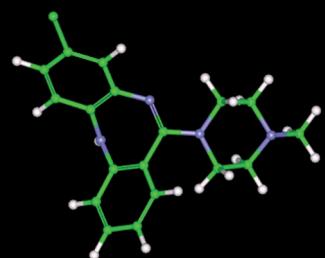
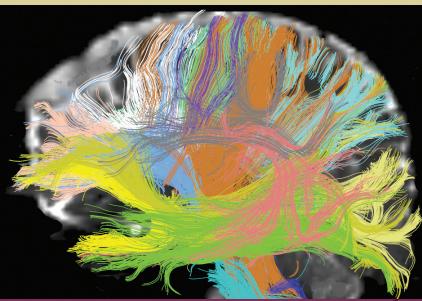
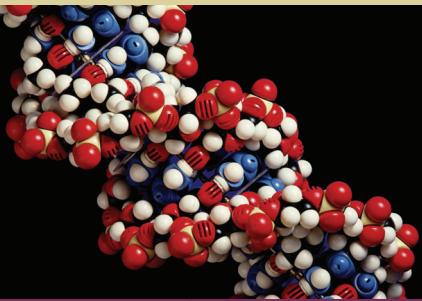


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PLENARY & SYMPOSIA SESSIONS, ORAL PRESENTATIONS AND WORKSHOPS

Special Session

ITALIAN RESEARCH DAY

Saturday, 5 April 2014

10:00 AM – 5:15 PM

This satellite meeting builds on a very successful similar day at the last SIRS meeting. It provides the opportunity to all attendees, and to all those interested in mental illness, to hear the best of Italian Research into Schizophrenia, both from those Italian research scientists now working in other countries and those carrying out research in major Italian Centres. We will hear of how the incidence of schizophrenia appears surprisingly low in different centres in Italy, of the relative importance in Italy and elsewhere of risk factors for schizophrenia such as child abuse, immigration and drug abuse (including novel internet drugs). We will also hear how imaging can predict outcome of psychosis and how it reflects genetic predisposition.

The afternoon will include sessions on the ways in which relatives are involved in care of people with psychosis in Italy. The day will close with a panel of very distinguished clinicians from across the globe discussing the merits and demerits of the care offered to people with schizophrenia in their respective countries.

The day will be in English and is open and free to all attendees at the SIRS meeting and indeed the general public (Italian and non-Italian alike). Those with experience of psychosis and their relatives are very welcome.

THE ROAD FROM DAMASCUS: A SCIENTIFIC JOURNEY

Huda Akil

University of Michigan, United States of America

In this talk, Dr. Akil will share her transition from Syria to the USA to become a scientist, witnessing the discovery of Endorphins, her current interests in neuroscience, and lessons she learned along the way about how to keep her love of science alive.

Plenary Session

IMPACT OF GENOMICS AND CONNECTOMICS APPROACHES ON SCHIZOPHRENIA RESEARCH

Chairpersons: Lynn DeLisi and René Kahn

Sunday, 6 April 2014

8:30 AM – 12:00 PM

Wikipedia defines "Omics" as an informal suffix that implies "the collective characterization and quantification of pools of biological molecules that translate into the structure, function, and dynamics of an organism or organisms." Thus, "genomics" describes all that is known about the multiple aspects of the genetic architecture of an organism or its disorders and

"connectomics" describes the complex cerebral architecture that is uniquely human and can develop in deviant ways in schizophrenia. In this session we thus aim to review the most up-to-date knowledge in the fields of both genomics and connectomics as they relate to improving our understanding about schizophrenia. Research findings are accumulating so rapidly now that even the latest published literature cannot keep up with the pace of progress in these fields.

In the genomics session, Dr. Patrick Sullivan will cover the latest Genome-Wide Association Study (GWAS) findings of common alleles with increased risk for schizophrenia from the large international collaborative effort, The Psychiatric Genomics Consortium (PGC). He will be followed by Dr. Jonathan Sebat who will discuss how rare genetic variants, such as Copy Number Variants (CNVs) can play a role in risk for schizophrenia. This will be followed by a discussion of environmental-gene interaction as led by Dr. Tiina Paunio. All panelists will then discuss the field of Next-Generation Sequencing and how it will be effective in finding genes for schizophrenia. We will end this session with a discussion of controversial ethical issues that the field of psychiatric genetics is now faced with, including commercial direct-to-consumer genome testing availability. This will be led by Dr. Francis McMahon, president of The International Society of Psychiatric Genetics. General audience participation will be encouraged.

The second half of this plenary will be devoted to "Connectomics" in the human brain and how connectivity is influenced by genetics. It will include Drs. Ed Bullmore, Jeff Lichtman and Deanna Barch. All of these researchers have developed innovative methods for viewing how the brain communicates and functions through its connectivity and how genes influence the variation that exists in human brain connections. Some of the latter variation may be relevant to neurodevelopmental disorders, such as schizophrenia. They will then lead a panel discussion session with audience participation to conclude this session.

Symposium

DEVELOPMENTAL STRESS IN SCHIZOPHRENIA: EPIDEMIOLOGY AND POSSIBLE MECHANISMS

Chairpersons: Preben Bo Mortensen and James Koenig

Discussant: James Koenig

Sunday, 6 April 2014

2:00 PM – 4:00 PM

Overall Abstract: The developing and maturing brain is highly sensitive to the detrimental effects induced by environmental adversities. Early-life exposure to environmental stressors such as prenatal maternal stress or childhood psychological trauma have been identified as possible risk factors of schizophrenia and related disorders. Despite epidemiological evidence for such associations, several controversial issues still exist in the field that warrant close examination, including the role of developmental timing and the specificity of developmental stressors. Moreover, the extent to which early-life exposure to stress interacts with other genetic or environmental

risk factors of schizophrenia is currently being investigated extensively, and so are the potential mechanisms mediating increased disease risk following developmental stress exposure. This symposium will bring together leading epidemiologists and basic researchers who use distinct scientific approaches to address some of these burning questions. Preben B. Mortensen (National Centre for Register-based Research, Aarhus University, Denmark) will present findings from register-based psychiatric epidemiology addressing the role of developmental stress in schizophrenia and will discuss epidemiological associations linking early-life stress and schizophrenia in relation to their conceptual and methodological strengths and limitations. Urs Meyer (Swiss Federal Institute of Technology, ETH Zurich, Switzerland) will discuss animal work showing that prenatal adversities in the form of in-utero immune challenge can function as a disease primer that increases the offspring's vulnerability to the detrimental neuropathological stress in puberty. Furthermore, he will present novel findings obtained in this two-hit model suggesting that developmental neuroinflammation may be one of the critical mechanisms mediating the pathological interaction between prenatal infection and pubertal stress exposure. Marco A. Riva (Center of Neuropharmacology, University of Milan, Italy) will focus on a well-established animal model of prenatal stress to highlight its impact on neuronal plasticity across distinct time windows of brain development and maturation. He will also show how epigenetic signatures in specific brain regions may allow the identification of novel genes and pathways that are affected as a consequence of antenatal stress exposure. Akira Sawa (Departments of Psychiatry and Neuroscience, Johns Hopkins University, USA) will discuss novel epigenetic mechanisms that can compromise adult neuronal networks following exposure to adolescent stress. In particular, he will present findings demonstrating altered DNA hypermethylation of dopaminergic systems and associated behavioral dysfunctions following adolescent stress exposure in a mouse model with a dominant-negative DISC1 (disrupted-in-schizophrenia-1) expression. Collectively, the epidemiological and experimental work described in this symposium corroborates the relevance of the developmental stress in schizophrenia and suggests several molecular mechanisms involved in this association. The latter may open new avenues to attenuate or even prevent long-term psychiatric outcomes following developmental stress exposures.

EPIDEMIOLOGICAL EVIDENCE FOR A ROLE OF DEVELOPMENTAL STRESS IN SCHIZOPHRENIA

Preben Bo Mortensen

National Centre for Register-based Research, Aarhus University

Epidemiological studies and other evidence have suggested a wide range of factors affecting fetal development to be associated with schizophrenia risk. Factors as maternal infections, dietary deficiencies, and pregnancy and birth complications have been repeatedly implicated, and also more general environmental factors as diverse as urban place of birth, stressful life events and war or natural disasters have been found to increase the risk of developing schizophrenia. Stressors during infancy, childhood and adolescence have been less well studied, but, again, a wide range of exposures, from frequent moves to severe injury or adversity, have been implicated in this context. This presentation will review some of the available evidence and present more recent and ongoing large scale register-based Danish studies that explore the epidemiological relevance of stress exposures over the early life course, from conception through adolescence.

TRANSIENT NEUROINFLAMMATION IS A KEY MECHANISM MEDIATING THE NEUROPATHOLOGICAL INTERACTIONS BETWEEN PRENATAL IMMUNE CHALLENGE AND PERIPUBERTAL STRESS

Urs Meyer¹, Sandra Giovanoli²

¹Swiss Federal Institute of Technology (ETH), Zurich, Switzerland; ²Physiology and Behavior Laboratory, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland

Prenatal infection and exposure to traumatizing experiences in peripubertal life have each been associated with increased risk for neuropsychiatric disease, especially schizophrenia and related psychotic illnesses. Our laboratory has recently developed a translational mouse model of combined expo-

sure to prenatal immune challenge and peripubertal stress to study possible neuropathological synergisms between these two adverse environmental factors. In this two-hit model, the first environmental hit is composed of prenatal viral-like immune activation induced by maternal administration of the synthetic double-stranded RNA poly(I:C) (polyribonucleic acid) during mid-gestation. The resulting offspring are then either left undisturbed or exposed to subchronic unpredictable stress during peripuberty. Using this two-hit environmental model, we reveal that prenatal immune activation and pubertal stress synergistically interact with each other to facilitate the emergence of schizophrenia-relevant behavioral and neurochemical abnormalities, including sensorimotor gating deficiency, hypersensitivity to psychotomimetic drugs, and dopaminergic imbalances in striatal and hippocampal areas. We further find that the prenatal insult markedly increases the vulnerability of the pubescent offspring to brain immune changes in response to stress. In particular, offspring subjected to combined prenatal immune challenge and peripubertal stress show marked signs of neuroinflammation that are characterized by microglia overactivation and hypersecretion of brain inflammatory cytokines. Based on these latter findings, we have recently begun to test whether normalizing acute neuroinflammation in the event of peripubertal stress exposure may prevent the subsequent emergence of schizophrenia-relevant deficits in prenatally primed offspring. As a first proof-of-principle supporting this hypothesis, we reveal that the adult onset of behavioral abnormalities induced by combined prenatal immune challenge and peripubertal stress can be prevented by administration of the broad-spectrum antibiotic minocycline during the course of peri-pubertal stress exposure. This anti-inflammatory drug regimen also prevents overactivation of microglia and altered pro-inflammatory cytokine secretion in prenatally primed offspring experiencing additional stress in puberty. Our experimental data highlight that stress exposure in puberty can unmask latent neuropathological consequences of early prenatal environmental insults such as prenatal maternal infection. Furthermore, anti-inflammatory strategies targeting microglia overactivation may represent a valid pharmacological approach to prevent full-blown brain abnormalities emerging in subjects exposed to multiple environmental hits such as prenatal infection and pubertal stress.

EPIGENETIC PROFILING OF PRENATAL STRESS AND LONG-TERM PSYCHOPATHOLOGICAL IMPLICATIONS

Marco A. Riva¹, Alessia Luoni², Alessandra Berry³, Renaud Massart⁴,

Francesca Cirulli³, Moshe Szyf⁴

¹Dept. of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy; ²Department of Pharmacological and Biomolecular Sciences, University of Milan, Italy; ³Department of Cell Biology and Neurosciences, Istituto Superiore di Sanità, Rome, Italy; ⁴Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada

Perinatal life is a period of high plasticity and vulnerability to adverse life conditions, which may program chronic diseases in adulthood, including psychiatric disorders. In particular, exposure to stress during gestation produces an array of behavioral alterations, including mood disturbance and cognitive deficits. We used the rat prenatal stress (PNS) model to investigate attentional impairment (object Recognition Test -ORT), as behavioral readout of cognitive function, and to characterize long-lasting molecular alterations that may contribute to late psychopathology susceptibility. We found that male and female rats exposed to PNS show a significant impairment in the ORT. At molecular level, PNS rats show a region- and time-specific reduction in the expression of the neurotrophin BDNF, a marker of neuronal plasticity that has an important role in mood and cognitive function. BDNF changes were particularly evident in the prefrontal cortex and were sustained by the modulation of specific neurotrophin transcripts with the contribution of epigenetic mechanism. In order to further characterize the epigenetic changes produced in response to PNS, we performed an epigenome-wide analysis in male prefrontal cortex using a 400K promoter tiling array. About 5% of genes were differentially methylated in PNS rats when compared to control animals, with a highly significant association for neuronal functions and psychiatric disorders, in particular schizophrenia. Finally, some of the modifications at epigenetic level display a high correlation with mRNA levels, indicating once again that the effects observed at adulthood are the consequence of a latent epigenetic system-wide regulation. We next employed a cross species study

comparing the list of genes differentially methylated in the PFC of PNS rats with similar results obtained in monkeys exposed to maternal separation as well as with a human cohort characterized by early life stress (ELS). Such analyses allowed us to prioritize the list of genes that may be affected by ELS and that may therefore play a relevant role for psychopathology and disease susceptibility. Collectively, our data provide further support to the notion that in-utero exposure to stress leads to permanent functional and molecular changes in the offspring. Moreover, these results highlight the importance of the identification of methylation signatures in a convergent approach that could serve as predictive and diagnostic markers. This will eventually lead to the identification of novel genes and pathways that are affected as a consequence of ELS and that may contribute to long-term susceptibility for mental illness.

ADOLESCENT STRESS-INDUCED EPIGENETIC CONTROL OF NEURONAL NETWORKS

Akira Sawa¹, Minae Niwa^{2,3}, Richard Lee³

¹Johns Hopkins University School of Medicine; ²Department of Chemical Pharmacology, Meijo University Graduate School of Pharmaceutical Sciences, Nagoya, Japan; ³Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

Environmental stressors during childhood and adolescence influence postnatal brain maturation and human behavioral patterns in adulthood. Accordingly, excess stressors result in adult-onset neuropsychiatric disorders. Here we present an underlying mechanism by linking adolescent stressors to epigenetic controls in neurons via glucocorticoids. A mild isolation stress in adolescence (for 3 weeks) affects mesocortical projection of dopaminergic neurons in which DNA hypermethylation of the tyrosine hydroxylase gene is elicited, only when combined with a relevant genetic risk for neuropsychiatric disorders (DISC1). Associated with these molecular changes several neurochemical and behavioral deficits occur in this mouse model, all of which are blocked by a glucocorticoid receptor antagonist. The face and predictive validities of the mice offer a model for psychotic depression, a common and debilitating psychiatric disease. Although preliminary, we will include two published new data as follows in our presentation: we have narrowed down the most critical term of isolation in adolescence for just one week. We have also extended our study on epigenetic impact of the gene-environmental interactions (e.g., adolescent isolation and DISC1) at the whole genome levels beyond the tyrosine hydroxylase gene.

Symposium

NEGATIVE SYMPTOMS AND SOCIAL COGNITION IN SCHIZOPHRENIA: NEURAL CIRCUITRY, FUNCTIONAL OUTCOMES, AND TREATMENT INNOVATION

Chairperson: Aristotle Voineskos

Discussant: Celso Arango

Sunday, 6 April 2014

2:00 PM – 4:00 PM

Overall Abstract: Individuals with schizophrenia spectrum disorders (SSDs; i.e., schizophrenia, schizoaffective disorder, schizopreniform disorder) exhibit a continuum of impairment in social functioning. This symposium will explore the neural correlates of lower-level and higher-level social cognitive processing impairment among people with SSDs. Effort will also be made to show how schizophrenia patients with prominent negative symptoms demonstrate impairments in similar brain systems that may be responsible for social cognitive performance. Finally, a novel intervention that can improve social function by targeting motivation and emotion recognition using an innovative neuroplasticity-based cognitive training approach will be described. First, Dr. Michael Green will present results from 3 fMRI studies and one EEG study that attempted to explore higher- and lower-level systems in schizophrenia. The higher-level mentalizing system was studied with selective belief attribution or emotion attribution tasks. The lower-level mirroring system was studied with a mirror neuron task in the scanner, and an EEG mu suppression task. The integration of these systems was also examined with an empathic accuracy task. Results suggest the mirroring system is largely intact in schizophrenia. However, individuals

with schizophrenia show impairment in other aspects of social cognition, including mentalizing. Dr. Aristotle Voineskos will then present data demonstrating heterogeneous findings in patients with schizophrenia in circuits that may underlie these two systems. He will show that schizophrenia patients with prominent negative symptoms, or deficit schizophrenia have impairment in right fronto-parietal circuit structure, which predicts impairment in social function. Such impairment was not found in other subjects with a major psychotic disorder, or healthy controls. Dr. Voineskos will also present preliminary results using a continuum-based approach that may illuminate apparent discrepancies regarding impairment of the mirroring system in schizophrenia. Dr. Anil Malhotra will then present data using resting state fMRI which shows that schizophrenia patients with the deficit subtype demonstrate alterations in the cortical midline network, which is considered important for mentalization, introducing the possibility that these more impaired patients may also have impairment in the higher-level mentalizing network. Dr. Robert Buchanan will then put the previous talks into context by utilizing the new Research Domain Criteria framework to integrate findings from patients with prominent enduring negative symptoms, with newer research on social cognitive impairment, both critical determinants of social function. Dr. Buchanan will describe the impact of social cognitive impairment on long-term functioning in SSDs and present data implicating right fronto-parietal white matter microstructural abnormalities in people with prominent negative symptoms, who are socially impaired. Finally, Dr. Sophia Vinogradov will present data on cognitive training approaches relevant to schizophrenia patients with negative symptoms, social cognitive impairment or both. The treatment approach that she will present uses a bottom-up approach to include behaviorally salient and ecologically meaningful social and emotional stimuli with the goal of restoring function in the neural correlates of reward anticipation and emotion recognition in people with schizophrenia. She will present preliminary data indicating that re-engaging the dopaminergic reward system through training facilitates the use of positive incentives to motivate behavior in social and nonsocial domains.

NETWORK TOPOLOGY IN DEFICIT SCHIZOPHRENIA, NONDEFICIT SCHIZOPHRENIA, AND BIPOLAR DISORDER: FROM CIRCUITS TO FUNCTIONAL OUTCOME

Aristotle Voineskos¹, Anne Wheeler², Jason Lerch³, Mallar Chakravarty², Anthony Jun², Philip R. Szczek⁴, Anil K. Malhotra⁴, Julia Linke⁵, Michele Wessa⁵

¹Centre for Addiction and Mental Health, University of Toronto; ²Centre for Addiction and Mental Health; ³Hospital for Sick Children; ⁴Zucker Hillside Hospital; ⁵University of Mainz

Purpose: Recent data suggests substantial shared etiology for the major psychoses (schizophrenia and bipolar disorder). However, a subset of patients with schizophrenia (with the "deficit" form of illness) may represent one end of a continuum of neurobiological and social impairment among patients with major psychoses. We sought to compare patients characterized by strong negative symptom burden and poor social function, who have been classified as "deficit syndrome", to nondeficit patients with minimal negative symptom burden and bipolar disorder patients, using a brain network connectivity approach, and relate abnormal brain circuitry to impairment in social function.

Methods: Following high resolution structural magnetic resonance imaging, and diffusion tensor imaging, brain-wide inter-regional correlations in cortical thickness were examined in schizophrenia subjects ranked in the top ($n=18$ deficit subjects) and bottom ($n=18$ nondeficit subjects) quartile of deficit scores. Then, $n=32$ deficit, $n=32$ nondeficit subjects, and $n=32$ healthy controls were combined from the Hillside and Toronto samples. In addition, $n=32$ bipolar subjects were compared to $n=32$ controls using the same network topology methods to investigate cortical thickness networks across the major psychoses. A subset of schizophrenia patients ($n=22$) completed the quality of life scale (QLS). Correlations with altered brain network structure in relation to social and functional outcome measures were examined.

Results: Deficit schizophrenia subjects demonstrated a larger number of strong positive correlations among cortical regions compared to individuals with nondeficit schizophrenia, bipolar disorder, or healthy controls subjects resulting in a network with increased density of connections. The network

in the deficit subjects contained an increased number of highly central nodes such as the supramarginal, superior temporal and inferior frontal gyri (i.e., fronto-parietal) that were less prominent in the nondeficit and control networks. In addition, highly central nodes were also found in cortical midline regions, specifically cingulate and parahippocampal gyrus. No network differences were detected between bipolar and matched healthy control groups. Mean diffusivity of the right arcuate fasciculus, the white matter tract connecting the fronto-parietal circuit was inversely correlated with the QLS interpersonal subscale ($r=-0.49$, $p=0.02$).

Discussion: Deficit syndrome subjects demonstrated an increased network density compared to nondeficit subjects, bipolar subjects, and healthy controls, who all demonstrated similar network density. Increased network density in deficit subjects was particularly prominent in fronto-parietal and cortical midline circuitry. Fronto-parietal circuitry in particular has been related to social impairment in autism spectrum disorders. Our findings clearly demonstrate differences in cortical regions comprising fronto-parietal circuitry in deficit patients, who have severe social impairment compared to other patients with major psychoses, who are less socially impaired. We directly related impairment in this circuit to impairment in social function using the QLS. These interregional fronto-parietal and cortical midline alterations may serve as neurobiological correlates of a subgroup of especially socially impaired (deficit) people with schizophrenia. The fronto-parietal circuit should be considered as a useful biomarker and treatment target of impaired social function in people with schizophrenia spectrum disorders.

NEUROSCIENTIFIC EXPLORATIONS OF TWO LEVELS OF SOCIAL COGNITION IN SCHIZOPHRENIA

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Social cognition has become an important focus of study in schizophrenia. The terminology and concepts in this area are still being refined. One useful distinction is to separate social cognition into two levels: higher and lower. An example of higher-level social cognition is the "mentalizing" system, which is involved in making inferences about people and their mental states (e.g., theory of mind), and the ability to take someone else's point of view (e.g., perspective taking). Key regions for the mentalizing system include the temporoparietal junction and the ventral prefrontal region. An example of a lower-level social cognition is the relatively automatic "mirroring" system, which is involved in experience sharing, emotional contagion, and common neural coding of action execution and observation. Key mirroring regions include the inferior parietal and premotor cortex. In this presentation, we will present results from 4 neuroscientific studies (3 fMRI studies and one EEG study) that explored higher-level and lower-level systems associated with empathy in schizophrenia. For the higher-level mentalizing system we conducted an fMRI study using tasks that selectively required belief attribution or emotion attribution. For the lower-level mirroring system we conducted a validated mirroring paradigm (imitation, execution, and observation tasks) in the scanner. We also conducted an EEG task of mirroring (mu suppression). Lastly, we examined the integration of mentalizing and mirroring systems by assessing empathetic accuracy in the scanner. For this task, subjects continuously rated changes in the mood of a social "target" shown in a video clip. We obtained a varied pattern of results. Patients showed a failure to activate key regions associated with mentalizing. In contrast, the fMRI and EEG results indicate that the mirroring system is largely intact in schizophrenia for the paradigms that were used. For empathetic accuracy, patients showed differences from controls in a broad range of both higher and lower-level regions. In particular, patients showed much fewer brain regions that modulated their activity with changes in the emotional expression of the social target. The pattern of results indicates clear group differences in mentalizing, but not mirroring, neural systems in schizophrenia. Group differences were also seen on the integrative task of empathetic accuracy. The reason for the different between-group results at higher versus lower levels may involve selective higher-level deficits, or reduced ability to connect lower and higher-level social cognitive systems in schizophrenia.

BEHAVIORAL AND NEURAL SYSTEM EFFECTS OF COMPUTERIZED SOCIAL COGNITIVE TRAINING EXERCISES IN SCHIZOPHRENIA

Sophia Vinogradov^{1,2}, Mor Nahum³, Karuna Subramaniam, Melissa Fisher, Christine Hooker

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Recent research suggests that underlying deficits in both neurocognition and social cognition contribute to motivational impairments in schizophrenia, which in turn, affect functional outcome. Accurate processing of socio-emotive stimuli is intimately integrated with neural systems related to reward, learning, and motivation. For example, positive social stimuli, such as happy faces, are highly rewarding and can serve as primary reinforcement, activating reward-related neural structures such as the ventral striatum and ventromedial prefrontal cortex. These data indicate that improvement in the accuracy and fidelity of social cognitive processing in schizophrenia could have beneficial effects in the neurobehavioral systems that underpin motivated behavior. We will report on preliminary results from intensive computerized neuroplasticity-based cognitive training studies that focus on improving incentive salience via the creation of strong and predictable associations between successful learning events and rewards. "Bottom up" training that emphasizes improved perceptual processing is expanded to include behaviorally salient and ecologically meaningful social and emotional stimuli with the goal of restoring function in the neural correlates of reward anticipation and emotion recognition in individuals with schizophrenia. We will present preliminary data indicating that re-engaging this dopaminergic reward system through training facilitates the use of positive incentives to improve motivated behavior in both social and non-social domains.

THE NEURAL CIRCUITRY OF SOCIAL IMPAIRMENTS IN SCHIZOPHRENIA SPECTRUM DISORDERS

Robert W. Buchanan¹, Laura M. Rowland, Philip R. Szczekko², Aristotle Voineskos³

¹University of Maryland School of Medicine; ²Zucker Hillside Hospital; ³Centre for Addiction and Mental Health, University of Toronto

Background: People with schizophrenia spectrum disorders (SSDs) are characterized by marked impairments in social function. These impairments severely impact quality of life, and predict relapse, poor illness course, and unemployment. Over the past decade, considerable progress has been made in delineating the social cognitive processes that underlie these impairments. However, much less is known about the neural circuitry that supports these processes. The NIMH RDoC initiative provides a framework for evaluating the neural basis of social cognition. In the context of the RDoC Systems for Social Processes Domain: the Perception and Understanding of Others, the right fronto-parietal network has been hypothesized to subserve "lower-level" social cognitive processes necessary for understanding the actions and basic emotions of others, and the cortical midline circuit, has been hypothesized to subserve "higher-level" processes necessary for understanding the perspective of others (theory of mind). In order to evaluate the hypothesized involvement of the fronto-parietal network in social function impairments, we have conducted diffusion tensor imaging (DTI) studies in three independent samples to examine this circuit in people with the deficit form of schizophrenia, a form of schizophrenia characterized by impaired social function.

Methods: Study 1: Twenty participants with DSM-IV schizophrenia or schizoaffective disorder (deficit: n=10 and nondeficit: n=10) and 11 healthy subjects participated in this study. Study 2: Thirty-six participants with DSM-IV schizophrenia (deficit: n=18 and nondeficit: n=18) and 18 healthy subjects participated in this study. Study 3: Fifty-one participants with DSM-IV schizophrenia (deficit: n=14 and nondeficit: n=37) participated in this study. DTI was used to assess the integrity of the superior longitudinal fasciculus (SLF), the major white matter tract connecting the frontal and parietal lobes.

Results: Study 1: There was a significant FA group difference for the right hemisphere SLF ($F=3.6$ df=2,27; $p=0.04$). The deficit group had lower FA than the healthy control group ($p<0.05$), with the deficit/nondeficit group difference approaching statistical significance ($p=0.07$). There were

no significant FA differences between the nondeficit and healthy control groups. Left hemisphere SLF FA values did not significantly differ among the groups. Study 2: There was a significant FA group difference for the right arcuate fasciculus, a component of the SLF ($F=3.4$ df=2,50; $p=0.04$), with the deficit group characterized by lower FA. There was also a significant mean diffusivity group difference for this tract ($F=5.5$ df=2,50; $p=0.007$). The deficit group had a higher mean diffusivity. There were no significant nondeficit/healthy control group differences on either of these measures. Study 3: The deficit group demonstrated significantly ($p<0.05$) lower FA compared to the nondeficit group within the right and left SLF, genu of the corpus callosum, splenium of the corpus callosum, posterior cingulate and right and left inferior longitudinal fasciculus.

Conclusions: The finding of lower FA in the right SLF/arcuate fasciculus in three independent samples is consistent with the hypothesis that disruptions in white matter integrity hypothesized to subserve "lower-level" social cognitive processes play a role in the pathophysiology of the deficit form of schizophrenia.

IDENTIFICATION OF NEUROIMAGING BIOMARKERS FOR NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

Anil K. Malhotra, Pamela DeRosse, Miklos Argyelan, Philip R. Szeszko
The Zucker Hillside Hospital

Negative symptoms and impaired cognitive processes are strong predictors of functional disability in schizophrenia; however the neural underpinnings of these critical features of illness are not well understood. We have previously identified cortical thickness as a potential mediator of outcome in schizophrenia (Szeszko et al. 2011), as well as recent data (Argyelan et al. 2013) suggesting that global connectivity, as assessed by resting state fMRI, may be associated with core features of schizophrenia and other psychotic disorders. We therefore examined networks of brain structure and resting state fMRI activity in a subgroup of patients with schizophrenia characterized by strong negative symptom burden and poor social functioning. Brain-wide inter-regional correlations in cortical thickness were examined in schizophrenia patients ranked in the top (N=14) and bottom (N=14) quartile of negative symptom ratings and compared to matched healthy volunteers (n=14 per group). Networks were derived by thresholding correlation matrices ($p<0.05$ corrected) and node centrality measures were used to identify brain regions that play the most important role in network organization. In a subgroup (N=27) of patients who completed resting state fMRI exams, we calculated spatial inter-correlations ("expression scores") among independent component templates (Biswal et al. 2010) and corresponding individual maps were obtained following dual regression analysis. Investigation of the structural neuroimaging data revealed a larger number of strong positive correlations in the network among patients with the greatest negative symptoms as compared with healthy volunteers and patients with the lowest negative symptom ratings. This pattern yielded an overall network that had an increased density of connections. Investigation of brain-wide correlations revealed frontoparietal and frontotemporal correlations that were stronger in the patients with more severe negative symptoms as compared to the healthy volunteers and correlations with the cingulate gyrus that were stronger in the negative symptom group as compared to the patients with low levels of negative symptoms. Analysis of resting state fMRI measures indicated that negative symptom ratings correlated ($p<0.05$) with expression scores. Specifically, greater negative symptom ratings were associated with lower expression scores within cortical midline structures including the posterior cingulate, which is responsible for self-integration and a parieto-frontal network encompassing the parietal lobes, inferior frontal gyrus and posterior temporal lobe that partially overlapped regions found to be abnormal in the structural imaging analysis. The increase in network density and decrease in resting state fMRI expression scores among patients with severe negative symptoms may reflect decreased specificity and potentially decreased differentiation of brain regions. These phenotypes may therefore represent biomarkers of negative symptom severity, and thus may be useful as targets for early assessment of treatments focused on this critical and disabling feature of psychotic illnesses.

Symposium

NEW VISTAS IN DOPAMINE RECEPTOR RESEARCH: IMPLICATIONS FOR NOVEL THERAPIES IN SCHIZOPHRENIA

Chairperson: Larry J. Siever
Discussant: René S. Kahn

Sunday, 6 April 2014

2:00 PM – 4:00 PM

Overall Abstract: New advances in our understanding of the dopamine receptors and their interactions with other systems have opened up possibilities of new therapeutic interventions for these receptors in the schizophrenia spectrum, including a novel D1 agonist and D2/D3 agents. Waddington will present new data utilizing mutant mouse technologies to evaluate the effects of knockouts of D1 receptors versus glutamate receptors as well as conditional progressive losses of D1 receptor expressing cells in cortex on activity in working memory suggesting that D1 receptors can influence spatial working memory but have no effects on sociability and appear to involve both cortical and subcortical brain regions. O'Donnell will cover dopamine-glutamate and dopamine-GABA interactions in the prefrontal cortex addressing their developmental trajectory suggesting that dopamine modulation of interneurons changes during adolescence with the D2 responses becoming more similar to those of D1 suggesting potential roles for a D2 partial agonist-like aripiprazole or D1 agonists in restoring interneuron activity and excitation/inhibition balance. Mailman will report on several new directions in the development of D1 agonists for human pharmacological use starting with dyhydrexidine, which increased cell activity when administered as the D-enantiomer and other modifications preserve the desirable pharmacodynamic properties but provide improvement in the pharmacokinetics in the potential candidate EFF0311. Progress in discovering non-catechol D1 agonists and mechanisms of signaling properties of these analysis ligands will also be discussed. Siever will discuss new post-mortem data genetic data suggesting the SNP rs5326 is associated with overall Clinical Dementia Rating (CDR) scores in a sample of 727 Caucasians with schizophrenia, Alzheimer's Disease and healthy controls and in the controls alone. This same SNP was associated with cognitive function in a Greek conscript cohort. New data with a selective D1 agonist DAR-100a, the active enantiomer of dyhydrexidine, in schizophrenia spectrum patients with working memory deficits demonstrating improved performance on tests of working memory after IV administration of this compound for three days compared to placebo administered in double-blind fashion. Finally, Burdick will discuss new studies using pramipexole evaluating the effects on reward processing which may have adverse effects as well as beneficial effects on measures of attention and working memory, related to dopamine transporter gene, with discussed in the context of how modulation of dopamine can influence brain function in clinical populations such as bipolar disorder with potential relevance to the schizophrenia spectrum.

