy was found to reduce the negative appraisals of unusual experiences over 12 months (Morrison et al., 2013).

Dr. Mark van der Gaag (VU University Amsterdam, Netherlands) presented findings from a meta-analysis evaluating the effects of CBT on delusions and auditory hallucinations. Five CBT trials showed the most robust effects with 48% risk reduction and a “Number Needed to Treat” of 13, indicating that early detection and intervention in people with UHR for developing psychosis is effective.

5. Studies of outcome

Dr. Peter Jones (University of Cambridge, Cambridge, UK) presented a ten-year outcome study of psychotic disorders: the AESOP-10 study. Schizophrenia was presented as an illness with a wide range of outcomes. The AESOP cohort followed 557 patients for 10 years, beginning with the first psychotic episode. A better course of illness was observed than that previously assumed, but social outcome was still poor.

Dr. Matti Isohanni (University of Oulu, Oulu, Finland) presented data from the Northern Finland 1966 birth cohort study (Molianne et al., 2013), showing that schizophrenia progresses in mid-life, with the higher the dose of anti-psychotics, the greater the brain volume loss. However, progression of clinical illness leads clinicians to give higher doses of neuroleptics, thus it cannot be assumed that neuroleptics are a cause of brain volume loss.

Dr. Rene Kahn (University Medical Center, Utrecht, The Netherlands) presented a 6-year follow-up of over 1000 patients (Korver et al., 2012). The data presented showed a 58% remission from psychosis at 6 years. Diagnosis other than schizophrenia, higher functioning, better quality of life and higher IQ were associated with higher rates of remission.

Dr. Arsim Demjaha (Institute of Psychiatry, London, UK) examined pathways to treatment resistance in a cohort of individuals with FEP who were followed-up 10 years later. In total, around 10% of the sample (74/323) were classified as being treatment resistant, these patients were more likely to be younger, male, have a diagnosis of schizophrenia, and a longer duration of untreated psychosis. Interestingly, the majority of these individuals were found to be resistant to anti-psychotic medication during the early stages of treatment, with less than 1 in 5 patients developing treatment resistance later in the course of illness. Differences were observed between these two groups, suggesting that there may be two distinct pathways to treatment resistance among individuals with schizophrenia.

Dr. Mark Weiser (Tel Aviv University, Israel) presented data that showed nation-wide employment status in patients with schizophrenia and bipolar disorders was poor even if they were admitted to the hospital only once. In summary, factors such as stigma, medication compliance, among other things play a role in predicting the outcome and prognosis of psychotic patients.

6. Substance abuse

Various substances are thought to be risks for later psychotic illness. Various amphetamines have long been implicated. Dr. Callaghan (University of Northern British Columbia, Canada) presented results of a large population based study of patients in California with methamphetamine related problems, showing that methamphetamine abusers may have a higher risk of schizophrenia than population matched controls. The level of risk was as high as cannabis and greater than cocaine and opioid users.

Dr. Suzanne Gage (University of Bristol, UK) reported on the association between psychotic experiences and tobacco use in adolescents from the UK, using evidence from the Avon Longitudinal...
Study of Parents and Children (ALSPAC). Analyses revealed that very few of the subjects reported any psychotic experiences. The association between cigarette use and psychotic experiences was confounded by cannabis use, but little evidence for a psychotogenic effect of tobacco smoking was found. Dr. Pedro Guirilo Munoz (Hospital de la Marina Baixa, Alicante, Spain) reported a review and meta-analysis of the association between tobacco smoking and psychosis. Daily tobacco smoking was associated with an increased risk of a psychotic disorder, with an earlier onset of psychosis than non-smokers. Dr. Marta Di Forti (Institute of Psychiatry, King’s College London) presented a case-control study of the association between tobacco use and first episode psychosis from the Genetics and Psychosis (GAP) study. The data analysis revealed that there is an elevated rate of first episode psychosis in tobacco users and the associations was unchanged after adjusting for lifetime cannabis use. Dr. Marco Boks (UMC Utrecht, the Netherlands) presented the nature of the relationship between cannabis use and psychotic-like experiences using data from a cross sectional survey of young adults. Analysis revealed that smoking is an important confounder of the relationship between cannabis and psychotic experiences. Perhaps many different exposures (e.g. skunk, cannabis, tobacco smoking) contribute to the development of psychosis, but further prospective studies are needed to clarify these risks.

Dr. Marta Di Forti focused on the ways in which high potency cannabis, i.e. sensimilla (Skunk) may lead to psychosis. The modern high yielding potent skunk plant has increased levels of THC compared with previous forms of marijuana. In a recent study, persons with first episode psychosis were about 5 times more likely to use highly potent cannabis (skunk-type) daily and the mean age of onset of psychosis in participants who used skunk was 6 years earlier than those who did not use cannabis (Di Forti et al., 2013). In addition, cannabis use preceding the onset of psychosis may interact significantly with a AKT1 rs2494732 genotype resulting in deficits in performance of certain tasks (Ozaita et al., 2007; Van Winkel et al., 2011).

Dr. Jim van Os (University Hospital of Maastricht, The Netherlands) reported that differential sensitivity for cannabis use was found in relatives. According to him, a large family based cohort of patients, their siblings and parents reveal that selective environmental exposures e.g. cannabis influence familiar correlation of psychosis (Smeets et al., 2010). This suggests that it raised the importance of selective gene-environment interactions in psychosis susceptibility.

Dr. Deepak D’Souza (Yale University School of Medicine, Dept of Psychiatry) attempted to explain how synthetic cannabinoids such as spice may relate to psychotic states. “Spice” products are sold under many different names and packaging and they contain synthetic cannabinoids that have been sprayed onto an herbal substrate. Psychosis is one of the most prominent side effects of synthetic cannabinoids. Unlike THC found in the marijuana plant, synthetic cannabinoids are high affinity full agonists for the CB1 receptor and consequently highly potent. The significant variability in the type and amount of synthetic cannabinoids in different types of ‘spice’ poses research challenges.

Dr. Tiziana Runio (University of Insubria) explored the molecular mechanisms that underlie the etiology of cannabis associated psychosis and cognitive deficits and studied adolescent rats after exposure to THC. Her results suggest that THC administration to adolescent rats may result in epigenetic changes in a dose dependent manner, and negatively affects the expression of genes involved in brain plasticity.

Dr. Amir Englund (Institute of Psychiatry, UK) discussed the endocannabinoid system and the phytocannabinoids including THC, CBD, and THCV. He presented his work on the administration of THC to healthy subjects. He found that the negative effects caused by THC were dose dependent and that CBD was therapeutic and able to offset the negative effects of high doses of THC. Additionally, THCV blocked some of the negative psychological effects of THC while possibly increasing anxiety and improving cognition.

Dr. Markus Leweke (Central Institute of Mental Health in Mannheim, Germany) proposed the binocular depth inversion test (DBI), a measurement tool sensitive to characterize impaired visual information processing, as an integrative neuropsychological test for assessment of psychosis, anti-psychotic treatment efficacy and psychopathology associated with Δ9-tetrahydrocannabinol in UHR adolescents as well as in patients with schizophrenia and healthy individuals.

Regardless of whether some substances can actually cause a psychosis, initiate one that would have occurred eventually, or interact with genetic risk factors to cause the disorder, substance abuse of several kinds is co-morbid with schizophrenia in clinical populations. The underlying biological interactions and how substance use is addressed clinically is of crucial importance, as it likely leads to poorer functional outcome.

Dr. Anissa Abi-Dargham (Columbia University, USA) presented studies showing that dopamine release in patients with schizophrenia and comorbid substance use is markedly blunted when compared with substance use alone. A recent raclopride positron emission tomography study with an amphetamine challenge showed that dopamine release was linked to transient amphetamine-induced positive symptom change (Thompson et al., 2013). These findings suggest that oversensitivity of D2 receptors or abnormality of the postD2 signaling pathway may be involved in substance use psychosis. Prof Robin Murray (Kings College, United Kingdom) suggested that the risk of cannabis related psychosis could be related to the potency and extent of drug use. This mechanism may be different from other forms of schizophrenia because of the postsynaptic abnormality observed (Bloomfield et al., 2013).

7. Violence and schizophrenia

Acts of violence by people with schizophrenia, particularly those who are untreated frequently make the news world-wide. Violent behavior is 4 times more frequent in people with schizophrenia than in the general population, although it is often noted that only a small portion of violent acts in total are completed by people with schizophrenia. Dr. Seena Fazel (University of Oxford, Oxford, UK) presented a systematic review and a meta-analysis of the risk and protective factors of violence in patients with psychosis (Witt et al., 2013). 110 such studies of a total of 45,533 patients have been published. In a meta-analysis of these studies risk factors for violence included: hostile behavior, recent drug misuse, non-adherence to psychological therapies, poor impulse control, recent substance misuse, recent alcohol misuse, and non-adherence to medications. Prior criminal history was also found as a risk factor. Dr. Jeffrey Swanson (Duke University School of Medicine, Durham, USA), challenged the assumption that delusions directly cause violence in schizophrenia patients. The heterogeneity of patients suffering from delusions and the multi-factorial nature of violent behavior were presented as key factors for the inability to define delusions as a single independent cause for violent behavior. Factors like age, sex, substance abuse, social disadvantage, developmental history, victimization and trauma and exposure to community violence, were presented as important associated factors. Other types of symptoms, such as explosive anger, impulsivity, disregulated mood, psychoactive drug effects, and anti-social personality, combined with delusions may exacerbate or mediate their impact on violence risk. Although psychopathology may contribute to violent behavior, it is rarely the single cause for such behavior.