THE D1 RECEPTOR AND COGNITION AND TRIAL OF A NOVEL D1 AGONIST IN THE SCHIZOPHRENIA SPECTRUM

Larry J. Siever¹, Daniel Rosell², Margaret McClure², Katherine Strike³, Deanna M. Barch⁴, Philip Harvey⁵, Ragy Gergis⁶, Jeffrey Lieberman⁷, Stella Giakoumaki⁸, Panos Bitsios⁸, Panos Roussos³, Vahram Haroutunian^{2,3}

¹Mount Sinai School of Medicine/James J. Peters VAMC; ²James J. Peters VAMC, Department of Mental Health, New York; ³Mount Sinai School of Medicine, Department of Psychiatry, New York; ⁴Departments of Psychology and Psychiatry, Washington University in St. Louis; ⁵University of Miami Miller School of Medicine, Department of Psychiatry and Behavioral Sciences, Miami, Florida; ⁶Columbia University, Department of Mental Health Services, New York; ⁷Columbia University, Department of Psychiatry, New York; ⁸University of Crete, Department of Psychiatry and Behavioral Sciences, Crete, Greece

Focused genotyping using the COGS 1,5K SNP array was conducted in a total of N=727 [N=349 with AD; N=230 with SZ and N=148 controls] Caucasian samples originated from the MSSM/JJPVAMC BB cohort. The genetic association with clinical dementia rating (CDR) was examined using linear regression models and age, sex and disease status as covariates. The rs5326 at DRD1 locus was associated with CDR in controls alone ($P=9.8E-5$; Beta=0.71) or in the combined sample ($P=9.3E-4$; Beta=0.74). No association

among the rs5326 and disease status (SCZ or AD) was found. The effect of rs5326 was furthered explored in N=1113 healthy controls in the LOGOS cohort and a strong association was found with a cognitive function related to Strategic Planning ($\chi^2=10.32$, df=2; P=0.006), an executive function that depends on working memory. In a clinical study medically/neurologically healthy, medication-free individuals with SPD (N=16), but without current major depressive episode, nor current/recent substance abuse, provided informed consent to participate in a randomized, double-blind, placebo-controlled trial of DAR-0100A (with subsequent open-trial for those randomized to placebo). Baseline cognitive testing (Day 1) consisted of: the Paced Auditory Serial Addition Task (PASAT), Modified AX-CPT, and N-Back task. On Days 2-4, individuals received either 15 mg of DAR-0100A or placebo intravenously over 30 minutes with close hemodynamic monitoring. Cognitive testing was repeated on Days 2 and 4, beginning 20 minutes after the start of infusion. Those randomized to placebo were invited to receive open-label DAR-0100A a minimum of two weeks after initial testing; four of the 8 randomized to placebo entered the open-label trial. The PASAT showed significant improvement from baseline to post-DAR-0100A in correct responses between drug and placebo [mean drug=26.3%, mean placebo=1.69%, d=1.14, t=2.64, p<0.05]. Trend-level improvements with moderate to large effect sizes in the N-back were also observed [d=0.81]. DAR-0100A was well tolerated. Our preliminary findings support the hypothesis that D1R agonists can ameliorate schizophrenia-spectrum working memory deficits. Cumulatively, these studies suggest that the D1 receptor plays a central role in cognition, particularly working memory, and that D1 agonists may improve cognition, especially working memory, in the schizophrenia spectrum.

MODULATION OF DOPAMINE USING A D2/D3 AGONIST IN PATIENTS WITH BIPOLAR DISORDER: EFFECTS ON COGNITION AND REWARD PROCESSING

Katherine Burdick, Raphael J. Braga, Anil K. Malhotra
Zucker Hillside Hospital -North Shore Long Island Jewish Health System

Pramipexole has been implicated in the emergence of risk-seeking behaviors such as pathological gambling in multiple case reports and cross-sectional studies in patients with Parkinson's disease (PD). A purported mechanism for this effect is related to pramipexole's high selective affinity for D3 receptors, which are primarily expressed in the mesocorticolimbic dopamine (DA) pathway – a circuitry that is active during impulsive decision-making. Indeed, several studies that have used pramipexole in single-dose challenge paradigms have confirmed its actions on reward-related neural networks, primarily at low doses and in healthy individuals (Riba et al, 2008; Ye et al, 2011); however, low doses of pramipexole (e.g. 0.25 – 0.5 mg) are thought to influence reward via a "paradoxical" effect related to activation of the presynaptic D2 autoreceptor, resulting in a blockade of phasic DA release and a blunted response to rewarding stimuli (Riba et al. 2008). In contrast, higher doses of pramipexole, including those in the range used to treat Parkinson's disease and in the range used in our cognitive enhancement trial in bipolar patients, act as specific agonists both presynaptically and postsynaptically to enhance DA activity (Mierau et al. 1995). These higher doses of pramipexole are the ones that have been linked to pathological gambling and anti-anhedonic (antidepressant) effects across several major psychiatric disorders. To date, the effects of pramipexole on reward processing have been limited to single-dose (low-dose) challenge paradigms and have not yet been extended to include higher, clinically-relevant doses. Preliminary evidence will be discussed which suggests that pramipexole (1.5 mg/day) has a direct effect on performance on the Iowa Gambling Task such that after 8 weeks of treatment, euthymic bipolar patients made more high-risk/high-reward choices as a result of an increased attention to feedback associated with monetary wins vs. losses (Burdick et al. 2013 Neuropsychopharmacology). These results stand somewhat in contrast to the beneficial effects of the agent on measures of attention and working memory in the same cohort (Burdick et al. 2012 J Clin Psychiatry). Preliminary data will also be presented with regard to the effects of variation within the dopamine transporter gene (DAT) on outcome after pramipexole treatment in our cohort. The results of this clinical trial will be discussed in the context of how modulation of dopamine through D2/D3 receptors influences brain function in healthy individuals and in patients with schizophrenia and bipolar illness with an eye toward future study design.

MUTANT MOUSE MODELS TO EXPLORE D1-GLUTAMATE INTERACTIONS AND CORTICAL VS SUBCORTICAL D1 DOPAMINE RECEPTOR FUNCTION: SCHIZOPHRENIA-RELATED PHENOTYPIC EFFECTS

John L. Waddington¹, Katsunori Tomiyama², Noriaki Koshikawa², Claire O'Leary³, John Drago⁴

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Background: Iterative advances have shaped the classical dopamine (DA) hyperfunction hypothesis of psychosis in terms of both pathobiological mechanisms and their capacity to explain psychopathology. One influential formulation posits positive, psychotic symptoms to be related to increased release of DA onto subcortical D2 receptors, with cognitive dysfunction, and perhaps negative symptoms, related to reduction in cortical release of DA, particularly involving D1 receptors in prefrontal cortex and their interactions with glutamatergic function. Advances in mutant mouse technologies now allow such putative processes to be investigated with increasing specificity, in terms of individual neuronal elements and their relationships to phenotypic behaviours held to reflect psychopathology and movement disorder.

Methodology: A first series of studies investigated the effects of constitutive [i.e. entire brain, from conception] knockout (KO) of D1 receptors vs glutamate (Glu) N2A, B or D receptors on activity and orofacial movements. A second series of studies investigated the effects of conditional [i.e. under regional/temporal control], progressive loss of D1 receptor-expressing cells in cortex vs striatum vs both cortex + striatum on activity, spatial working memory and sociability/social novelty preference.

Results: In adult mice, while constitutive KO of D1 receptors resulted in hyperactivity and reduction in orofacial movements, KO of GluN2A receptors resulted in hyperactivity but did not effect orofacial movements, KO of GluN2B receptors resulted in hypoactivity and increase in orofacial movements, and KO of GluN2C receptors did not effect activity but resulted in increase in orofacial movements; responsiveness to the D1-like agonist SKF 83959 was little altered by KO of either GluN2A, B or D receptors. In adult mice, progressive loss of D1 receptor-expressing cells, whether from the striatum, cortex or both, was without effect on activity. Loss of D1 receptor-expressing cells from both the cortex + striatum, but not loss from either region alone, resulted in impairment in spatial working memory. Loss of D1 receptor-expressing cells, whether from the striatum, cortex or both, was without effect on either sociability or social novelty preference.

Conclusions: These findings indicate, firstly, that D1-glutamate interactions are not ubiquitous; rather, D1 receptors can both (a) interact with, and (b) function independently of, individual glutamate receptor subtypes in relation to behaviours held to reflect psychosis and movement disorder. Secondly, D1 receptors can influence cognition [spatial working memory] while exerting no effect on negative symptom-related behaviours [sociability/social novelty preference]. Furthermore, the influence of D1 receptors on cognition appears to involve both cortical and subcortical brain regions. These studies were supported by Science Foundation Ireland.

CHEMICAL, MOLECULAR, AND CELLULAR FACTORS INFLUENCING THE DISCOVERY AND DEVELOPMENT OF DOPAMINE D1 AGONISTS

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The D1 dopamine receptor is both the most highly expressed dopamine receptor in brain, as well as one shown in numerous preclinical studies to affect many functions. Despite this, there is no approved centrally available selective D1 agonist, and only one compound in use for clinical experimentation. The development of D1 agonists has been hampered by several factors. For one, it has been assumed that high intrinsic activity ("full agonism") requires drugs to have a catechol moiety on the drug, leading to little oral bioavailability and/or rapid metabolism. In addition, some experimental D1 agonists have caused toxicity (e.g., seizures), whereas others cause extremely rapid tolerance. There are a few approved drugs (e.g., rotigotine

and apomorphine) that have high D1 intrinsic activity, but these all are D2 selective and cause a host of dose-limiting D2-mediated pharmacological effects. These issues have provided a neuropsychopharmacological conundrum for decades, but recent advances in medicinal and computational chemistry have offered potential for the immediate future. The availability of high resolution crystal structures of relatively homologous receptors like the β-adrenergic receptor have, when combined with molecular manipulation of receptors, allowed a degree of study of ligand docking and activation mechanisms not previously possible. This, in turn, can permit the discovery or rationale modification of non-catechol-containing chemical backbones that may lead to novel drugs. In addition, has been widely recognized recently that it is possible to design novel drugs using two non-traditional strategies. One is the use of allosteric ligands that can affect signaling by interacting with the receptor and influence the actions of dopamine itself. The other is the ability to discover functionally selective ligands that would differentially activate signaling pathways mediated by the D1 receptor, leading to an improvement in therapeutic index. This presentation will report on several new directions in this area. We shall provide insights on how one can change the pharmacokinetic properties of molecules while retaining the desirable pharmacodynamic properties. One example to be presented will be the potential drug candidate EFF0311, in which a subtle chemical modification to dihydrexidine retained the desirable pharmacodynamic properties but provided a great improvement in pharmacokinetics. We shall also present data relating to the signaling properties of D1 receptor ligands, and how different signaling pathways affect functional responses *in vivo*. Finally, we shall summarize recent progress into the understanding and discovery of non-catechol D1 agonists. The therapeutic promise of D1 agonists has been extant for several decades. The utility for improving aspects of cognition has been suggested by animal studies for two decades, and as reported by others in this symposium, is now starting to be confirmed in human studies. Similarly, D1 agonists have been shown to have dramatic effects in the symptomatic treatment of Parkinson's disease, and have been suggested as have potential in ADHD and substance abuse among other disorders. We believe that this presentation will show that contrary to a popular view, that the D1 receptor is druggable and may lead to important new symptomatic medicine.

DOPAMINE RECEPTORS AS TARGETS FOR COGNITIVE DEFICITS IN SCHIZOPHRENIA: LESSONS FROM ANIMAL MODELS

Patricio O'Donnell

Pfizer

As current antipsychotics are inefficient against cognitive deficits in schizophrenia, there is intense effort to unveil approaches that could improve prefrontal cortical function in this disorder. A convergent observation in many different developmental and genetic animal models is the alteration in postnatal maturation of a subset of inhibitory cortical interneurons. Fast-spiking interneurons mature during adolescence in naïve animals, and this maturation is evidenced by a dramatic change in the manner they are modulated by dopamine. While in juvenile rats and mice D1 and D2 receptor activation has opposite effects on interneuron excitability, in adult animals both D1 and D2 activation strongly enhances excitability. This adolescent maturation is affected in several different models with genetic (DISC1 dominant negative) or developmental (neonatal ventral hippocampal lesion) manipulations. Our data indicate the adult profile of dopamine modulation of interneurons is critical for correct cognitive performance and suggests enhancing interneuron and pyramidal cell function by augmenting D1 receptor activity can be a useful strategy to restore excitation-inhibition balance in an altered cortical circuit.

Symposium

NO SMOKE WITHOUT FIRE: COULD TOBACCO SMOKING HAVE A CAUSAL ROLE IN PSYCHOSIS?

Chairpersons: James H. MacCabe and Robin M. Murray

Discussant: John J. McGrath

Sunday, 6 April 2014

2:00 PM – 4:00 PM

Overall Abstract: The emerging findings on cannabis as a risk factor for psychosis and psychotic symptoms are still stimulating debate. It is proving difficult to disentangle biological effects from confounding by social factors and reverse causality (self-medication). However, cigarette smoking has been largely overlooked, despite the very high (~80%) prevalence of cigarette smoking in patients with schizophrenia. Almost all smokers of cannabis also smoke tobacco, but not vice-versa. However, cigarette smoking is rarely adjusted for, so any association between cannabis use and psychosis could, in theory, be almost entirely confounded by cigarette smoking. We present four recent studies on this topic, all of which show convergent and complementary findings. The first two studies concern subclinical psychotic symptoms. Dr Marco Boks of UMC Utrecht will present findings from a cross-sectional survey of 1,900 young adults in The Netherlands. Cigarette smoking was associated with psychotic symptoms as strongly as was cannabis, but when both were included in the same model, cigarette smoking remained significantly associated with psychotic symptoms, whereas cannabis smoking did not. Suzanne Gage (University of Bristol) will present longitudinal data from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. Smoking cigarettes or cannabis at age 16 predicted psychosis-like experiences at age 18. The effect of cigarette smoking persisted after adjustment for confounders including cannabis, but the effect of cannabis did not persist after adjusting for cigarette smoking. But does tobacco smoking increase clinically significant psychosis? Dr Marta di Forti (Institute of Psychiatry, King's College London) will present case-control data from a first episode study. Tobacco use was four times more common in cases than controls, and the association persisted almost unchanged after adjusting for lifetime cannabis use. Lifetime cannabis use, on the other hand, showed no association with psychosis; although more frequent cannabis use and the use of more potent forms did. Lastly, Dr Pedro Muñoz Gurillo (Hospital de la Marina Baixa, Alicante) will present a series of systematic reviews and meta-analyses examining associations between tobacco smoking and psychosis. The results show that tobacco smoking is more common in first episode psychosis than in controls, that tobacco smokers have an earlier onset of psychosis than non-smokers, that patients with psychosis have an earlier uptake of tobacco smoking than controls, and that patients who smoke tobacco have more positive symptoms than non-smoking patients. Taken together, these findings raise the possibility that tobacco smoking may be an independent risk factor for psychosis. Given the collinearity between cannabis and tobacco smoking, it is even plausible that the reported associations between cannabis and psychosis may be driven by nicotine rather than cannabis. Many of the epidemiological difficulties complicating the study of cannabis, such as the role confounding and reverse causality, apply equally well to tobacco, with the added problem of collinearity between tobacco and cannabis smoking. These factors make this area very difficult to study. However, we argue that the problem may be tractable, for example by studying people who smoke tobacco but not cannabis, or who take cannabis without tobacco. We conclude that epidemiological and biological research on associations between tobacco smoking and psychosis has been neglected for too long, and should be pursued.

TOBACCO USE AND PSYCHOTIC EXPERIENCES IN UK TEENAGERS - EVIDENCE FROM THE ALSPAC LONGITUDINAL STUDY

Suzanne H. Gage¹, Matthew Hickman¹, Jon Heron¹, Marcus Munafò¹, Glyn Lewis², Stanley Zammit²

¹University of Bristol; ²University of Cardiff, UK

A consistent association between cannabis use and psychotic experiences (PEs) has been described, but confounding by tobacco is hard to rule out due to the practice of smoking cannabis with tobacco. We attempt to assess the independent effect of tobacco on PEs, as there are more tobacco users

who do not use cannabis than there are cannabis users who do not use tobacco. This means that while collinearity is a problem when assessing cannabis' independent association with PEs, this is not the case for tobacco. We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort (N=2050). Tobacco use at 16 was assessed via self-report questionnaire. PEs at 18 were assessed via semi-structured interview. Confounders (pre-birth: family history of mental illness, maternal education; childhood: childhood depression, borderline personality traits, conduct disorder; and teenage: alcohol (AUDIT), cannabis use and other illicit drug use) were measured by questionnaire or interview. Ordered logistic regression analyses were conducted to investigate the associations between frequency of tobacco use at 16 (never/experimenter/weekly/daily) and severity of PEs at 18 (none/suspected/definite/definite plus problems). Anyone who was deemed to have PEs at interview at age 12 was excluded. There was a strong association between frequency of tobacco use at 16 and severity PEs at 18 (Odds Ratio (OR) 1.66, 95% CI: 1.38, 2.00). Adjustment for pre-birth confounders did not alter the relationship. Further adjustment for childhood confounders attenuated the relationship slightly, although a strong association remained (OR 1.63, 95% CI: 1.34, 1.98). Additional adjustment for teenage confounders further attenuated the relationship, but a strong association still remained (OR 1.49, 95% CI: 1.12, 1.97). The association between tobacco and PEs was robust to confounding by all measured variables. This was unexpected, and contrary to findings in the same sample investigating cannabis' effect on PEs, where adjustment for illicit drug or tobacco use greatly attenuated the previously similar relationship. There is little evidence as yet for a psychogenic effect of tobacco, so our findings may be due to confounding. If so, there are implications for interpreting cannabis and psychosis associations, as not all studies adjust for tobacco, and those that do often use crude measures. As there is a genetic basis for tobacco use, future research could employ Mendelian Randomisation to assess tobacco's independent causal effect on PEs, without confounding from cannabis or other illicit drugs.

ANOTHER GOOD REASON TO STOP SMOKING: A CASE-CONTROL STUDY OF THE ASSOCIATION BETWEEN TOBACCO USE AND FIRST EPISODE PSYCHOSIS

Marta Di Forti¹, Arianna Marconi², Pedro Gurillo Muñoz³, Francesca Bianconi⁴, Matteo Bonomo⁴, Saffron H. Mirza⁴, Anna Kolliakou⁴, James H. MacCabe⁴, Robin M. Murray¹

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The prevalence of tobacco smoking among people affected by schizophrenia is approximately three times that in the general population and two times that in people suffering from affective disorders. Two recent meta-analyses support the evidence of a consistent association. However, it is frequently suggested that the smoking is an attempt to self-medicate to ameliorate symptoms or antipsychotic side effects. To address this issue we analysed the association between tobacco use and psychosis at the time of the first onset comparing several measures of tobacco use between first episode psychosis patients (FEP) and a sample of healthy population controls. We also aimed to investigate the independent and combined contribution of tobacco smoking and cannabis use to the onset of psychosis. As part of the Genetics and Psychosis (GAP) case-control study, FEP patients who met ICD10 criteria for non-affective and affective psychosis were invited to participate. Socio-demographic data and history of tobacco and cannabis use were collected for 677 individuals (358 cases, 319 population controls) using the Medical Research Council Social Schedule, the Cannabis Experience Questionnaire, and the Nicotine Dependence Questionnaire. Gender, ethnicity and cannabis use were found to be differently distributed amongst smokers and non-smokers; therefore these variables were controlled for in the logistic regression analyses. Results FEP patients were almost four times more likely (OR=3.84; 95% CI: 2.74–5.38) to have been smoking tobacco at some point before onset and almost 4 times more likely to be current smokers compared to controls (OR=3.98; 95% CI: 2.43–6.53). When in the same model, we controlled for socio-demographic variables, and we analysed the effect of both life time tobacco and cannabis use, the probability of suffering from a psychotic disorder remained significantly increased for both life time history of tobacco use (OR=4.84; 95% CI: 3.04–7.71) and cur-

rent use (OR=3.59; 95% CI: 1.93–6.67). After controlling for life time history of tobacco use, the association with increased probability of experiencing a psychotic disorder was significant for daily cannabis use (OR=3.04; 95% CI: 1.91–7.76; p=0.020) and use of high potency cannabis (skunk) (OR=2.91; 95% CI: 1.52–3.45; p=0.001) but not for lifetime cannabis use (OR=0.91; 95% CI: 0.55–2.29; p=0.731).

Conclusions: Both ever and current tobacco use are associated with a 4 fold increased probability to suffer from a psychotic disorder compared to never users and past users. When we analysed the effect of tobacco and cannabis use in the same model: 1) Tobacco use both lifetime and current significantly increased the probability of suffering a psychotic disorders; 2) Daily cannabis use and skunk use were still significantly associated with an increased probability of suffering a psychotic disorder. Finally, as our data were collected from cases within few weeks of the onset of their first episode, this indicates that FEP patients tobacco consumption is unlikely to be merely an attempt to 1) counteract the effects of antipsychotic medications; or 2) ameliorate psychotic symptoms. Neither is it just a proxy for cannabis use.

SYSTEMATIC REVIEW AND META-ANALYSIS ON ASSOCIATIONS BETWEEN TOBACCO SMOKING AND BOTH THE DIAGNOSIS AND THE CLINICAL SYMPTOMS OF PSYCHOSIS?

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Background: Despite acknowledgement that a significant number of people with psychosis smoke cigarettes [1], it is still unclear whether smoking has a role in the aetiology of psychosis [2], and whether it has an effect on clinical symptoms in those with established psychosis.

Methods: We conducted systematic reviews and meta-analyses of the published literature on cigarette smoking, incorporating prospective, cross-sectional, case-control and retrospective studies reporting rates of smoking and clinical symptoms scores in people with psychosis. Specifically we wished to examine rates of daily cigarette smoking, age of initiation of nicotine use and age of onset of psychosis in those with psychosis versus controls, and the effects of smoking on positive and negative symptoms in those with psychosis who smoked cigarettes versus those who did not. Statistical analysis Analysis was carried out using the metan command in Stata 11.2

Results: 29 studies and 32 samples were identified, that gave rates of daily cigarette smoking, with a total sample of 3328 smokers and 3010 non-smokers. Longitudinal Prospective Studies: overall risk ratio of new psychotic disorders in daily smokers versus non-smokers (RR)=1.33 (95% CI, 1.17–1.53). Case-Control Studies: overall odds ratio of first episode of psychosis in daily smokers versus non-smokers (OR)=1.77 (95% CI, 1.09–2.88). Age of onset of psychosis: people with psychosis who were daily smokers and developed psychotic illness at an earlier age than non-smokers (SMD=−0.2). Age of initiation of smoking: there was an earlier age of smoking cigarettes in those with psychosis compared to healthy controls (SMD=−0.34). 14 samples (from 13 studies) were identified with symptom data on people with psychosis by smoking status. These showed greater symptomatology in smokers than non-smokers with a standardized mean difference of 0.43, (95% CI 0.34 to 0.52), z=9.26, p<0.001 for positive symptoms (taking data from PANSS, BPRS and SAPS), 0.089 for negative symptoms, (95% CIs 0.023–0.155), z=2.64, p=0.008 (taking data from PANSS, BPRS and SANS).

Discussion and conclusions: Daily smoking is associated with a modestly increased risk of psychotic disorder. Smokers have an earlier onset of psychosis than non-smokers and people with psychosis have an earlier age of initiation of smoking than controls. Cigarette smoking is also linked to an increase in positive symptoms, though the cross sectional nature of the data means that causality cannot be inferred.

References:

- [1] De Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophrenia research*. 2005;76(2-3):135–57.
- [2] Myles N, Newall HD, Curtis J, Nielssen O, Shiers D, Large M. Tobacco Use Before, At, and After First-Episode Psychosis: A Systematic Meta-Analysis. *The Journal of clinical psychiatry*. 2012;73(4):468–7.

CIGARETTE SMOKING IS EQUALLY STRONGLY ASSOCIATED WITH PSYCHOTIC-LIKE EXPERIENCES AS CANNABIS USE

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Background: Cannabis use has been implicated as a risk factor for psychotic symptoms, ranging from subclinical psychotic-like experiences (PLE) to clinically defined schizophrenia. However, the nature of the long-term association between cannabis use and psychotic symptoms remains subject to debate. A possibility is that the association between cannabis consumption and psychotic symptoms is confounded by cigarette smoking.

Methods: In a large internet-based cross-sectional study in the Netherlands 1,929 young adults aged 18–30 years were included. We analysed the association of cannabis use and cigarette smoking with frequency of psychotic-like experiences and associated distress as measured by the Community Assessment of Psychic Experiences (CAPE).

Results: Cigarette smoking and monthly cannabis use were independently and equally strongly associated with frequency of PLE ($\beta=0.10$, $p<0.01$ and $\beta=0.08$, $p=0.02$ respectively). Cannabis use was associated with distress from PLE in a model adjusted for an elaborate set of confounders excluding smoking ($\beta=0.081$, $p<0.02$). However, when cigarette smoking was included in the model, cannabis use was no significant predictor of psychotic-like experiences but cigarette smoking remained associated with distress from PLE ($\beta=0.106$, $p<0.01$)

Conclusion: Smoking is an equally strong independent predictor of frequency of PLE as monthly cannabis use. The relationship between monthly cannabis use and distress from psychotic-like experiences may be explained by confounding with cigarette smoking. The results suggest that nicotine has a similar or stronger impact on psychotic like experiences in the general population as cannabis. This finding is consistent with the hypothesis that a large part of the association of cannabis with PLE is due to an increased propensity of PLE prone individuals to commence cannabis smoking. The results highlight the need to revisit the role of nicotine in psychosis susceptibility and the evidence for a causal relationship between moderate cannabis use and psychotic like experiences.

Symposium

OLIGODENDROCYTES AS A TARGET FOR TREATMENT IN SCHIZOPHRENIA

Chairpersons: Johann Steiner and Natalya Uranova

Discussant: Andrea Schmitt

Sunday, 6 April 2014

2:00 PM – 4:00 PM

Overall Abstract: Convergent data from different research fields have described the dysfunction of oligodendrocytes as an important feature in schizophrenia pathogenesis, especially due to their implication in brain connectivity. Apart from brain imaging, a wide range of techniques such as light and electron microscopy, morphometry, mass spectrometry, shotgun proteomics, animal and cell culture experiments have been applied to explore the potential role of oligodendrocytes in schizophrenia, as well as analyzing direct effects of antipsychotic drugs on these glial cells. This symposium will provide an update on the role(s) of oligodendrocytes in the pathogenesis of schizophrenia and will outline the latest advances in the area. Natalya Uranova (Moscow, Russia) will present postmortem data which indicate ultrastructural alterations of myelinated fibers and oligodendrocytes, reduced oligodendrocyte densities in the dorsolateral prefrontal and parietal cortex in schizophrenia subjects and clinical-pathological correlates. Daniel Martins-de-Souza (Munich, Germany) will summarize results of proteome analyses of postmortem brain structures using two-dimensional gel electrophoresis in conjunction with mass spectrometry and shotgun proteomics. He will discuss the role of oligodendrocyte proteins as potential biomarkers candidates. The two following talks will discuss if these observations in postmortem studies are disease-inherent, side effects

of medication or if they are ameliorated by antipsychotic drugs. Specifically, consistent with cell-cycle studies in postmortem brain, the animal experiments presented by Lan Xiao (Chongqing, China) will show that certain atypical antipsychotic drugs have a beneficial influence on the proliferation or differentiation of oligodendrocyte precursor cells. Vahram Haroutunian (New York, USA) will discuss recent findings derived from weighted gene co-expression network analysis (WGCNA) of genetic and gene expression in schizophrenia with a focus on the interactions of neurons, oligodendrocytes and astrocytes and their potential grouping into functional units. Finally, Johann Steiner (Magdeburg, Germany) will close the symposium, outlining experiments that suggest that clozapine (but not haloperidol) promotes glycolysis and myelin lipid synthesis in OLN-93 oligodendrocytes. If similar effects occur in vivo, an improvement of brain connectivity may be an important aspect of the superior efficacy of clozapine. In summary, the symposium aims to contribute to a better understanding of schizophrenia pathogenesis. Novel oligodendrocyte-directed therapies of schizophrenia should be established in the future.

ULTRASTRUCTURAL ABNORMALITIES AND DEFICIT OF OLIGODENDROCYTES IN SCHIZOPHRENIA: CLINICAL-PATHOLOGICAL CORRELATES

Natalya Uranova, Natalya S. Kolomeets, Victor M. Vostrikov
Lab. of Clinical Neuropathology, Mental Health Research Center

Background: Neuroimaging and postmortem studies provide evidence for oligodendrocyte (Ol) dysfunction and myelin abnormalities in schizophrenia (SZ), associated with clinical symptoms. Electron microscopy demonstrated dystrophy, necrosis and apoptosis of oligodendrocytes (Ols), the most severely affected cells, in postmortem brains of subjects with SZ. Morphometric evidence for altered Ol-axon, Ol-neuron and Ol-capillary interactions in SZ brains suggests a key role of damage and deficit of Ols in altered neuronal connectivity in SZ. Previously we found a significant reduction of the numerical density of Ols and ultrastructural alterations of Ols in the prefrontal cortex in the subgroup of SZ subjects with predominantly negative symptoms as compared to the normal control group. The deficit of Ols has been consistently reported in different cortical and subcortical areas in patients with SZ, and alterations in the clustering pattern of Ols in the white matter have been found in SZ. Recently it has been shown that Ol progenitors proliferate in the adult mammalian brain to form Ol clusters (OIC). We previously found a deficit of Ols in layer 3 of the inferior parietal lobule, BA 39, in subjects with SZ. This deficit was more pronounced in subjects with poor insight into their disorder. We hypothesized that the number of OIC might also be reduced in SZ subjects having poor insight. This research looked specifically at OIC, in contrast to our previous work looking at density or proximity to neurons of these cells.

Methods: Nissl-stained sections from the Stanley "Parietal Collection" from male SZ subjects (n=24) that have poor, fair, or good insight into the nature of their disorder and normal matched controls (n=24) were studied. The numerical density (Nv) of OIC was estimated in layer 3 of BA 39 and BA 40 by optical disector method.

Results: The Nv of OIC was 23% lower in BA 39 and 30% lower in BA 40 in the SZ group as compared to the control group ($p<0.01$). Normal hemispheric differences in the Nv of OIC were absent in the SZ group. The Nv of OIC was significantly decreased in BA 39 in the subgroup with poor insight and in BA 40 in the subgroups with fair and good insight as compared to controls. In BA 40 lower Nv of OIC (~40%, $p<0.01$) was found in the subgroup with adolescent onset of disease as compared to controls.

Conclusions: Abnormalities of OIC in the inferior parietal cortex in SZ are associated with insight. The deficit of OIC may be associated with altered proliferation and/or maturation of Ol progenitors in SZ. Together with the previous results these data provide a basis for the new therapeutic strategy directed to compensate prominent deficits of Ols and OIC in SZ.

Acknowledgments: Supported by the Stanley Medical Research Institute.

OLIGODENDROCYTE-TARGETED PROTEOMICS: INSIGHTS ABOUT SCHIZOPHRENIA

Daniel Martins-de-Souza

Ludwig Maximilians University of Munich

Background: Despite all scientific efforts, the molecular mechanisms of schizophrenia pathogenesis still need to be comprehended and proteomics are a suitable tool to this end. Our group has contributed with more evidence about the potential role of oligodendrocytes/myelination as well as energy metabolism pathways in schizophrenia, while analyzing the proteome of postmortem brain tissue. At this point, we were driven to verify these affected pathways in a compartmentalized manner.

Methods: Thus, we employed state-of-the-art proteomics in the proteome analyses of primary cultures of human oligodendrocytes treated with MK-801, a NMDA receptor antagonist modeling glutamatergic impairments observed in schizophrenia. Additionally, effects of overexpression and knock-down of oligodendrocytes markers such as CNP were assessed.

Results: Interestingly, we observed in MK-801-treated and CNP-overexpressed/knockout oligodendrocytes proteome differences similar to our findings in postmortem tissue, especially regarding energy metabolism.

Conclusion: Our data support the notion that oligodendrocytes might be the responsible brain compartment to display energy metabolism dysfunction in schizophrenia brains. Our results provide insights to understand the molecular mechanisms of schizophrenia and may even reveal molecular targets for improving treatment strategies.

ANIMAL EXPERIMENT DATA REGARDING THE EFFECT OF ANTIPSYCHOTIC DRUGS ON OLIGODENDROCYTE TURNOVER

Lan Xiao

Department of Histology and Embryology, TMM University, Chongqing

Background: Schizophrenia is a severe psychiatric disorder and its etiology remains largely undefined. Epidemiological studies revealed that young individuals aged between 15 to 35 years are the major schizophrenia-affected population. Recently, more and more evidences suggested that demyelination and/or dysfunction of oligodendrocytes play an important role in the pathogenesis of schizophrenia.