Dr. Giovanni De Girolamo (IRCCS Fatebenefratelli, Brescia, Italy) discussed an ongoing and yet unpublished review of the prevalence and risk factors for interpersonal violence in acute psychiatric units. The main finding was that 20% of patients were violent in acute inpatient settings. Age, sex and schizophrenia were clear risk factors, while others were inconsistent. Dr. Olav Nielsens (St. Vincents Hospital, Sydney, Australia) presented a review of case linked studies
psychotic relapse early in the course of illness (Øie et al., 2010). 10 years of neurocognitive follow-up data, and con

University of Oslo, Oslo, Norway). This study included 1

An association between decline in certain aspect of IQ and total

in how their cognitive function changed over time, with the exception

Cohort members with schizophrenia were broadly similar to controls

12,000 individuals born in the two most Northerly provinces of Finland

change in cognitive performance over a nine-year period in middle-age

Dr. Graham Murray (Cambridge University, UK) presented results of

the inability of risk assessment based interventions to reduce violence

and presented an approach based on the stage of illness. The data

suggest that intervention aimed at reducing violence should include:

early treatment of first psychotic episodes, reduction of substance

abuse and long term supervision.

8. General cognition

Dr. James MacCabe (King’s College, London, UK) discussed a cog-
nitive trajectory between ages 10, 13 and 18 and risk for psychosis in

adulthood for a Swedish longitudinal cohort study. Previous studies

postulated that cognitive deficits are assumed to result from

neurodevelopmental changes (Murray and Lewis, 1987). He report-
ed that poor cognitive function is associated with increased risk of

depression; alcohol dependence, cardiovascular disease, and mortal-

ity. Further, findings suggested that psychosis is characterized by

relative decline in pre-morbid verbal score between age 13 and 18

years old. The timing of these verbal score deficits suggested that

this may reflect an abnormality in late development, and are

consistent with data from neuroimaging, which show acceleration

of gray matter loss.

Dr. Eileen Joyce (University Hospital, London, UK) studied

neurocognitive functioning at the first episode of schizophrenia

and over the first four years of illness. Both premorbid and current

IQs were evaluated. Previously, strong dissociation between current

IQ and social function were observed. It was hypothesized that

fronto-parietal networks serve as multiple demand systems which

undertake the information processing requirement common to dif-

ferent cognitive tasks. Cognitive impairment was found to be linked

with brain abnormalities at the onset of psychosis (Gutiérrez-Galve

et al., 2010) and specifically reduction of cortical thickness in frontal,

temporal and parietal cortices were found on follow-up. Patients

with psychosis showed significant impairment in tasks including

current IQ, working memory span and planning. Furthermore, IQ

impairment was predicted by fronto-parietal cortical thickness and

seems to be related to its disconnectivity.

A 10 year longitudinal follow-up of first episode patients (FEP) in

the Scandinavian TIPS study was presented and discussed by Dr. Bjørn Rund

(University of Oslo, Oslo, Norway). This study included 1–3, 5 and

10 years of neuropsychological follow-up data, and confirmed that previous

findings suggested long-term stability in neuropsychological functioning,

with the exception of decline in verbal memory in patients with

psychotic relapse early in the course of illness (Øie et al., 2010). In

addition, significant correlations were observed between performance on

working memory and verbal learning at 1, 2, 5 and 10 years. An

association between decline in certain aspect of IQ and total
duration of psychosis after initiation of treatment was also found.

Dr. Graham Murray (Cambridge University, UK) presented results of

change in cognitive performance over a nine-year period in middle-age

in the Northern Finland 1966 Birth Cohort study, which consists of over

12,000 individuals born in the two most Northerly provinces of Finland

in 1966 and followed from the prenatal period to the present day.

Cohort members with schizophrenia were broadly similar to controls

in how their cognitive function changed over time, with the exception of

an executive function test involving abstraction with memory,
in which schizophrenia individuals deteriorated to a greater degree than controls. Moreover, a measure of infant motor development

(age of learning to stand without support) predicted the decline in

this measure in middle-age in schizophrenia, providing a hint that
developmental and degenerative aspects of schizophrenia could be

inter-related. He also showed that while cohort members with

schizophrenia exhibit a significant decline in verbal learning during

middle-age, cohort general population controls also decline in verbal

learning in this follow-up study, making the schizophrenia verbal

learning decline difficult to interpret.

Dr. Michel Mazilade (Laval University, Quebec, Canada) reported

data from a longitudinal study exploring cognitive decline in children

born to a parent affected by schizophrenia. A 5 year follow-up revealed

that the entire cohort experienced some cognitive decline. There was

no difference in diagnosis or global functioning of those with steep

versus minimal decline. It remains to be explored whether this loss

of IQ should be characterized as a true decline in function or simply a

failure to mature.

9. Social cognition, negative symptoms and their treatments

Dr. Michael Green (UCLA, Los Angeles, USA) contrasted high and low

levels of social cognition in schizophrenia. Mentalizing, an example of

high level social cognition, was impaired in schizophrenia, and associat-
ed levels of functional neural activity were also aberrant. In contrast,
depression; alcohol dependence, cardiovascular disease, and mortal-

ity. Further, findings suggested that psychosis is characterized by

relative decline in pre-morbid verbal score between age 13 and 18

years old. The timing of these verbal score deficits suggested that

this may reflect an abnormality in late development, and are

consistent with data from neuroimaging, which show acceleration

of gray matter loss.

Dr. Anil Malhotra (The Zucker Hillside Hospital, New York, USA)

used resting state measures of brain connectivity as a potential

biomarker for negative symptom severity. Specific aberrations in
cortical midline regions such as fronto-parietal and posterior cingulate
areas, which are associated with social cognition, were predictive of
negative symptom severity. Dr. Aristotle Voineskos (University of
Toronto, Toronto, Canada) further expanded upon the relationship
between brain connectivity and negative symptoms. He discussed the
use of graph theory to analyze neural data, measuring centrality
between specific nodes in the brain, and suggested that this may be a
more useful biomarker than white matter integrity. Early data using
this analysis technique is focusing on brain regions involved with
lower lever social cognition, such as emotional mirroring behavior.
Dr. Sophia Vonogradov (UCSF, San Francisco, USA) discussed therapeu-
tic treatment of negative symptoms. Motivational deficits in adoles-
cence are among the earliest precursors to schizophrenia, and deficits in
social cognition and working memory are mediated by motivation.
Therefore, therapies that target the dopaminergic reward system may
be useful when treating both social and cognitive deficits in psychotic
disorders. Dr. Vinogradov also discussed the effectiveness of the
addition of social cognitive training to more general cognitive training
in patients with schizophrenia. Vinogradov presented work suggesting
that combining cognitive and social cognitive training improves neural
activity in areas associated with social cognition. She found that
computer-based training programs improved the areas of facial
emotion recognition and reality monitoring and that this translated
into better social functioning in patients.

Very few researchers have focused on the link between musical
ability and cognitive functioning (Hatada et al., 2014). Dr. Ken Sawada
(University of British Columbia, Vancouver, Canada) investigated
the musical ability of schizophrenia patients and suggested that
schizophrenia patients, compared to controls, perform worse on a test
measuring musical ability. In schizophrenia there was an association
between poor musical ability, the degree of cognitive impairment and
the severity of symptoms. In particular there seems to be a link between
negative symptoms and poor musical ability.

Dr. Michael Green (UCLA Semel Institute for Neuroscience and
Human Behavior, Los Angeles, USA) referred to the association between
negative symptoms and poor functional outcome. He suggested that
in addition to clinical interviews more objective measures of negative
symptoms are required to treat them. Green and colleagues used
performance-based measures to assess negative symptoms related to
motivation and effort. Their work suggests that in comparison to controls, some patients exhibited less effort and gave up more easily, while other patients were more persistent than controls. Dr. Deanna Barch (Washington University St. Louis, USA) addressed the complexities involved in schizophrenia patients' apparent lack of motivation. She referred to studies in which she and her team used the Effort-Expenditure for Rewards Task and the Probabilistic Selection Task together with fMRI imaging to better understand the underlying mechanisms involved in motivation, effort and reward learning. The studies suggest that there are no significant differences between controls and schizophrenia patients when it comes to learning from negative feedback. However, schizophrenia patients are less likely to learn from positive feedback.

Dr. Eleanor Simpson (Columbia University, New York, USA) presented work she had done on mice to understand the mechanisms involved in impaired motivation and the role played by dopamine. Mice exposed to selective overexpression of striatal D2Rs and D3Rs were less inclined to work for a reward and this was not due to anhedonia. Dr. Jared Young (University of California, San Diego, USA) presented work he and his team did on Sp4 mutant mice to gain insight into motivation and reward learning. He compared Sp4 hypomorphic mice to wild type mice and found that Sp4 mutant mice performed worse in terms of attention, learning and motivation. In addition, he tested the effect of GLYT1 inhibition treatment and found that it did not reverse impaired learning and motivation; however, it was effective in reversing impaired attention.

Schizophrenia makes it difficult for patients living with the disease to function effectively in their daily lives (Keefe, 2007). The work done by Dr. Peter Falkai (Ludwig-Maximilians University, Munich, Germany) and colleagues suggests that exercise may improve patient functioning. He presented data showing that aerobic exercise has a positive impact on cognition and leads to a reduction in negative symptoms. Initially, patients experienced stress, since they were not used to exercising. However three months into the study the aerobic exercise regimen had a positive impact on patient symptoms and cognitive function. Dr. Eric Chen (University of Hong Kong, Hong Kong) presented a study in which he investigated whether patients with early psychosis benefit from yoga. The study suggests that yoga has a positive impact on cognition and correlated with an improvement in clinical symptoms such as depression. In addition, it was found that yoga in comparison to aerobic exercises has a more beneficial impact on attention and concentration.

10. Social defeat as a risk factor

It is widely accepted that a hyperactive mesolimbic dopamine system is associated with the positive symptoms of schizophrenia. While the causes of such a dysregulation are not clear, a hypothesis known as social defeat (Selten and Cantor-Graae, 2005) postulates that social risk factors such as migration or particular health conditions (experienced as a stigma) may induce social defeat, sensitize the mesolimbic dopamine system and increase the risk of developing schizophrenia. Dr. Andreas Meyer-Lindenberg (Central Institute of Mental Health in Mannheim, Germany) presented data on the relationship between environmental risk factors such as urbanicity and neuronal mechanisms. Using the social evaluative stress during functional magnetic resonance imaging (fMRI) his group found a specific association of city living with amygdala activity and urban upbringing with perigenual cingulate cortex.