Methods: To test this hypothesis, we performed a series of examinations including experiment on animal and pharmacological studies.

Results: We showed that: (1) Cuprizone (CPZ), a copper chelator treatment induces demyelination and concomitant in the spatial working memory impairment in C57BL/6 mice; and more severe demyelination are displayed in the juvenile and young-adult mice than that in the middle-aged mice. (2) Chronic administration of atypical antipsychotic drug quetiapine (QUE) can prevent or alleviate myelin breakdown and decrease the activity of astrocytes and microglia in CPZ-exposed mice; (3) In the chronic demyelination mice model, administration of QUE after cuprizone withdrawn can significantly improve the spatial working memory, decrease accumulation of NG2+ cells and microglia, and promote remyelination; (4) Different from QUE, the typical antipsychotic drug haloperidol (HAL) can promote the proliferation but inhibit the differentiation of oligodendrocyte progenitor cells (OPCs), and administration of HAL in C57BL/6 mice even worsen myelin breakdown.

Conclusion: Our data imply that certain atypical antipsychotic drugs, like QUE, may protect the white matter from demyelination and thus improve the negative symptoms of schizophrenia. We also provide supporting evidence for better understanding of the susceptibility of young population to the onset of schizophrenia.

A SYSTEMS BIOLOGY APPROACH TOWARD UNDERSTANDING SCHIZOPHRENIA

Vahram Haroutunian^{1,2}

¹Mount Sinai School of Medicine; ²James J Peters VA Medical Center

We aimed to identify abnormalities in the transcriptome organization of the brain among cases with SZ and controls by gene co-expression network analysis. Gene expression was analyzed in postmortem samples from

four different cerebrocortical regions (dorsolateral prefrontal cortex, middle temporal area gyrus, temporopolar area and anterior cingulate cortex) in SZ (N=21) using several microarray platforms. The co-expression analysis identified modules within oligodendrocyte, microglia, mitochondria and neuron (GABAergic and glutamatergic) networks to be associated with disease status. Combining the network analyses with genome-wide association studies in schizophrenia and other illnesses demonstrated that oligodendrocyte and neuronal (GABAergic and glutamatergic) modules are enriched for genetically associated variants, whereas the microglial and mitochondrial modules are not, providing independent support for more direct involvement of these gene expression networks in schizophrenia. Inter-regional coexpression network analysis showed that the gene expression patterns that typically differentiate the frontal, temporal and cingulate cortices in controls diminish significantly in schizophrenia. These results support the existence of convergent molecular abnormalities in schizophrenia, providing a molecular neuropathological basis for the disease.

Symposium
SUICIDE AND PSYCHOSIS: THE CONTEXT AND MEANING OF EARLY RISK

Chairperson: Stephen Wood

Discussant: Stephen Wood

Sunday, 6 April 2014

2:00 PM – 4:00 PM

Overall Abstract: Suicide and Psychosis: the Context and Meaning of Early Risk Suicide accounts for the major part of excess mortality accompanying psychotic illness. The impact of suicide is widely felt, with lasting effect on families, careers, friends and health care workers. We know the risk factors for completed suicide in general terms, however predicting and preventing suicide on an individual basis is a major challenge. A significant majority of patients with psychotic disorder may face all the concomitant risk factors for suicide, yet do not act. In clinical practice much emphasis in risk assessment is put on the role of positive symptoms, with limited evidence as to how psychosis conveys risk. The early years of psychotic illness are the highest period of suicidal behaviour and completed suicide, and we know there is an increase in suicidal behaviour, and self harm, in young people. Understanding the potential associations between self harm, psychosis and suicide is an essential step to improving outcome in schizophrenia. This symposium will present the context in which early risk of suicide in schizophrenia is experienced. We will present an overview of key recent findings with studies of increasing depth; from population effects and self harm in young people, to detailed studies exploring the relationships between suicidal ideation and psychotic symptoms. Studies on completed suicide in early psychosis will conclude with themes for novel interventions featured throughout. There remains a distinct lack of knowledge to explain mechanisms through which self harm and psychosis conveys influence on completed suicide, and whether this can be ameliorated. Our ability to reduce risk of suicide depends on first understanding the context and development of these risks.

SUICIDE-RELATED BEHAVIOUR IN YOUNG PEOPLE: RATES, RISK FACTORS AND INTERVENTION

Jo Robinson¹, Georgina Cox², Sarah Hetrick²

¹Orygen Youth Health Research Centre; ²Orygen Youth Health Research Centre: University of Melbourne, Australia

Background: Suicide-related behaviours are common among young people. At least 100,000 adolescents complete suicide every year, and worldwide, suicide ranks in the top five causes of mortality among 15 - 19 year olds. Suicide attempt and suicidal ideation are more common, with just under 10% of adolescents reporting lifetime rates of attempted suicide, and almost 30% reporting a lifetime prevalence of suicidal ideation. A number of countries have developed national suicide prevention strategies with youth as one of the groups to be targeted, yet despite this, and despite the extent of this problem, little is known about the effectiveness of interventions to reduce risk, in both general and clinical populations. Thus the aims of this paper are to briefly describe the rates and risk factors associated with

suicide-related behaviour in young people and the to examine in more detail the evidence for a range of interventions designed to reduce risk that could inform both clinical practice and government policy.

Methods: Three systematic reviews, and one narrative review, were conducted in order to examine the range, and effectiveness, of interventions designed to reduce suicide risk among young people, in clinical, school-based and online settings. For each of the reviews conducted suicide-related behaviour had to be a primary outcome of interest.

Results: Suicide prevention in clinical settings: Fifteen published trials were included. Of them two targeted young people with mood disorders, one targeted young people with borderline personality disorder and one study targeted young people with a psychotic disorder. Interventions included (but are not restricted to): medication, a family-based intervention, dialectical behavioural therapy, problem-solving therapy, cognitive behavioural therapy and group therapy. No differences were found between treatment and control groups except in one study that found a difference in rates of suicidal ideation between individual cognitive behavioural therapy and treatment as usual. Suicide prevention in school settings: Forty-three studies were included here, of which 15 reported on universal education or awareness programs, 23 reported on selective interventions (e.g. gatekeeper training and screening programs), 3 reported on targeted interventions, and 2 examined a postvention response in schools. Of these studies the most promising appeared to be gatekeeper training and screening programs, although more research is necessary. Suicide prevention in online settings: These reviews found that, despite the number, and potential effectiveness of, online programs for young people with depression and/or anxiety disorders, there are currently no published studies reporting on the effects of online therapy for suicidal youth. Similarly a number of studies have been found that discuss the relationship between suicide and social media, however despite the popularity and the potential reach of social media, no actual interventions studies were identified.

Discussion: Overall it is concluded that whilst we know much about the epidemiology of suicide among youth, there is a dearth of well-conducted studies that provide adequate evidence regarding what works in youth suicide prevention. This has implications both clinically and at a policy level. A greater emphasis on intervention studies – including novel interventions – would lead to better practice in terms of detecting and supporting suicidal young people, and could also contribute to a better informed, and more evidence-based, policy agenda around the world.

PSYCHOTIC EXPERIENCES AS A PREDICTOR OF THE NATURAL COURSE OF SUICIDAL IDEATION: A SWEDISH COHORT STUDY

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¹Royal College of Surgeons in Ireland, Karolinska Institutet, Stockholm, Sweden; ²Karolinska Institutet, Department of Medical Epidemiology and Biostatistics, Nobels vag 12A, 17177 Stockholm, Sweden

Background: Psychotic experiences are far more prevalent in the population than psychotic disorders and are associated with a wide range of depressive, anxiety and behavioral disorders, as well as increased risk for psychotic disorder. Recently, psychotic experiences have been highlighted as a potentially valuable clinical marker of risk for suicidal behavior. There have been few studies to date, however, to assess psychotic experiences as a predictor of suicidality over time.

Method: We wished to assess whether young persons with suicidal ideation at baseline assessment who reported psychotic experiences were at higher risk for persistence of suicidal ideation at follow up than young persons who also reported suicidal ideation at baseline but who did not report co-occurring psychotic experiences. A total of 2,263 Swedish adolescents were assessed at ages 13 to 14 years for psychotic experiences, suicidal ideation and internalizing and externalizing psychopathology. Participants were re-assessed at ages 16 to 17 years and 19 to 20 years.

Results: Among 13- to 14-year olds with suicidal ideation, co-occurring psychotic experiences did not predict an increased odds of persistence of suicidal ideation to 16 to 17 years ($OR=0.94$, $95\%CI=0.19-4.78$). Among 16- to 17-year olds with suicidal ideation, however, co-occurring psychotic experiences predicted a 6-fold increased odds of persistence of suicidal ideation to ages 19 to 20 years ($OR=5.53$, $95\%CI=1.33-23.00$). This finding was not explained by internalizing or externalizing psychopathology or by cannabis use.

Discussion: Although most suicidal ideation is transient and does not require close clinical attention, for some individuals, suicidal ideation becomes persistent, causing long-term morbidity, mental distress and ultimately increasing the risk of attempted and completed suicide. Identification of individuals whose suicidal ideation is likely to become persistent, then, is an important, if complex, challenge in clinical psychiatry. Our results show that psychotic experiences are an important, but under-recognized, marker of risk for persistence of suicidal ideation, in particular from mid-adolescence. An increased emphasis on the clinical assessment of psychotic experiences in mental health services should be a priority

DEPRESSION AND SUICIDALITY IN FIRST EPISODE PSYCHOSIS: SUBORDINATION AND SHAME

Rachel Upthegrove^{1,2}, Jonathan Ives³, Amrita Sandhu³, Lisa Jones³, Kerry Ross⁴, Katherine Brunet⁴

¹University of Birmingham; ²Early Intervention Service; ³School of Clinical and Experimental Medicine, University of Birmingham; ⁴Early Intervention Service, Birmingham and Solihull Mental Health Trust

Suicidal behaviour in early psychosis is linked to depression and hopelessness, however the meaning and mechanisms of this association is understudied. We may accept a depressive dimension in psychosis, in keeping with a dimensional rather than categorical approach, however our concepts of this depression here has been transported wholesale from unipolar affective disorders. It is not clear that this is a valid approach. We will present a series of short papers exploring the development and phenomenology of depression and suicidal thinking in early psychosis. We aimed initially to have a clearer understanding of the ebb and flow of depression and suicidal thinking in the early phase of psychosis, whether these events are predictable and how they relate to the early course of psychotic symptoms. Ninety-two patients with first episode psychosis (FEP) completed measures of self harm, hopelessness, depression, and duration of untreated psychosis. Follow-up took place over 12 months. A combination of depression and suicidal thinking was present in 63%. Depression in the prodromal phase was the most significant predictor of future depression and acts of self-harm and thus may be key to the development of future depression and suicidal thinking. Exploring the relationship between early psychotic symptoms and suicidal ideation in detail, we examined the relationship of depression and suicidal thinking with appraisal of illness, voices and persecutors. Prospective data was gathered on 72 patients with acute FEP on depression, severity and experience of positive symptoms, insight and appraisals of illness using validated interviews over 12 months. Malevolent voices, use of safety behaviours and subordination to persecutors was associated with depression and suicidal behaviour in acute FEP. Loss, shame, low level continuing positive symptoms and longer duration of untreated psychosis were associated with post psychotic depression. Negative appraisals remained stable despite recovery in other symptom domains. Thus depression in early psychosis may be propagated by the personal significance and content of positive symptoms experienced in FEP. In recovery, low level symptoms, longer period of illness and negative appraisals are significant factors. Using novel qualitative methodology, we went on to explore the subjective experience and phenomenological features of post-psychotic depression using photo-elicitation and unstructured interviews. The psychotic episode was a traumatic event followed by subjective doubt, shame and embarrassment. Common biological symptoms of depression did not feature. Participants rather felt that the psychotic episode had destroyed their personality and identity, leading to a loss of role, status and suicidal ideation; "It's a feeling of worthlessness, feeling of no hope, feeling of you're useless to anything, anyone ... you got nothing to look forward to, it's all taken away from you." Efforts to predict and reduce suicide in psychosis may need to target the early phase of illness to reduce later risk. Understanding this dimension of psychosis in and of itself has the potential to improve and aid development of more effective and appropriately targeted interventions.

THE LONG-TERM RISK OF SUICIDE FOLLOWING FIRST ONSET PSYCHOSIS AND POTENTIAL EARLY RISK FACTORS

Rina Dutta^{1,2}, Robin M. Murray³, Matthew Hotopf³, Judith Allardyce⁴, Peter Jones⁵, Jane Boydell³

¹King's College London; ²Institute of Psychiatry and The Maudsley Hospital, London; ³Institute of Psychiatry, King's College London, UK; ⁴Department of Psychiatry, Maastricht University, The Netherlands; ⁵Department Psychiatry, University of Cambridge

Background: The long term risk of suicide following first onset of psychosis is unknown, because previous studies have (1) been based on prevalence cohorts, (2) been biased to more severely ill, hospitalised patients, (3) extrapolated from short follow-up times and (4) made a distinction between schizophrenia and other psychoses. Previous research has identified risk factors in the period leading up to suicide in psychotic illness, but little is known about whether factors identifiable early in the course of illness might be markers for later suicide.

Objectives: (i) To determine the epidemiology of suicide and (ii) to investigate potential early risk factors for suicide in a clinically representative, retrospective inception cohort of n=2,723 first onset psychosis patients.

Method: All 2,723 patients who presented for the first time to secondary care services with psychosis in three defined geographical catchment areas in London (1965-2004; n=2056), Nottingham (1997-1999; n=203) and Dumfries and Galloway (1979-1998; n=464) were traced after a mean follow-up period of 11.5 years and death certificates were obtained to identify deaths by suicide and open verdicts according to ICD-7-10. Potential early risk factors for suicide were identified from the Operational Checklist for Psychotic Disorders rated for the first year following presentation.

Results: Overall there were 53 suicides and 391 deaths from other causes. Case fatality from suicide was considerably lower than expected from previous studies: 1.9% (53/2723); proportionate mortality was 11.9% (53/444). Although the rate of suicide was highest in the first year after presentation, risk persisted late into follow-up, with median time to suicide being 5.6 years. Suicide occurred approximately 12 times more than expected from the general population of England and Wales (SMR 11.65; 95%CI 8.73-15.24), and 49 of the 53 suicides were excess deaths. Even a decade after first presentation, suicide risk remained almost 4 times higher than in the general population (SMR 3.92; 95%CI 2.22-6.89): a time when there may be less intense clinical monitoring of risk. Male gender (RR 2.84, 95% CI 1.20-6.69, p<0.02) and a cumulative threshold effect of symptoms early in the illness (RR 6.81, 95% CI 2.33-19.85, p<0.001) were associated with a higher propensity for later completed suicide. There was also a suggestion that early manic symptoms might increase the risk of later suicide irrespective of initial diagnosis.

Conclusions: The highest risk of suicide following a psychotic episode occurs soon after presentation, yet clinicians should still be vigilant in assessing risk a decade or more after first contact. The widely held view that "10-15% die from suicide" is misleading as it refers to proportionate mortality, not "lifetime risk". Nonetheless, there is a substantial increase in risk of suicide compared with the general population. Suicide risk was associated with a cumulative threshold effect of symptoms noted early in the course of the illness as well as with manic symptoms.

Symposium

ICOSR SYMPOSIA: THE ADVANCES IN STRUCTURAL AND FUNCTIONAL BRAIN IMAGING IN SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS

Chairperson: S. Charles Schulz

Discussant: S. Charles Schulz

Sunday, 6 April 2014

4:15 PM – 6:15 PM

Overall Abstract: Brain imaging has been a major instrument for the study of mental illnesses for over 30 years now. The early studies utilizing CT scanning demonstrated structural differences in patients with schizophrenia compared to control groups, and then further studies illustrated that there were structural differences for bipolar disorder as well. As the CT scan studies increased in size and number, other studies looking at the functioning of the brain were performed using PET scans and the early

studies illustrated a hypofrontality in patients with schizophrenia compared to controls. The PET scanning introduced the idea of the ability to look at not only structure but function as well. The discovery of MRI led to a very clear picture of the brain and allowed the field to examine not only the structure of the brain but also connectivity utilizing such measures such as DTI. With the discovery of fMRI, then there was the possibility to see how the brain was working and to also test how the brain reacted to certain stimuli or how it worked when it was performing cognitive tasks. The purpose of this symposium is to discuss a number of the latest techniques in brain imaging, to examine ways to understand which treatments may be possibly successful, to examine how functional imaging responds when a person is performing cognitive tasks, the use of brain imaging to examine the domains of psychosis – similarities and differences – and the latest techniques in utilizing brain imaging in psychiatry. The emergence of the treatments of neuromodulation has substantial revolutionary potential in treating patients with psychiatric illness. As some of the imaging studies led to sites for stimulation, it is thought to be very important to utilize brain imaging in understanding which patients may respond to treatment and also to identify areas of the brain which may be stimulated by imaging. The utilization of functional imaging in the cognitive neuroscience task reliability and clinical applications (CNTRACS) is a multi-site trial in which brain imaging was performed using fMRI while subjects were undergoing cognitive processes. The differences between the patients and the controls are highly informative about these cognitive processes. The emergence of examining the domains of psychosis has led to the large study (BSNIP) which has examined five different techniques to determine similarities and differences between people with schizophrenia, schizoaffective disorders, and psychotic bipolar patients. The study will now report on 917 people participating and is finding many similarities in brain structure and function across the domains of psychosis. However, there are areas of substantial differences as well. During the symposium, these results will be described. Further advanced strategies to assess connectivity networks have been developed and in a study of people with schizophrenia and controls, the patients had weak connectivity compared to the controls. Further, the controls showed faster recruiting connectivity resources. The symposium will focus on the advanced techniques for examining schizophrenia and other domains of psychosis. An important step in the symposium is to hear reports of the latest techniques in brain imaging.

DYNAMICS OF INTRINSIC CONNECTIVITY NETWORKS IN SCHIZOPHRENIA

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Background: Schizophrenia is a mental disorder that has been ascribed to dysfunctional integration among distant neural systems. Intrinsic connectivity networks (ICNs) obtained using independent component analysis (ICA) of resting-state functional magnetic resonance imaging (fMRI) data seem to provide valuable insights in understanding the properties of these networks but such studies have primarily been focused on static measures of ICNs. In this study, we explore dynamic whole brain resting-state functional network connectivity (FNC), defined as pairwise correlation between the time courses of ICNs, differences between healthy controls (HC) and patients with schizophrenia (SZ) who took part in the FBRIN Phase III multi-site fMRI study.

Methods: Six minute resting fMRI scans were obtained from 163 healthy controls (HC) and 151 age-and-gender-matched patients with SZ on seven 3 Tesla scanners. A high model order (C=100) group ICA analysis was performed on the resting fMRI data. Out of the 100 components, 47 ICNs were identified. Subject time courses were then detrended, orthogonalized to subject motion, and bandpass filtered between [0.01–0.15] Hz. We estimated dynamic FNC by computing pairwise correlations between ICNs in a sliding windowed fashion (44 s window length) with an additional sparsity constraint on the inverse covariance matrix. These dynamic FNC states were then clustered using k-means clustering.

Results: The identified 47 ICNs were broadly categorized into 8 sub-networks: subcortical, auditory, sensorimotor, visual, default-mode, higher order associative, frontal, and cerebellar networks. Clustering of dynamic FNC states revealed similar centroid FNC states for both HC and SZ subjects

for several cluster sizes searched ($K=2$ to 9), but the FNC window states of patients with SZ were more commonly assigned to a particular state of weak connectivity among subsystems whereas HC switched between different FNC states more often.

Conclusions: Dynamic FNC analysis suggests that patients with SZ tend to linger in a state of "weak" and relatively "rigid" connectivity among different sub-networks. In contrast HC are probably faster in recruiting necessary resources as task demands change by dynamically switching between different FNC states while varying connectivity among sub-networks. Furthermore, patients with SZ showed weaker connectivity among sensory systems and hyper-connectivity between thalamus and sensory systems in different FNC states.

GUIDING NEUROMODULATION WITH NEUROIMAGING

Kelvin Lim^{1,2}

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The pace of medication development for psychotic disorders has slowed. In order to continue to improve treatment for patients suffering from psychotic disorders, innovative approaches need to be developed. Non-pharmacological interventions such as cognitive based approaches have shown promise for the management of a variety of symptoms observed in psychotic disorders. These cognitive based approaches depend on learning (brain plasticity), which can be impaired in psychotic disorders. Non-invasive neuromodulation methods can both probe and modulate brain plasticity and may be useful to enhance the effectiveness of existing treatments. It is likely that there is interindividual variation in brain network abnormalities as measured with current neuroimaging approaches. In order to be successful, neuromodulation interventions targeting putative brain network abnormalities will need to take this variation into account. Neuroimaging may be an important tool to identify neuromodulation targets.

NEW NEUROSCIENCE BASED COGNITIVE PARADIGMS FOR BIOMARKER RESEARCH IN SCHIZOPHRENIA

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Background: Cognitive neuroscience has seen an explosion of technical advances and new knowledge regarding the neural basis of cognition. This presentation will overview of the results of the Cognitive Neuroscience Task Reliability & Clinical Applications (CNTRACs) Consortium work developing imaging biomarkers for three of the cognitive tasks developed by the consortium: Goal Maintenance (Dot Probe Expectancy Task; DPX), Episodic Memory (Relational and Item Specific Encoding Task; RISE), and Visual Integration (Jittered Orientation Visual Integration Task; JOVI).

Methods: The CNTRACs Consortium conducted a five-site imaging study, with a demographically matched sample of 55 patients with schizophrenia and 50 healthy controls. Participants completed a behavioral practice session within one week of their baseline scan, and then completed a baseline scan session followed by a retest scan within 28 days. Three of the scanners were Siemens' Tim TRIOs using a 12 channel headcoil, one was a Siemens' Allegra using an 8 channel headcoil, and one was a Phillips Achieva using a 12 channel head coil. Each imaging session including high resolution T1 imaging based on ADNI sequences, a T2 acquisition (to aid in co-registration), 2 sets of field maps, and 11 BOLD runs using an EPI sequence. Participants completed 4 runs of the DPX, 3 runs of the JOVI, and 4 runs for the RISE (1 during encoding, 2 during item recognition and 1 during relational recognition). Order of task administration was counterbalanced across participants and all participants took a break half way through the session. fMRI data were pre-processed using standard procedures with the FMRI Expert Analysis Tool (FEAT) in the FMRI Software Library (FSL version 4.1). Statistical analysis was performed using the general linear model in FEAT, with research site added as a co-variate.

Results: For the RISE, controls had greater activation than patients in medial temporal lobe regions (right hippocampus and parahippocampal

gyrus) when successfully retrieving objects that had undergone relational encoding. In addition, when participants made errors following relational encoding controls showed greater activation than patients in a set of bilateral prefrontal regions (inferior and middle frontal gyrus, anterior cingulate gyrus) often associated with error detection. Conversely, in the item encoding condition, there were no group differences observed in medial temporal or prefrontal activation during either successful or unsuccessful item recognition. For the DPX, controls had greater activation than patients in dorsolateral prefrontal cortex in the comparison of cues signifying greater versus lesser need for goal maintenance. For the JOVI, all participants showed linear increases in activation in visual, frontal and parietal regions as demands on visual integration increased and patients showed altered activation in superior parietal and inferior frontal regions. There were few site differences that interacted with group, and minimal differences in QA indices across sites. Analyses of test-retest reliability are ongoing.

Discussion: These results illustrate the successful development and implementation of imaging biomarkers paradigms of tasks developed as part of the CNTRACs Consortium, and provide evidence for the validity of these paradigms as measures of the neural systems associated with specific cognitive processes. These results also illustrate the sensitivity of these measures to identifying neural changes associated with cognition impairment in schizophrenia and pave the way for their use as outcome and predictor measures in studies focused on evaluating treatments to enhance cognitive function in psychosis.

STRUCTURAL AND FUNCTIONAL NEUROIMAGING FINDINGS IN THE BSNIP PSYCHOSIS CONSORTIUM

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Background: increasing evidence suggests that brain-based biological marker data tend to cross traditional psychiatric diagnostic boundaries. Clinical symptoms used in psychiatric diagnosis tend to be diagnostically non-specific, and risk genes discovered to date are similarly broad with regard to illness risk. Given the above, the BSNIP 5-site endophenotype study quantified multiple endophenotype candidates, derived from cognitive, oculomotor, electrophysiological and neuroimaging domains across DSM-diagnosed schizophrenia (SZ), schizo-affective (SA) and psychotic bipolar (PBP) patients and their first-degree relatives and controls. For neuroimaging, we explored whether abnormalities were more associated with classic psychiatric syndromes/disease diagnoses or alternatively with symptom dimensions, i.e. "psychosis", and crossed traditional diagnostic boundaries. We determined if abnormalities were heritable and if so, were they found in all first-degree relatives or only the subset with psychotic spectrum diagnoses.

Methods: We report here data on 917: SZ, N=149; SA, N=90; PBP, N=115; Healthy controls (HC) N=200; and patients' relatives (SZ-R, N=134; SA-R, N=100; and PBP-R, N=129). Participants underwent imaging at 3-T that included structural (s)MRI, functional (f)MRI during a 5 min. resting period at all sites and DTI at 2 sites (subject N=513). sMRI data were processed using (a) VBM and (b) Freesurfer, DTI with tract-based spatial statistics to define fiber tracts and voxel-based analysis on skeletonized data using threshold-free cluster enhancement to correct for multiple comparisons. fMRI used the Group-ICA toolbox deriving within-and between-component connectivity measures and ALFF analyses implemented in Matlab. Statistical analyses were done blind to diagnosis with research site as a covariate.

Results: For VBM, widespread cortical and subcortical gray matter (GM) volume reductions were related with psychosis across diagnoses, including relatives with cluster-A features. Using DSM, there were progressive GM deficits from PBP to SA to SZ. With DTI, patients across diagnoses shared white matter (WM) FA deficits, most consistently within corpus callosum genu and body: SC-R displayed similar WM deficits while PBP-R resembled controls. Again, cluster-A relatives resembled patients, so that corpus callo-

sum FA abnormalities were strongly associated with the clinical psychosis state and trait. For fMRI ALFF, SZ and SA shared marked, widespread deficits that were seen to a lesser extent in PBP; none of these were heritable, with all relatives resembling controls. With regard to resting network connectivity, 7 networks revealed abnormalities. Two of these were unique to schizophrenia probands (fronto-temporal/and cerebellum/midbrain), other abnormalities including the posterior default mode network, and were shared by probands. Thus, SZ, SA, PBP probands and their relatives shared both unique and overlapping brain connectivity abnormalities, some of which were seen in unaffected relatives.

Discussion: these results reveal that neuroimaging data can be integrated across multiple sites without introducing site-by-diagnosis confounds. Different imaging measures clearly display different properties; in general, simpler measures (sMRI, DTI) tended to be more heritable. Many measures emphasize the predominant effect of these biological, quantitative abnormalities tracking more reliably with the symptom dimension of psychosis than with DSM diagnostic categories. While some imaging measures such as DTI-derived FA were strongly heritable, others such as fMRI functional connectivity were more variable.

Symposium

SHOULD WE CONTINUE TO DO PLACEBO-CONTROLLED MEDICATION TRIALS IN SCHIZOPHRENIA? AN ETHICO-CLINICAL DEBATE

Chairperson: Anthony S. David

Discussant: William T. Carpenter

Sunday, 6 April 2014

4:15 PM – 6:15 PM

Overall Abstract: Therapeutic trials of medication in schizophrenia research, especially those sponsored by the pharmaceutical industry, often contain a placebo arm. Given that there are available several proven therapeutic agents for the treatment of this disorder, why is this necessary? Should not all trial compare a new trial agent with an established, efficacious one? In this symposium, we will debate the clinical, research, regulatory and ethical context behind placebo-controlled trials in schizophrenia therapeutics. This will be chaired by Anthony David, who is currently co-chair of the SIRS Ethical Committee. Each contributor has considerable experience of conducting such trials in various capacities. The symposium will start with Professor Wolfgang Fleischhacker a well-known clinical researcher from Austria, who will begin with an overview of the practical and methodological concerns which face researchers carrying out such trials. From his experience working with different companies as well as on academic studies, he will draw attention to the fact that methodological issues impinge on ethical ones and vice versa. After all a methodologically flawed study is arguably an unethical one and a ethically perfect study which is impossible to carry out in the real world will not benefit anyone. Next we will hear from Dr Luca Pani, a psychiatrist and representative from Italian Medicines Agency (AIFA)'s General Directorate, part of the European regulatory framework. He will explain how current guidelines allow for the safe use of placebos in clinical trials provided certain rules are adhered to. A view from the pharmaceutical industry will be provided by Dr Rob Conley who currently holds the position of distinguished scholar employed by Eli Lilly but has a long background in schizophrenia research in non-commercial settings. He will discuss the strengths and weaknesses of placebo controlled trials and will highlight some of the necessary safeguards for doing ethical research in this area. The issues of autonomy versus paternalism; informed consent and capacity to make decisions will be elaborated. The foregoing will set the stage for Paul Appelbaum, a US clinical psychiatrist and professional ethicist. Starting with the Declaration of Helsinki, he will go through how risk and harms can be balanced to enable useful, ethical research to proceed. Finally Will Carpenter will discuss all the contributions. Dr Carpenter has written on many of these topics and has unrivalled experience in the field of biological and social research in schizophrenia. He will broaden the consideration from placebos to the more general challenge of off-medication research. The symposium will attempt to explore and resolve the tension that sometimes develops between: the requirements of regulators to ensure that drugs may only be licensed after rigorous efficacy and safety checks; the aims of the pharma industry to produce novel agents and ensure profits for their shareholders and for the company to reinvest in

further discovery; the objectives of researchers to ensure that trial design and methodology succeeds in answering the questions they have posed; the aspirations of clinicians who are seeking ever better treatments for their patients. It is hoped that the symposium will lead to recommendations that may be considered by the SIRS Ethical Committee for dissemination.

THE USE OF PLACEBO IN RANDOMIZED CONTROLLED TRIALS IN SCHIZOPHRENIA: A REGULATOR'S VIEW

Luca Pani

Segreteria Tecnica Direzione Generale Agenzia Italiana del Farmaco

The use of placebo represents a major challenge for CNS drug development. In the field of schizophrenia, in recent trials, the difference in efficacy between active treatments and placebo has tended to be smaller than the differences seen in the past. This has contributed to the increasing failure of registration trials and has raised ethical concerns. Informative data in clinical trials are those defined by a negative placebo response and a positive drug response. High placebo response rates are inversely related to the signals of efficacy thus reducing the efficiency of a trial. From a regulatory point of view, assay sensitivity cannot be guaranteed even in well designed and conducted trials if a placebo arm is not included. The latest version of the "Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia" (EMA, 2012), states that predefined escape criteria, rescue medication and stopping rules, as well as a stringent follow up should be applied to safeguard patients' safety in placebo controlled trials. Provided that, the benefits of using a placebo arm will generally override any ethical reservations in short term controlled efficacy trials. A placebo arm can still be possible and appropriate in long term studies if a randomized withdrawal design is applied to demonstrate maintenance of effect. On the other hand, recent work has shown that many factors could be identified affecting the level of placebo response, including both patients characteristics and trial design factors. New experimental designs, which control these factors, are being tested to verify if the likelihood to detect antipsychotic effect could be increased. A common effort is therefore needed among all stakeholders, such as patients, regulators, industry and research centers with Health Care Providers, which are involved in the drug development process and strategy to collaborate to optimize trial design in order to increase its efficiency, in terms of reducing the number of patients needed and reducing the placebo response rate with clear positive ethical implications.

THE ETHICS OF PLACEBO-CONTROLLED TRIALS IN SCHIZOPHRENIA: A VIEW INFORMED BY WORKING WITH INDUSTRY

Robert R. Conley^{1,2}

¹Eli Lilly and Co; ²Adjunct Professor, University of Maryland School of Medicine

People with schizophrenia present a challenge in the consideration of placebo controlled trials. Although there are commonly accepted standards of care in regard to medication worldwide it is recognized that the majority of people with this syndrome are not well treated by these current medications, which have serious problems with safety and efficacy. When there are no established effective interventions for the treatment of a disease, the use of a placebo control is not controversial. However, when an established effective intervention exists, the ethical acceptability of using a placebo control is sometimes challenged. If placebo control presents a serious risk, it is unethical. However, when the use of placebo control can reasonably be expected to result in only temporary or minor discomfort, it can be ethical. In addition to a low probability of morbidity, the use of a placebo control may be justified in situations in which existing treatments are minimally effective or have serious safety issues. Placebo-controlled trials are one of the most reliable ways to demonstrate the safety and efficacy of an investigational intervention because they provide a valid baseline against which the intervention can be compared. Placebo-controlled trials therefore have a great ability to distinguish between effective and ineffective treatment. This is crucial in conditions where treatments are not fully effective. Active-controlled trials are less sensitive and usually require a larger sample size than placebo-controlled trials. Therefore, a safety advantage of placebo-controlled trials is that they expose fewer

participants to the risks associated with the investigational intervention. This is important in the testing of novel interventions in people. People with schizophrenia are also considered to be a vulnerable patient population. Benefit-risk analyses must take into account relevant vulnerabilities (including cognitive and social harm) that create unique risks, as well as the potential for research participants to benefit. If there are scientifically sound methodological reasons to use a placebo control and the risks are reasonable, then it is ethical to for consent. Consent must be valid, which is also an issue in people with schizophrenia. Research participants must be fully informed of alternative available treatment options; the probability they could be randomized to a placebo arm; the consequences of delaying treatment; the risks and benefits associated with the trial; the options to receive treatment if symptoms worsen; and the right to withdraw from the study. Competent research participants are capable of assessing the relative merits and risks of a trial. Denying research participants the option to evaluate a trial and consent to participate is overly paternalistic and a violation of their autonomy. Decisions on whether a vulnerable person or population should be included or excluded from a placebo-controlled trial should be made on a case-by-case basis.

ETHICS OF PLACEBO USE IN SCHIZOPHRENIA TRIALS

Paul S. Appelbaum
Columbia University

The ethics of placebo use in schizophrenia research has been a matter of contention for several decades. Opponents of placebo use once relied on the Declaration of Helsinki, which formerly required that "[i]n any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method". However, the Declaration now admits the possibility of using placebos, at least in studies in which "no current proven intervention exists; or where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm." This formulation suggests that two elements are critical to the ethical use of placebos – establishing necessity and minimizing risk – to which obtaining meaningful informed consent of research participants must be added. Necessity may involve any of the following, which may apply to given schizophrenia protocols: standard medications may not be effective with the population under study; the condition being studied is susceptible to substantial fluctuation in severity or to spontaneous remission; the measurement techniques being used in the study are unavoidably imprecise; substantial reduction of risk of exposure to experimental interventions is possible with placebo use; or substantial benefits are likely as a result of more rapidly determining whether the experimental intervention is effective. Minimization of risk can involve: selection of subjects who are less likely to be adversely affected by placebo; minimizing the number of subjects receiving placebo and the duration of its use; making available other forms of treatment during the study that have the potential to mitigate adverse consequences; and having procedures in place for close monitoring of subjects and prompt restoration of active treatment. To insure meaningful consent, investigators may want to screen potential subjects for decisional capacity, use multiple approaches to communicating information, emphasize the potential consequences of being off medication, and quiz potential subjects' understanding of the study. Placebo use in schizophrenia studies requires clear justification and efforts to minimize harms, but using these approaches can be done in conformance with acceptable ethical standards.

PLACEBO CONTROLLED TRIALS IN PATIENTS SUFFERING FROM SCHIZOPHRENIA: METHODOLOGICAL ISSUES WITH AN INDIRECT EFFECT ON ETHICAL CONSIDERATIONS

W. Wolfgang Fleischhacker
Medical University Innsbruck, Austria, Department of Psychiatry and Psychotherapy

Placebo controlled randomized clinical trials continue to be required by regulatory authorities for the licensing of new drugs for schizophrenia

and many experts also consider this methodology as the gold standard of evaluating antipsychotics. This is hotly debated in the field, mostly from an ethical perspective. Yet, there are a number of issues associated mostly with methodological challenges, which only indirectly impinge upon ethical concerns. These include feasibility, patient selection, attitudes and expectations, all of which have an impact on the generalizability of data acquired from placebo controlled clinical trials. Given that there is an increasing difficulty in convincing both patients and clinicians to participate in placebo controlled studies and taking into account high drop out rates in such studies, even in the active treatment arms, the concern has been raised that such data will not be informative for everyday clinical practice.

Symposium

THE LONG SEARCH FOR AN INFLAMMATORY COMPONENT IN SCHIZOPHRENIA

Chairpersons: Iris Sommer and Sabine Bahn

Discussant: Cynthia Shannon-Weickert

Sunday, 6 April 2014

4:15 PM – 6:15 PM

Overall Abstract: In the 19th century, Sigmund Freud already examined the blood of psychotic patients for the presence of infectious agents. At that time, it was the spirochette he searched for, as a sign of tertiary syphilis. Today, tertiary syphilis is rare, but psychiatrists still examine blood samples of patients with psychosis in search for inflammatory or infectious components to rule out Lyme Disease, for example, which can present with psychotic symptoms. The reason for their vigorous search is the important consequences an inflammatory or infectious cause would have for the treatment of these patients. This symposium will provide an update on the long search for an inflammatory component in schizophrenia. We will present recent findings portraying a wide range of scientific approaches (ie proteomics, virology, cognition and RCTs) that investigate the immune hypothesis of schizophrenia. Bob Yolken will present findings from recent investigations on infectious agents in patients with schizophrenia. Faith Dickerson will present findings about the increased risk of schizophrenia associated with infectious and inflammatory markers including IgG antibodies to Toxoplasma gondii, IgG antibodies to gliadin, and C-reactive protein. The third speaker, Sabine Bahn, will provide an overview of recent findings from her lab on the expression of immunological and other protein analytes in peripheral blood, especially providing evidence of the existence of schizophrenia sub-groups. Bart van Berckel will present findings using the PK11195 tracer in PET studies, which identified increased activation of microglia cells in patients with schizophrenia, most pronounced in the medial temporal lobe. Finally, Iris Sommer will review the evidence from RCTs adding different types of anti-inflammatory components to antipsychotic treatment for patients with schizophrenia. All speakers provide evidence for an inflammatory, possibly an infectious cause, in patients with schizophrenia. This suggests that immune modulation could have beneficial effects for (some) patients with schizophrenia. Together, this symposium will provide an overview of the contemporary findings of infectious and inflammatory causes in schizophrenia and provide an update of the current literature on efficacy of anti-inflammatory drugs.

META-ANALYSES ON DOUBLE-BLIND RCTS ADDING DRUGS WITH ANTI-INFLAMMATORY PROPERTIES TO ANTIPSYCHOTIC MEDICATION

Iris Sommer¹, Roos van Westrenen, Marieke Begemann, Lot de Witte, Stefan Leucht, René Kahn²

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Background: The inflammatory hypothesis of schizophrenia is not new, but recently it has regained interest as more data suggest a role of the immune system in the pathogenesis of schizophrenia. If increased inflammation of the brain contributes to the symptoms of schizophrenia, reduction of the inflammatory status could improve the clinical picture. Lately, several trials have been conducted investigating the potential of anti-inflammatory

agents to improve symptoms of schizophrenia. This study provides an update regarding the efficacy of anti-inflammatory agents on schizophrenic symptoms in clinical studies performed so far.

Methods: An electronic search was performed using PubMed, Embase, the national institutes of Health Web site clinicaltrials.gov, Cochrane Schizophrenia Group entries in PsiTri <http://psitri.stakes.fi/EN/psitri.htm>, and the Cochrane Database of systematic reviews. Only randomized, double-blind, placebo-controlled studies that investigated clinical outcome (PANSS) were included.

Results: Our search yielded 26 double blind RCTs that provided information on the efficacy on symptom severity of the following components: aspirin, celecoxib, davunetide, EPA/DHA fatty-acids, estrogens, minocycline and N-Acetylcysteine (NAC). Of these components aspirin (mean weighted effect size (ES) 0.3, 95% CI 0.06–0.537, I²=0), estrogens (ES 0.51, 95%CI 0.043–0.972, I²=69%) and NAC (0.45, 95% CI 0.112–0.779) showed significant effects. Celecoxib, minocycline, davunetide and fatty acids showed no significant effect.

Conclusion: The results of aspirin addition to antipsychotic treatment seem promising, as does the addition of NAC and estrogens. These three agents are all very broadly active substances and it has to be investigated if the beneficial effects on symptom severity are indeed mediated by their anti-inflammatory aspects.

SERUM BIOMARKERS FOR PSYCHIATRIC DISORDERS

Sabine Bahn^{1,2}

¹Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, UK; ²University of Rotterdam

Objective: Schizophrenia is a heterogeneous disorder traditionally diagnosed using DSM criteria, which do not necessarily reflect potential differences in underlying molecular phenotypes. I will present results exploring whether schizophrenia patients can be divided into subgroups with distinct molecular alterations in growth factors or immune molecules.

Method: Multiplexed immunoassays were used to measure 147 molecules in the serum of 180 acutely ill antipsychotic-naïve schizophrenia patients and 350 controls. 50 of these molecules were related to growth factor and immune pathways and were selected for a hypothesis driven approach to identify subgroups within the schizophrenia cohort. This analysis aimed to evaluate whether each patient subgroup had specific abnormalities in molecules associated with the two molecules classes.

Results: Schizophrenia patients could be separated into two significantly distinct subgroups each of which demonstrated predominant molecular abnormalities in either growth factors or immune molecules. Immune molecules were largely increased whereas growth factor levels showed both increased and decreased levels in the respective patient subgroups. Findings were validated in an independent validation cohort.

Conclusion: This study suggests that abnormalities in growth factors and immune molecules, which have been associated reproducibly with the molecular manifestation of schizophrenia, do not coincide in the same group of patients. This may be of relevance for intervention studies that specifically target particular molecular mechanisms and could be a first step to deconstruct the complex schizophrenia syndrome based on molecular alterations.

THE MICROBIOME-THE MISSING LINK IN THE PATHOGENESIS OF SCHIZOPHRENIA

Robert Yolken¹, Faith Dickerson²

¹Johns Hopkins School of Medicine; ²Sheppard Pratt Hospital, Baltimore, MD, USA

Recent studies indicate that individuals with schizophrenia have evidence of immune activation that may contribute to disease pathogenesis. The source of this immune activation has not been identified but is likely to be related to both genetic and environmental components. Recently it has become apparent that the composition of microbes on mucosal surfaces, termed the microbiome, represents an important modulator of the immune response in humans and in experimental animals. The microbiome has been linked to the generation of an aberrant immune response and also

been shown to modulate brain development and behavior in animal model systems. We employed high throughput sequencing to characterize the complete oro-pharyngeal microbiome of 41 individuals with schizophrenia and 32 controls without a psychiatric disorder. We also examined the role of probiotics in modulating the microbiome. Interim analysis indicates that there are large differences between case and control individuals in terms of bacterial, viral, and fungal composition. Individuals with schizophrenia had increased levels of lactic acid bacteria including *Lactobacillus casei*, *Lactobacillus salivarius*, *Lactobacillus lactis*, and *Streptococcus thermophilus* as well as several other species of streptococci including *S mitis* and *S mutans*. Several of these bacteria have been associated with altered Th2 immune responses, an immunological change also noted in schizophrenia. On the other hand individuals with schizophrenia had decreased levels of many non-pathogenic bacteria such as strains of *Neisseria*, *Haemophilus*, *Prochlorococcus*, and *Shewanella*. Within the group of individuals with schizophrenia, altered levels of microorganisms were associated with an increased prevalence of the deficit syndrome as well as increased levels of intestinal immune activation as indicated by antibodies to food and intestinal antigens. In terms of fungi, individuals with schizophrenia had higher levels of pathogenic yeasts such as *Candida glabrata* and *Candida tropicalis*, but lower levels of the relatively less pathogenic *Candida albicans*. We also characterized a number of known human viruses such as Herpesviruses and Papillomaviruses, as well as bacteriophages and novel viruses. The microbiome was significantly altered by probiotic therapy, with a tendency towards normalization following treatment. Furthermore, many of the species which are increased in the oral microbiome of individuals with schizophrenia, such as streptococci, are modifiable by the administration of antibiotic medications. These studies indicate that the oral microbiome is altered in individuals with schizophrenia and that the microbiome is a potential target for novel therapies.

INFECTIONS, INFLAMMATORY MARKERS AND SCHIZOPHRENIA

Faith Dickerson, R.H. Yolken

Sheppard Pratt from Johns Hopkins University, Baltimore, MD

Background: A number of markers of infectious and inflammatory diseases have been associated with schizophrenia. However previous investigations have not yielded definitive conclusions about the role of these agents in disease pathogenesis. Previous studies have been limited by the examination of single or small groups of agents within a single population.

Methods: In this study, we examine multiple antibodies to infectious agents and food antigens as well as protein markers of inflammation in well-characterized cohorts of individuals with established schizophrenia (those with a duration of illness at least two years, N=261), individuals with a recent onset of psychosis (within the previous two years, N=106), and non-psychiatric controls (N=233). Some individuals had markers evaluated at several time points and some markers were not measured in some individuals due to limited sample volumes. Linear regression methods were used to calculate the association between the markers in recent onset and in established schizophrenia patients in comparison with controls adjusting for demographic factors such as age, race, gender, and maternal education. Regression models were also adjusted for the performance of multiple measurements in samples obtained from the same individual at different time points.

Results: For the recent onset group, significant associations were found for IgG antibodies to measles ($t=8.31$, $p<0.001$); markers of intestinal inflammation, gliadin ($t=5.90$, $p<0.001$) and bovine casein ($t=4.74$, $p<0.001$); human coronavirus ($t=2.89$, $p=0.004$); *Toxoplasma gondii* ($t=2.20$, $p=0.029$), and the group D retroviruses, Mason-Pfizer monkey virus ($t=3.97$, $p<0.001$) and murine leukemia virus ($t=3.27$, $p=0.001$). For the established schizophrenia group, significant associations were found for a general marker of inflammation, C-reactive protein ($t=7.47$, $p\leq0.001$); IgG antibodies to wheat gliadin ($t=2.58$, $p=0.010$) and another marker of intestinal inflammation, *Saccharomyces cerevisiae* ($t=-2.78$, $p<0.006$), measles ($t=2.37$, $p=0.018$), Herpes simplex virus type 2 ($t=2.56$, $p=0.011$), and human coronavirus (2.67 , $p=0.008$). No significant case control differences were found in either group for IgG antibodies to cytomegalovirus, Epstein-Barr Virus, varicella-zoster virus, or influenza A or influenza B viruses. Case control differences were not found in the levels of antibodies to Herpes simplex virus type 1. However, antibodies to this virus were associated with lower

cognitive performance in the individuals with established schizophrenia and in controls.

Conclusions: These results indicate overlap between the markers of infectious and inflammatory diseases found in recent onset psychosis and those found in established schizophrenia. Markers of intestinal inflammation were elevated in both groups but a marker of systemic inflammation, C-reactive protein, was only elevated in the established schizophrenia patients. Future studies that assess patients from the start of the illness and throughout the illness course may further identify the infectious and inflammatory factors that contribute to disease pathogenesis.

NEUROINFLAMMATION IN TEMPORAL CORTEX OF PATIENTS WITH RECENT ONSET SCHIZOPHRENIA

Bart van Berckel

VUmc, Nucleaire geneeskunde & PET research

Background: There is increasing evidence that neuroinflammation is associated with schizophrenia. Neuroinflammation is characterized by the activation of microglial cells. Increased expression of the translocator protein is a biomarker for microglial activation and can be measured in vivo using the positron emission tomography ligand ((R) -[^{11}C]PK11195). The purpose of this study was to compare the regional distribution of (R)-[^{11}C]PK11195 binding in schizophrenia patients with that in healthy controls.

Methods: (R)-[^{11}C]PK11195 binding potential was studied in ten patients with recent onset schizophrenia and ten age-matched healthy controls. Psychopathology was measured using the Positive and Negative Syndrome Scale (PANSS). Dynamic (R)-[^{11}C]PK11195 scans were acquired using an ECAT EXACT HR+ scanner. Binding potential was obtained using receptor parametric mapping in combination with supervised cluster analysis to derive the reference tissue input function. Subsequently, gray matter regions of interest (ROIs) were delineated on a T1-weighted structural MRI scan using an automatic procedure, resulting in the following regions: frontal, temporal, parietal and occipital cortex, and cerebellum. Multivariate analysis of variance (MANOVA) was used to test for differences in binding potential between patients and controls with group as the between-subjects factor, region of interest as the within-subjects factor, and age as covariate. **Results:** MANOVA showed an overall significant effect of group ($F(5)=5.7$, $p=0.005$). Schizophrenia patients showed increased (R)-[^{11}C]PK11195 binding potential in the temporal cortex ($F(1)=5.5$, $p=0.03$). There were no significant differences in mean (R)-[^{11}C]PK11195 binding potential in the other areas tested. Patients with schizophrenia had minimal to moderate symptoms of the disease at the time of PET scanning (PANSS total score = 52.5 ± 9.5).

Discussion: This study provides preliminary evidence for neuroinflammation in the temporal cortex of recent onset schizophrenia patients. This may provide an explanation for progressive tissue loss in this area in schizophrenia. Further studies are warranted to assess anti-inflammatory treatment in this disease. This is an ongoing study and results of a larger patient and control group will be presented.

Symposium

USING NEUROIMAGING TO PREDICT OUTCOMES IN SUBJECTS AT HIGH RISK

Chairpersons: Philip McGuire and Tyrone Cannon

Discussant: Ed Bullmore

Sunday, 6 April 2014

4:15 PM – 6:15 PM

Overall Abstract: A key problem in the clinical management of people at high risk for psychosis is that it is difficult to predict the prognosis for a given individual. Within a high risk sample, some subjects will make a good recovery, but others will go on to develop psychotic disorder. Recent neuroimaging research indicates that there are differences in brain structure, function, chemistry and connectivity between high risk subjects with good and poor outcomes. The aim of this symposium is to review these differences, and consider whether they can be used to facilitate the prediction of outcomes in individuals at high risk. Ty Cannon will discuss

the segregation of biomarkers of risk for psychosis from biomarker for progression to psychosis, drawing upon recent evidence from neuroimaging studies in genetic and clinical high-risk samples. Oliver Howes will present cross-sectional and longitudinal PET data on the relationship between dopamine dysfunction in high risk subjects and the risk of psychotic disorder. Alice Egerton will describe alterations in brain glutamate function in the high risk phase, and the relationship between these findings and subsequent clinical and functional outcomes. Steven Lawrie will describe how integrating network measures, MRI, clinical and genetic data in a support vector machine analysis can be used to predict outcomes at the individual subject level. Ed Bullmore will lead a discussion on the findings presented in the symposium and on the prospects for translating these into tools that can be used in clinical practice.

IDENTIFYING BIOMARKERS OF RISK FOR AND PROGRESSION TO PSYCHOSIS USING HIGH-RISK STRATEGIES

Tyrone Cannon

Yale University

The nature of schizophrenia and related psychotic disorders is such that some factors that predispose to the illness are present premorbidly but do not change over time, while other factors show evidence of progression in the pre-onset and early phases of disorder. While at least some stable markers of risk may be necessary contributors, they are unlikely to be sufficient in provoking illness expression, given that they are present pre-onset and may also appear in clinically unaffected first-degree relatives. Markers that progress during the periods immediately preceding and following onset have the potential to play mechanistic roles in the emergence of psychosis – that is, they could represent proximal, sufficient conditions for psychosis onset – but this interpretation depends on the unambiguous dissociation of such factors as reflecting the natural course of illness rather than secondary (e.g., iatrogenic) phenomena. This talk will address criteria and research strategies used in the segregation of biomarkers of risk for versus progression to psychosis, using markers of brain structure, physiology, and metabolism as assessed by neuroimaging as primary examples and drawing upon recent evidence from genetic and clinical high-risk studies. This body of work supports that view that the emergence of psychosis is marked by a dynamic and potentially reversible process that results in a reduced structural and functional connectivity in circuits involved in cognitive control, learning and memory, emotional regulation, and auditory-verbal processing.

RELATIONSHIP BETWEEN BRAIN GLUTAMATE CONCENTRATIONS AND FUNCTIONAL OUTCOME IN INDIVIDUALS AT ULTRA HIGH RISK OF PSYCHOSIS

Alice Egerton¹, James Stone², Christopher A. Chaddock³, Gareth J. Barker⁴, Ilaria Bonoldi³, Kate Merritt³, Paul Allen⁵, David J. Lythgoe⁴, Ruth L. O'Gorman^{4,6}, Philip McGuire¹

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Background: There is increasing interest in predicting functional outcome in individuals at ultra high risk of psychosis (UHR). Magnetic resonance spectroscopy (1H-MRS) studies have indicated abnormalities in glutamate concentrations in UHR individuals. In this longitudinal study, we explored the associations between glutamate levels and functional outcome in UHR individuals.

Methods: 1H-MRS spectra (PRESS – Point RESolved Spectroscopy; TE=30 msec; TR=3000 msec; 96 averages) were acquired at 3 Tesla in voxels positioned in the anterior cingulate cortex (ACC) and left thalamus of 75 UHR participants at clinical presentation and again after a mean of 18 months. 56 age and gender-matched healthy volunteers were also assessed. Spectra were analysed with LCModel version 6.14F and metabolite concentrations were corrected for voxel cerebral spinal fluid content. Overall social

and occupational functioning was assessed using the Global Assessment of Functioning (GAF) scale. The UHR group was subsequently subdivided into those that showed a >5 point decline (GAFdeclined, n=15) or improvement (GAFimproved n=22) in GAF over the study period.

Results: Relative to control, at presentation UHR subjects showed lower levels of glutamate ($t(127)=2.15$; $P=0.03$), NAA ($t(129)=3.56$; $P=0.0007$) and total choline ($t(128)=2.67$; $P=0.009$) in the thalamus. Metabolite levels were not associated with the level of overall functioning at baseline, but lower thalamic glutamate levels at baseline were associated with a subsequent decline in overall functioning over the study period (GAFdeclined versus GAFimproved, $t(35)=3.25$; $P=0.003$). Baseline ACC metabolite levels did not differ between UHR and control, or between GAFdeclined versus GAFimproved groups. However, at follow-up ACC glutamate levels were negatively correlated with GAF scores ($r=-0.37$; $df=46$, $P=0.01$) and higher in UHR subjects whose functioning had declined over the study period (GAFimproved vs. GAFdeclined $t(34)=2.75$; $P=0.01$).

Conclusions: These results suggest that lower levels of thalamic glutamate at presentation may be associated with subsequent functional decline in individuals at ultra high risk of psychosis. Conversely, higher ACC glutamate levels are present in those UHR individuals whose functioning has deteriorated. This latter result is consistent with our recent observations in established schizophrenia of elevated ACC glutamate levels in patients who have responded poorly to treatment, and a negative association between ACC glutamate levels and overall functioning in first episode psychosis. These observations may suggest that glutamatergic agents may have therapeutic benefit in improving functional outcome in UHR individuals.

CLINICAL AND IMAGING PREDICTION OF SCHIZOPHRENIA IN PEOPLE AT HIGH FAMILIAL RISK

Stephen Lawrie, E. Zarogianni, B. Tijms, A.M. McIntosh, D.G. Owens, E.C. Johnstone
University of Edinburgh

Background: Structural differences between the brains of people with schizophrenia and matched controls are highly replicated but the timing and clinical correlates of these changes remain to be established. In the Edinburgh High Risk Study (EHRS), we have followed up 162 individuals at high genetic risk of schizophrenia and 36 healthy controls over 10 years, during which time 20 with adequate data developed schizophrenia.

Methods: Participants received detailed clinical assessments and structural MRI scans of the brain at intake assessment. We developed a novel method of extracting network properties from single subjects scans, as well as a means of combining clinical, cognitive and genetic data with imaging for a Support Vector Machine (SVM) analysis, to predict subsequent schizophrenia.

Results: 17 HR subjects with one or more scans and assessments developed schizophrenia, after a mean of 929 days. None were treated with antipsychotics during the study. On standard univariate analyses, baseline pre-frontal cortical folding, schizotypy, COMT Val/Met status and psychotic symptoms were the strongest positive predictors of schizophrenia. Network properties out-performed all of these, with around 70% predictive power. Combinations of these data in the SVM analysis had up to 100% positive and negative predictive qualities.

Conclusions: Neuroimaging measures are now well established in research settings as a means of the early detection of schizophrenia. Increasingly refined analysis techniques show great promise for clinical applications.

OUTCOME IN SUBJECTS AT ULTRA HIGH RISK OF PSYCHOSIS: RELATIONSHIP TO DOPAMINERGIC FUNCTION

Oliver Howes, Paul Allen, Chris Chaddock, Alice Egerton, Isabel Valli, Philip McGuire
Institute of Psychiatry, King's College London

Background: People meeting clinical criteria for an at risk mental state show a greatly increased risk of psychosis. However, the majority do not go on to develop a psychotic disorder, although many continue to experience sub-clinical symptoms, whilst symptoms resolve in others. This presents a major clinical problem as it is not possible to identify who is at risk of

which outcome based on clinical indices. People at risk of psychosis show a number of functional and structural brain changes, including altered presynaptic dopamine function. Here we investigate the relationship between presynaptic dopamine function and clinical outcomes in people who meet clinical at risk criteria, and in people who experience long-term sub-clinical symptoms.

Method: We studied subjects at high clinical risk of psychosis who met CAARMS criteria indicating an at risk mental state and an ultra high risk of psychosis, and compared them to matched controls. All subjects received [¹⁸F]-DOPA PET imaging to index dopamine synthesis capacity, an aspect of presynaptic dopamine function known to be elevated in schizophrenia. The subjects received follow-up over at least two years to determine their clinical outcome. Additionally we compared dopamine synthesis capacity in people with long sub-clinical psychotic-like symptoms to controls.

Results: Presynaptic dopaminergic function was significantly elevated in the UHR subjects who went on to develop psychosis compared to those UHR subjects who did not develop psychosis (effect size=0.8, $p<0.05$), and was positively associated with severity of delusional thinking in the subjects who went on to develop psychosis ($\rho=0.75$, $p=0.03$) but in those who did not go on to develop psychosis ($\rho=0.004$, $p=0.9$). At follow-up there was no significant difference in dopamine synthesis capacity between those UHR subjects who continued to meet criteria at follow-up and those UHR subjects who no longer met criteria ($p=0.9$). Similarly, there was no significant difference in dopamine synthesis capacity in people with long-term sub-clinical symptoms compared to controls ($p>0.3$).

Conclusions: Elevated dopamine synthesis capacity is specifically linked to people in the prodrome of psychosis and is not seen in people who are indistinguishable on the basis of symptoms, or in people with long-term sub-clinical symptoms who have not developed schizophrenia.

Symposium

WHEN DOES THE TROUBLE START? OBESITY, DIABETES RISKS AND METABOLIC DISTURBANCES IN YOUNG PEOPLE WITH PSYCHOSIS

Chairperson: Cherrie Galletly

Discussant: Benno G. Schimmelmann

Sunday, 6 April 2014

4:15 PM – 6:15 PM

Overall Abstract: People with psychotic disorders have higher mortality rates compared to the general population. Most deaths are due to cardiovascular (CV) disease, reflecting high rates of CV risk factors such as obesity and diabetes.

Treatment with antipsychotic drugs is associated with weight gain in clinical trials. However, there is little information about how these drugs affect children and young people, and how early in the course of treatment the elevation in CV risk factors begins. This information is essential in understanding the costs and benefits of these treatments in young people, and establishing preventive and early intervention services to address physical health comorbidities.

This symposium reports both prospective and naturalistic data from children and adolescents treated with antipsychotic drugs. These studies demonstrate that adverse effects on cardiometabolic measures, notably BMI and insulin resistance, become apparent very soon after treatment is initiated. Further, children and adolescents appear to be even more sensitive to these effects than adults.

Population-wide studies are also informative. Danish data showing that young people exposed to antipsychotics have a higher risk of diabetes, compared with young people who had a psychiatric diagnosis but were not exposed to antipsychotic drugs, will be presented. In addition, an Australian comparison between a large, nationally representative sample of people with psychosis and a general population sample shows that higher rates of obesity and other cardiometabolic abnormalities are already evident in people with psychosis by the age of 25 years.

Young people living with psychosis are already disadvantaged by the demands of living with mental illness, stigma, and social factors such as unemployment and low income. The addition of obesity, diabetes and other comorbidities adds a further burden. The data presented highlights the need for careful selection of antipsychotic drugs, regular monitoring of physical health and early intervention when weight gain, glucose dysregulation, or other cardiometabolic abnormalities are detected.

DYSGLYCEMIC SIGNALS IN CHILDREN AND ADOLESCENTS TREATED WITH ANTIPSYCHOTICS FOR THE FIRST TIME

Christoph Correll¹, M. Olfson, C. Blanco, S.M. Liu, S. Wang, P. Manu, V. Olshanskiy, B. Napolitano, J.M. Kane¹, A.K. Malhotra¹, M. De Hert, J. Detraux, R. van Winkel², W. Yu

¹The Zucker Hillside Hospital, Psychiatry Research, North Shore – Long Island Jewish Health System, Glen Oaks, New York, USA; ²Maastricht University

Background: Antipsychotics, which are used increasingly in youth for psychotic and non-psychotic disorders (1) are associated with significant weight gain and metabolic abnormalities, particularly in youth (2). However, disruptions of glucose metabolism in pediatric patients has received less attention (3).

Methods: Data from the ongoing Second-generation Treatment Indications, Efficacy and Tolerability in Youth (SATIETY) study (2), a prospective inception cohort study, were collected in 272 antipsychotic-naïve youth. At baseline, week one, 4, 8, 12 and three-monthly thereafter, body composition and fasting metabolic values were assessed. Primary outcome for these analyses was insulin resistance, measured as the homeostatic model assessment (HOMA). Secondary outcomes included body weight, sex- and age adjusted BMI z-scores and lipid changes/abnormalities.

Results: In prospectively assessed antipsychotic-naïve youth (mean age: 13.9 years) body weight increased after a mean of 10.8 weeks by 19.0 (95% CI: 16.4, 21.5) lbs=15.2 (13.2, 17.2)% with olanzapine (N=45), 13.5 (10.9, 16.0) lbs=10.4 (8.5, 12.3)% with quetiapine (N=36), 11.9 (10.7, 13.1) lbs=10.4 (9.4, 11.3)% with risperidone (N=135), and 9.9 (8.2, 11.5) lbs=8.1 (7.0, 9.5)% with aripiprazole (N=41). Weight gain >7% occurred in 84.4% on olanzapine, 64.4% on risperidone, 58.4% on aripiprazole, and 55.6% on quetiapine. Increasing insulin resistance (HOMA) was not significantly associated with sex, age, race, diagnostic group or leptin: fat mass ratio at baseline. HOMA change was significantly associated with various measures of body weight increase, being the most associated with fat mass change ($p=0.0001$). Individually, only olanzapine was associated with significant HOMA increase at 3 months, with glucose increase being mediated by olanzapine dose >10 mg/day ($p<0.05$). 6-month data on weight gain and metabolic effects as well as data on the predictive value of week 1 changes in lipid and glucose metabolism will become available and will also be presented.

Conclusions: Antipsychotics are associated with a relevant, but differential risk for insulin resistance and diabetes risk, especially when used early on. Careful choice of antipsychotics, proactive monitoring, risk factor identification, and the development of novel treatments for the amelioration and, ideally, prevention of glucose metabolism perturbations in antipsychotic-treated youth and adults are urgently needed.

RESULTS FROM THE NIMH-FUNDED METABOLIC EFFECTS OF ANTIPSYCHOTICS IN CHILDREN (MEAC) STUDY

John W. Newcomer

Charles E. Schmidt College of Medicine, Florida Atlantic University

Background: Rates of antipsychotic prescription in children have increased, largely driven by off-label use for disruptive behavior. Antipsychotics have well characterized effects on the development of obesity and cardiometabolic risks in adults, but this aspect of safety and tolerability has been less well studied in treatment naïve individuals, in particular for off-label uses such as the treatment of disruptive behavior in children, where non-randomized trials have shown clinical efficacy. The randomized, NIMH-funded Metabolic Effects of Antipsychotics in Children study (MEAC, PI Newcomer, MH072912) characterized the metabolic effects of 12 weeks of antipsychotic treatment in a population where antipsychotics are commonly used to treat disruptive behavior across a range of diagnoses, using gold-standard metabolic techniques.

Methods: Antipsychotic-naïve youth ages 6-18 with clinically significant aggression/irritability in the setting of one or more DSM-IV diagnoses indicating a disruptive behavior disorder were randomized to 12 weeks of treatment with aripiprazole, olanzapine or risperidone. Baseline and 12 week measures included body composition analysis with Dual Energy X-ray Absorptiometry (DEXA), a single stage hyperinsulinemic-euglycemic glucose clamp using stable isotopomer tracing, anthropomorphic assessment and plasma measures. Primary endpoints were change in whole body and

abdominal adiposity, and whole-body and tissue-specific insulin sensitivity. ANCOVA was used to test effects of time and treatment condition on adiposity and insulin sensitivity. Regression analyses were performed to test the predictive effect of baseline DEXA-measured total % body fat on baseline insulin-stimulated changes in glucose and lipid metabolism during treatment.