Dr. Romina Mizrahi (Centre for addiction and Mental Health, Toronto, Canada) reported studies demonstrating potentiated striatal dopaminergic transmission induced by the social stress of immigration. Comparing people at high risk and schizophrenia using positron emission tomography, an association was found between immigration and dopamine hyperactivity in the associative striatum and measures of social stress.

Dr. Vincent Vialou (Inserm, Paris, France) presented data on an animal model of social defeat stress demonstrating that ΔFosB is specifically induced in the medial prefrontal cortex (mPFC) of vulnerable mice as measured in several behavioral tests. Such induction worsened the effect of stress as evidenced by its overexpression in medial prefrontal cortex. ΔFosB was then linked to the cognitive deficit of schizophrenia, providing evidences of an increased expression of the protein after treatment with anti-psychotic drugs and increased startle response and glutamate-mediated anxiety in those mice overexpressing ΔFosB in mPFC.

Mr. Martin Gevonden (Brain Imaging Center, Amsterdam, The Netherlands) spoke on alterations in the dopaminergic system of people with hearing impairment (HI), a group who experience social defeat and are at increased risk for psychosis. Comparing striatal dopamineD2/3 receptor binding and amphetamine-induced dopaminergic release using single-photon emission computed tomography (SPECT) between HI and normal hearing subjects, Mr. Gevonden found that the HI group had greater dopamine release after an amphetamine challenge but did not differ from the control group in baseline tracer binding. The sensitized dopaminergic response to amphetamine was however neither associated with social defeat scores on questionnaires nor with positive symptoms in response to amphetamine. Together these studies suggest the role of social defeat as an environmental risk factor in the development of schizophrenia.

11. Reward processing

Dr. Nicholas Simon and Dr. Bita Moghaddam (University of Pittsburgh, USA) reported dissociations in electrophysiological signals between adolescent and adult rats in the orbital frontal cortex (OFC) during the performance of a reward-driven operant behavior using single unit recording. Phasic neuronal activity in the OFC was increased in adolescent rats, during reward collection, whereas OFC activity was inhibited in adults.

Dr. Alison Adcock (Center for Cognitive Neuroscience, Duke University, Durham, USA) reported on the role of the dorsolateral prefrontal cortex (dlPFC) in mediating reward-motivated behaviors. Using dynamic causal modeling (DCM) to interpret fMRI data obtained from healthy and ultra-high risk (UHR) adolescent humans performing reward anticipation tasks, Dr. Adcock identified the dlPFC as the exclusive entry point of reward-related information in healthy individuals. The reward-related signal then activated the ventral tegmental area (VTA) and the nucleus accumbens (NAC). However, this hierarchical network proved to be altered in UHR subjects due to their dysfunctional dlPFC activity.

Dr. Matthijs Vink (UMC Utrecht, the Netherlands) reported on dysfunctional development of the fronto-striatal network in adolescent offspring of patients with schizophrenia. He measured brain activation using functional MRI while offspring and controls performed an inhibition task and a reward task. The results revealed impaired development of the fronto-striatal network in offspring of patients, characterized by hypoactivation of the striatum and frontal cortex during both tasks.

Professor Birte Glenthaj (Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Copenhagen University Hospital, Mental Health Centre Glostrup, Denmark) presented data relating striatal and extrastriatal dopamine D2/3 receptor binding to psychopathology, reward processing, and treatment outcome in two cohorts of schizophrenia patients. The two cohorts of patients and matched controls are both part of longitudinal cohorts of initially anti-psychotic-naive first-episode schizophrenia patients. The patients were comparable in catchment area and inclusion criteria. One of the two cohorts (CINS cohort A) went through an examination program including SPECT scans using [123I] epidepride as the D2,3-receptor radio ligand. This ligand is suitable for examinations of extrastriatal receptors in contrast to the D2,3-receptor ligand (O.N. Nielsen et al., 2012; M.O. Nielsen et al., 2012) labeled iodobenzamid (IBZM), which was used in the other cohort (CINS cohort B). IBZM is suitable for examinations of striatal D2,3-receptors. The Positive and
12. Studies using brain imaging

“Connectomics” is a new field that has emerged from brain imaging and provides an approach to understanding brain functioning based on data from shared imaging studies. His approach has been in development since 2005 with new concepts of trackable networks (“hubs and nodes”, “rich clubs”). Dr. Ed Bullmore (University of Cambridge, Cambridge, UK) gave a brief description of connectivity-based functional magnetic resonance brain image parcellation, which results in the statistical brain-map model of the anatomical connections in the nervous system. As an example of interconnection abnormalities, Dr. Bullmore presented amyloid-related destruction of “rich hubs” in Alzheimer disease (Buckner et al., 2009), abnormalities of prefrontal, limbic, temporal, and parietal hubs (Rubinov and Bullmore, 2013) and abnormal synchronized cortical thickness (Alexander-Bloch et al., 2014) in schizophrenia.

Dr. Martijn van den Heuvel (Brain Centre Rudolf Magnus, Department of Psychiatry, Utrecht, The Netherlands) underlined the role of high connectivity hubs (rich club hubs, RCH) in the pathology of schizophrenia. RCH represent the general system of communication and integration of the information. In the series of studies the reduced connectivity between the rich club nodes of the brain was detected in patients with schizophrenia (Van den Heuvel et al., 2013), in siblings of patients and in their healthy offsprings (Collin et al., 2014).

Dr. Deanna Barch (Washington University St. Louis, USA) presented work applying graph theory to brain connectivity. She found that the basic brain network structure was intact among individuals with schizophrenia. However, several core brain networks that are involved in higher cognitive and behavioral functioning such as the cingulo-opercular (CO), frontal parietal (FP) and cerebellar (CER) networks suggest that functional disconnectivity between these networks (Repovš and Barch, 2012) may affect cognitive and psychological functioning. Other studies provide evidence that schizophrenia is a “disconnectivity disease”, showing a significant reduction in rich club connections in superior frontal, parietal regions and insula regions in schizophrenia (Van den Heuvel et al., 2013).

Dr. Mark Drakesmith (Cardiff University, Cardiff, UK) shared his findings examining the properties in the structural brain networks using Graph theory in individuals with psychotic experiences. Individuals with psychotic experiences had decreased network efficiency and network density as compared to controls thus a lack of integrity, particularly in critical rich club hub regions.

Dr. Holly Moore (Columbia University, New York, USA) stressed that although schizophrenia involves many different neural pathways, it is not a disease of the whole brain. Using animal models, she described substantial pathogenic roles of subcortical regions and cortical–subcortical connectivity, showing interactions between multiple brain systems (prefrontal cortex, limbic system, thalamus, ventral midbrain, striatum and pallidum).

Dr. Kelvin O. Lim (University of Minnesota, Minneapolis VAHCS, USA) stressed the importance of studying substance abuse due to its high prevalence in schizophrenia and its sharing of similar circuits and neurotransmitters systems[01] as schizophrenia. He gave an overview of task based fMRI studies that were used to predict substance use relapse. He then presented recent work that used resting fMRI to show that higher connectivity between prefrontal cortex (PFC) and nucleus accumbens (NAC) was found in subjects with 7 years of alcohol abstinence compared with non-using controls. In 11 week abstinent alcohol abusers, a lower PFC-NAC connectivity predicted relapse use within six months. A longitudinal study examining stimulant users at 5 weeks and 13 weeks of abstinence found that connectivity patterns changed during this period and that a reduction in PFC-NAC connectivity from 5 to 13 weeks was a strong predictor of relapse within 6 months. Based on these data, it was suggested that non-invasive brain modulation methods might be used to increase PFC-NAC connectivity as an intervention to reduce relapse.

Dr. Godfrey Pearlson (Olin Neuropsychiatry Research Centre and Yale University, Hartford, USA; Institute of Living, USA) presented the evidence from several structural and functional studies of a Bipolar and Schizophrenia Network on Intermediate Phenotypes (BSNIP) Consortium. He demonstrated a substantial schizophrenia/bipolar disorder overlap in the structure and function of the brain using the parameters of gray matter volume (Ivleva et al., 2013), cortical thickness (Nanda et al., 2013), fractional anisotropy (Skudlarski et al., 2013) and functional connectivity (Unschuld et al., 2014). Most substantial similarities were found that in prefrontal regions, the degree of deficits is always higher in schizophrenia patients, but it is not different in kind and is close to schizoaffective disorder. Thus, none of the obtained structural and functional imaging findings are specific to schizophrenia. He emphasized a need to reclassify psychiatric illnesses based on brain biomarkers rather than phenomenology.
Dr. Deanna Barch (Washington University in St. Louis, USA) discussed new advances in the Cognitive Neuroscience Task Reliability & Clinical Applications (CNTRACs) Consortium that is aimed to: 1) access cognitive mechanisms and neural systems that are related to fundamental components of human behavior; 2) optimize cognitive tasks by simplifying, minimizing task length, standardizing the task administration, maximizing sensitivity and selectivity and maintaining construct validity, enhancing reliability; 3) address imaging biomarkers; 4) translate tests into clinical research and practice. She reported the data on the differences in behavioral and imaging correlates in patients with schizophrenia and healthy individuals using the Modified AX-Continuous performance test, Relational Encoding and Retrieval Test, also demonstrating the association of fMRI tasks and Proxy functional measures. She highlighted further steps toward the development of a different set of measures on working memory capacity; implicit negative reinforcement learning, explicit positive and negative reinforcement learning and stressed the importance of applying tests in patients with schizoaffective disorder and bipolar disorder in order to elicit the common patterns that come across diagnostic categories.