Results: MEAC participants had a baseline prevalence of overweight or obesity of 34% (13% overweight, 21% obese) that was similar to the 32% of overweight (15%) or obese (17%) youth in the general population according to 2008 NHANES data. During 12 weeks of initial antipsychotic exposure, differential effects of treatment were observed on measures of adiposity and other endpoints. Specifically, time by treatment condition effects were detected on DEXA %fat ($F[2,123]=8.81, p<0.0001$). Pooling treatment groups to test the relationship of baseline and change in adiposity to baseline and change in insulin sensitivity, respectively, the magnitude antipsychotic treatment-induced increases in adiposity over 12 weeks of treatment were associated with the magnitude of adverse changes in SI at both adipose ($F[1,95]=4.973, p=0.028$) and hepatic ($F[1,95]=2.839, p=0.095$) tissues. Importantly, treatment resulted in marked improvement in Aberrant Behavior Checklist irritability/aggression subscale scores, with a mean decrease of 16.59 points ($p<0.0001$).

Conclusions: Adverse metabolic effects of antipsychotic are rapidly detectable within 12 weeks of treatment, but importantly occur within the context of significant clinical benefit for disruptive behavior. Randomized clinical trials like the MEAC study, which incorporate adaptive or practical design elements to enhance generalizability to real-world prescribing practices, can be valuable in understanding safety and tolerability issues, developing strategies for effective risk mitigation, and in assessment of costs and benefits of treatment. Data regarding primary outcomes in the NIMH-funded MEAC study, including time by treatment group and main effect of time analyses on adiposity and insulin sensitivity measures, are unique and unpublished.

RISK FACTORS FOR DEATH AND DISABILITY IN YOUNG PEOPLE WITH PSYCHOSIS

Cherrie Galletly^{1,2}, Debra L. Foley³, Andrew Mackinnon³, Gerald F. Watts⁴, Jonathan Shaw⁵, Dianna Magliano⁵, David Castle⁶, John McGrath⁷, Anna Waterreus⁸, Vera A. Morgan⁸

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People with psychotic disorders die 10-20 years prematurely, so would be expected to have higher rates of the risk factors associated with common causes of death. However, whilst it is well known that risk factors such as smoking and metabolic syndrome are more prevalent in people with psychotic disorders than in the general population, much less is known about when in the lifespan these risk factors develop. The World Health Organisation has identified 10 leading risk factors for death and disability in high income countries, and we used this as a framework to examine the physical health of young people living with psychosis in Australia.

Methods: The second Australian survey of psychosis was a population based survey of Australians aged 18 to 64 years with a psychotic disorder. A total of 1087 men (60%) and 738 women (40%) participated. Their mean age was 38.36 (SD 11.16) years; 773 (42%) were aged 18-34 years and 1052 (58%) 35-64 years. Seventy percent (N=1285) of participants provided fasting blood samples. This large sample size enabled us to compare the prevalence of the WHO-defined risk factors in younger vs older participants. We were also able to compare people with psychosis with the general population sample collected for the Australian Diabetes, Obesity and Lifestyle Study (AusDiab), a large national study of risk factors for diabetes and cardiovascular disease.

Results: Young people living with psychosis had high rates of most WHO-defined risk factors for death and disability. Their rates of tobacco use were more than double the general population, and virtually all were sedentary or had very low rates of physical activity. Most did not eat daily recommended amounts of fruit and vegetables. Obesity was common, and comparison with the AusDiab sample showed that the psychosis population had higher rates of obesity even from the age of 25 years. In addition, from age 25 years, people with psychosis had significantly higher diastolic blood pressure, triglycerides and glucose (in women), and lower HDL-cholesterol. There were gender differences, for example tobacco use was more common in young men whilst young women were more likely to meet criteria for at-risk waist circumference.

Conclusions: Many of the risk factors for premature death are present from a young age in people with psychosis. It is therefore likely that people with these disorders will continue to experience poor physical health and premature mortality, unless measures are put in place to address these risk factors. Such measures need to be an integral component of early intervention services for young people with psychotic disorders, and to continue to be provided as an essential part of comprehensive mental health care across the lifespan.

WEIGHT GAIN AND METABOLIC CHANGES AFTER SIX MONTHS OF TREATMENT WITH SECOND-GENERATION ANTIPSYCHOTICS IN ANTIPSYCHOTIC-NAÏVE PEDIATRIC AND ADULT PATIENTS

Celso Arango¹, Diaz Caneja Covadonga, Laura Pina, Cecilia Tapia,

Jessica Merchán, David Fraguas, Mara Parelada

¹Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón Universidad Complutense

Background: Second-generation antipsychotics (SGAs) have been associated with increased risk of metabolic adverse events such as weight gain, insulin resistance, dyslipidemia and metabolic syndrome. Pediatric patients seem to be at higher risk of some of these adverse effects than adults, but empirical data on differential metabolic changes in antipsychotic-naïve youth and adults are still scarce.

Aims: To compare weight gain and metabolic changes between a sample of antipsychotic-naïve adult and pediatric patients and to explore the effect of age on these metabolic changes.

Methods: Naturalistic longitudinal study comparing anthropometric (weight, body mass index (BMI) Z-scores) and metabolic changes (fasting cholesterol, LDL cholesterol, HDL cholesterol, fasting glucose, insulin and Homeostasis Model of Insulin Resistance (HOMA-IR)) after 6 weeks, 3 and 6 months of treatment with SGAs in antipsychotic-naïve (exposure to SGAs \leq 10 days) pediatric and adult patients.

Results: 204 patients (60 adolescent patients, age: 15.7 ± 1.3 years, 68.3% male and 144 adult patients, age: 44.7 ± 18.1 years, 54.2% male) comprised the study sample. At baseline, adults presented with significantly higher fasting glucose ($p < 0.001$), HbA1c ($p = 0.008$), triglycerides ($p < 0.001$), total cholesterol ($p < 0.001$), LDL cholesterol ($p < 0.001$) and HOMA-IR ($p = 0.02$). After six months of treatment with SGAs, significant increases were found in weight and BMI Z-score both for adolescent ($p < 0.001$) and adult patients ($p < 0.001$). Adolescents experienced greater weight gain (7.3 vs. 3.5 kg; $t = -2.53$, $p = 0.02$) and greater increase in BMI Z-score (0.57 vs. 0.3, $t = -2.34$, $p = 0.02$). A significant age group-by-time interaction was found for changes in weight ($F = 7.13$, $p = 0.009$) and BMI Z-score ($F = 4.64$, $p = 0.03$). In adolescents, but not in adults, most weight gain occurred within the first three months of treatment, with no significant increases in weight or BMI Z-score between month 3 and 6. Age was negatively correlated with increase in BMI Z-score at month 6 ($r = -0.401$, $p < 0.001$). In the pediatric, but not in the adult group, a positive correlation was found between increase in BMI Z-score and increase HOMA-IR at month 6 (pediatric patients: $r = 0.661$, $p = 0.003$, adult patients: $r = 0.175$, $p = 0.194$). No significant age group-by-time interaction was found for changes in the lipid profile (triglycerides ($F = 0.002$, $p = 0.961$), total cholesterol ($F = 0.058$, $p = 0.811$), LDL cholesterol ($F = 0.294$, $p = 0.589$) or HDL cholesterol ($F = 2.11$, $p = 0.150$)). There were also no significant differences in the percentage of patients developing metabolic syndrome at month 3 (9.5% of adolescents vs. 11% of adults, $p = 0.789$) and 6 (7.7% of adolescents vs. 11.8% of adults, $p = 0.256$).

Conclusion: The effect of SGAs on weight and some metabolic changes appears to be age-dependent, with younger patients experiencing greater

and more rapid increases in BMI Z-scores during the first six months of treatment and greater impact of weight gain on the development of insulin resistance.

PHARMACEUTICAL PIPELINE SESSION

Chairperson: John Kane

Sunday, 6 April 2014

4:15 PM – 6:15 PM

EFFICACY AND SAFETY OF ADJUNCTIVE BITOPERTIN VERSUS PLACEBO IN SUBJECTS WITH PERSISTENT PREDOMINANT NEGATIVE SYMPTOMS OF SCHIZOPHRENIA TREATED WITH ANTIPSYCHOTICS – UPDATE FROM THE SEARCHLYTE PROGRAMME

Dragana Bugarski-Kirola¹, Celso Arango², W. Wolfgang Fleischhacker³, Rodrigo Bressan⁴, Henry Nasrallah⁵, Stephen Lawrie⁶, Thomas Blaettler¹, George Garibaldi¹, Carol Reid⁷, Stephen Marder⁸

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Background: Schizophrenia is a chronic and debilitating disorder characterized by three categories of symptoms – positive, negative and cognitive. Available antipsychotics have limited impact on negative symptoms and do not fully suppress positive symptoms. Thus, a significant unmet medical need remains in the pharmacotherapy of schizophrenia. NMDA receptor hypofunction is thought to contribute to all core symptoms of schizophrenia. Bitopertin is an oral investigational glycine reuptake inhibitor that may enhance NMDA receptor functioning. The effect of bitopertin on negative symptoms of schizophrenia was assessed in a placebo-controlled Phase II study. Results from this study indicated efficacy at 10 and 30 mg and lack thereof at 60 mg. The SearchLyte phase III trial program was undertaken to investigate the efficacy and safety of adjunctive bitopertin treatment in patients with persistent and predominant negative symptoms (3 studies) and those with sub-optimally controlled symptoms (3 studies) of schizophrenia.

Methods: FlashLyte (NCT01192867; NN25310) and DayLyte (NCT01192906; WN25309) are multi-centre, randomized, 24 week, double-blind, parallel-group, placebo-controlled studies to evaluate the efficacy and safety of adjunctive bitopertin in stable patients with persistent, predominant negative symptoms of schizophrenia treated with antipsychotic drugs. For both studies, participants were aged ≥ 18 years with a DSM-IV-TR diagnosis of schizophrenia, and a score ≥ 40 on sum of the 14 Positive and Negative Syndrome Scale (PANSS) negative symptoms and disorganized thought factors (items scored 1–7 for a maximum possible score of 98). They were clinically stable for 6 months prior to study entry and had antipsychotic treatment stability. After clinical stability was confirmed, patients were randomized 1:1:1 to receive bitopertin 10 mg, 20 mg or placebo (FlashLyte) or bitopertin 5 mg, 10 mg or placebo (DayLyte) once daily for 24 weeks. The primary efficacy endpoint was the change from baseline in PANSS negative symptoms factor score (NSFS) measured at Week 24. The key secondary endpoint was mean change from baseline in Personal and Social Performance (PSP) total score at Week 24. In addition, analyses of PANSS NSFS and PSP for the biomarker CFHR1 high subpopulation were defined as key secondary analyses.

Results: In January it was announced that the first two studies (FlashLyte and DayLyte) conducted in patients with persistent and predominant negative symptoms did not meet their primary endpoints. The results of both studies will be presented at SIRS (Blaettler et al; Arango et al).

Discussion: In these studies conducted in patients with persistent predominant negative symptoms receiving antipsychotics there was no statistically significant effect of adjunctive bitopertin treatment at doses of 5, 10 or 20 mg compared with placebo on primary or key secondary endpoints after 24 weeks of treatment. Bitopertin was well tolerated.

RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED, PHASE 2/3 STUDY TO DETERMINE THE SHORT-TERM (6-WEEK) AND LONG-TERM (6 MONTH) COGNITIVE AND ANTI-PDYCHOTIC EFFICACY, SAFETY AND TOLERABILITY OF CYP-1020 COMPARED TO RISPERIDONE

Jonathan Rabinowitz
Bar Ilan University

Background: CYP-1020 (aka BL-1020) is a γ -aminobutyric acid (GABA) enhanced antipsychotic that combines dopamine antagonism with GABA agonist activity. A previous study found possible pro-cognitive effects of CYP-1020 (20–30 mg) as compared to placebo and risperidone (2–8 mg/d) in chronic schizophrenia. The objective of the current study was to test the hypothesis that CYP-1020 would have pro-cognitive benefits as compared to risperidone after 6 weeks of treatment in patients experiencing acute exacerbations of schizophrenia. Secondary objectives included evaluating pro-cognitive benefits after 12 and 24 weeks and to compare antipsychotic efficacy of the treatments after 6, 12 and 24 weeks.

Methods: Two hundred and sixty nine patients, out of 450 planned, aged 18 to 50 meeting criteria for DSM-IV-TR diagnosis of chronic schizophrenia were randomized double-blind to receive CYP-1020 (15–35 mg per day), or risperidone (2–6 mg/day) and treated for up to 24 weeks. The primary efficacy measure, MCCB (MATRICS Consensus Cognition Battery) and secondary measures, UPSA-B (University of California Performance-Based Skills Assessment-Brief Version) and PSP (Personal and Social Performance scale), were administered at baseline and week 6, 12 and 24 or end point. The PANSS and CGI-S were administered at all study weeks except for week 1. Readiness for discharge was rated at weeks 2, 4, 6 and 8. Patients underwent weekly assessments of vital signs, safety which included the SAS (Simpson Angus Scale), AIMS (Abnormal Involuntary Movement Scale), BAS (Barnes Akathisia Scale) and inventory of concomitant medications.

Results: The study was terminated after the interim analysis suggested that the study would not reach its primary endpoint. There was no statistically significant difference on cognitive benefits on the MCCB total composite score. However, on the Mayer-Salovey-Caruso Emotional Intelligence Test, which was used to measure social cognition, and included in the MCCB total score, differences were found favoring CYP-1020. This difference was noticeable starting at week 12, and reached significance ($p=0.051$) at week 24 endpoint. On the PANSS there was a significant treatment by country interaction with CYP-1020 group showing significantly greater reduction on the PANSS total score than Risperidone group in Romania at weeks 6, 12 and 24. There were no significant or treatment group differences on the CGI, PSP, UPSA or RDQ. There were no notable differences on vital signs, TAE's, SAE's, SAS, BAS and AIMS. Increase in prolactin was substantially lower in CYP-1020 as compared to risperidone.

Discussion: The current study does not support a superiority of CYP-1020 over risperidone on general cognition. However, results suggest a superiority on social cognition. It should be noted that social cognition is not highly correlated with general cognition. There is an emerging literature that examines the role of antipsychotics in improving social cognition. This could be a future area to explore for CYP-1020.

ITI-007, A NEW APPROACH TO THE TREATMENT OF SCHIZOPHRENIA

Kimberly E. Vanover, Robert E. Davis, Sharon Mates
Intra-Cellular Therapies, Inc

Background: ITI-007 represents a new approach to the treatment of schizophrenia and other neuropsychiatric disorders through the dose-dependent modulation of serotonergic, dopaminergic and glutamatergic neurotransmission. ITI-007's unique pharmacological profile translates into broad efficacy as a monotherapy against a myriad of psychiatric symptoms designed to improve positive and negative symptoms, reduce depression, and enhance social function. ITI-007 is a potent 5-HT2A receptor antagonist, a dopamine phosphoprotein modulator (DPPM) with activity as a pre-synaptic partial agonist and post-synaptic antagonist at dopamine D2 receptors, a glutamate GluN2B receptor phosphoprotein modulator and a serotonin reuptake inhibitor. ITI-007 has shown efficacy in animal models predictive of antipsychotic and antidepressant efficacy with reduced liability for motoric side effects. At low doses evaluated in a Phase 2 clinical trial in patients with primary insomnia, ITI-007 improved sleep maintenance.

Low doses are also predicted to reduce behavioral disturbances associated with dementia, including Alzheimer's disease. Most recently, ITI-007 was evaluated in a randomized, double-blind, placebo- and active-controlled Phase 2 clinical trial designed to evaluate the efficacy and safety of ITI-007 in patients with acute schizophrenia.

Methods: Patients with an acutely exacerbated episode of schizophrenia were randomized to receive one of four treatments in a 1:1:1:1 ratio: 60 mg ITI-007, 120 mg ITI-007, 4 mg risperidone (positive control) or placebo. Patients received study treatment orally once daily in the morning for 28 days. The primary endpoint was change from baseline on the total Positive and Negative Syndrome Scale (PANSS) on study Day 28. Secondary endpoints included weekly assessments of the total PANSS as well as its subscales. Safety and tolerability were assessed.

Results: ITI-007 at a dose of 60 mg, but not 120 mg, improved schizophrenia as measured by change from baseline on the total PANSS score, compared to placebo, after 28 days of once daily administration in the morning. Moreover, ITI-007 (60 mg) demonstrated a differentiating response profile with improvements across a wide range of symptoms consistent with improved social function. ITI-007 was safe and well tolerated, especially at 60 mg, with no signal of extrapyramidal side effects, including no signal for akathisia, and no hyperprolactinemia with a favorable metabolic profile.

Discussion: ITI-007 demonstrated antipsychotic efficacy in a well-controlled Phase 2 clinical trial. Moreover, robust efficacy was observed at a moderate dose of ITI-007, 60 mg, which was safe and well tolerated, with a response profile consistent with improved social integration and enhanced social function. The higher dose of ITI-007 produced frequent sedation when administered in the morning and might be more appropriately administered in the evening. ITI-007 represents a new approach to the treatment of schizophrenia and other neuropsychiatric and neurological disorders.

RESULTS OF A PHASE 2B CLINICAL TRIAL OF TC-5619, A SELECTIVE ALPHA 7 NEURONAL NICOTINIC RECEPTOR (NNR) AGONIST, IN THE ADJUNCTIVE TREATMENT OF NEGATIVE SYMPTOMS AND COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

David Hosford
Targacept, Inc.

Background: There are no approved medicines to treat negative symptoms or cognitive dysfunction in people with schizophrenia. These are common features of the condition that often prevent those whose positive symptoms are well-controlled from resuming or achieving their premorbid potential. TC-5619, a selective alpha 7 NNR agonist, showed statistically significant benefit in preclinical models of cognition and negative symptoms; and also showed statistically significant benefit in cognitive and negative symptoms in an early phase 2 adjunctive clinical trial in schizophrenia that was conducted in the US and India.

Methods: This phase 2B clinical trial was a double-blind, randomized, parallel group, fixed dose, placebo-controlled trial comparing TC-5619 vs. placebo in the adjunctive treatment of negative symptoms or cognitive dysfunction in well-controlled outpatients with schizophrenia. Sixty-six sites in the US, Russia, Ukraine, Hungary, Romania and Serbia randomized 477 patients into a 24-week treatment period in which they received either TC-5619 (5 mg or 50 mg po qd) or placebo in a 1:1:2 ratio. All atypical antipsychotics were permitted except clozapine. The primary endpoint, negative symptoms, was measured using the Scale to Assess Negative Symptoms (SANS), and the key secondary endpoints, cognition and functional ability, were measured using the Cogstate Schizophrenia Test Battery (CSTB) and the UCSD Performance-Based Skills Assessment-Brief version (UPSA-B). A variety of other endpoints included global clinical outcome, adverse events, vital signs, physical exam, laboratory and ECG measurements, movement disorders, suicidality, depression, and tobacco craving.

Results: The majority of the randomized subjects were tobacco users and the demographic profile was consistent with other trials in this population. None of the primary, key secondary or secondary efficacy outcome measures showed a statistically significant benefit favoring either dose of TC-5619. Withdrawals of any kind including those due to adverse events were low, and there were few serious adverse events. The previously established safety and tolerability profile was not altered by any unanticipated findings.

Discussion: This well-conducted and robust phase 2B study did not confirm benefits of TC-5619 in negative or cognitive symptoms, but it did confirm that the compound was generally safe and well-tolerated. Reasons for the lack of benefit do not appear to include dose selection, site performance, or subpopulation factors.

DOPAMINE-1 RECEPTOR STIMULATION IN SCHIZOPHRENIA: A RANDOMIZED, CLINICAL TRIAL

Ragy Girgis

Columbia University Medical Center

Background: Cognitive deficits are a core feature of schizophrenia. Evidence from preclinical and human studies suggest that cortical hypodopaminergia may contribute to cognitive deficits in schizophrenia. The purpose of this trial was to test whether stimulation of dopamine-1 receptors via a full, selective agonist of the dopamine-1 receptor (DAR-0100A) would improve cognitive deficits in schizophrenia.

Methods: We first performed a phase I, single, ascending dose trial of DAR-0100A in order to identify a maximal tolerated dose of DAR-0100A and to characterize the safety of DAR-0100A. We then randomized 49 clinically stable individuals with schizophrenia to 3 weeks of intermittent treatment with high dose (15 mg), low dose DAR-0100A (0.5 mg) or placebo (normal saline). fMRI BOLD imaging was used to evaluate the effects of drug administration on patterns of brain activity during performance of a working memory task. Effects on cognition were also assessed using the N-Back, MATRICS, and CogState batteries. Secondary objectives were to investigate the effects of DAR-0100A on negative symptoms.

Results: The maximal tolerated dose of DAR-0100A as identified in the phase I trial was 15mg over 30 minutes, limited by hemodynamic side effects. In addition, scores on the N-Back working memory task (adjusted hit rate) improved after administration by 8.5% (1-Back; p=0.08) and 61% (3-Back; p=0.03). Data from the double blind, randomized, placebo controlled phase II trial are currently being analyzed and will be presented at the meeting.

Discussion: As this drug was limited by its pharmacokinetic profile, better D1 agonists are needed to more fully test the efficacy of this mechanism for cognitive enhancement in schizophrenia.

EARLY CLINICAL RESULTS OF THE PHOSPHODIESTERASE 10 INHIBITOR OMS643762 IN DEVELOPMENT FOR THE TREATMENT OF SCHIZOPHRENIA AND HUNTINGTON'S DISEASE

Albert Yu

Omeros Corporation

Background: Phosphodiesterase 10 (PDE10) is a cyclic nucleotide phosphodiesterase that is selectively expressed in brain, in particular in the striatum, with limited expression in the periphery. PDE10 plays a key role in the signalling of medium spiny neurons in the striatum and targeting its activity may have utility in disorders affecting the basal ganglia circuit. OMS643762 is an orally available small molecule that potently and selectively inhibits PDE10. OMS643762 is in clinical development for the treatment of central nervous system disorders including schizophrenia and Huntington's disease.

Methods: Three clinical trials were conducted in the early development program: a Phase 1 first-in-man trial in healthy subjects, a Phase 1 positron emission tomography (PET) trial in healthy subjects to evaluate PDE10 target occupancy, and a Phase 2a trial in psychiatrically stable schizophrenia subjects. The objectives of these trials were to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of OMS643762 administered as a single dose or multiple doses for up to 14 days. Safety was evaluated by adverse events, vital signs, laboratory tests, and electrocardiograms. The concentration of OMS643762 was measured using a validated liquid chromatography/mass spectrometry/mass spectrometry assay. PET imaging with [¹⁸F]MNI-659, a highly specific PDE10 PET ligand, was completed at baseline and on the last day of dosing to determine target occupancy.

Results: Participants: The three trials enrolled a total of 149 subjects, consisting of 116 healthy male subjects and 33 schizophrenia subjects, with 125 subjects receiving OMS643762 and 24 subjects receiving placebo.

Safety: Single- and multiple-dose administration of OMS643762 were well tolerated. Adverse events were mild or moderate in severity and resolved during dosing. Adverse events that were dose-related included somnolence, jaw tightness, and restlessness. The tolerability of OMS643762 was similar between healthy and schizophrenia subjects and unaffected by concomitant antipsychotic medications. There were no clinically significant effects on other safety measures.

Pharmacokinetics: OMS643762 displayed linear pharmacokinetics over the dose range evaluated with a half-life that supports once-a-day dosing. OMS643762 was detected in cerebrospinal fluid at concentrations that are consistent with extent of plasma protein binding. The pharmacokinetic parameters were similar in schizophrenia subjects with or without concomitant antipsychotic medications.

Pharmacodynamics: PDE10 target occupancy in the striatum increased with dose up to approximately 70% at the highest dose. Mean plasma concentration during the PET scan similarly increased with dose.

Discussion: OMS643762 administration is well tolerated in healthy and schizophrenia subjects; tolerability is not impacted by concomitant antipsychotic medications. OMS643762 displays linear pharmacokinetics with a long half-life that supports once-a-day dosing. OMS643762 achieves dose-dependent target occupancy in the striatum, with a high of approximately 70% occupancy at a well-tolerated dose. These data support continued development of OMS643762 for the treatment of schizophrenia and other neuropsychiatric disorders.

EFFICACY AND SAFETY OF NOVEL DOPAMINE SEROTONIN STABILIZER RP 5063 IN ACUTE SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

Marc Cantillon

Reviva Pharmaceuticals

Background: RP5063 is a novel dopamine-serotonin system stabilizer with an optimum balance of potent partial agonist activity at the dopamine D₂, D₃, D₄, serotonin 5-HT_{1A} and 5-HT_{2A} receptors, and antagonist activity at the serotonin 5-HT₆ and 5-HT₇ receptors. Positive initial PK, safety and efficacy in stable outpatient schizophrenia patients has already been presented.

Methods: REFRESH, the Phase 2 study was a global randomized placebo-controlled inpatient trial. RP5063 (15 mg, 30 mg and 50 mg) was administered to subjects with an acute exacerbation of schizophrenia or schizoaffective disorder and efficacy was measured by change from baseline to week 4 on the Positive and Negative Syndrome Scale (PANSS). A total of 234 patients randomized to one of the three doses of RP5063 (15 mg/day or 30 mg/day or 50 mg/day), placebo, or aripiprazole (15 mg/day) in a ratio of 3:3:3:2:1. Safety was assessed by blood labs, centralized ECG, EPS scales and standard AE reporting throughout the study.

Results: RP5063 showed remission level superior efficacy across all three doses (15, 30, and 50 mg) tested when compared to aripiprazole (15 mg), an assay sensitivity comparator or placebo. RP5063 was well tolerated at all three dose levels and no clinically relevant adverse effects, tolerability or safety issues were reported. RP5063 showed highly predictable and linear pharmacokinetic profile, with a PK-PD profile showing no demographic or ethnic contributing factors. Furthermore, depression and cognition also showed trends toward improvement despite being a small and short study. All the three dose groups of RP5063 were safe and well tolerated by the study subjects. Body weight, cardiac assessments, metabolic factors and EPS measurements were not different from placebo. Serum prolactin levels significantly decreased in RP5063 groups and returned higher levels upon restarting patients' former antipsychotics.

Discussion: RP5063 showed robust efficacy and safety in the Phase 2 trial, Phase 3 trials are now under development at various global clinical trial sites including India. With a unique receptor balanced profile and efficacy across psychotic, anxiety-depressive and cognitive domains of schizophrenia/schizoaffective disorder, this novel agent may offer significant therapeutic improvement over current treatments.

DOPAMINE D₃ RECEPTOR OCCUPANCY AND D₃ RECEPTOR-MEDIATED ACTIONS OF CARIPRAZINE, A DOPAMINE D₃/D₂ RECEPTOR PARTIAL AGONIST ANTIPSYCHOTIC CANDIDATE

Ashok Rakshit¹, Suresh Durgam¹, Nika Adham¹, István Gyertyán², Béla Kiss², Yih Lee¹, Mark Slifstein³, Ragy Gergis³, Anissa Abi-Dargham³

¹Forest Research Institute, Jersey City, NJ, USA; ²Gedeon Richter Plc, Budapest, Hungary; ³Department of Psychiatry, Columbia University, New York, NY, USA

Abstract not received.

Plenary Session
BEHAVIORAL AND IMAGING TRANSLATIONAL PARADIGMS IN DRUG DEVELOPMENT

Chairpersons: Holly Moore and Barbara Sahakian

Monday, 7 April 2014 8:30 AM – 12:00 PM

Many would agree that we are currently in the “Decade of Neuroconnectomics”. Advances in genetic, electrical and biochemical engineering have made it possible to map and measure function in specific circuits in animal models with levels of selectivity and precision never before achieved. Complementing this revolution are advances in brain stimulation and imaging methods that allow us to map interactions between anatomically defined regions of the human brain, and, further, examine how these maps change with psychiatric disease. But as we embark on this journey into new territories opened by these new technologies, it is valuable to review what we already think we know from the previous century of neuroanatomical and electrophysiological studies of the brain circuits most commonly implicated in psychiatric disorders. The goal of this talk will be to take iconic cortico-basal ganglia and limbic circuits known to mediate appetitive motivation, fear, memory and decision-making and use the structural and functional connectivity to review “motifs of connectivity” within these systems.

Symposium
DEBATE: ATTENUATED PSYCHOSIS SYNDROME IS A NEEDED DIAGNOSTIC CATEGORY

Chairperson: Robin M. Murray

Discussant: Robin M. Murray

Monday, 7 April 2014 2:00 PM – 4:00 PM

Overall Abstract: There is an explosion of new information relating to the overlapping constructs of at risk mental states and attenuated psychosis syndrome. Controversy is intense and the DSM-5 handling of the issue hotly contested. A debate format provides an opportunity for an interesting, and perhaps entertaining, sharing of information and perspective. The debate question is: Attenuated Psychosis Syndrome: a New Disorder is Needed. Fusar-Poli will answer yes and detail validating data. He will establish that APS identifies persons with a mental disorder, and that vulnerability for progression to a psychotic disorder is high. van Os will answer no and show how the disorders associated with APS can be addressed with current classification and argue future progress depends on a different conceptual framework than that offered by APS. Carpenter will state why APS is essential to therapeutic discovery. Castle will state the case for advances in therapeutics being supported without the need for a new classification.

ATTENUATED PSYCHOSIS SYNDROME = COMMON MENTAL DISORDER WITH SUBTHRESHOLD PSYCHOSIS

Jim van Os

Maastricht University Medical Centre

Traditionally, phenomena such as delusions and hallucinations (hereafter, psychosis) were thought to be diagnostic indicators of psychotic disorders such as schizophrenia. However, psychotic symptoms are more common than was previously realised. They are present – at various degrees of

severity – in about 5% of the general population who are not seeking help; in about 25% of people with (non-psychotic) common mental disorders, such as anxiety and depression; and in around 80% of patients with psychotic disorders. Low grade psychotic phenomena in those not seeking help are associated with an increased relative risk – albeit low absolute risk – of later psychotic disorder, and, more surprisingly, also of non-psychotic mental disorder. Furthermore, low grade psychotic symptoms in people with common mental disorders predict a poorer prognosis, similar to the more severe course traditionally associated with psychotic illness. Therefore, the boundaries between normal mentation, common mental disorder, and schizophrenia become blurred if positive psychotic phenomena are used as a distinguisher. It is important to deconstruct the concepts of “ultra high risk” and “transition” in relation to psychotic illness. Much of the literature that promotes the idea of a state of ultra high risk of progression to psychotic illness reduces this complex psychopathological reality to an unrealistically clear picture. The implicit assumption is that this state is a “schizophrenia light” condition that is a reliable and valid binary concept, and that treatment of this condition can prevent the equally valid simple concept of transition to frank psychosis. Frank psychosis is defined according to an (arbitrary) cut off of psychosis severity or a (similarly arbitrary) diagnostic concept of “schizophrenia spectrum.” However, reality may not be quite so black and white. Firstly, definitions of transition, which are usually arbitrarily applied, vary between centres. These definitions basically express the shift from a little or moderate expression of psychosis to severe expression of psychosis. However, the expression of psychosis naturally fluctuates in intensity, severity, duration, and functional impact within individuals over time. Temporary amelioration of psychosis in people with existing psychotic disorder at the time of the baseline assessment may cause them to be wrongly assigned to the ultra high risk group rather than the psychotic group. Secondly, populations in studies of ultra high risk groups consist largely of people already diagnosed with mental disorders (mostly common mental disorders such as anxiety and depression) who seek help at mental health services. Thus, “transition” is not the transition from health to disorder, but mostly from a common mental disorder with a certain degree of psychosis to one with a greater degree of psychosis. Given the flexibility of diagnostic criteria in psychiatry, and the large degree of heterogeneity within groups of patients with a certain diagnosis, a new diagnosis within the schizophrenia spectrum can often be applied in the context of such transitions. Thirdly, given the arguably arbitrary distinction between transition and non-transition, it is not surprising that prospective research has established that transition is not relevant to longer term outcome. So what can we conclude? It may make sense to focus on treating psychosis in non-psychotic disorders. For patients diagnosed as having common mental disorder with psychotic symptoms of varying severity, which is usually associated with poorer outcome, early treatment of psychotic symptoms may have beneficial effects on the course of psychosis expression.

THE PSYCHOSIS HIGH RISK STATE: IS IT VALID?

Paolo Fusar-Poli¹, S. Borgwardt, A. Bechdolf², J. Addington, A. Riecher-Rössler³, F. Schulte-Lutter, M. Keshavan⁴, S. Wood⁵, S. Ruhrmann⁶, L.I. Seidman⁷, L. Valmaggia, T. Cannon⁸, E. Velthorst, L. de Haan⁹, B. Cornblatt, I. Bonaldi¹⁰, M. Birchwood¹¹, T. McGlashan, W.T. Carpenter¹², A. Yung¹³

¹Department of Psychiatry Studies, Institute of Psychiatry, King's College London, London, UK; ²Klinik für Psychiatrie, Psychotherapie und Psychosomatik, Vivantes Klinikum am Urban, Akademisches Lehrkrankenhaus Charité-Universitätsmedizin Berlin, Germany; ³University of Basel;

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⁵University of Birmingham; ⁶Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany; ⁷Harvard University; ⁸Yale University; ⁹Dept. of Psychiatry, Academic Medical Centre, Amsterdam, The Netherlands; ¹⁰King's College London; ¹¹School of Psychology, University of Birmingham; ¹²University of Maryland School of Medicine; ¹³Orygen Youth Health Research Centre and University of Melbourne

During the past 2 decades, a major transition in the clinical characterization of psychotic disorders has occurred. The construct of a clinical high-risk (HR) state for psychosis has evolved to capture the prepyschotic phase, describing people presenting with potentially prodromal symptoms. The

importance of this HR state has been increasingly recognized to such an extent that a new syndrome is being considered as a diagnostic category in the DSM-5. The present lecture will reframe the HR state on the progress that has been made while also recognizing the challenges that remain. We will critically review the available HR research of the past 20 years from PubMed, books, meetings, abstracts, and international conferences. We will address HR historical development, inclusion criteria, epidemiologic research, transition criteria, outcomes, clinical and functional characteristics, neurocognition, neuroimaging, predictors of psychosis development, treatment trials, socioeconomic aspects, nosography, and future challenges in the field. The present lecture will provide evidence that the relatively new field of HR research in psychosis is exciting. It has the potential to shed light on the development of major psychotic disorders and to alter their course. It also provides a rationale for service provision to those in need of help who could not previously access it and the possibility of changing trajectories for those with vulnerability to psychotic illnesses.

DEBATE: ATTENUATED PSYCHOSIS SYNDROME IS A NEEDED DIAGNOSTIC CATEGORY

David J. Castle

The University of Melbourne and St. Vincent's Hospital

Evidence-based treatment needs to be developed for APS with clinical targets focused on treatment of current psychopathology, improving functional capacity, enhancing resiliency, and secondary prevention of psychosis. These data have not been developed with existing classification, but a robust beginning has emerged using the APS or related constructs. Eleven RCTs to date provide evidence that several therapeutic approaches are superior to treatment as usual and, perhaps, substantially better than no treatment. This includes data on symptoms, function, and secondary prevention of psychosis. APS provides an opportunity to organize early detection and intervention with the current best hope for altering the life course of afflicted persons.

DEBATE: ATTENUATED PSYCHOSIS SYNDROME: A NEW DIAGNOSTIC CLASS IS NEEDED

William T. Carpenter^{1,2}

¹*Maryland Psychiatric Research Center; ²University of Maryland School of Medicine*

Evidence-based treatment needs to be developed for APS with clinical targets focused on treatment of current psychopathology, improving functional capacity, enhancing resiliency, and secondary prevention of psychosis. These data have not been developed with existing classification, but a robust beginning has emerged using the APS or related constructs. Eleven RCTs to date provide evidence that several therapeutic approaches are superior to treatment as usual and, perhaps, substantially better than no treatment. This includes data on symptoms, function, and secondary prevention of psychosis. APS provides an opportunity to organize early detection and intervention with the current best hope for altering the life course of afflicted persons.

Symposium

EXPOSURE TO INFECTION/INFLAMMATION DURING BRAIN DEVELOPMENT AND RISK FOR PSYCHOTIC DISORDERS

Chairperson: Christina Dalman

Discussant: Robert Yolken

Monday, 7 April 2014

2:00 PM – 4:00 PM

Overall Abstract: Infection during neurodevelopment is proposed as a risk factor to psychotic disorder. However, the scientific support is scattered and for example have specific infectious pathogens as well as broader groups of infections (e.g. viral infections) been investigated in several studies with often contradicting results. The somewhat vague but nevertheless increasing evidence of a range of pathogens associated with psychosis have led

to the theory of an effector common to all agents in the pathogenesis of psychosis, such as the immune system. Several hypotheses have emerged, e.g. the theory of maternal immune activation (MIA) including the cytokine hypothesis, and the hypothesis of a dysfunctional immune response. The former have sparse epidemiological evidence, only two small studies reports on elevated maternal cytokines during pregnancy and development of schizophrenia in offspring. However, extensive research from animal models of the effect by MIA and cytokines on brain development strongly supports this hypothesis. The immune deficiency hypothesis is supported by one study reporting on low levels of acute phase proteins (APPs) in the neonatal period in patients with non-affective psychosis, and by continuous reports of minor risk alleles in the major histocompatibility complex (MHC) which is rich in genes involved in immune response regulation. In spite of these efforts the underlying mechanisms of infection are not yet understood. Currently there are multidisciplinary approaches involving register data, biological samples and animal models to understand the mechanisms behind infection/inflammation contribution to psychosis development. This symposium intends to summaries the current knowledge of infection/inflammation in the ethiology of psychotic disorders including schizophrenia, and to present novel findings of the area. Dr Khandaker will present findings from a longitudinal study of the association between early-life exposure to EBV, childhood IQ and the risk of psychotic experiences (PE) in early adolescence. He has used a population based birth cohort from eastern England. Dr Brown will discuss new findings from serological samples of the specificity of maternal influenza to schizophrenia as compared to bipolar disorder. A Blomstrom will report on hospital admission with infection during childhood and risk of non-affective psychosis from a population-based birth cohort from Sweden. And discuss novel data from biological samples of maternal immune activation affecting neonatal immune response and potential immune deficiency in psychosis patients. Dr Patterson will discuss MIA mouse model use in schizophrenia research. Dr Dalman will summaries the present state of knowledge on infection/inflammation as risk factor to psychotic disorders.

MANGANESE-ENHANCED MAGNETIC RESONANCE IMAGING REVEALS INCREASED HALLUCINATION-LIKE BRAIN ACTIVITY IN A MOUSE MODEL OF A SCHIZOPHRENIA RISK FACTOR

Paul H. Patterson

California Institute of Technology

Maternal infection during pregnancy increases the risk for schizophrenia in the offspring. In rodent models, maternal infection or maternal immune activation (MIA) in the absence of pathogens yields offspring with schizophrenia-like behaviors. None of these behaviors are, however, specific to schizophrenia. The presence of hallucinations is a key diagnostic symptom of schizophrenia that is not shared with most other mental disorders. In mice, this symptom can be defined as the brain activation in the absence of external stimuli, which can be mimicked by administration of hallucinogens. We find that, compared to controls, adult MIA offspring display increased stereotypical behavioral response to the hallucinogen 2,5-dimethoxy-4-iodoamphetamine (DOI), an agonist for serotonin receptor 2A (5-HT2AR). This may be explained by our finding of increased levels of 5-HT2AR and downstream signaling molecules in unstimulated MIA prefrontal cortex (PFC). Imaging techniques capable of mapping hallucination-like activity would greatly enhance our understanding of such episodes and possibly provide a framework for assessing interventions. Using manganese-enhanced magnetic resonance imaging (MEMRI) to identify neuronal activation elicited by DOI administration we find that, compared to controls, MIA offspring exhibit a greater manganese (Mn^{2+}) accumulation in several brain areas, including frontal cortex. Thus, the MIA mouse model can be successfully used to investigate hallucination-like activity in awake, behaving mice. Moreover, MEMRI is a useful, non-invasive method for accurately measuring this type of activity.

EARLY-LIFE EXPOSURE TO EPSTEIN BARR VIRUS, CHILDHOOD IQ AND THE RISK OF PSYCHOTIC EXPERIENCES IN THE ALSPAC BIRTH COHORT

Golam Khandaker¹, Jan Stochl¹, Stanley Zammit², Glyn Lewis³, Peter Jones⁴

¹University of Cambridge; ²University of Cardiff, UK; ³UCL; ⁴Department Psychiatry, University of Cambridge

Background: Early-life infection is associated with the increased risk of adult psychotic illness. Cross-sectional studies have reported increased prevalence of Epstein Barr virus (EBV), a member of the herpes family in schizophrenia; also, a possible role of herpes virus in cognitive dysfunction in schizophrenia and healthy controls. Using data from the general population-based Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, we report a longitudinal study of the association between early-life exposure to EBV, childhood IQ and the risk of psychotic experiences (PE) in early adolescence.

Methods: Serum IgG antibodies to EBV were measured at age 4 years in a representative subsample of the cohort (N=530). The assessments for IQ at age 9 years and PE at age 13 years were attended by 392 and 366 of these individuals, respectively. Logistic regression calculated odds ratios (OR) for PE in the EBV-exposed compared with the unexposed individuals. Mean IQ scores were compared between these exposure groups; mediating effects of IQ on the EBV-PE association was examined. Potential confounders included age, gender, ethnicity, social class, household crowding, and depression at the time of assessment of PE.

Results: About 25% of the sample was exposed to EBV at age 4 years. EBV exposure was associated with a five-fold risk of PE; OR for definite PE 5.37 (95% CI 1.71- 16.87), which remained significant after adjusting for confounders. EBV-exposed individuals performed worse on all measures of IQ; mean difference in full-scale IQ between EBV-exposed and unexposed groups was 4.55 (95% CI 0.88- 8.23); however, this was explained by socio-demographic differences.

Conclusions: Early-life exposure to EBV is associated with the increased risk of PE in early adolescence; an association not mediated by IQ. Thus, CNS alterations arising from early-life infections that lead to an increased risk of psychotic outcomes may be independent of childhood cognitive deficit as captured by IQ test. Scientific endeavour to unravel the mechanisms underlying the link between psychosis and early-life infection should, therefore, consider alternative pathways possibly immune and genetic.

SEROLOGICALLY DOCUMENTED MATERNAL INFLUENZA AND BIPOLAR DISORDER IN ADULT OFFSPRING

Alan Brown^{1,2}, Sarah E. Canetta³, Yuanyuan Bao³, Mary Dawn T. Co⁴, Francis A. Ennis⁴, John Cruz⁴, Masanori Terajima⁴, Ling Shen⁵, Christoph Kellendonk³, Catherine A. Schaefer⁵

¹Columbia University Medical Center; ²New York State Psychiatric Institute;

³Department of Psychiatry, Columbia University of Physicians and Surgeons, New York State Psychiatric Institute, New York, NY; ⁴Division of Infectious Diseases and Immunology, Department of Medicine, University of Massachusetts Medical School, Worcester, MA; ⁵Division of Research, Kaiser Permanente, Oakland, CA

Background: Elevated maternal antibody to influenza has been associated previously with schizophrenia. In order to assess the diagnostic specificity of the association, we examined whether serologically documented maternal influenza antibody is related to bipolar disorder (BD) in adult offspring from the same birth cohort as in the study of schizophrenia.

Methods: Cases with BD were followed up by linkages between the Child Health and Development Study and the Kaiser Permanente Medical Care Plan (KPNC) and Alameda County Behavioral Health Care Services databases, as well as by a large survey of the cohort. Potential cases were diagnosed with the SCID for DSM-IV-TR by consensus of three experienced psychiatric diagnosticians supplemented by medical records. Maternal archived serum specimens corresponding to cases with BD (N=85) and control (N=170) offspring matched 1:2 on date of birth, sex, availability of archived maternal sera, and KPNC membership/Alameda County residence were assayed for influenza antibody by hemagglutination inhibition. Conditional logistic regression analyses were conducted.

Results: Serologically documented influenza at any time during pregnancy

was significantly increased in cases with BD with psychotic features (38.9%) compared to controls (18.1%) (OR=5.03, 95% CI=1.38–18.4, p=0.015). There was no relationship between maternal influenza and all BD cases nor among BD cases without psychotic features.

Conclusion: These findings suggest that second trimester exposure to influenza may be a risk factor for BD with psychotic features in offspring, suggesting that this infection may not be specific to schizophrenia among major psychiatric disorders.

FETAL AND CHILDHOOD INFECTIONS AND LATER RISK OF DEVELOPING PSYCHOSES; IN SEARCH OF POSSIBLE UNDERLYING MECHANISMS BY COMBINING DIFFERENT RESEARCH DISCIPLINES

Åsa Blomström¹, Håkan Karlsson², Anna Svensson³, Thomas Frisell⁴, Henrik Dahl³, Cecilia Magnusson³, Renee M. Gardner³, Susanne Wicks³, Christina Dalman³

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At present, psychotic disorder is considered a neurodevelopmental disorder. As fetal life is a crucial period of brain development maternal infection during pregnancy has been pointed out as a risk factor for psychosis in offspring. However, brain development proceeds continuously throughout childhood. Nevertheless, the effect of infection during these ages is insufficiently examined. In this study, all individuals born in Sweden 1973–85, (N=1,172,879) were followed up regarding first time in-patient care with non-affective psychosis from 14 years until 2006, (N=4 638), and on somatic inpatient care with a diagnosis of infection during childhood (0–13 years). Hazard ratios (HR) of non-affective psychosis were calculated with Cox regression. Potential confounders included differences in sex, socioeconomic status, family history of psychosis and hospital admissions involving non-infectious and non-psychiatric care. A small but significant association was observed between hospital admissions with any infection throughout childhood (0–13 years) and a later diagnosis of non-affective psychosis, HR=1.10 (95% CI 1.03–1.18). This association was driven by bacterial infection, HR=1.23 (95% CI 1.08–1.40). More specifically, bacterial infection and CNS-infection during preadolescence (10–13 years) conferred the strongest risk, HR 1.59 (95% CI 1.22–2.08), and HR 1.96 (95% CI 1.06–3.65) respectively. Patients with non-affective psychosis had more admissions with infection during childhood; HR 1.37 (95% CI 1.06–1.78) for ≥4 admissions, after adjusting for confounders. Preadolescence appears to be a vulnerable age period to acquire an infection, and bacterial infections the most severe in relation to psychosis development. However, the present findings could also indicate an increased susceptibility to hospital admission for infections among children who will later develop psychosis due to social or familial/genetic factors. In fact, adjusting for admission with other diagnoses and parental psychiatric disease had an attenuating effect on the estimates. The underlying mechanisms are unknown but inflammatory processes may be involved. Recently we reported that neonates who will develop non-affective psychosis have lower levels of some acute phase proteins (APPs) as compared to controls indicating deficits in the innate immune defense of these newborns, which potentially increase either their risk of contracting infections or the severity of contracted infections. The pathogenesis however remains obscure but can potentially involve direct effect of infectious agents and/or indirect effects of maternal immune activation (MIA) modulating the development during fetal life and childhood, including the innate immune system. We conducted a case control study including 198 individuals born in Sweden 1975–85, diagnosed with non-affective psychoses, and 524 controls matched on sex, birth day, and birth hospital. Maternal exposure status of Toxoplasma gondii (T. gondii), cytomegalovirus (CMV), and Herpes simplex virus type 1 (HSV-1) and -2 (HSV-2) was known for all participants. Levels of 9 APPs in archived neonatal dried blood samples from these individuals were determined. Controls exposed to T. gondii and CMV had significantly higher levels of all APPs compared to unexposed controls. Among cases however the levels remained low irrespective of exposure status. Maternal exposure to HSV-1 or -2 did not affect APP levels in neither group. Thus it seems as specific maternal infections alter the child's innate immune response and as psychosis patients have deficiencies in the response which could render the child vulnerable to later infections.

EARLY INFECTION/INFLAMMATION AND LATER DEVELOPMENT OF PSYCHOSES: AN OVERVIEW OF THE RESEARCH AREA

Christina Dalman

Karolinska Institutet

A lot has happened in the field of infection during early life and risk of later psychotic disorder since Mednick et al published there seminal paper in 1988. Several periods have emerged and passed starting with the era of ecological studies of influenza, passing over to the era of studies of persistent agents with CNS-affinity in limited biological samples and lately the era of large population based register studies covering a broad range of infectious agents have emerged. The different eras fill different knowledge gaps but are not fully consistent. Parallel to this an extensive literature on Maternal Immune Activation (MIA) in rodents have attracted a lot of interest as well as research on genes involved in immune activity in the MHC-region. The results from these diverse eras will be summarized and discussed in this presentation, incorporating recent results presented during the symposia, as a starting point for future directions.

Symposium
NOVEL TREATMENT OPTIONS FOR IMPAIRED COGNITION IN SCHIZOPHRENIA: COMBINING DIFFERENT MODES OF COGNITIVE REMEDIATION

Chairpersons: Peter Falkai and William Honer

Discussant: William Honer

Monday, 7 April 2014

2:00 PM – 4:00 PM

Overall Abstract: Cognitive dysfunction is one of the key debilitating symptoms in schizophrenia and contributes substantially to an unfavourable prognosis in many patients. Treatment of dysfunction of cognitive symptoms however, is difficult and therefore new pharmacological but especially psychosocial interventions are needed to improve them. In single, psychosocial interventions like cognitive remediation have shown moderate facts to improve cognitive dysfunction in negative symptoms. The proposed symposium will outline strategies to combine different psychosocial interventions with each other or other means to improve its effectiveness. Falkai et al. will demonstrate that the combination of exercise with cognitive remediation seem to have a beneficial effect especially on global psychosocial functioning. Sawada will investigate the question whether improving the ability to participate in music therapy will subsequently improve basic cognitive functions. Chen et al. have demonstrated a better effect of Yoga compared to exercise and the question whether cultural or other factors contribute to this finding will be raised. Finally Vinogradov et al. will show that the combination of cognitive and social cognitive approaches is better than the single intervention.

COMBINING EXERCISE AND COGNITIVE REMEDIATION

Peter Falkai

Department of Psychiatry, LMU University of Munich

Affective and non-affective psychoses are severe and frequent psychiatric disorders. Amongst others, they not only have a profound impact on affected individuals through their symptomatology, but also regarding cognition, brain structure and function. Cognitive impairment influences patients' quality of life as well as their ability to work and being employed. While exercise therapy has been implemented in the treatment of psychiatric conditions since the days of Kraepelin and Bleuler, the underlying mechanisms have never been systematically studied. Since the early 1990s, studies emerged examining the effect of physical exercise in animal models, revealing stimulation of neurogenesis, synaptogenesis and neurotransmission. Based on that body of work, clinical studies have been carried out in both healthy humans and in patient populations. These studies differ with regard to homogenous study samples, sample size, type and duration of exercise, outcome variables and measurement techniques. Based on their review, we draw conclusions regarding recommendations for future research strategies showing that modern therapeutic approaches should

include physical exercise as part of a multimodal intervention programme to improve psychopathology and cognitive symptoms in schizophrenia and affective disorders.

YOGA EXERCISE FOR COGNITIVE IMPAIRMENT IN PSYCHOTIC DISORDERS

Eric Yu Hai Chen¹, Jingxia Lin², Edwin Ho Ming Lee², Wing Chung Chang², Sherry Kit Wa Chan², Christy Lai Ming Hui²

¹University of Hong Kong; ²Department of Psychiatry, the University of Hong Kong

Background: Cognitive impairment is evident in early stage of psychosis and can result in severe and longstanding functional impairment. Pharmacological interventions for cognitive impairments have been largely unsuccessful. The current study aimed to explore the effects of yoga exercise and aerobic exercise on cognitive functions, clinical conditions and brain structure in female patients with psychotic disorders.

Methods: Eighty-five female patients with psychotic disorders were recruited from three early intervention service units for psychosis. They were randomized into integrated yoga exercise group, aerobic exercise group and control group. At baseline and 12 weeks, clinical symptoms, cognitive functions, quality of life and fitness levels were assessed in all patients. Thirty-nine patients completed structural MRI assessment to compare the brain volume and cortical thickness. Repeated measures ANOVA and ANCOVA analyses of the clinical, cognitive, quality of life and fitness data were done between baseline and 12 weeks among the three groups. Post-hoc Bonferroni test was used for comparison between yoga exercise group and aerobic exercise group.

Results: Both yoga and aerobic exercise groups demonstrated significant improvements in verbal encoding ($p < 0.01$), short-term memory ($p < 0.05$), long-term memory ($p < 0.01$), and working memory ($p < 0.01$) with moderate to large effect sizes compared to control group. The yoga group showed significantly enhanced attention and concentration ($p < 0.05$). Both yoga and aerobic exercise significantly improved overall clinical symptoms ($p < 0.05$) and depressive symptoms ($p < 0.05$) after 12 weeks. Significant increase was observed in the thickness of the left superior frontal gyrus and the right inferior frontal gyrus in the aerobic exercise group. Significant increase was observed in the volume of the postcentral gyrus and the posterior corpus callosum in the yoga exercise group. There was a statistically significant correlation between improvements in working memory and changes in the postcentral gyrus ($r = 0.54$, $p < 0.01$).

Conclusion: Both yoga and aerobic exercise improved memory in patients with psychotic disorder and yoga exercise showed a superior effect on attention than aerobic exercise. The improvement in working memory was associated with change in the volume of postcentral gyrus. The present study indicates possible interventions for cognitive impairments in the patients with psychotic disorder. The application of yoga and aerobic exercise as adjunct treatments in early intervention of psychosis in the clinical setting should be advocated.

UNDERSTANDING OF MUSICAL IMPAIRMENT MAY FACILITATE THE DEVELOPMENT OF INSIGHT FOR COGNITIVE REMEDIATION

Ken Sawada¹, Sanae Hatada², Allen E. Thornton³, William G. Honer⁴

¹Aki General Hospital; ²Department of Neuropsychiatry, Kochi Medical School, Kochi, Japan; ³Department of Psychology, Simon Fraser University, Burnaby, Canada; ⁴Department of Psychiatry, University of British Columbia, Vancouver, Canada

Introduction: Like language, music is a universal human-specific cultural experience. Perception, interpretation, and production of music are linked to language, emotion, cognitive function, and social communication in everyday life. The association between musical ability and cognitive function has been investigated in patients with neurologic illnesses. However, assessment of the musical ability of persons with schizophrenia has attracted little interest despite the diverse and substantive findings of impairments in sound perception and processing, and the therapeutic effect of music in the illness. Our group investigated the musical ability of persons with schizophrenia and the relationship with psychiatric symptoms and cognitive functions.

Methods: We recruited 50 patients with chronic schizophrenia and 58 healthy control subjects. To measure musical ability and cognitive function, we used the Montreal Battery of Evaluation of Amusia (MBEA) and the Brief Assessment of Cognition in Schizophrenia (BACS). We carried out a mediation analysis to investigate a possible pathway to a deficit in musical ability.

Results: Compared to controls, the MBEA global score in schizophrenia was significantly lower ($p < 0.001$), and was strongly associated with both the composite cognitive function score ($r = 0.645$, $p < 0.001$) and the negative symptom score ($r = -0.504$, $p < 0.001$). Our mediation study showed an approximately 43% indirect and 57% direct association between negative symptoms and musical deficit via cognitive impairment, indicating that the effects of negative symptoms on musical disability in patients with schizophrenia are only partially explained by cognitive impairment.

Conclusion: In our study, negative symptoms were correlated with the MBEA global score. Patients with schizophrenia also showed a correlation between overall cognitive functions and MBEA global musical score. Examining the relationships between musical deficits, negative symptoms and cognitive dysfunction in schizophrenia may identify shared biological mechanisms. Greater understanding of the connection between musical deficits and cognitive dysfunctions could improve our understanding of the neural substrates of functional impairment in people with this illness, facilitating the development of insight for cognitive remediation through music.

COMBINING COGNITIVE AND SOCIAL COGNITIVE TRAINING FOR INDIVIDUALS WITH SCHIZOPHRENIA

Sophia Vinogradov^{1,2}, Karuna Subramaniam, Bruno Biagianti, Christine Hooker, Melissa Fisher

¹University of California, San Francisco; ²Associate Chief of Staff for Mental Health, SFVA MEdical Center

In a previous path analysis examining the relationship of neurocognition, self-referential processing, and social cognition to motivation and functional outcome in patients with schizophrenia, we demonstrated that: 1) Neurocognition (attention and executive functioning) and self-referential processing are independent, and each uniquely contributes to social cognition, 2) Social cognition and motivation are associated, 3) Motivation, in turn, predicts outcome (social and occupational functioning). The results of these analyses raised several key questions for the design of maximally effective cognitive treatments in schizophrenia: 1) Is social cognition amenable to computerized neuroplasticity-based training? 2) By enhancing both social cognitive and general cognitive abilities through neuroadaptive training, can we optimize motivation and functional outcome? We will present preliminary data on the behavioral and neural system findings from a randomized controlled trial which performs a direct contrast of general cognitive training delivered alone to individuals with schizophrenia, vs. general cognitive training plus social cognitive training. The purpose of this study is to investigate factors that have often been ignored in computer-based cognitive training programs – those related to social cognition – and to delineate their relationship to motivation, functional outcome, and the neural substrates of reward anticipation and emotion processing.

Symposium

SCHIZOPHRENIA INTERNEURON PATHOLOGY: LOST IN MIGRATION

Chairperson: Cynthia Shannon-Weickert

Discussant: Bita Moghaddam

Monday, 7 April 2014

2:00 PM – 4:00 PM

Overall Abstract: An increased density of neurons below the cortical grey matter represents reproducible cellular evidence for altered neurodevelopment in schizophrenia. In this session we will examine the nature of these cells and consider that white matter neurons (WMNs) may be GABAergic interneurons related to the cortical interneuron deficit in schizophrenia. In this view, excess WMNs could represent improper migration of interneurons to the cortex. In an attempt to illuminate the nature of WMNs in schizophrenia, we will consider data on how laser capture of WMNs combined with RNAseq may help us to determine global transcriptional profiles

of these cells and their changes in schizophrenia. We will also provide evidence that interneuron deficits and activation of immune responses within the cortex of people with schizophrenia may be linked to excess WMNs. Next, we will review experimental evidence that birth and migration of new GABAergic interneurons can be seen in the early postnatal rodent brain and that these neurons can migrate to the cortex. This knowledge suggests a further interpretation: that increased WMNs in schizophrenia could represent the harnessing of new neurons in a rebuilding effort. We will then present evidence that in rodent models of schizophrenia elevated oxidative stress, particularly in GABAergic interneurons, precedes symptom onset and may represent a cortical injury-like pathology in disease that could induce recruitment of new interneurons to the cortex. Finally, we will discuss why viewing increased WMNs as part of neurodevelopment, neuropathology or neurorepair, may constrain or inform our efforts to determine the causes of schizophrenia.

INCREASED WHITE MATTER NEURON DENSITY IS RELATED TO HIGH NEUROINFLAMMATION IN PEOPLE WITH SCHIZOPHRENIA

Cindy Shannon-Weickert^{1,2}, S.J. Fung³, D. Joshi³, S.G. Fillman³, V.S. Catts³

¹UNSW; ²SRI; ³Schizophrenia Research Institute, Neuroscience Research Australia, and University of New South Wales; Sydney, Australia

Background: Increased white matter neuron density is linked to reductions in cortical interneuron mRNA in people with schizophrenia, suggesting aberrant interneuron migration to the cortex may be implicated in the neuropathophysiology. Proinflammatory cytokines are also elevated in the disease and we hypothesize that reduced viability of interneurons relates to increased neuroinflammation and recruitment of interneurons to the cortex in schizophrenia.

Methods: Immunohistochemistry (NeuN, GAD65/67) was used to identify white matter neurons, and quantitative RT-PCR of cDNA from 37 people with schizophrenia and 37 matched controls was used to determine expression of cytokines (IL-6, CXCL12), cytokine receptors (CXCR4, CXCR7), interneuron marker (somatostatin), and cell death related mRNAs (FASR, APRIL) in the frontal cortex.

Results: A subgroup of individuals with high proinflammatory cytokines (primarily IL-6) was identified (14/37 people with schizophrenia) (Fillman et al, 2012, Mol Psychiatry). Density of white matter neurons was increased in individuals with schizophrenia with high compared to low neuroinflammation ($p < 6 \times 10^{-4}$). Somatostatin was reduced in people with schizophrenia with high compared to low inflammation ($p = 8.8 \times 10^{-4}$), and the cytokine receptor CXCR7 mRNA was increased in the DLPFC of schizophrenics with high neuroinflammation ($p = 4 \times 10^{-4}$).

Conclusion: Our findings suggest that inflammation in the brain of people with schizophrenia may be associated with an interneuron deficit, cell death pathways, increased white matter neuron density, and increased expression of cytokine receptor CXCR7. We propose that white matter neurons may represent immature, migrating interneurons increased in people with schizophrenia in response to a cortical neuron deficit.

SUBCORTICAL WHITE MATTER NEURONS IN AUTISM, SCHIZOPHRENIA AND DEPRESSION

Schahram Akbarian¹, Cong L. Lin², Aslihan Dincer³, Eustathia

Lela Giannaris⁴, Yin Guo², Adriana Akintobé², John Neary²,

Vahram Haroutunian^{5,6}, Andree Lessard⁷, William E. Bunney Jr.⁸,

Juerg Straubhaar⁹, Scott E. Hemby⁹, Schahram Akbarian^{2,5}

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Increased numbers and densities of subcortical white matter neurons

(WMN) have been reported for a subset of cases diagnosed with schizophrenia and related disease including depression and autism. While it is often incurred that this type of alteration reflects a fixed lesion of early brain development, it is not known whether there is ongoing dynamic regulation of WMN numbers beyond the postnatal period, and a unifying molecular pathology. We determined the proportion of neuronal nuclei in frontal lobe white matter of 140 brains, including 65 controls from newborn to 93 years of age, and 56 cases diagnosed with schizophrenia, depression or autism, and 19 non-human primates treated daily with typical or atypical antipsychotic for a period of 6 months. We also deeply sequenced 26 gray and white matter transcriptomes.

Results: The authors report that 18% of disease cases, including 6/39 subjects with schizophrenia, exceeded the 99th percentile of controls. Normal aging was associated with a step-wise, 3-fold decline in WMN from childhood to early-/mid-adult (16–40 years) to advanced age. Gray to white matter redistribution of neuronal (including GABAergic) transcripts was observed in 1/7 cases with excess WMN. Frontal lobe WMN decline during the course of normal aging, a process that continues into the 4th decade. Disease cases with excess WMN lack a unifying molecular signature, indicating heterogeneous etiologies for this cellular phenotype.

OXIDATIVE STRESS IN PARVALBUMIN INTERNEURONS IN A DEVELOPMENTAL RODENT MODEL OF SCHIZOPHRENIA

Patricia O'Donnell¹, Kim Q. Do², Danielle Counotte³, Jan Harry Cabungcal²
¹Pfizer; ²University of Lausanne; ³University of Maryland

Abnormal development can lead to deficits in adult brain function, a trajectory likely underlying adolescent-onset psychiatric conditions such as schizophrenia. Developmental manipulations yielding adult deficits in rodents provide an opportunity to explore mechanisms involved in a delayed emergence of anomalies driven by developmental alterations and to test hypotheses about pathophysiological scenarios for these disorders. We assessed whether oxidative stress during pre-adolescent stages causes adult anomalies in rats with a neonatal ventral hippocampal lesion, a widely used developmental model of schizophrenia. Juvenile and adolescent treatment with the antioxidant N-acetyl cysteine prevented the reduction of prefrontal parvalbumin interneurons observed in this model, as well as behavioral and electrophysiological deficits relevant to schizophrenia. These findings suggest that oxidative stress during presymptomatic stages can confer vulnerability for abnormal adult brain function in a developmentally compromised brain, and highlight redox modulation as a potential target for early intervention.

PATTERNS OF NEURONAL MIGRATION FROM THE EARLY POSTNATAL SUBVENTRICULAR ZONE: POTENTIAL RELEVANCE FOR SCHIZOPHRENIA

Dragos Inta¹, Juan M. Lima-Ojeda², Andreas Meyer-Lindenberg², Peter Gass²

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Background: The subventricular zone (SVZ) is the main site of neurogenesis in rodents in postnatal life. Generally it is thought that migration of neuroblasts from the SVZ is restricted to tangential migration to the olfactory bulb and that SVZ neurogenesis may play a role only in olfaction. Here we investigated using a multimodal approach in transgenic mouse models the pattern of neuroblast migration from the SVZ during early postnatal life.

Methods: Transgenic 5-HT3-EGFP and D3-EGFP mice were generated by bacterial artificial chromosome (BAC) technology. Identification, migration and differentiation of neuroblasts from the early postnatal SVZ were done by immunohistochemical methods, time-lapse imaging and birthdating analysis.

Results: Unexpectedly, we found massive migration of neuroblasts from the SVZ that was not restricted to the RMS and OB, but included numerous cortical and subcortical regions. Neuroblasts from the early postnatal SVZ migrate along all elongations of the callosal system into adjacent regions

(prefrontal cortex, striatum, nucleus accumbens) and differentiate into specific, mainly calretinin-positive GABAergic interneurons, similar to granule cells in the olfactory bulb and hippocampus.

Conclusions: Early postnatal SVZ neurogenesis is not restricted to the olfactory bulb. The functional relevance of these new identified patterns of neurogenesis/migration for schizophrenia needs further evaluation considering the important modulatory role of susceptibility genes like neuregulin-1 and the possible link to the postnatal development of the dopamine system.