Dr. Vince Calhoun (The Mind Research Network; The University of New Mexico; UC Irvine, USA) discussed dynamic functional connectivity assuming that the resting state is not homogeneous and consists of several alternating states. The resting state data were obtained from a simultaneous fMRI and EEG study in a large cohort of healthy individuals. Based on a spatial and temporal independent component analysis (ICA) by clustering the time series of commonly recurring states, Allen et al. (2014) were able to identify distinct states and their alterations. Dr Calhoun provided the evidence of weak resting state connectivity in patients with schizophrenia, the decreased number of distinct states and reduced dynamic fluidity (changes) between the states, and these were associated with negative symptoms.

Dr. Letizia Squarcina (Department of Public Health and Community Medicine, Italy) assessed hemodynamic changes in first episode psychosis using brain perfusion imaging. The aim of the study was to automatically classify psychosis using Dynamic Susceptibility Contrast (DSC) MRI. Combining perfusion imaging and machine learning, First Episode-Psychosis patients were distinguished from controls with an accuracy of over 80%.

Dr. Renaud Jardri (Lille University Medical Centre, France) investigated different sensory hallucinatory experiences using multi-modal connectivity analysis on the hippocampal complex (HP) connectivity and the mesolimbic pathway (ventral tegmental area and nucleus accumbens (NAcc)) known to be involved in hallucinatory pathophysiology. Patients with visual and auditory hallucinations exhibited greater resting state connectivity between the NAcc network, HP and the prefrontal cortex. Additionally, further analysis revealed greater white matter connectivity in the HP pathways connecting visual areas than in the patients that had only auditory hallucinations.

Dr. Marco Picchioni (Institute of Psychiatry, London, UK) and coworkers examined an fMRI during phonological verbal fluency task in a large cohort of twin-sibling subjects. Patients and their unaffected relatives developed greater activation in the left inferior frontal gyrus, and greater deactivation in the left hippocampal and middle temporal gyril bilaterally compared to HC.

Dr. Deepak Cyril D’Souza (Yale University, New Haven, USA) gave an overview of the Cannabinoid 1 Receptor (CB1R) availability using PET in schizophrenia. 19 male patients showed reduced CB1R in the posterior cingulate cortex compared to age-matched HC using a PET resting state High Resolution Research Tomography and the 11C-OMAR CB1 tracer. Moreover, treatment with Dopamine D2 antagonists decreased CB1R availability, suggesting a possible normalization effect of CB1R in schizophrenia. Surprisingly, they showed that the more CB1R density in the posterior cingulate cortex, the more the emotional distress symptoms (PANSS excitative dimension).

Dr. Alan Anticevic (Yale University, New Haven, USA) Based on the NMDA receptor dysfunction hypothesis for working memory deficits seen in schizophrenia, a computational model of specific behavioral and neural predictions was created. BOLD imaging revealed ketamine disrupted task-dependent activation and connectivity during working memory. This work suggests disinhibition as a neural model of working memory deficits in the early course of schizophrenia and ketamine as a suitable pharmacological model for them.

Dr. Dennis Hernaas (Maastricht University, Maastricht, The Netherlands) investigated the role of stress-induced dopamine activity in Prefrontal cortex using PET in 3 groups, 1) patients under medication, 2) unmedicated patients and 3) healthy controls. Regression analysis revealed large differences in stress-induced changes in Fallypride binding in ventromedial PFC and dorsolateral PFC. Patients under medication showed a low stress-induced dopaminergic response, the unmedicated patients slightly higher and controls the highest. Differences in stress-induced changes in D2/D3 receptor occupancy between medicated and unmedicated could suggest that the stress response depends on treatment or illness phase.

Dr. Remko van Luttenveld (University Medical Centre Utrecht, the Netherlands) compared cortical thickness in 3 populations alongside the continuum of psychotic symptoms. Using rank analysis for levels of cortical thickness, he demonstrated the highest thickness in controls, whereas the non-clinical group of individuals with auditory hallucinations showed a similar but milder pattern of cortical thinning than patients with psychotic disorders.

Dr. Nikolaos Koutsouleris (Ludwig-Maximilian University Munich, Germany) applied a machine learning analysis (support vector analysis, SVM) to investigate the abnormal trajectories of aging in schizophrenia, depression and personality disorder in order to predict the age and patients’ status from structural MRI images (Koutsouleris et al., 2013). There was an overlap of predictive patterns of age and the patient’s status and detected brain regions suggesting that the brain areas that undergo strong changes over a life span are substantially affected by the disease.

Dr. Elias Mouchianitis (Medical Research Council Clinical Sciences Centre, Imperial College London, UK) presented a study examining glutamate level differences in the anterior cingulate cortex (ACC) between treatment resistant and treatment responsive schizophrenia patients, showing elevated glutamate in chronic treatment resistant patients with a relatively large effect size of 0.76.

Dr. Hilleke Hulshoff Pol (Brain Centre Rudolf Magnus, University Medical Centre Utrecht, the Netherlands) presented her findings from 7-T MRI study that support the mechanism of altered GABA level distinguished from glutamate levels in medial prefrontal cortex in schizophrenia, particularly in patients with higher IQ. She assumed the compensatory role for GABA through altered inhibitory neurotransmission in the prefrontal cortex which may be ongoing in particularly high functional patients with schizophrenia.

Dr. Edith Liemburg (University Medical Centre Groningen, The Netherlands) reported the results of the study that investigated levels of glutamate/glutamine and n-acetyl aspartate (NAA) in the prefrontal cortex in psychotic disorders and in ultra high risk subjects (UHR) in a large cohort study. She showed that along with an increasing age there is a stronger decline in NAA and glutamate level in psychotic patients compared to healthy controls. In UHR subjects there was an increase of NAA and glutamate level with increasing age. Machteld Marcelis (Maastricht University, the Netherlands) presented data from a longitudinal DTI study of patients with schizophrenia and their healthy siblings at risk for psychosis. Patients showed reduced white matter integrity in comparison to healthy controls, although no reduction was detected in white matter tracks over a 3 year period, while fractional anisotropy (FA) declined in the siblings over time.

Dr. Peter Uhlhaas (University of Glasgow, UK) spoke about his study in which magnetoencephalographic (MEG) responses of medication naïve first-episode patients (FE-patients) with SCz were assessed and
compared with chronically medicated SCZ patients and a group of healthy individuals who were administered sub anesthetic dose of ketamine. The potential differences in their neural oscillations and event related fields (ERFs) at task-and resting-state were examined. Increased excitability of neural circuits was observed in FE-SCZ compared with the effects of ketamine using MEG-data. The study results established that MEG was well tolerated by FE-SCZ patients but there were certain deficits in both neural oscillations and ERFs which were specific to FE-SCZs and not observed in chronically medicated SCZ patients. There was an overlap with the effects of ketamine on neuromagnetic activity which provides evidence that cortical activity in FE-SCZ may be characterized by disinhibition, possibly involving NMDA-hypofunction.

13. Oligodendrites and glia

Dr. Natalya Uranova (Russian Academy of Medical Sciences, Moscow, Russia) and her group have studied white and gray matter in prefrontal cortex of postmortem brains. They found evidence of a deficiency of glial cells and damage of oligodendrocytes in schizophrenia when compared with healthy controls. The frequency of pathological fibers in gray matter was increased in patients with predominately positive symptoms and in contrast, the frequency of altered fibers in white matter was increased in elderly patients, in patients with predominately negative symptoms, and correlated with illness duration (Uranova et al., 2011).

Dr. Andrea Schmitt (Ludwig-Maximilians-University, Munich, Germany) presented a comparative proteome analysis of the prefrontal cortex in patients with schizophrenia and in healthy controls to identify possible alterations in protein expression. He found a reduction in proteins for energy metabolism, cytoskeleton, and cell-signaling proteins as well as oligodendrocyte-marking proteins in schizophrenia (Martins-de-Souza et al., 2009).

Dr. Lan Xiao (TMM University, Chongqing, China) and her group have studied whether the demyelination in schizophrenia could be linked to the use of typical anti-psychotic medication (Niu et al., 2010). They examined mice treated with a typical anti-psychotic drug, and showed that young mice were more vulnerable to drug-induced demyelination in the white matter of the forebrain, and the demyelination was associated with schizophrenia-like behavior. Additionally, they also showed that mice treated with atypical anti-psychotic drugs prevent demyelination and actually facilitate myelination of neocortical cells.

Pavel Katsel (Mount Sinai Medical Center, New York, United States) presented his work on possible abnormalities in neuron and oligodendrocyte interactions at the Nodes of Ranvier (NOR) in schizophrenia. In a case–control analysis of postmortem brain samples, his group found that patients with schizophrenia had decreased expression of multiple NOR genes. They also found that lower expression of the allele ANK3 increased the risk of schizophrenia. Additionally, they saw that the expression of genes for oligodendrocytes and microglial cells were down-regulated and this was significantly associated with schizophrenia (Roussos et al., 2012). The potential of the findings for new therapeutic strategies in schizophrenia, such as drugs regulating the differentiation of oligodendrocytes. There is still need for more evidence of whether oligodendrocytes play a central role in the disease mechanisms.

14. Pharmacologic treatment

Dr. Anthony Grace (University of Pittsburgh, USA) proposed that a better approach to treat schizophrenia would be to target the site of pathology. He reported the effects of a selective GABA-A alpha-5 benzodiazepine in the MAM (methylazoxymethanol acetate) developmental model of schizophrenia. The drug decreased ventral hippocampal excitability, but the effect was not observed in animals treated with haloperidol for three weeks, which raises the possibility that clinical trials fail because the subjects are medicated with anti-psychotics for years.

Dr. Pierre Trifilieff (University of Bordeaux, France) covered intriguing animal studies showing that specifically boosting striatal D2 receptors in the nucleus accumbens led to an increase in motivation (Trifilieff et al., 2013). This provides insight into the potential of future pharmacological strategies that enhance D2 receptors signaling in the striatum.