Symposium

THE BIOLOGY OF SOCIAL DEFEAT

Chairpersons: Jean-Paul Selten and Andreas Meyer-Lindenberg

Discussant: Oliver Howes

Monday, 7 April 2014

2:00 PM – 4:00 PM

Overall Abstract: According to the social defeat hypothesis (Selten & Cantor-Graae, 2005; Selten et al., 2013) the negative experience of being excluded from the majority group leads to increased baseline activity or sensitization of the mesolimbic dopamine system (possibly through prefrontal regulation of subcortical structures) and puts the individual at increased risk for schizophrenia. This hypothesis may provide a parsimonious explanation for the association between risk for schizophrenia and ethnic minority status, childhood trauma, low IQ, urban upbringing, drug abuse, hearing impairment, unmarried status, unemployment and autistic spectrum disorder. This symposium brings together researchers from four countries who have examined the biology of social defeat from different angles. Two researchers performed neuroreceptor imaging studies to investigate the dopamine system in high risk groups. Romina Mizrahi (Canada) compared the dopamine response to the Montreal Stress Task (MIST) in immigrants to that in natives using Positron Emission Tomography (PET) and found evidence for dopaminergic sensitization in immigrants. Martin Gevonden (the Netherlands) used Single Photon Emission Computed Tomography (SPECT) to test the hypothesis that psychologically normal young adults with a serious hearing impairment release more dopamine after intravenous administration of amphetamine than peers without such impairment. The preliminary results were in the hypothesized direction, but just failed to reach statistical significance. Andreas Meyer-Lindenberg (Germany) interrogates associations from epidemiology with functional Magnetic Resonance Imaging (fMRI). Subjects are exposed to the stress of negative evaluation using a social evaluative stress paradigm. A previous study showed an increased activation and functional connectivity in the perigenual anterior cingulate cortex (pACC) among people raised in urban areas versus those raised in rural areas (Nature, 2011). The study to be presented in Florence demonstrates similar differences between second-generation migrants and natives. Before his return to France Vincent Vialou worked for many years in Eric Nestler's lab at Mount Sinai, New York. He is an expert on social defeat in animals and will present novel work on stress-related molecular adaptations in the limbic system, in particular the medial prefrontal cortex. His work on mice shows that induction of DeltaFosB by social stress leads to more social avoidance. Viral-mediated overexpression of DeltaFosB induces inhibitory avoidance, increased startle response in Prepulse Inhibition Tasks and increased anxiety-like behaviours. Interestingly, antipsychotic drugs have also been shown to induce DeltaFosB. Finally, we are pleased to inform you that Oliver Howes (Institute of Psychiatry, UK) will act as discussant.

References:

- [1] Selten JP, Cantor-Graae E (2005). Social defeat: risk factor for schizophrenia? Br J Psychiatry, 187, 201–205.
- [2] Selten JP, van der Ven E, Rutten B, Cantor-Graae E (2013). The social defeat hypothesis of schizophrenia: an update. Schizophrenia Bulletin (in press).

ABNORMALITIES OF NEURAL SOCIAL STRESS PROCESSING AND EXPOSURE TO ENVIRONMENTAL RISK FACTORS FOR SCHIZOPHRENIA

Andreas Meyer-Lindenberg¹, Heike Tost²

¹Central Institute of Mental Health; ²ZI Mannheim

Social stressors like social defeat have been hypothesized to play a key role in mediating environmental risk factors such as urban birth or migra-

tion. Recently (Lederbogen et al. *Nature* 2011) we provided experimental evidence for a role of perigenual cingulate cortex (pACC) hyperactivity during social stress processing in urban upbringing. In this presentation, we apply the same experimental paradigm to study migration-associated risk. In a series of studies, we identified specific neural alterations during social stress processing in German second-generation migrants. We found hyperactivity in a key regulatory system for negative emotion and stress including perigenual anterior cingulate cortex (pACC) and downstream effector sites linked to schizophrenia risk such as frontoinsular cortex and ventral striatum. These findings were specific to social stress, not explained by a social distance effect, present across a range of ethnicities, and strongly related to participant's perceived social discrimination. By linking altered neural stress processing to migration, our results provide evidence for a long-standing hypothesis in the field, identify a neural system where multiple genetic and environmental risk factors for schizophrenia converge, and highlight potential targets for early intervention and prevention.

EXAGGERATED DOPAMINE RELEASE IN IMMIGRANTS DURING SOCIAL STRESS: A RISK MECHANISM FOR PSYCHOSIS

Romina Mizrahi¹, J. Addington, P.M. Rusjan, I. Suridjan, A. Ng, I. Boileau, J.C. Pruessner², G. Remington³, S. Houle, A.A. Wilson

¹*University of Toronto; ²Douglas Mental Health Institute, Department of Psychiatry, McGill University, Montreal, Quebec, Canada; ³Department of Psychiatry, University of Toronto*

Psychosocial stressors such as migration and urbanicity have been implicated in the pathogenesis of schizophrenia, but the neurochemical processes involved remain unidentified. Psychosocial stress (e.g. marginalization, social defeat, etc) may sensitize the brain dopaminergic system, changing its reactivity and increasing the amount of dopamine released during stressful situations. Since psychosis has been linked to altered striatal dopamine release in response to both amphetamine and stress, this suggests a pathophysiological model in which elevated stress-induced dopamine in migrants predisposes this population to schizophrenia. Using a previously validated psychosocial stress procedure (Montreal Imaging Stress Task – MIST), and combining a published cohort of healthy volunteers and patient populations, we studied seventeen non-immigrants (9 healthy volunteers (HV), 4 patients with schizophrenia (SCZ) and 4 subjects at clinical high risk (CHR) of developing the disease) and fifteen first and second generation immigrant subjects (3 HV, 5 SCZ and 7 CHR), aged 18–35 years and matched for age, and gender. We measured dopamine release in the striatum using a previously described positron emission tomography (PET) displacement paradigm involving scans under stress and control conditions with the tracer [11C]-(+)-PHNO. Binding potential relative to non-displaceable ligand (BPND) was quantified using the simplified reference tissue model in the whole striatum, associative striatum (AST), limbic striatum (LST) and sensorimotor striatum (SMST), with cerebellum as a reference region. Self-reporting measures confirmed the efficacy of the stress paradigm ($F=36.31$ $df=1,56$ $p<0.0001$), regardless of the immigration status. A statistical model (including clinical vulnerability (HV, CHR, SCZ) and immigration as predictors) explained 39% of the variance in stress-induced dopamine release in the whole striatum ($F=5.98$, $df=3,28$ $p=0.002$), with a significant vulnerability group effect ($F=3.49$, $df=2,28$ $p=0.04$) confirming previous findings (Mizrahi et al., 2012), and a significant immigration effect ($F=5.97$, $df=1,28$ $p=0.02$). In the entire striatum, displacement in immigrant subjects was significantly higher compared to the non-immigrant subjects (8.06% and 0.96%, respectively, figure panels A and B). In analyzing the striatal subregions, the same model accounted for 49% of the variance in stress-induced dopamine release for the AST ($F=9.08$, $df=3,28$ $p=0.0002$), with a significant immigration effect ($F=7.24$, $df=1,28$ $p=0.01$). The same model explained 12% of total variance in the LST and 24% for the SMST. Same findings were observed when using a voxel-wise analysis showing clusters of significantly decreased BPND at the level of striatum for immigrants, but not in non-immigrants. Furthermore, dopamine release in the AST significantly correlated with several measures of social stress. This result is, to our knowledge, the first report of stress-induced dopaminergic sensitization in immigrants. Our data are in agreement with a model in which dopamine sensitization mediates risk for schizophrenia, suggesting that altered dopamine responsiveness is a part of the neural mechanisms underlying the elevated risk for schizophrenia in immigrant populations. Abnormal dopaminergic sen-

sitivity may be one pathway through which the social world interacts with biology to confer a higher risk of schizophrenia. Further elucidation of this mechanistic linkage would open the road for possible interventions that address the underlying neurobiological vulnerability and protect against environmental risks possibly even allowing for a preventive approach.

ΔFOSB IN THE PREFRONTAL CORTEX, SUSCEPTIBILITY TO SOCIAL STRESS AND ANTIPSYCHOTIC TREATMENT

Vincent Vialou

INSERM

Among current rodent models of affective disorders, chronic social defeat stress is an ethologically valid approach, which induces long-term physiological and behavioral alterations, including social avoidance, anhedonia, cognitive deficits and anxiety-like symptoms, involving activation of several neural circuits and neurochemical systems. It is a model for stress-related disorders such as depression, PTSD and schizophrenia. Using this model, we identified persistent molecular adaptations occurring in the limbic brain in particular the medial prefrontal cortex (mPFC) driving such susceptibility to stress. We first quantified by immunohistochemistry levels of ΔFosB, a protein implicated in the persistent neuronal alterations induced by chronic exposure to stress. Here we show that ΔFosB is induced in the mPFC of susceptible mice. Such induction increased social avoidance induced by social stress. Molecular alterations in the mPFC could be implicated in the cognitive deficits associated with schizophrenia. Both first and second generation antipsychotic drugs, which are used to alleviate these symptoms, have been shown to induce ΔFosB in mPFC. Viral-mediated overexpression of ΔFosB in the PFC of rodents induced cognitive deficits as measured by inhibitory avoidance, increased startle responses in PPI tasks, and increased MK-801-induced anxiety-like behaviors. All together, these results suggest that induction of ΔFosB by social stress might precipitate schizophrenia- and depressive-like symptoms. Furthermore, ΔFosB induction in PFC by antipsychotic treatment contributes to the deleterious effects of these drugs and not to their therapeutic actions. We looked at potential molecular targets of ΔFosB and tested the role of cortical projections from mPFC to its various target regions using optogenetic stimulation.

SOCIAL EXCLUSION AND SENSITIZATION OF THE DOPAMINE SYSTEM:

A [¹²³I]IBZM-SPECT STUDY IN YOUNG ADULTS WITH SERIOUS HEARING IMPAIRMENT

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Aim: According to the social defeat hypothesis (Selten & Cantor-Graae, 2005), chronic experience of exclusion from the majority group leads to enhanced baseline activity and/or sensitization of the mesolimbic dopamine (DA) system and puts the individual at increased risk for psychosis. Such increased risk has been found in migrants and in people with hearing impairment. Hearing loss, even when compensated with modern hearing aids, can hinder participation in conversations and result in feelings of exclusion and loneliness. This study tests the social defeat hypothesis by comparing dopaminergic function between young adults (age 18–30) with a serious hearing impairment (HI) and normally hearing peers. Subjects and methods: Nineteen subjects with HI (3 males; 4 smokers, mean age 25y 10m, SD=8m) and 19 control subjects individually matched on age, sex and smoking behaviour (mean age 26y 2m, SD=9m), were examined using SPECT imaging with the well-validated DA D_{2/3} receptor tracer [¹²³I]iodobenzamide ([¹²³I]IBZM) on a brain-dedicated scanner (Neurofocus; 12 detectors). In one session, baseline striatal D_{2/3} receptor binding and endogenous DA release after stimulation with D-amphetamine sulphate (0.3 mg/kg i.v.) were assessed (bolus/constant infusion technique). Main hypotheses were tested using profile analysis with age, sex and cigarette smoking as covariates.

Results: Overall striatal [¹²³I]IBZM binding potentials did not differ between groups, $F(1,36)=1.28$, $p=0.27$, adjusted $F(1,33)=1.67$, $p=0.21$). The decrease in binding potential after administration of D-amphetamine sul-

phate was greater in the HI group (18.7%) than in the control group (10.5%), reflecting greater DA release in the striatum in the HI group ($F(1,36)=3.75$, $p=0.061$, adjusted $F(1,33)=4.57$, $p=0.040$). HI subjects reported more social defeat, $t(38)=-2.44$, $p=0.019$, loneliness, $t(37)=-3.33$, $p<0.01$, and depression, $t(38)=-2.20$, $p=0.034$. However, none of these measures were substantially associated with DA release (range $r=0.07$ – 0.20).

Discussion: These preliminary results provide some support for sensitization of the dopamine system in individuals experiencing chronic exclusion, but the results are not conclusive.

Symposium

VIOLENCE AND SCHIZOPHRENIA: RISK FACTORS AND MEDIATORS

Chairperson: Seena Fazel

Discussant: John J. McGrath

Monday, 7 April 2014

2:00 PM – 4:00 PM

Overall Abstract: Violence perpetrated by patients with schizophrenia remains one of the most important adverse outcomes in such patients, and a robust body of work has concluded that the odds of violent outcomes in individuals with schizophrenia are around 4 times higher than general population controls. What remains uncertain, however, is what risk and protective factors moderate such risk. This symposium will present a series of new reviews examining risk and protective factors for violence in patients with schizophrenia. The first review is an overall examination of all risk factor research and a meta-epidemiological approach synthesizing information across similar factors. The second reviews the epidemiologic work on the relationship between delusions and violence, and discusses the implications of this research for psychiatric treatment and public mental health policy. The third is a systematic review of the prevalence and risk factors for violence among inpatients with schizophrenia-spectrum disorders. The final paper brings together research on protective factors and discuss interventions that might reduce the incidence of violence in schizophrenia.

RISK FACTORS FOR VIOLENCE IN PSYCHOSIS: FINDINGS FROM A META-ANALYSIS

Seena Fazel¹, Katrina Witt¹, Richard Van Dorn²

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Previous reviews on risk and protective factors for violence in psychosis have produced contrasting findings. Therefore we conducted a systematic review and meta-analysis of the direction and strength of association of risk and protective factors for violent outcomes in individuals with psychosis. We searched 6 databases for studies that reported factors associated with violence in adults diagnosed, using DSM or ICD criteria, with schizophrenia and other psychoses. Risk and protective factors were meta-analysed if reported in three or more primary studies. Meta-regression examined sources of heterogeneity. A novel meta-epidemiological approach was used to group similar risk factors into one of 10 domains. Sub-group analyses were then used to investigate whether risk domains differed for studies reporting severe violence (rather than aggression or hostility). There were 110 eligible studies reporting on 45,533 individuals, of whom 39,995 (87.8%) were diagnosed with schizophrenia. Dynamic (or modifiable) risk factors included hostile behaviour, recent drug misuse, non-adherence with psychological therapies (p values <0.001), higher poor impulse control scores, recent substance misuse, recent alcohol misuse (p values <0.01), and non-adherence with medication (p value <0.05). We also examined a number of static factors, the strongest of which were criminal history factors. When restricting outcomes to severe violence, these associations did not change materially. In conclusions, we found certain dynamic risk factors are strongly associated with increased violence risk in individuals with psychosis. Their role in risk assessment and management warrants further examination.

DELUSIONS AND VIOLENCE

Jeffrey Swanson

Duke University School of Medicine

This presentation will review and evaluate key evidence for the link between violent behavior and psychotic symptoms in general, and delusions in particular. The presenter will reexamine conflicting findings for the "threat/control-override" and "rationality-within-irrationality" hypotheses that emerged in the 1990s, focusing in detail on comparative evidence from the MacArthur Violence Risk Study and the more recent Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) from the USA. That delusions directly cause violence in schizophrenia has been widely assumed, yet remains contested in the literatures of psychiatry and its neighboring sciences. Populations with psychosis are heterogeneous, manifesting the full range of risk and protective factors for violence. For every threatening delusional patient, clinicians in nonforensic settings may see 9 who will not harm. Epidemiological studies describe violence in mental illness as a multi-factorial problem, with salient predictors including age, gender, substance abuse, social disadvantage, developmental history, victimization and trauma sequelae, and exposure to community violence. Clinical studies of aggression implicate other types of symptoms—such as explosive anger, impulsivity, dysregulated mood, psychoactive drug effects, and antisocial personality—that may combine with delusions to exacerbate or mediate their impact on violence risk. These other vectors of violence provide a context and a matrix within which to understand the role of delusions in precipitating aggressive and violent acts. Psychopathology may contribute to assaultive acts, but is rarely, if ever, the sufficient explanation for them. The lecture concludes with general implications for antipsychotic pharmacotherapy, involuntary treatment law, criminal justice, and policy in behavioral healthcare services delivery.

SYSTEMATIC REVIEW OF THE PREVALENCE AND RISK FACTORS FOR INTERPERSONAL VIOLENCE IN ACUTE PSYCHIATRIC UNITS

Giovanni De Girolamo, Laura Liozzino

IRCCS Fatebenefratelli

Using standard systematic reviewing methods, we have estimated the prevalence of patients admitted to acute psychiatric wards who have committed at least one violent act against persons (staff, other patients, visitors) during the hospitalization. Our aim is to study the socio-demographic, clinical characteristics of these patients, and to identify risk factors that can predict their violent behaviours. The study is ongoing and will be completed early in 2014. To date, we have identified over 50 studies for the review.

PREVENTING VIOLENCE IN SCHIZOPHRENIA

Olav Nielssen

St Vincents Hospital, Sydney

Background: High rates of violence have been reported in clinical samples of patients with schizophrenia, especially of first episode psychosis, and there is an over-representation of people with schizophrenia among samples of violent offenders.

Method: A review of case linkage studies, studies of violence and stage of illness, studies of factors associated with violence in schizophrenia, and outcome studies, to identify strategies that might reduce the incidence of violence by people with schizophrenia.

Results: Case linkage studies show a peak in violent offending in the period before the diagnosis of schizophrenia. Studies of stage of illness and violence show that most serious violence is committed prior to initial treatment for schizophrenia, often after long period of untreated psychosis. The main factors associated with violence in schizophrenia are comorbid substance abuse and delusional beliefs in which the patient believes they are in danger or have been seriously wronged. Outcome studies suggest that long term supervision of treatment after committing an act of violence reduces the incidence of further violent offences. There were no studies showing that the routine use of any form of risk assessment was able to reduce rates of violence among people with schizophrenia.

Conclusions: Interventions that might reduce the incidence of violence in schizophrenia include earlier and adequate treatment of the first episode of psychosis, improvement in methods of treating substance abuse in people with schizophrenia, including involuntary treatment for those who have committed offences associated with intoxication, assertive treatment of patients with alarming symptoms, and long term supervision of patients who have committed serious violent offences. The low base rates of serious violence and the absence of specific risk factors that might predict which patients might commit an act of violence means that the best way to reduce violence is not by attempting to predict which patients might commit an act of violence, and is instead by reducing barriers to care and by systems of care for the continued treatment for all patients, especially those with a history of violence.

Symposium

CANNABIS, SKUNK AND SPICE: THE EVOLVING RISK OF PSYCHOSIS

Chairperson: Marta Di Forti

Discussant: Robin M. Murray

Monday, 7 April 2014

4:15 PM – 6:15 PM

Overall Abstract: Intravenous administration of cannabinoids has proven an excellent method of exploring differences in the effect of the different constituents of cannabis on psychopathology and memory functions. Amir Englund will present two such studies in which Δ9-tetrahydrocannabinol (THC) was administered intravenously to healthy volunteers; cannabidiol (CBD) was used as a pre-treatment in one study and Δ9-tetrahydrocannabivarin (THCV) in the other. Pretreatment with CBD or THCV was able to reduce the effects of TCH on both cognitive performance and psychopathology, effects that were clearly dose dependent. Which biological mechanisms underlie the etiology of cannabis associated psychosis and cognitive deficits? Emerging evidence has suggested that epigenetic processes may contribute to the development of several psychiatric disorders including schizophrenia. Tiziana Rubino will describe an investigation into the occurrence of epigenetic changes after chronic THC administration in adolescent rats. Specifically, histone modification changes were analysed in genes closely related to the endocannabinoid system or involved in synaptic plasticity. The results indicate that THC administration to adolescent rats affects Histone modifications in a dose dependent manner, and impairs the steady state expression of genes involved in brain plasticity. Such alterations might play a role in the development of the psychosis induced by THC exposure in adolescence. Might the now widely availability of high potency cannabis, Sinsemilla (Skunk), be reshaping the magnitude of the association between cannabis use and psychosis onset? Sinsemilla, from the female plant which is at the seedless stage, contains very high levels of THC and virtually no CBD. Using data from 410 first episode psychosis (FEP) patients and 370 population controls, Marta Di Forti showed that Skunk use is associated with: 1) a greater probability to experience a psychotic disorder; 2) on average, a 6 years earlier onset of psychosis compared to never users; 3) a significant interaction with the COMT Val158 genotype in further increasing the probability of developing a psychotic disorder. Assuming a causal role of cannabis in the aetiology of psychosis, 32% of psychotic cases in this study population could be prevented by abolishing skunk use. The link between cannabinoids and psychosis is almost exclusively based on observations of the effects of naturally occurring cannabinoids. However, the dramatic increase in the recreational use of synthetic cannabinoids can further inform the link between cannabinoids and psychosis. In the U.S., Spice, a synthetic cannabinoid, has become the second most frequently used illicit substance after cannabis. DR D'Souza will demonstrate that unlike THC, the synthetic cannabinoids in Spice are high-potency full agonists at the brain CB1 receptor and Spice lacks in CBD. Spice is sold under the guise of potpourri or incense. Since standard urine toxicology does not test for synthetic cannabinoids, Spice is often used by those who want to avoid detection of drug use. Psychoses induced by Spice may represent the future of cannabinoid associated psychopathology. Finally, given 1) that exposure to cannabis in adolescence is thought to contribute to an increased risk of later psychosis, 2) the dose-response relationship, with greater exposure increasing the risk for psychosis, and 3) the high potency of Skunk and of Spice relative to THC and absence of CBD, there is concern that the growing use of Skunk and

Spice may lead to an increase in the number and in the severity of cases of psychosis.

HOW SINSEMILLA (SKUNK) USE HAS RESHAPED THE ASSOCIATION BETWEEN CANNABIS AND PSYCHOSIS

Marta Di Forti¹, A.S. David², P. Dazzan², Marta Di Forti², M.A. Falcone², A. Kolliakou², A. Marconi², T. Reis Marques², V. Mondelli³, C. Morgan⁴, R.M. Murray², C. Pariente³, J. Powell⁵, M. Russo², S.A. Stilo⁴, C. Yedgye⁵

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On most European street markets, the types of cannabis on offer are marijuana, hash, and more recently the high potency sinsemilla (skunk). Skunk is from the female plant which at this seedless stage (sinsemilla=without seeds) contains very high levels of Delta-9-Tetrahydrocannabinol (THC) and virtually no Cannabidiol (CBD). UK hash samples seized by London Metropolitan Police contain on average 2–4% THC compared to the 12–18% present in the skunk samples (Potter et al. 2008). It has been suggested that the risk of the harmful effect to mental health posed by cannabis use might be conditional on the potency of the type of cannabis such as skunk, which contains a very high concentration of THC and no CBD. We set to investigate how the wide spread use of skunk in South East London has reshaped the strength of the associated between cannabis and psychosis. We applied logistic regression models to 410 first episode psychosis (FEP) patients and 370 population controls from the GAP (Genetic and Psychosis) study to investigate the effect of exposure to skunk use compared to other types of cannabis; and also the modifying effect of the COMT (Catechol-O-Methyltransferase) Val allele on the risk to develop psychosis. In the FEP sample, using cox regression, did we test the effect of skunk use on age of illness onset. Finally we calculated the proportion of new cases of psychosis attributable (PAF) to skunk use in South East London, where our cases and controls come from. FEP patients were more likely to be daily users of skunk than controls ($\chi^2=58.08$, $p<0.01$). Skunk users were twice as likely to be diagnosed with a psychotic disorder if they used it less than weekly (Adj OR=1.9; 95% CI 1.08–2.62; $p=0.020$), over 3 times more likely to be diagnosed with a psychotic disorder if they used it at week ends (Adj OR=3.6; 95% CI 1.40–9.14; $p=0.0008$), and over 5 times more likely to be diagnosed with a psychotic disorder if they were daily users (Adj OR=5.4; 95% CI 2.81–11.31; $p<0.01$), compared to never users. Among those with a history of skunk use, G/G (Val/Val) carriers had a significant 5 fold increase in risk of psychotic disorder compared to those with the A/A (Met/Met) genotype (LR=9.14, $p=0.0461$; OR=5.4; 95% CI 1.26, 12.53; $p=0.025$). Among FEP patients, daily skunk users had the earliest onset (mean years = 25.2, SD=6.3, median years=24.6) compared to never users among all the groups tested (HR=1.99; 95% CI: 1.50–2.65; $p<0.0001$), which on average was 6 years earlier than that of non-cannabis users. Given a 49.2% prevalence of skunk use among our FEP, the PAF for skunk use in our geographical area ($p(OR-1)/OR$; Bruzzi, et al. 1985) was 32.2%. Daily use of skunk is significantly associated with: 1) the greatest probability of psychotic disorders; 2) on average, a 6 years earlier onset of psychosis compared to never users; 3) a significant interaction with the COMT Val158 genotype in further increasing the probability of developing a psychotic disorder. Finally, assuming a causal role of cannabis in the aetiology of psychosis, 32% of psychotic cases in this population could be prevented by abolishing skunk use.

SPICING THING UP - WHAT CAN WE LEARN FROM SYNTHETIC CANNABINOID ABOUT THE LINK BETWEEN CANNABINOID AND PSYCHOSIS

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The link between cannabinoids and psychosis is almost exclusively based on observations of the effects of naturally occurring cannabinoids. The recent trend in the recreational use of synthetic cannabinoids can further inform the link between cannabinoids and psychosis. These synthetic cannabinoids present in Spice include classical cannabinoids, naphtoylindoles, benzoylindone or phenylacetylindole. Since the mid2000s products containing synthetic cannabinoids, collectively referred to as Spice, have started being used recreationally. In the U.S., Spice has become the second most frequently used illicit substance after cannabis (NIDA 2012). Unlike delta-9-tetrahydrocannabinol (THC), the principal active component of cannabis, the synthetic cannabinoids in Spice are high-potency full agonists at the brain CB1 receptor. Moreover, Spice lacks cannabinoids such as CBD that may offset some of the effects of THC. Spice is sold under the guise of potpourri or incense. Since standard urine toxicology does not test for the synthetic cannabinoids in Spice, it is often used by those who want to avoid detection of drug use. There are no controlled data on the effects of Spice and the synthetic cannabinoids in Spice have not yet been subjected to rigorous testing in humans. The main source of information about the effects of Spice comes from Poison Control Centers, law enforcement, case reports in the medical literature and media reports. Another important source of information are self-reports posted on Erowid. The acute psychoactive effects include changes in mood, anxiety, perception, thinking, memory, and attention. Adverse effects include anxiety, agitation, panic, dysphoria, psychosis, and bizarre behavior. Psychotic symptoms associated with Spice include perceptual alterations, illusions, auditory and visual hallucinations, paranoia, agitation, aggression, catatonia, depersonalization, and dissociation. The reported psychosis outcomes associated with synthetic cannabinoids that have varying chemical structures but all have in common agonist effects at brain cannabinoid receptors, provide further support for the link between cannabinoids and psychosis. Given that 1) exposure to cannabis in adolescence is thought to contribute to an increased risk of psychosis later in life, 2) there appears to be a linear dose-response relationship, with greater exposure increasing the risk for psychosis, and 3) the higher potency of synthetic cannabinoids relative to THC, there is concern that the growing use of Spice may lead to new cases of psychosis and may precipitate psychosis in individuals with a psychotic disorder.

EPIGENETIC AND TRANSCRIPTIONAL CHANGES ASSOCIATED WITH THE DEVELOPMENT OF THE SCHIZOAFFECTIVE-LIKE PHENOTYPE INDUCED BY ADOLESCENT EXPOSURE TO THC IN RATS

Tiziana Rubino¹, Pamela Prini², Daniela Parolaro²

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We recently reported that adolescent exposure to THC in rats induces a complex behavioural and biochemical phenotype at adulthood that closely resembles a schizoaffective disorder. When the same protocol of treatment was applied to adult animals, no significant enduring changes were observed, suggesting a specific vulnerability of adolescent animals to THC adverse effects. However, the molecular basis of this vulnerability is still largely unknown. Emerging evidence suggests that epigenetic mechanisms may contribute to the development of several psychiatric disorders such as depression, drug addiction and schizophrenia. Thus, to study the occurrence of possible epigenetic changes after chronic THC administration in adolescent rats, we examined total levels of some histone modifications in the prefrontal cortex, since this brain region seems to be the most affected by THC treatment and particularly relevant for the schizoaffective-like phe-

notype. To this aim, adolescent female rats were treated with increasing doses of THC twice a day from 35 to 45 post-natal day (PND). Twenty-four hours after the last THC injection the prefrontal cortices were collected and processed for Western blot experiments. THC exposure induced a significant increase in global histone H3 acetylation at lysine 14 (H3K14Ac, that increases transcriptional activity), whereas no changes were observed in global histone H3 trimethylation at lysine 27 (H3K27-3met, that decreases transcriptional activity). In contrast, animals exposed to THC in adulthood showed a slight but significant reduction in H3K27-3met and no changes in H3K14Ac. Since histone modifications impact transcriptional activity, we then investigated the effect of adolescent THC exposure on gene expression 24 hours after the last THC injection. We examined genes closely related to the endocannabinoid system or involved in synaptic plasticity (e.g. belonging to the glutamatergic and gabaergic system as well as coding for proteins or pathways related to plasticity), because adolescence is characterized by intense remodeling in neuronal connectivity and the endocannabinoid system seems to play a role. Real-Time PCR arrays revealed that THC exposure induced an intense and wide spread decrease in mRNA levels of the considered genes. Again, a different picture was observed when the same analysis was performed in adult-exposed rats. However the observed reduction in gene expression did not correlate with the increased H3K14Ac. Thus, to investigate the time course of the altered gene expression, the same analyses were performed 2 and 48 hours after the last THC injection. Adolescent THC exposure decreased several mRNA levels analyzed immediately after the treatment. In contrast, 48 hours later, all the mRNA analyzed returned to control levels or even increased. To understand the stability of these alterations the same analyses were also performed at 60 and 75 PND. An increase of several mRNA levels was still present at 60 PND, while only the expression of two genes (Gria1 and Gad1, known to be of relevance for schizophrenia both in patients and animal models) resulted altered at 75 PND. As a whole, these data suggest that adolescent THC treatment impaired the steady state expression of a set of genes involved in brain plasticity. These alterations might play a role in the development of the schizoaffective disorder induced by adolescent THC exposure.

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"THE GOOD, THE BAD, THE UGLY": EXPERIMENTAL HUMAN STUDIES OF CBD, THC, AND THCV

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Background: Experimental studies using intravenous administrations of drugs are an excellent method of exploring specific interactions between cannabis compounds. Here we will present results of two studies in which Δ9-tetrahydrocannabinol (THC) was administered intravenously to healthy volunteers, one in which Cannabidiol (CBD) was used as a pre-treatment and Δ9-tetrahydrcannabivarin (THCV) in the other.

Methods: The first study used a between subjects design with 48 participants, pre-treatment of CBD (600mg oral) or placebo was followed by iv. Injection of 1.5mg THC. The second study used a within subjects design where participants were dosed for 5 days with THCV (10mg/day oral) or placebo, followed by 1mg iv. THC. Both studies used standardised cognitive and psychopathology measures. Results In the first study, CBD significantly attenuated THC induced paranoid symptoms ($t=2.28$, $p<0.05$), impaired delayed verbal recall ($t=2.39$, $p<0.05$) and reduced the number of clinically significant psychotic symptoms ($\chi^2=4.74$, $p<0.05$). In the second study, 1mg iv. THC did not produce significant paranoia or psychotic symptoms. THCV did however significantly impair delayed verbal recall ($t=2.74$, $p<0.05$), an effect that was absent when THCV was co-administered ($t=1.48$, $p=0.17$).

Conclusion: The negative effects of THC on psychopathology and memory are highly dose dependent and may also be eliminated or reduced by co-administration of CBD or THCV.

Symposium**IS THE ASSOCIATIVE STRIATUM A LOCUS OF VULNERABILITY FOR TRANSITION TO PSYCHOSIS?****Chairperson: Anissa Abi-Dargham****Discussant: Anissa Abi-Dargham****Monday, 7 April 2014****4:15 PM – 6:15 PM**

Overall Abstract: Studies examining dopamine transmission across the anatomical striatal subdivisions using Positron Emission Tomography (PET) techniques have recently shown that the rostral caudate is the striatal substructure where the dysregulation is greatest and where it first starts during the prodromal phase of the illness. These findings disproved the long held belief by researchers in the field that the ventral striatum is the main area of abnormal dopamine transmission underlying the positive symptoms of the illness, referred to as the “mesolimbic hypothesis”, and shifted the focus to the associative striatum, and in particular, to the rostral caudate within the associative striatum. This structure receives input from the dorso-lateral prefrontal cortex (DLPFC), and, in addition, some input from limbic cortical regions, thus processing cognitive information, and also serving to integrate across limbic and cognitive domains. Enhanced dopamine transmission during development in the dorsal striatum has also been shown to have profound effects on the function of the cortex and on the circuitry in a developmental transgenic mouse model of D2 overexpression. This panel will focus on the role of the associative striatum in the early stages of the disease by examining the imaging phenotypes in this region in patients at risk for developing schizophrenia. Oliver Howes (UK) will present the findings relating to presynaptic dopamine synthesis using [18F]f-dopa imaging scans, and their relationships to the emergence and progression of symptoms. Camilo Sandoval (Mexico) will present his findings on dysregulated glutamate transmission in the dorsal striatum at disease onset and its modulation by antipsychotic treatment, using Magnetic Resonance Spectroscopy (MRS). Tiziano Colibazzi (USA) will present results from a large cohort using bold fMRI showing functional and anatomical disruption of connections between the DLPFC and the dorsal (associative) striatum. Finally, Bita Moghaddam (USA) will present data contrasting the local variations in dopamine transmission within the striatal substructures in adolescent versus adult rats, suggesting a mechanistic understanding of the observations in patients during the transition from prodromal stages to overt psychosis, and provide rationale for a possible therapeutic strategy. Anissa Abi-Dargham (USA) will integrate and discuss the relevance of these convergent findings to the field of schizophrenia research.