Dr. Davide Amato (Friedrich-Alexander University of Erlangen-Nürnberg, Germany) discussed possible mechanisms of anti-psychotic treatment failure. He showed that haloperidol lost efficacy after 14 days of chronic treatment in rats, which was explained by increased activity of the dopamine transporter and consequent decrease in extracellular dopamine basal levels.

Dr. Anthony Vernon (King’s College, London, UK) showed the impact of chronic anti-psychotic treatment on rat brain morphology. Long-term exposure to anti-psychotics decreased total cortical volume (Vernon et al., 2011), which was reversed after drug withdrawal (Vernon et al., 2012). There was no loss of neurons or astrocytes, suggesting alterations in synaptic or dendritic architecture (Vernon et al., 2014).

Dr. Margaret Hahn (University of Toronto, Canada) shared clinical insights derived from rodent models of anti-psychotic-induced metabolic perturbations. She showed that anti-psychotics directly influence body tissues implicated in glucose metabolism depending on their receptor binding profiles. Effects at the central nervous system level may also contribute to these metabolic alterations.

Dr. Karl-Anton Dorph-Peterson (Aarhus University, Denmark) spoke on evidence from a study showing reduced brain weight and volume in a group of healthy male macaque monkeys who were administered doses of anti-psychotic medication such as Haloperidol and Olanzapine for approximately two years. The results of the study showed the presence of subtle structural brain changes in schizophrenia patients having history of prolonged medication. Thus it was concluded that the evidence of reduced brain size in schizophrenia is confounded by anti-psychotic medication.

By examining transgenic mice overexpressing D2 receptors, Dr. Christoph Kellendonk (Columbia University, New York, USA) showed that there is a pronounced anatomical plasticity in the basal ganglia of adult mice that is regulated by these receptors. The transgenic animals exhibit working memory deficits that persist even after the transgene has been switched off (Kellendonk et al., 2006), and deficits in incentive motivation that are reversible (Simpson et al., 2011).

Dr. Henrik Klitgaard (UCB Pharma, Braine-l’Alleud, Belgium) presented a new pharmacological target for cognitive impairment in schizophrenia. He described SV2A (a synaptic vesicle protein) as a potential target, on which anti-epileptic drugs (e.g. Levetiracetam; Lynch et al., 2004) are already used. Ligands work by decreasing neurotransmitter release to obtain the clinical effect. Their group has developed a new drug, UCB0255, which has better affinity and selectivity for SV2A. The drug has shown to improve cognition in rat recognition tests and could have future treatment potential for the cognitive impairment seen in schizophrenia.

Dr. Lex Wunderink (University of Groningen, The Netherlands) and colleagues investigated long-term effects of dose reduction/discontinuation of anti-psychotic medication among patients with first-episode psychosis in a year of follow-up. They found that the number of patients in recovery with dose reduction/discontinuation of anti-psychotic medication at the follow-up was higher (40%) when compared with patients that had been maintained on anti-psychotic medication (17%; Wunderink et al., 2013).

There is a need for clinical trials incorporating a D1 agonist to improve cognition in schizophrenia and some of the challenges that this would present. Dr. John Waddington (Royal College of Surgeons, Dublin, Ireland) presented recent research using mouse models with
selective loss to Drd1a dopaminergic cells in the striatum, cortex and both (forebrain) to demonstrate the role of dopamine in the striatum versus the cortex. Early loss of Drd1a cells in only the forebrain and cortex led to a loss in preference for social novelty but not sociability. Furthermore, early loss of D1 receptors in only the forebrain led to working memory impairments.

Dr. Richard Mailman (Penn State University, Hershey, USA) discussed some of the problems with D1 agonists in clinical trials. In addition to seizures, and hypotension, rapid tolerance is a major problem with D1 agonists, where tolerance can be achieved after one day. A D1 dopamine agonist, dinapsole, was given over two weeks with acute administrations without producing tolerance. This study shows that the D1 receptor is druggable using modern tools.

Dr. Patricio O’Donnell (Pfizer, Cambridge, USA) explored both D1 and D2 dopamine receptors and how they act as targets for cognitive deficits in schizophrenia using animal models to demonstrate these interactions. The excitatory and inhibitory modulation of D1 and D2 receptors matures during adolescence and is affected by developmental manipulations. Mice with a ventral hippocampal lesion were found to demonstrate a disinhibited cortex and aberrant cortical interneuron functioning which was not properly activated by dopamine, similar to deficits observed in schizophrenia.

Dr. Larry Siever (Mount Sinai School of Medicine, New York, USA) presented the D1 receptor as a potential treatment target in schizophrenia by associating preclinical findings to current findings in clinical populations and calling for clinical trials to test D1 agonists, particularly the potential of DAR100a. There is a compensatory upregulation of D1 receptors in the dorsolateral prefrontal cortex which negatively correlates with worse cognitive performance (Abi-Dargham et al., 2002) suggesting that a D1 receptor agonist could help improve cognition in schizophrenia.

Dr. Kathryn Burdick (Mount Sinai School of Medicine, New York, USA) presented a pharmacological trial of pramipexole, a partial/full agonist for D2/D3 dopamine receptors to enhance cognition in bipolar disorder. Pramipexole appeared to produce improvement from baseline, but was not significant. In a substudy examining euthymic patients, pramipexole produced improvement in processing speed and working memory.

Dr. Richard Keeffe (Duke University Medical Center, Durham, USA) gave an overview of ways to increase signal detection in trials targeted at enhancing cognition by presenting current data using the MATRICS consensus cognitive battery. He emphasized that it is important to recruit young patients with a recent illness onset, administer tests at the same time of day, account for different “norms” between countries as well as differences in social cognition due to cultural differences and to acquire objective informant data.

Chris Schmidt (Pfizer, Cambridge, USA) presented a recent negative clinical trial using a cyclic nucleotide phosphodiesterase, PDE10A.

Bruce Kinon (Eli Lilly, Indianapolis, USA) presented findings from clinical trials examining a pomaglametad metionil selective agonist for mGlu2/3, LY2140023. Initially, LY2140023 showed significant clinical improvement compared to placebo and olanzapine. However, these findings failed to replicate in subsequent trials. However, when he examined only the subgroup of patients with recent illness onset, significant response to the drug was seen.

Dr. Jonathan Rabino-witz (Bar Ilan University, Ramat Gan, Israel) talked about the need for advanced data analysis techniques and some findings to inform data design to shorten trials. In general, drug efficacy will not change between weeks four and six; females show a more pronounced placebo active difference; younger patients ≤ 30 with ≥ 4 years of illness and patients with high positive and negative symptoms show a greater response to treatment. Using this knowledge results in less subjects needed to retain the same effect size.

John Kane (Hofstra North Shore-LIJ School of Medicine, Hempstead, USA) also explored the implications of a failed trial and the challenges in the design and conduct of clinical trials in schizophrenia. Biomarkers are a potential way to determine early treatment responders that will show greater improvement to treatment. It may be useful to only randomize early responders but this introduces ethical confounds. Smart phone use for illness monitoring could be beneficial for both the studies and for the patients.

Dr. Mark Weiser (Tel Aviv University, Israel) presented a posthoc analysis which administered add-on aspirin or placebo to patients with schizophrenia receiving anti-psychotics. It was found that patients who received aspirin with high C-reactive protein (CRP) levels were more likely to have improvements in the PANSS positive scores, whereas patients with intermediate CRP or low CRP levels were not. Deanna Kelly (Maryland Psychiatric Research Center, USA) studied an efficacy of adjunctive minocycline in clozapine treated schizophrenia patients. There were significant improvements in avolition, working memory, and anxiety/depressive symptoms. A modest trend toward positive symptoms improvement was found, although it was not statistically significant.

Dr. Jaime Hallak (Ribeirão Preto Medical School, Brazil) examined the use of sodium nitroprusside (SNP) for the treatment of schizophrenia. BPRS scores and PANSS negative scores were significantly reduced after the SNP infusion. SNP infusion also appeared to improve cognition.

Dr. Joshua Roffman (Massachusetts General Hospital, USA) showed that folate plus B12 improved negative symptoms of schizophrenia when genotype was taken into account, An interaction of the 484T→C variant of FOLH1 with treatment was observed. MRI scans found that patients received folate plus B12 showed increased cortical thickness and working memory-related activation.

Dr. Luca Pani (Italian Medicines Agency, Italy) stated that the difference in efficacy between treatment and placebo has tended to be smaller in recent trials compared with that in the past. This has led to the increasing failure of the trials and has raised ethical concerns. Predefined escape criteria, rescue medication, stopping rules, and stringent follow-up should be applied in placebo controlled trials to assure patients’ safety.

Dr. Robert Conley (Eli Lilly, USA) suggested that placebo controlled trials may be ethically preferred in some situations as they require fewer patients and they are often methodologically superior to active controlled trials. Research participants must be informed of the purpose of a trial, the chance they could be randomized to the placebo arm, the benefits associated with being on an established effective intervention, the risks of foregoing this intervention if randomized to the placebo arm, and their right to withdraw from the study at any time.

Dr. Wolfgang Fleischhacker (Medical University Innsbruck, Austria) stated that placebo control trials may be ethically questionable in testing treatments with well-known acute efficacy or pharmacological principles in long-term trials. By doing these studies, patients were exposed to research of questionable significance. Dr. Paul Appelbaum (Columbia University, USA) presented a review of the evolution of the Declaration of Helsinki. The Declaration of Helsinki originally appeared to bar all but add-on testing of new treatments when partially effective treatments exist, and prohibited the use of placebos in such cases. Since 2002, however, placebo use has been permitted, but the appropriateness of use must be determined on a case-by-case basis. Close oversight is likely to continue, and burden will be on investigators to demonstrate that conditions for use have been met.

Dr. William Carpenter (University of Maryland School of Medicine, USA) stated that placebo was not the same as no treatment. Being involved in the clinical trials generally benefits patients regardless of group assignment. A case for safe and ethical off-medication research in schizophrenia has been published (Carpenter et al., 2003).

Dr. Robin Emsley (Stellenbosch University, South Africa) questioned whether it is ethically appropriate to continue to conduct placebo-controlled relapse-prevention randomized controlled trials (RCT) due to the high risk of relapse. In a systematic review of 12 relapse-prevention RCT evaluating second-generation anti-psychotics (Emsley and Fleischhacker, 2013), relapse rates among those assigned to placebo were far higher than among those receiving active treatment.
(56% vs. 17%, respectively). Only one study investigated the consequences of relapse, and adverse outcomes (e.g., suicide, death, and readmission) were not consistently reported across studies. It was concluded that further research is needed to determine the extent to which placebo exposure has harmful consequences, and that without this knowledge it is difficult to justify placebo use in RCT.

Wolfgang Gaebel (Heinrich Heine University, Germany) described a review of studies examining predictors of relapse in schizophrenia and additionally presented results from the German First-Episode Study (Gaebel et al., 2011). While the results were inconsistent across studies, factors such as poor premorbid adjustment, residual symptoms, male gender, anti-psychotic discontinuation, and longer duration of untreated psychosis appear to be associated with illness relapse (Gaebel and Riesbeck, 2014). It was suggested that, in line with the Vulnerability-Stress-Coping model (Zubin and Spring, 1977), it may be useful to examine interactive relationships between predictors of relapse. Ofer Agid (University of Toronto, Canada) presented data from a trial investigating pathways to relapse in a sample of patients with FEP. A clinical response to treatment was observed in 38 of the patients, however, within two years all had relapsed due to medication non-adherence. It was observed that among these patients, a second treatment trial with the same medication resulted in significantly smaller improvements in symptoms, thus suggesting that anti-psychotic medication may have a diminished effect in those who re-start treatment. Robert Zipursky (McMaster University, Canada) reported the results of a recent systematic review examining the risk of relapse among patients with FEP who cease treatment (Zipursky et al., 2014). Across six studies, the weighted one-year recurrence/relapse rate among those who discontinued treatment was 77% (range: 57 to 91%), which increased to over 90% after two years. In contrast, the estimated rate in those who continued with treatment was 3%. These findings suggest that the majority of patients are likely to require long-term anti-psychotic treatment.

Dr. Dragana Bugarski-Kirola (Hoffmann-La Roche) investigated the efficacy and safety of adjunctive bitopertin for persistent negative symptoms of schizophrenia. NMDA receptors are thought to be important contributors in positive, negative and cognitive symptoms of schizophrenia and bitopertin functions as a glycine reuptake inhibitor that could improve NMDA receptor functioning (Martin-Facklam et al., 2013). Although bitopertin was well tolerated, no statistical significance was found for the efficacy of bitopertin in doses of 5, 10 and 20 mg. compared to placebo in a 24-week trial.

Dr. Daniela Alberati (Hoffmann-La Roche) presented data on the effects of a glycine reuptake inhibitor, bitopertin, in animal models. In vitro bitopertin was shown to enhance firing of hypofunctioning dopaminergic neurons. In vivo animal studies showed improvement in working memory and reversal of social deficits.

Dr. Jonathan Rabinowitz (Bar Ilan University, Ramat Gan, Israel) assessed the efficacy, safety and tolerability of the cognitive and anti-psychotic effects of CYP-1020 (a dopamine antagonist and GABA agonist) compared to risperidone at 6 weeks and 6 months. No statistical significance was showed for CYP-1020 as a pro-cognitive enhancer. However, it seemed to be superior to risperidone in a measure of social cognition included in the MCCI battery (MSEICT): an independent factor from the rest of cognitive domains (Mancuso et al., 2011).

A new approach for the treatment of schizophrenia (ITI-007) was presented by Dr. Kimberly E. Vanover (Intra-cellar Therapies Inc., New York, USA). This group demonstrated the efficacy of ITI-007 (a 5HT2A antagonist, dopamine and glutamatergic phosphoprotein modulator and serotonin reuptake inhibitor) (Li et al., 2014) at 60 mg. dose on negative symptoms. Doses of 60 mg. showed great efficacy for the treatment of depressive symptoms and social function. Therefore, ITI-007 may become an innovative approach for the treatment of schizophrenia.

15. The metabolic syndrome and other medication side-effects

People with psychotic disorders are at high risk for obesity, metabolic abnormalities, and early cardiovascular morbidity and mortality. Clinical trials demonstrate the role of anti-psychotic treatment on these parameters; however there is limited data on how anti-psychotic medication affects children and adolescents. This symposium seeks to bridge this knowledge gap. Dr. Cherrie Galletly (University of Adelaide, Adelaide, South Australia) presented the analyses of data from the 2010 Australian National Survey of High Impact Psychosis (SHIP) and the 1999–2000 Australian Obesity, Diabetes, and Lifestyle Study population surveys, focusing on the subset of young adults between the ages of 18 and 24 years old. She addressed the earlier age of death observed in patients with psychosis versus the general population by analyzing in these populations the occurrence of leading risk factors for death, such as physical inactivity, obesity, hypertension, and high cholesterol. The most prevalent of the risk factors are all immediately modifiable; therefore interventions targeting these risk factors in young patients with psychosis should be implemented.

Dr. Celso Arango (Hospital General Universitario Gregorio Marañón Universidad Complutense, Madrid, Spain) then presented the results of a one-year longitudinal study of drug-naïve children who were prescribed second-generation anti-psychotics (SGAs), as well as a six-month longitudinal study comparing drug-naïve pediatric patients and adults who have been prescribed SGAs. Noteworthy findings include an increase in BMI z-scores and weight gain among pediatric patients, most of which occurred during the first three months of administration of SGAs. Furthermore, pediatric patients evidenced a marked increase in BMI z-score and weight gain from SGA administration compared to adult patients.

Dr. David Hosford (Targacept Inc., Winston-Salem, USA) performed a phase 2B clinical trial to prove the efficacy, safety and tolerability of TC-5619, a selective alpha 7 nicotinic receptor agonist (Lieberman et al., 2013) for the treatment of negative and cognitive symptoms of schizophrenia. There was no significant improvement in either negative or cognitive symptoms. However, it was safe and well-tolerated.

The improvement in cognitive symptoms by the stimulation of D1 receptors via DAR-0100A agonist (Allean et al., 2000) was studied by Dr. Ragy Girgis (Columbia University Medical Center, New York, USA). Although there was an improvement on cognitive tasks in phase I, the results from phase II showed no significant differences between DAR-0100A and placebo and between DAR-0100A doses in working memory.

Dr. John Steve Whitaker (Omeros Corporation, Seattle, USA) showed the results obtained from the use of OMS643762 for the treatment of schizophrenia and Huntington’s disease. The OMS643762 is a phosphodiesterase 10 inhibitor at the striatum. The results from clinical trials showed that it was well tolerated and supported once-a-day dosing. Phase II clinical programs are in progress.

Dr. Marc Cantillon (Reviva Pharmaceuticals, San Jose, USA) presented a dopamine-serotonergic stabilizer: RP5063 is a partial agonist for D2, D3, D4, 5HT1A and 5HT2A receptors and antagonist for 5HT6 and 5HT7. The results showed significant efficacy for the treatment of positive and negative psychotic symptoms at 15, 30 and 50 mg doses compared to aripiprazol. Robust efficacy for the treatment of depression symptoms was also found. Phase III trial is currently under development.

Dr. René Nielsen (Aalborg University Hospital, Denmark) described an epidemiological non-randomized nationwide study of patients under the age of 18 treated with anti-psychotics. Patients treated with anti-psychotic were diagnosed with diabetes at a faster rate with double the hazard (hazard ratio — 2.01) of being treated with an oral anti-diabetic. Number needed to harm was greater than 200.
effects of anti-psychotics on parameters such as body weight, fasting total cholesterol, fasting glucose, and fasting triglycerides (Correll et al., 2009). These findings are consistent with the differential effects of anti-psychotics on weight gain, as well as lipid and/or glucose abnormalities that were evidenced by De Hert et al. (2011), and additionally, the increased diabetes risk from use of anti-psychotics demonstrated by Nielsen et al., 2010. Medical risk management strategies for patients on anti-psychotic medications were additionally addressed (Correll, 2007). Dr. John Newcomer (Florida Atlantic University, USA) presented the results from his NIMH-funded study, “Metabolic Effects of Antipsychotics in Children.” Anti-psychotic-naive patients aged 6 to 18 years old were followed during 12 weeks of anti-psychotic treatment for clinically significant symptoms of aggression/irritability. Adverse metabolic effects were detectable; however, anti-psychotic treatment resulted in a marked improvement in clinical symptoms.

Neutropenia is a rare side effect of clozapine. Sophie Legge (Cardiff University, United Kingdom) identified possible genetic variants that indicate risk of developing neutropenia in clozapine treated individuals. The authors observed a significant association in the gene SLC4 interacting protein in severe clozapine associated neutropenia compared to clozapine treated controls.

16. Non-pharmacologic treatment

Studies have identified possible subgroups of patients who can obtain remission of psychotic symptoms without using anti-psychotic medication on a long-term basis. Dr. Ditte Gottfredsen (University of Copenhagen, Denmark) presented a Danish cohort study of patients diagnosed with schizophrenia spectrum disorders. At the 10-year follow-up, the proportion of patients who obtained stable remission without the use of anti-psychotic medication was 30% of the patient population. Remission was positively associated with female gender, shorter duration of untreated psychosis, participation in the labor marked and no substance abuse.

The efficacy of cognitive behavioral therapy is an ongoing debate in the research field of schizophrenia (Nielsen, 2011). A series of novel cognitive treatments can control psychotic symptoms with profound clinical implications. Auditory hallucinations are able to drive injurious behavior to oneself and others because of the belief that these voices not only possess bad intentions toward the patient, but also the power to act upon these intentions. Dr. Max Birchwood (Warwick University, Coventry, UK) presented the results of the COMMAND trial, which assessed the effects of Cognitive Therapy for Command Hallucinations (CTCH) in psychotic patients. CTCH was designed to reduce perceptions of the omniscience, ability to predict the future, and control over the patient by auditory hallucinations. This novel therapy in conjunction with traditional treatment yielded interesting results in patients that had previously been prone to hallucination-induced harmful behavior.

Dr. Tom Craig (King’s College London, UK) discussed results of the recently developed AVATAR therapy, in which patients create a computerized representation of the face and voice of the entity that produces their auditory hallucinations. The patients then engage in a discussion with this avatar, altering the passive relationship with the voice to a controlled, two-way relationship. Preliminary results indicate that this treatment can reduce both the frequency of the auditory hallucinations, and the subsequent emotional distress and depression.

An abundance of research has reported the importance of alternative medication besides anti-psychotic drugs (Warner et al., 2006; Morrison et al., 2014). Researchers have found that cognitive therapy are safe and acceptable and can be used in patients with psychosis who are not taking anti-psychotics. The results also show that cognitive therapy reduces severity of symptoms and improves cognitive functioning. Cognitive therapy showed the stronger results in young ages, and the effect size was similar to patients who receive anti-psychotics. However, findings suggested that psychological intervention is most effective when delivered in conjunction with anti-psychotic medication (Bola et al., 2012).

Dr. Anthony Morrison (University of Manchester, UK) presented their study on cognitive therapy for people with schizophrenia spectrum disorders. The results showed that psychotic symptoms were consistently lower in the cognitive therapy group than the usual care group over 18 months. Their findings proved the effectiveness of cognitive therapy in reducing psychotic symptoms and suggested that it might be an alternative to anti-psychotic treatment for people with schizophrenia spectrum, but further testing is still needed (Morrison et al., 2014).

Dr. Mark van der Gaag (VU University Amsterdam, Netherlands) talked about eye movement desensitization and reprocessing (EMDR) and prolonged exposure (PE) therapy in patients with posttraumatic stress disorder (PTSD) and chronic psychotic disorder. Previous studies have represented high prevalence of PTSD in all regions (Kessler et al., 2005; Creamer et al., 2001; Alonso et al., 2004). However, its importance in clinical practice is misdiagnosed in psychosis (Howgego et al., 2005). The results of this study suggested that PE and EMDR are both effective in treating PTSD in chronic psychosis.

Neurostimulation as a treatment option for psychotic symptoms is becoming more and more popular as a clinical and research option. Data from four research groups investigating the efficacy and neural mechanisms of neurostimulation techniques: 1-Hz repetitive magnetic stimulation (rTMS), theta-burst magnetic stimulation (TBS), transcranial direct current stimulation (tDCS) and magnetic seizure therapy (MST). The findings are detailed in the summaries below.

Dr. Jerome Brunelin (Centre Hospitalier Le Vinatier, Bron, France) presented a study of the effects of tDCS on resistant psychotic symptoms in patient suffering from schizophrenia (Brunelin et al., 2012). The study presented showed that tDCS improved global symptoms: hallucination (−31%) and general symptomatology (−12%) including negative (−12%), positive (−15%) and depressive (−17%) symptoms. It also demonstrated that tDCS had resulted in a significant decrease of functional connectivity in fronto-temporal network, a decrease of functional connectivity between the TPJ and the PFC and the inferior frontal gyrus (including Broca’s area) and a decreased connectivity between the PFC and the TPJ and the inferior frontal gyrus. The tDCS treatment is a promising tool to modulate brain networks underlying clinical symptoms in schizophrenia.

Dr. Philipp Homan (University Hospital of Psychiatry, University of Bern, Switzerland) spoke about the neurobiological mechanism of verbal auditory hallucinations (AVH) and presented data implying that AVH are associated with altered neuronal activity in cerebral areas that are responsible for language production and perception. The current literature suggests that in addition to primary and secondary sensory cortices, dysfunctions in prefrontal premotor, cingulate, subcortical and cerebellar regions contribute to AVH. The dominance of AVH in schizophrenia and the partial effect and dominant side effects of the current pharmacological treatment call for the extension of the therapeutic regimens. Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) were presented as potential and safe methods to relieve the hallucinatory burden in those, who did not respond to conventional approaches. The main study presented (Homan et al., 2014) demonstrated involvement of the language system in the generation of AVH. The superior temporal lobe, including primary auditory cortex and its connections, was identified as a region involved in the generation, modulation and therapy of AVH.

Dr. Daniel Blumberger (Department of Psychiatry, University of Toronto, Canada) presented a pilot case series of magnetic seizure therapy in refractory schizophrenia. Data indicate that rTMS has demonstrated some efficacy in attenuating auditory hallucinations, although replication of the initial findings has not been consistent (Blumberger et al., 2010).
Dr. Remko van Lutterveld (University Medical Center Utrecht, The Netherlands) presented data on the effect of Theta-burst Repetitive Transcranial Magnetic Stimulation in treating AVH. The significant main effects of treatment were lower hallucination severity scores after treatment. No significant interaction effects were observed for any of the hallucination severity scales, indicating that AVH did not significantly improve after theta-burst stimulation compared to sham stimulation.

17. Clinical staging for specific treatments in psychosis

Dr. Seetal Dodd (Deakin University, Burwood, Australia) discussed clinical staging in schizophrenia in the context of neuroprogression and neuroprotection. Dodd reviewed evidence of neuroprogression, describing changes in brain structure over time, and potential mechanisms of change. Dodd proposed that inflammatory oxidative and nitrosative stress (IO&NS) may be driving neuroprogression at a biological level (Brown and Derkits, 2010; Song et al., 2009). Strategies discussed involved agents that inhibit mechanisms associated with neuroprogression (Dodd et al., 2013), instead of treatments that focus on symptom reduction and relapse prevention. Dodd proposed that psychotropic agents may be neuroprotective, as well as some conventional pharmaceuticals and natural products (e.g. omega-3 fatty acids).

Dr. Nilufar Mossaheb (Medical University of Vienna, Austria), presented research on fatty acid markers of psychosis progression and treatment, on behalf of Paul Amminger (Orygen Youth Health Research, Australia). Altered levels of membranes of fatty acids are a robust biological finding in schizophrenia and are associated with psychopathology. Mossaheb focused on research pertaining to omega-3 fatty acids, known for their anti-inflammatory properties, their role in modulating neurotransmitter systems (Gomez-Pinilla, 2008) and also have shown to be lower in the ultra high risk for psychosis population, than in healthy controls. Mossaheb presented 6 year follow-up data on the efficacy of omega-3 fatty acids in a randomized, placebo controlled trial with young people at risk of schizophrenia (Amminger et al., 2010). This study provided evidence that long chain omega-3 PUFAs reduced the risk of progression to psychotic disorder and offered a safe and efficacious strategy for indicated prevention in young people with sub-threshold psychotic states.

Dr. Stephen Wood (University of Birmingham, West Midlands, UK) reviewed examples of changing brain abnormalities observed across different stages of illness. These included gray matter decreases over time in the prefrontal and temporolimbic areas (Fornito et al., 2009; Fusar-Poli et al., 2012b; Pantelis et al., 2005; Takahashi et al., 2009), ventricular enlargement from early psychosis to later stages (Pantelis et al., 2005) as well as a reduction in hippocampal volume seen in later stages (Velakoulis et al., 2006). Moving between illness stages suggests that there are neurobiological changes with relapse and illness progression, with each relapse appearing to have a toxic effect (Croyele et al., 2013). Exacerbation of psychosis in schizophrenia is accompanied by evidence of brain swelling (Garver et al., 2000), which could provide a potential relapse signature. Due to these progressive changes, treatment should be more effective in early stages, as well as more benign (Wood et al., 2011).

Dr. Marta Rapado-Castro (The University of Melbourne, Parkville, Australia) discussed stage specific treatments, and the effect duration of illness (DOI) has on response to treatment. It has previously been shown that DOI influences course, outcome, prognosis (Insel, 2010) and is associated with poorer clinical and functional outcomes (Hill et al., 2012), brain changes (Hajima et al., 2013) and an increased risk of relapse (Alvarez-Jimenez et al., 2011). Novel therapies with benign adverse effect profiles, such as N-acetyl cysteine (NACc), are showing promise as a potentially effective treatment strategy in late stage illness (Rapado-Castro, unpublished). Rapado-Castro discussed results from a trial investigating the interaction of treatment response to NACc and DOI, in an established schizophrenia sample. This study illustrated that DOI may impact on response to NACc in schizophrenia, with the potential advantage of adjunctive NACc over placebo on positive symptoms and functional outcomes in participants with a longer duration (> 20 years) of illness. Rapado-Castro concluded that the potential of glutamatergic compounds such as NACc could constitute an important step forward on the development of novel therapies for schizophrenia.

18. Oxytocin, social cognition and schizophrenia

Dr. Robert Buchanan, presenting the findings of James Koenig (Maryland Psychiatric Research Center, Catonsville, USA), discussed the use of animal models to evaluate the known risk factors for developing schizophrenia and the implications for future treatments. The study exposed offspring rats to prenatal stress conditions by subjecting the rats’ mothers to malnutrition, psychological stress, and immune system challenges during gestation. The prenatally stressed rats showed significant social impairments in interaction time, social memory, and social communication as compared to normal controls. Furthermore, they found a change in the expression levels of oxytocin mRNA and receptors in the prenatally stressed rat brains and infusion of oxytocin resulted in normalization of social behavior. Lastly, the study showed that alpha-7 nicotinic receptors activate oxytocin neurons in the rat hypothalamus and treatment of rats with agents that modify nicotinic mechanisms can improve schizophrenia-related cognitive and social deficits by normalizing oxytocin mechanisms.

Dr. Andreas Meyer-Lindenberg (Central Institute of Mental Health, Mannheim, Germany) used human brain imaging studies to show the importance of the prosocial neuropeptide oxytocin on the activity of different brain regions. Oxytocin decreases the interactions of the amygdala with brainstem effector sites of fear and aggression, leading to increased levels of trust in patients infused with oxytocin. The presentation proceeded with the implications of such findings on the development of neuropsychotherapy, in which patients with social cognitive disabilities can learn social functioning with oxytocin infusion combined with prosocial behavioral psychotherapy.

Dr. Gregory Strauss (State University of New York, Binghamton, USA) used data from a human population study to show how oxytocin can affect social cognition tasks and symptoms in schizophrenia patients. He implemented a variety of social cognition evaluations, such as eye-tracking and behavioral responses to emotional stimuli, in order to quantify the differences between patients and controls before and after oxytocin administration. One procedure, called the facial affect morphing test, evaluated the test subjects’ ability to identify a specific emotion presented by images of faces displaying progressive intensities of the emotion. The schizophrenia patients had less response to negative emotions with high intensity scales as compared to the control subjects. Furthermore, when administered oxytocin and asked to complete the same task, the schizophrenia patients showed significant improvement in the ability to accurately recognize intense emotional faces. Therefore, the combined effects of oxytocin and visual scanning patterns may be important predictors of emotional perception in this patient population.

Dr. Stephen Marder (UCLA Department of Psychiatry, Los Angeles, USA) presented on the effectiveness and limitations of social cognition training, and the approach to studying pharmacological facilitation for social cognition training given the short term effectiveness of oxytocin. He posed whether increasing the salience of social information by oxytocin administration just prior to each training session would facilitate learning for schizophrenia patients in social cognition training. In order to distinguish the drug and learning effects of this study, the assessments were performed at the end of treatment and later when the patient was not receiving oxytocin. Both placebo and oxytocin groups improved in social cognition; and the training alone was effective on lower level measures of cognition. However, the oxytocin
appeared to facilitate learning of higher level social cognition abilities, particularly empathy.

The discussant, Shitij Kapur, deliberated that the negative symptoms and socially odd behavior of schizophrenia patients are often the most obvious and first noted signs of the disease; the most debilitating deficit is arguably the inability to have adequate social functioning and to gain willful employment. Therefore, more research and focus should be placed on the social functioning aspect of this disease in order to find acute treatments for this deficit in social cognition. One challenge that the field currently faces is the diversity of paradigms used to study social cognition changes in the prefrontal cortex of schizophrenia patients.

19. Modeling schizophrenia using patient derived cells

The use of patient derived cells as an in vitro preclinical model for brain disorders has become increasingly popular since the advent of induced pluripotent stem cells (iPSC) during the last decade (Takahashi and Yamanaka, 2006). The olfactory epithelium is another important source of patient derived neurons, although their potency is limited compared to iPSC (Mackay-Sim, 2013). Dr. Jane English (Royal College of Surgeons, Dublin, Ireland), reported analysis of olfactory derived neurospheres from patients and controls which suggested that protein translation is disrupted in schizophrenia. Converging proteomic and functional analyses in the patient derived cells also agreed with genomic analysis they conducted using data from the psychiatric genetic consortium, which found two SNPs in genes involved in protein translation to be significantly associated with schizophrenia. Dr. Alan Mackay-Sim (Gillfith University, Brisbane, Australia) showed that mRNA expression of genes involved in cellular adhesion and migration were also dysregulated in olfactory derived neurospheres from schizophrenia patients. Migration assays were used to support these findings, and more recently the group has found changes in DNA methylation in cellular motility related genes, using both olfactory derived cells and iPSC. Dr. Akira Sawar (John Hopkins University, Baltimore, USA) showed reduced phosphorylation of DISC-1 in olfactory derived neurons from patients with schizophrenia, at a specific site which was previously shown to regulate neuronal migration during development. iPSC derived neurons were also examined, and they showed higher proliferation compared to control neuroblasts. When they assessed patients who donated tissue, they found that reduced DISC1 phosphorylation in olfactory derived neurons was associated with volume changes in the frontal cortex and working memory deficits. Dr. Kristen Brennan (Mount Sinai Medical Center, New York, USA) presented ongoing work in her laboratory exploring changes in cellular adhesion and oxidative stress pathways. Functional assays which can be performed in patient derived neurons have been particularly informative to understand the consequences of genomic changes which were identified using pathway analysis. Thus, these findings support the utility of patients’ derived cells as a complementary approach to other studies in live patients.

20. Addressing measurement variability in schizophrenia research

Dr. Janet Williams (Columbia University Medical Center, New York, USA; SVP Global Science, MedAvante, New Jersey, USA) focused on issues related to variability in reporting symptom scores in clinical trials, and different types of reporting ranging from clinician-based assessment to self rating to centralized rating. Self-reporting by the patient, although firsthand information, is subjective and not reliable in patients with lack of insight and cognitive dysfunction. Ratings using professionals has inter-rater variability and raters cannot be blinded completely. To overcome these problems, centralized rating through mass media communication is an alternative. This involves, establishing a centralized rating center with experienced and trained raters using video interviews. The proposed advantages are that the raters are blind to the protocols of the study. Several studies have also demonstrated the effectiveness of experienced, trained and calibrated raters over other methods. This requires less man power and is cost-effective. However, the challenges with this system are, proper training and calibration of the raters, maintaining confidentiality, the need for the presence of same clinician throughout the trial.

Dr. Ilan Rabiner (King’s College London, UK), discussed variability with respect to data assessment and interpretation in multi-site PET studies. He stressed the need for checking data variability due to type of scanner, quantitative methods, and clinician rated assessments. Dr. Alan Anticevic (Yale School of Medicine, New Haven, USA), speaking on other imaging modalities, highlighted different scan acquisition parameters, analytical approaches and imaging modalities not complimenting each other. He suggested standard image acquisition parameters as used in ‘Human Connectome Project’ (HCP) i.e. 0.8 mm thickness for MPRAGE images, 2 mm thickness for fMRI and 1.8 mm for DWI and a proper workflow/pipeline during analysis. He also stressed the need for use of one standard paradigm for a cognitive task.

Methodological considerations for sleep EEG studies in schizophrenia were discussed by Dr. Keshavan/Beth Israel Hospital, Boston, USA). Key sleep EEG findings in schizophrenia include decrease in efficiency, onset latency, total sleep time, slow wave sleep, REM latency and increased onset latency. Several sleep parameters, especially reduced spindle density could be a potential target for treatment of cognitive symptoms in schizophrenia since they are shown to correlate with IQ. However, the paucity of multi-site sleep studies, methodological variations and inconsistent replications of findings in smaller studies warrants a large scale multi-site sleep study with uniform and standardized methodology. There are multiple confounding factors that affect sleep EEG studies: (1) machine variation with respect to its calibration, filter settings and rate of digitization of signals, (2) the place of study affects the sleep quality, (3) artifacts from muscle contraction, lead movement and the 50 Hz electrical artifacts, and (4) the scoring of sleep data. Dr Keshavan proposed uniform calibration of EEG machines and their filter settings, uniform placement of electrodes, a minimum acceptable range for electrode impedance, explicit description of study settings, well trained personnel, study to be conducted in a familiar environment to the subject, and inter-rater scoring reliability established across centers.

21. The road forward to deconstruction of the psychoses into biologically meaningful constructs

Dr. Werner Strik (University of Bern, Switzerland) discussed brain systems underlying thought disorder, hallucinations and catatonia. Strik proposed that formal thought disorder and auditory verbal hallucinations are related to abnormalities in certain neuronal systems, especially brain regions associated with language (e.g., left dominant fronto-temporal regions, such as Broca’s and Wernicke’s areas, and the arcuate fascicle). Strik presented research linking paranoid anxiety in schizophrenia to abnormally dopaminergic regulation, via the mechanism of the attribution of aberrant salience (Heinz and Schlagenauf, 2010). Motor symptoms, e.g., catatonia, were discussed as being closely related to the neurodevelopmental disturbances of schizophrenia (Walther and Strik, 2012). Strik concluded that regrouping of psychotic symptoms into biologically meaningful dimensions may help to disentangle the contribution of the generating brain systems. Dr. Jim Van Os (Maastricht University Medical Centre, The Netherlands) proposed that instead of viewing psychotic symptoms as indicative of a latent construct (ie schizophrenia), it is better to consider symptoms interacting on each other in relational networks. He showed that the co-occurrence of delusions and hallucinations was more strongly associated with transition to psychosis, compared to either one in isolation (Smeets et al., 2012). These symptoms also tended to cluster together more often than would be expected by chance, the presence of one symptom being influenced by the presence
of the other. Van Os discussed the concept of ATOMS (altered transfer of
momentary states) as the basic unit of psychosis liability in interaction
with environment and emotions, which moderate the persistence/ change
of emotional states (Wigman et al., 2013). Van Os proposed that persistent changes in affect were mediated by changes in mood
network and that mental disorders may represent sets of symptoms,
connected through a system of causal relations.
Dr. Sophia Frangou (Mount Sinai School of Medicine, New York,
USA) introduced a neural network model approach to the classification
of psychotic syndromes. This provides opportunity for improved biolog-
ical validity and biologically targeted treatments. She gave examples of
studies using a supervised classification approach that involved struc-
tural MRI scans and pattern recognition algorithms of white and gray
matter densities (Nieuwenhuis et al., 2012; Rocha-Rego et al., 2014).
These were able to achieve moderate to high sensitivity scores (around
70%) in classification of pathologic subjects, similar to diagnostic scores
achieved in medicine. Another classification method that may be prom-
ising uses MRI data on resting state functional brain organization in
healthy individuals (Power et al., 2011; Yang et al., 2012). Frangou
concluded that further research is needed to establish whether
neuroimaging can indeed provide evidence for a biosignature for
syndromally manifest conditions, and to confirm or reassess current
syndromal boundaries.
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