DEVELOPMENTAL AND DIETARY SENSITIVITY OF DOPAMINE IN DORSAL STRIATUM**Bita Moghaddam, Nick Simon, YunBok Kim, Jesse Wood****University of Pittsburgh**

Recent studies in individuals at high risk to develop schizophrenia consistently point to dysregulated striatal-prefrontal cortex (PFC) interactions that are, in part, reflected in elevated presynaptic striatal dopamine availability. Briefly, these findings indicate that a dopamine abnormality (i) predates the onset of schizophrenia in individuals with prodromal symptoms, (ii) is predominantly localized in the associative/dorsal striatum, and (iii) is correlated with the severity of symptoms and neurocognitive dysfunction. These findings also provide evidence that the onset of frank psychosis is preceded by reduced gray matter volume in several cortical regions and direct correlations between altered PFC function and subcortical dopamine synthesis capacity. In addition, there are reports of disrupted activity of substantia nigra/VTA activation using fMRI in first episode psychosis patients during an instrumental reward conditioning task. The regions and associated circuits identified in these studies parallel the regions where we find dopamine and task-related unit activity differences in adolescents versus adults suggesting that disruption of cortical networks that regulate dopamine projections to the dorsal regions of the striatum are loci of vulnerability during adolescence. For example, we find that dopamine synthesis capacity as measured by tyrosine hydroxylase (TH) levels is significantly lower in the dorsal striatum of adolescent rats, suggesting that attenuated striatal activity may

be a component of normal development during adolescence that may be disrupted in individuals at high risk to develop schizophrenia. In addition we find that dietary manipulation of omega-3 fatty acids that has been reported to influence transition to psychosis in at-risk individuals uniquely disrupts dopamine synthesis in the dorsal striatum. Collectively, our animal studies identify key differences in presynaptic dopamine activity in the dorsal striatum, and in the processing of salient information in the dorsal striatum and PFC of adolescent compared to adult rats. These data complement the emerging clinical findings that suggest that the disruption of cortical networks that regulate dopamine projections to cortical and the dorsal/associative regions of the striatum may be relevant to increased vulnerability to transition to psychosis.

ABNORMALITIES OF FRONTOSTRIATAL CIRCUITS IN THE PSYCHOSIS PRODRome

Tiziano Colibazzi¹, Anissa Abi-Dargham², Guillermo Horga¹, Yuankai Huo¹, Zhishun Wang¹

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The development of psychotic illness is preceded by a long phase, in mid-to late adolescence, characterized by attenuated or brief psychotic symptoms as well as functional decline. This prodromal phase is of particular interest because the absence of a variety of confounding factors such as chronicity, medication use or institutionalization allows one to separate more clearly state- and trait-related effects. Over the last six years, we have been collecting longitudinal imaging data in multiple modalities (anatomical, diffusion, resting state, task-based fMRI as well as MRS data) in a cohort now consisting of sixty subjects deemed at ultra-high risk (UHR) for psychosis as well as and age- and gender matched healthy controls. So far, eight individuals in this cohort have developed psychotic illness. Recently, published anatomical, fMRI and PET studies of UHR cohorts have suggested the presence of abnormalities in fronto-striatal networks, predating the onset of psychotic illness. Using our multimodal dataset, we investigated whether abnormalities of frontostriatal circuits are present before the onset of psychosis. Analyses of baseline functional data during performance of a task engaging cognitive control (Simon task) has revealed decreased BOLD activation, in prodromal individuals, in the head of the right caudate as well as in the ipsilateral dorsolateral prefrontal cortex (DLPFC). Subsequent preliminary analyses of resting state data in this same cohort seem to suggest abnormal functional coupling of the caudate nucleus with executive fronto-parietal networks. Finally, diffusion data in the same sample has revealed abnormalities within frontal white matter tracts connecting the DLPFC to the dorsal striatum. Taken together, our findings converge to suggest both functional and anatomical disruptions of the connections between the DLPFC and the associative striatum. We discuss these findings in the context of a model of psychosis positing an imbalance between direct and indirect pathway due to abnormal cortical input to the dorsal striatum.

STRIATAL GABAERGIC AND GLUTAMATERGIC DYSREGULATIONS AS POTENTIAL PREDICTORS OF CONVERSION TO PSYCHOSIS IN INDIVIDUALS AT ULTRA-HIGH RISK

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The current hypothesis for the origin of schizophrenia proposes that the dis-

order stems from neurodevelopmental deficits that result in a disturbance of glutamatergic neurotransmission, especially for N-methyl-D-aspartate receptor-mediated signaling. The deteriorating course of the disease maybe partially explained by cortical neuronal toxic effects secondary to enhanced glutamatergic exposure, and dopaminergic dysregulation may be the final common pathway that results from altered glutamatergic neurotransmission. Recently, we and others reported the results of proton magnetic resonance spectroscopy (1H MRS) studies that found elevated glutamate levels in the associative striatum of subjects at ultra-high risk for psychosis (UHR), as well as in antipsychotic-naïve subjects during their first episode of psychosis (Cohen's effect sizes = 0.9 and 1, respectively). Subsequently, by longitudinally following these UHR subjects over 2 years, we demonstrated that the subjects with higher glutamate levels at baseline later transitioned to psychosis (Cohen's effect size = 1.39), suggesting the involvement of this excitatory amino acid neurotransmitter in the early or prodromal phases of schizophrenia. On the other hand, these glutamate system elevations could be explained in terms of pyramidal cell disinhibition by impairment of fast-spiking γ-aminobutyric acid (GABA) interneuron function. A recent 1H MRS study performed in a second cohort of UHR subjects found increased levels of GABA ($p < 0.001$, effect size = 1.3) and of the combined resonance of glutamate and glutamine – Glx ($p = 0.007$, effect size = 0.84) in the associative striatum compared to healthy controls. These results warrant multi-site, longitudinal studies to assess whether these neurotransmitter abnormalities can serve as noninvasive biomarkers of conversion risk to psychosis, as well as of illness progression and treatment response.

IS THE ASSOCIATIVE STRIATUM A LOCUS OF VULNERABILITY FOR TRANSITION TO PSYCHOSIS?

Oliver Howes, Alice Egerton, Paul Allen, Chris Chaddock, Philip McGuire
Institute of Psychiatry, King's College London

Background: The hypothesis that the dopamine dysfunction in schizophrenia is localized to mesolimbic pathways has been very influential despite the lack of direct evidence from patient studies. We therefore sought to investigate the localization of dopamine dysfunction in schizophrenia and people at clinical risk of the disorder and the link to symptoms and cortical function *in vivo* using PET and fMRI imaging.

Method: We used PET to study striatal dopamine synthesis capacity in patients ($n=36$) with schizophrenia and subjects at high clinical risk of psychosis ($n=54$; all meeting the CAARMS criteria for an at risk mental state [ARMS]) who show prodromal signs of schizophrenia and matched controls ($n=41$). The ARMS subjects received assessment of verbal fluency and clinical follow-up to determine who developed psychosis. The striatal regions of interest were the whole striatum (S), and its limbic (LS), associative (AST) and sensorimotor (SMST) subdivisions. Additionally we investigated dopamine synthesis capacity in the nigral origin of the dopaminergic projections to the dorsal striatum in schizophrenia in complementary PET and post-mortem studies. A sub-sample of the ARMS subjects and controls also received fMRI imaging using a task that activates the frontal cortex to investigate fronto-striatal interactions.

Results: Striatal dopamine synthesis capacity was significantly elevated in the associative striatum in the ARMS subjects ($p < 0.05$), and was significantly related to symptoms and cognitive performance ($p < 0.05$), and to fMRI activation during the cognitive task ($p < 0.05$). In contrast dopamine synthesis capacity was not significantly elevated in the limbic striatum ($p > 0.1$). The elevation in dopamine synthesis capacity was specific to the ARMS subjects who went on to develop psychosis. In schizophrenia dopamine synthesis capacity was significantly elevated in associative ($p=0.001$), sensorimotor ($p=0.001$) and limbic striatum ($p=0.017$), although this was relatively less marked in the limbic striatum. Furthermore the uptake of labeled-DOPA indexed using PET *in vivo* and tyrosine hydroxylase staining *ex vivo* were both elevated in the substantia nigra.

Conclusion: These findings indicate that i) dysfunction in associative striatal dopamine function, rather than limbic dysfunction, predates the onset of psychosis, ii) in schizophrenia dorsal striatal dysfunction is more marked than limbic alterations; and iii) dopamine synthesis capacity is also altered in the nigral origin of dopaminergic projections to the dorsal striatum in schizophrenia. These findings link dorsal striatal dopamine dysfunction to the development of psychosis and do not support the mesolimbic hypothesis.

Symposium

POTENTIAL ROLE OF NMDA-RECEPTOR ANTIBODIES IN SCHIZOPHRENIA: OVERLAP AND DISTINCTION FROM NMDA-RECEPTOR ENCEPHALITIS

Chairpersons: Johann Steiner and Hannelore Ehrenreich

Discussant: Souhel Najjar

Monday, 7 April 2014

4:15 PM – 6:15 PM

Overall Abstract: NMDA-receptor encephalitis has been discovered by J. Dalmau in 2007. Many of these patients develop a multistage illness that progresses from psychosis, memory deficits, seizures, and language disintegration to a state of unresponsiveness with catatonic features often associated with abnormal movements, as well as autonomic and breathing instability. It has been suggested that mild or incomplete forms of the disorder (formes frustes) with predominant or isolated psychiatric symptoms could occur. This symposium aims to summarize recent studies on the prevalence of NMDA-receptor antibodies in schizophrenia. In this context, we will discuss the influence of diagnostic criteria (definition of "schizophrenia") on the study results. Belinda Lennox (Oxford, UK) will present data on first-onset schizophrenia, estimating that the prevalence of NMDA-receptor antibodies in first episode psychosis is approximately 4%. She will present the clinical and cognitive characteristics of a cohort of NMDAR receptor antibody positive patients with a primary psychotic illness, without other features of encephalitis, and their response to treatment with immunotherapy. Takashi Kanbayashi (Akita, Japan) detected NMDA-receptor antibodies not only in encephalitis, but also in schizophrenia and narcolepsy with psychotinic features. Notably, most of these seropositive patients showed catatonic or disorganized features. Johann Steiner (Magdeburg, Germany) analyzed serum from 459 acutely ill patients admitted with the DSM-IV diagnoses of schizophrenia, major depression (MD), and borderline personality disorder (BLPD) or matched controls. Diverse NMDA-R antibodies were identified in subjects with an initial diagnosis of schizophrenia (9.9%), opposed to MD (2.8%), BLPD (0), and controls (0.4%). Retrospectively, 2 patients initially classified as having catatonic or disorganized schizophrenia were reclassified as having misdiagnosed NMDA-R encephalitis (presence of specific serum and cerebrospinal fluid IgG NR1a antibodies). Hannelore Ehrenreich (Göttingen, Germany) will report on an overall 10% seroprevalence of NMDA-R antibodies in >2800 individuals, ranging from healthy to schizophrenic, affective disorder, stroke and Parkinson patients, as well as on genetic and environmental risk factors predisposing to antibody formation. Blood-brain-barrier (BBB) integrity seems to be crucial (only those individuals with circulating NMDA-receptor antibodies who suffer from BBB dysfunction may experience neuropsychiatric symptoms). Urs Meyer (Zurich, Switzerland) will guide through these presentations as an international expert in the field of psychoneuroimmunology (invited discussant).

INCREASED PREVALENCE OF DIVERSE N-METHYL-D-ASPARTATE GLUTAMATE RECEPTOR ANTIBODIES IN PATIENTS WITH AN INITIAL DIAGNOSIS OF SCHIZOPHRENIA

Johann Steiner¹, Martin Walter², Jolja Schiltz², Bernhard Bogerts², Hans-Gert Bermstein², Wenzel Glanz³, Stefan Vielhaber³, Zoltan Sarnyai⁴, Christine Klingbiel⁵, Klaus-Peter Wandinger⁵, Winfried Stoecker⁵

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Evidence for symptomatic convergence of schizophrenia and N-methyl-D-aspartate glutamate receptor (NMDA-R) encephalitis highlights the need for an assessment of antibody prevalence and specificity for distinct disease mechanisms in patients with a diagnosis of schizophrenia among glutamatergic pathophysiologic abnormalities in psychiatric disorders. Serum from 459 patients admitted with acute schizophrenia, major depression (MD), and borderline personality disorder (BLPD) or individuals serving as matched controls was obtained from our scientific blood bank. To explore epitope specificity and antibody subtype, IgA/IgG/IgM NMDA-R (NR1a or NR1a/NR2b) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole-

propionate receptors (AMPA-R) (GluR1/GluR2) serum antibodies were determined. Two hundred thirty matched healthy controls were compared with patients (unmedicated for at least 6 weeks) with schizophrenia (n=121), MD (n=70), or BLPD (n=38). Diverse NMDA-R antibodies were identified in 15 subjects, primarily those with an initial schizophrenia diagnosis (9.9%), opposed to MD (2.8%), BLPD (0), and controls (0.4%). Retrospectively, 2 patients initially classified as having catatonic or disorganized schizophrenia were reclassified as having misdiagnosed NMDA-R encephalitis (presence of specific serum and cerebrospinal fluid IgG NR1a antibodies). In all other seropositive cases, the antibodies consisted of classes IgA and/or IgM or were directed against NR1a/NR2b (not against NR1a alone). None of the patients or controls had antibodies against AMPA-R. In conclusion, acutely ill patients with an initial schizophrenia diagnosis show an increased prevalence of NMDA-R antibodies. The repertoire of antibody subtypes in schizophrenia and MD is different from that with NMDA-R encephalitis. The latter disorder should be considered as a differential diagnosis, particularly in young females with acute disorganized behavior or catatonia.

NMDA RECEPTOR ANTIBODIES IN FIRST EPISODE PSYCHOSIS: PREVALENCE AND CLINICAL PHENOTYPE

Belinda Lennox¹, Michael S. Zandi², Julia B. Deakin³, Alasdair Coles², Linda Scorielis³, Peter Jones³, Ester Coutinho⁴, Angela Vincent⁴

¹University of Oxford; ²Department of Clinical Neuroscience, University of Cambridge; ³Department of Psychiatry, University of Cambridge; ⁴Nuffield Department of Clinical Neuroscience

Objective: Autoantibodies associated with central nervous system encephalopathies have been defined over around the last decade to now include those directed against the voltage-gated potassium channel (VGKC) complex, glutamic acid decarboxylase (GAD) and the N-methyl, D-aspartate receptor (NMDAR). NMDAR-antibodies were initially described in a paraneoplastic encephalitis affecting young women with ovarian teratomas. Removal of the tumour with concurrent immunotherapies often improved the clinical outcomes. The core features of the disease include behavioural changes, delusions, memory disturbances, seizures, and a movement disorder. We aimed to describe whether a proportion of patients with psychosis, without other features of encephalitis also had antibodies to NMDA receptors.

Methods: We tested the serum of patients with a first episode of psychosis using a cell based assay expressing NR1/NR2b subunits of the NMDA receptor.

Results: 6.5% of our initial cohort of patients had antibodies against the NMDAR or VGKC complex. A further cohort of patients have been identified through clinical testing. All 16 patients with NMDAR antibodies had primary psychiatric diagnoses, and none progressed to become encephalopathic. Six patients have been treated solely with immunotherapy and psychotic symptoms have improved.

Conclusion: A proportion of patients with first episode psychosis, without other features of encephalitis have been shown to have antibodies against the NMDA receptor. The clinical and cognitive profile of patients will be discussed, and the early experience of treating patients with immunotherapy rather than antipsychotics.

ANTI-NMDA-RECEPTOR ANTIBODY DETECTED IN LIMBIC ENCEPHALITIS, SCHIZOPHRENIA AND NARCOLEPSY WITH PSYCHOTIC SYMPTOMS

Takashi Kanbayashi¹, Kou Tsutsui², Keiko Tanaka³, Akane Mori², Ayalmanishi², Yohei Sagawa², Yuka Kikuchi², Eriko Narita², Seiji Nishino⁴, Tetsuo Shimizu²

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Introduction: Causative role of encephalitis in major psychotic features, dyskineticias (particularly orofacial), seizures, and autonomic and respiratory changes has been recently emphasized. These symptoms often occur in young females with ovarian teratomas and are frequently associated with serum and CSF autoantibodies to the NMDA receptor (NMDAR).

Methods: The study included a total of 86 patients from age 15 to 72 and was carried out between January 1, 2005, and Dec 31, 2012. The patients were divided into the following three clinical groups for comparison. Group A; Patients with typical clinical characteristics of anti-NMDAR encephalitis. Group B; Patients with narcolepsy with severe psychosis. Group C; Patients with schizophrenia or schizo-affective disorders.

Results: Seventeen out of 86 cases were anti-NMDAR antibody positive in typical encephalitis cases (group A: 7 of 10 cases) and cases in a broader range of psychiatric disorders including narcolepsy (group B: 3 of 5 cases) and schizophrenia (group C: 7 of 71 cases).

Discussion: In addition to 7 typical cases, we found 10 cases with anti-NMDAR antibody associated with various psychotic and sleep symptoms, which lack any noticeable clinical signs of encephalitis (seizures and autonomic symptoms) throughout the course of the disease episodes. Several groups measured this antibody in patients with schizophrenia. British group (Zandi2011), German group (Steiner2013) and us (Tsutsui2012) report an increase in the positivity of the antibody in the patients with schizophrenia, while Dalmau's group (2011, 2012) did not. Therefore, the positivity of the antibody is still controversial, but another important aspect is the type of schizophrenic patients who are positive for the antibody. Although 8 patients were the paranoid type and 2 patients were the catatonia type in an article by Steiner, they also described that the representative feature of the cases are young females with disorganized behavior or catatonia. We also reported NMDAR positive patients of young females with acute florid psychiatric symptoms without clinical signs of encephalitis. The features of these patients mirror-those of "Atypical psychosis" proposed by Mitsuda and colleagues (1965) in Japan, a notion derived from "Cycloid psychosis" conceptualized by German psychiatrist, Leonhard (1999). Both cycloid and atypical psychosis have coinciding features of acute onset, emotional disturbances, psychomotor disturbances, alternations of consciousness, high prevalence in women, oriented premorbid personality and a phasic course with generally a good prognosis, the characteristics that are shared with those of Steiner's initial two cases and our psychiatric cases (Tsutsui2012). Unfortunately, since both atypical and cycloid psychosis, comprise a widely varied and poorly understood collection of psychiatric disorders, both concepts and terminology were removed from the current diagnostic criteria, including DSM-IV and ICD-10. As involvements of brain organic changes in atypical psychosis were suspected by the original authors (Mitsuda1965), we have to reconsider these concepts in relation to NMDAR and other immune-mediated encephalopathy, and further research is critical.

NEUROPSYCHIATRIC DISEASE RELEVANCE OF CIRCULATING ANTI-NMDA RECEPTOR AUTOANTIBODIES DEPENDS ON BLOOD BRAIN BARRIER INTEGRITY

Hannelore Ehrenreich^{1,2}, Christian Hammer³, Beata Stepienak³, Anja Schneider^{4,5}, Sergi Papiol^{3,5}, Martesa Tantra^{3,5}, Martin Begemann³, Anna-Leena Sirén⁶, Luis A. Pardo⁷, Swetlana Sperling³, Suhaidah Mohd Jofrry³, Artem Gurvich³, Niels Jensen³, Katrin Ostmeier³, Fred Lüdmer⁸, Christian Probst⁹, Henrik Martens¹⁰, Meyke Gillis¹¹, Gesine Saher¹², Klaus-Armin Nave^{5,12}

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In 2007, a multifaceted syndrome, associated with anti-NMDA receptor autoantibodies (NMDAR-AB) of immunoglobulin-G isotype, has been described which variably consists of psychosis, epilepsy, cognitive decline, and extrapyramidal symptoms. Prevalence and significance of NMDAR-AB

in complex neuropsychiatric disease versus health, however, have remained unclear. We tested sera of 2817 subjects (1325 healthy, 1081 schizophrenic, 263 Parkinson and 148 affective-disorder subjects) for presence of NMDAR-AB, conducted a genome-wide genetic association study (GWAS), comparing AB-carriers versus non-carriers, and assessed their influenza AB status. For mechanistic insight and documentation of AB functionality, in vivo experiments involving mice with deficient blood-brain-barrier (ApoE-/-) and in vitro endocytosis assays in primary cortical neurons were performed. In 10.5% of subjects, NMDAR-AB (NR1 subunit) of any immunoglobulin isotype were detected, with no difference in seroprevalence, titer, or in vitro functionality between patients and healthy controls. Administration of extracted human serum to mice influenced basal and MK-801 induced activity in the open field only in ApoE-/- mice injected with NMDAR-AB positive serum but not in respective controls. Seropositive schizophrenic patients with a history of neurotrauma or birth complications, indicating an at least temporarily compromised blood-brain-barrier, had more neurological abnormalities than seronegative patients with comparable history. A common genetic variant (rs524991, p=6.15E-08) as well as past influenza A (p=0.024) or B (p=0.006) infection were identified as predisposing factors for NMDAR-AB seropositivity. The >10% overall seroprevalence of NMDAR-AB of both healthy individuals and patients is unexpectedly high. Clinical significance, however, apparently depends on association with past or present perturbations of blood-brain-barrier function.

Symposium

RELAPSE – RISK AND PREVENTION

Chairpersons: Robert Zipursky and Robin Emsley

Discussant: S. Charles Schulz

Monday, 7 April 2014

4:15 PM – 6:15 PM

Overall Abstract: The treatment of schizophrenia can now be expected to result in a remission of symptoms for a majority of people with schizophrenia. Relapses, however, are very common and are often considered to be an expected characteristic of the natural course of the illness. The risk of relapse and the extent to which they may be preventable has been the subject of much ongoing research. This symposium will focus on research that has addressed key questions about the risk of relapse, the causes and predictors of relapse, as well as methodological and ethical considerations in studying relapse. Relapses may occur for a myriad of reasons. Some may be a manifestation of the underlying biology of schizophrenia while others may be better understood as a reflection of factors indirectly associated with illness such as non-adherence to treatment and concurrent substance abuse. Making the distinction between primary and secondary causes of relapse has important implications for understanding and preventing relapses. While maintenance treatment with antipsychotic medication has been considered to be a mainstay for relapse prevention, little is known about how much medication is required and how often it needs to be administered to be effective. In a recent meta-analysis, relapse rates have been estimated to be lower in patients receiving maintenance antipsychotic treatment (27%) in comparison with those receiving placebo (64%). The extent to which these estimates are affected by the degree of improvement and the level of treatment adherence remains to be determined. A systematic review of antipsychotic discontinuation in stable remitted patients who were treated for a first episode of non-affective psychosis will be presented. The estimated rate of symptom recurrence was found to be much higher than previously described for those who discontinued medication and much lower for those who continued treatment. The implications of this finding for clinical care and for the design of future research will be discussed. The high risk of relapse associated with the use of placebo in medication discontinuation studies raises important ethical considerations for future research. Little is known about either the short-term or long-term consequences of relapse. The distress experienced by those affected directly and indirectly may be considerable. The possibility that discontinuation studies involving placebo assignment may result in long-term harm cannot yet be excluded. The design of future studies will need to be informed by this consideration. The identification of valid predictors of relapse would be valuable in minimizing the risks associated with relapse in clinical care and in the research setting. Research addressing this issue will be described. Future studies of relapse, including its predictors, consequences

and prevention, will need to incorporate design features that ensure that this research can be carried out in ways that are both safe and informative.

CAN THE ONGOING USE OF PLACEBO IN RELAPSE-PREVENTION CLINICAL TRIALS IN SCHIZOPHRENIA BE JUSTIFIED?

Robin Emsley¹, Wolfgang W. Wolfgang Fleischhacker²

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Background: Placebo-controlled randomised controlled trials (RCTs) continue to be required or strongly recommended by regulatory authorities for the licensing of new drugs for schizophrenia, despite concerns of risks to trial participants. The risk is likely to be greatest in relapse-prevention RCTs where patients are stabilized and then switched to placebo. Active treatment is sometimes withheld for considerable periods, and substantial numbers of relapse events need to occur before a treatment effect can be statistically demonstrated.

Methods: In this presentation we systematically review the relapse-prevention RCTs with second-generation antipsychotics (SGAs) in schizophrenia and examine the risks of harm associated with exposure to placebo in such trials. Results are interpreted in the context of ethical and scientific pros and cons and current regulatory guidelines.

Results: We identified 12 studies involving 2842 participants of which 968 received placebo. Relapse rates were 56% for placebo and 17.4% for active treatment groups. Only one of the studies investigated the consequences of relapse, in a post-hoc analysis. There is a lack of well-designed longitudinal studies investigating the psychosocial and biological consequences of exposure to placebo, to treatment discontinuation and to relapse in schizophrenia.

Discussion: In the absence of such studies it is risky to assume that patients experiencing relapses are not at risk of significant distress or lasting harm, and it is difficult to justify the on-going use of placebo in relapse-prevention trials in schizophrenia, particularly in view of the difficulties in identifying early warning signs and the ineffectualness of rescue medication in preventing full-blown relapse.

ARE THERE CLINICALLY USEFUL PREDICTORS AND EARLY WARNING SIGNS FOR RELAPSE IN SCHIZOPHRENIA?

Wolfgang Gaebel

Heinrich-Heine-University Duesseldorf, Dept. of Psychiatry and Psychotherapy

Background: Despite the availability of effective long-term treatment strategies in schizophrenia, relapse is still common. Relapse prevention is one of the major treatment objectives, because relapse represents burden and costs for patients, their environment, and society and seems to increase illness progression at the biological level. Valid predictors for relapse are urgently needed to enable more individualized recommendations and treatment decisions to be made.

Methods: Mainly recent evidence regarding predictors and early warning signs of relapse in schizophrenia will be reviewed. In addition, data from the first-episode (long-term) study (FES; Gaebel et al. 2007, 2011) performed within the German Research Network on Schizophrenia will be presented.

Results: On the basis of FES data, premorbid adjustment, residual symptoms and some side effects are significant predictors. Although a broad spectrum of potential parameters have been investigated in several other studies, only a few and rather general valid predictors were identified consistently. Data of the FES also indicated that predictive power could be enhanced by considering interacting factors, as suggested by the vulnerability-stress-coping model. Respective studies, however, are rare. In addition, prodromal symptoms as course-related characteristics likewise investigated in the FES add substantially to early recognition of relapse and may serve as early warning signs, but prediction nevertheless remains a challenge.

Discussion: Comprehensive and well-designed studies are needed to identify and confirm valid predictors for relapse in schizophrenia. In this respect, broadly accepted and specifically defined criteria for relapse would greatly facilitate comparison of results across studies.

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PATTERNS OF RESPONSE AND THE NEUROBIOLOGY OF RELAPSE IN SCHIZOPHRENIA

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Background: Dopamine's proposed role in psychosis provides a starting point for our understanding of the neurobiology of relapse in schizophrenia. While perturbations in dopamine have been proposed as the final common pathway in psychosis, it is evident that relapse, like response, cannot be conceptualized as a singular process. Similarly, the relationship between response and relapse appears to be multidimensional, with patterns of response defining relapse, and trajectories of response translating to different trajectories of relapse. Relapse can be defined as either primary (i.e. idiopathic) or secondary (e.g. substance abuse, medication non-adherence). Primary relapse occurs in the absence of clear precipitants and thus may better reflect the biology that underlies schizophrenia. Evidence suggests, however, that secondary relapse is more common and may be associated with a more attenuated response to antipsychotics than found in the treatment of the initial episode of psychosis.

Methods: Antipsychotic-naïve individuals diagnosed with first-episode schizophrenia were treated following an algorithm that involved treatment with risperidone or olanzapine. Each trial consisted of 3 stages (low, full, or high-dose) lasting up to 4 weeks at each level and adjusted according to response and tolerability. Clinical response was defined as resulting in a Clinical Global Impression Inventory - Improvement (CGI-I) of "much" or "very much improved", or a Brief Psychiatric Rating Scale (BPRS) Thought Disorder subscale of <6. Clinical data was collected on a monthly basis over a period of 6 months. In the case of relapse due to non-adherence, the same medication and dose where response was previously noted was offered again for the second episode. Results A total of 38 individuals (82% male; average age=22) reached that point following treatment with the first antipsychotic where they met criteria for response. Over a period of 2 years, each of these individuals relapsed due to non-adherence and went through a second trial with the same treatment. We observed that the BPRS (total/core psychosis scale) improvement was significantly greater for the first episode compared to the second episode at every time point over the first 6 months of treatment. The shape of trajectory was, however, similar for both first and second episodes.

Discussion: Reinitiating antipsychotic treatment for a second episode of psychosis was found to be associated with an attenuated response to antipsychotic medication. This finding raises questions about the nature of changes that may be taking place in the dopamine system in patients who have relapsed after discontinuing their antipsychotic medication. Whether this observation reflects the progression of biological changes associated schizophrenia or the impact of previous treatment or its withdrawal is not yet understood. The doses of antipsychotic medication and the frequency of administration required to prevent relapse also remains to be elucidated. In a recent 6-month placebo-controlled trial, we found that administering antipsychotic medication on alternating days was not associated with an increased risk of relapse. These lines of evidence raise a number of important questions about the prevention and treatment of psychotic relapses. Our results challenge the assumption that sustained D2 antagonism is the singular requirement for preventing relapse and the expectation that reconstituting the previous level of D2 antagonism is likely to result in a return to a remitted state. Taken together, these findings indicate that response and relapse must be viewed as multidimensional and are likely mediated by distinct mechanisms.

RISK OF SYMPTOM RECURRENCE WITH MEDICATION DISCONTINUATION IN FIRST-EPIISODE PSYCHOSIS: A SYSTEMATIC REVIEW

Robert Zipursky, Natasja M. Menezes, David L. Streiner

Department of Psychiatry and Behavioural Neurosciences, McMaster University

Background: The large majority of individuals with a first episode of schizophrenia will experience a remission of symptoms within their first year of treatment. It is not clear how long treatment with antipsychotic medications should be continued in this situation. The possibility that a percentage of patients may not require ongoing treatment and may be unnecessarily exposed to the long-term risks of antipsychotic medications has led to the development of a number of studies to address this question.

Methods: We carried out a systematic review to determine the risk of experiencing a recurrence of psychotic symptoms in individuals who have discontinued antipsychotic medications after achieving symptomatic remission from a first episode of non-affective psychosis (FEP).

Results: Six studies were identified that met our criteria and these reported a weighted mean one-year recurrence rate of 77% following discontinuation of antipsychotic medication. By two years, the risk of recurrence had increased to over 90%. By comparison, we estimated the one-year recurrence rate for patients who continued antipsychotic medication to be 3%.

Discussion: These findings suggest that in the absence of uncertainty about the diagnosis or concerns about the contribution of medication side effects to problems with health or functioning, a trial off of antipsychotic medications is associated with a very high risk of symptom recurrence and should thus not be recommended.

Symposium

REWARD PROCESSING, COGNITION AND PERCEPTION DURING ADOLESCENT BRAIN DEVELOPMENT AND VULNERABILITY FOR PSYCHOSIS

Chairpersons: Richard S.E. Keefe and Bita Moghaddam

Discussant: Philip McGuire

Monday, 7 April 2014

4:15 PM – 6:15 PM

Overall Abstract: Adolescence is a stage in which many neural processes are still maturing. Brain networks involved in context-based perception and reward processing are in frequent transition during this critical developmental stage. Although psychosis does not usually emerge until young adulthood, subtle neurobiological changes and the cognitive and behavioral manifestations of these changes may be present during adolescence. It is thus important to determine to what extent an abnormal maturation of reward networks contributes to these conditions. Social interaction, development of perceptual systems, and processing of rewarding information may have a strong impact on sculpting these circuits during adolescence. Cortical inhibitory processes that are essential for response selection and error detection may not be mature during adolescence. Alterations in the maturation of these processes may lead to vulnerability for psychosis. Bita Moghaddam will present single unit and local field potential data suggesting that during value processing and reinforcement expectation tasks, adolescent rats had local field potentials demonstrating that adolescent phasic neural activity is less inhibited and more variable during motivated/reward-driven behaviors. Specifically, diminished inhibitory response of orbitofrontal cortex neurons to salient events and the accompanying detrimental impact on coordinated large-scale activity may lead to reduced efficiency in the processing of cortical neural activity and related behaviors in adolescents. Alison Adcock will present fMRI data from young healthy subjects and ultra high risk participants suggesting a directional prefrontal influence on dopaminergic regions during reward anticipation. These data suggest a model in which the dlPFC integrates and transmits representations of reward to the mesolimbic and mesocortical dopamine systems, thereby initiating motivated behavior. Hypoactivation in the high-risk group during reward anticipation may be explained by failures in prefrontal regulation of mesolimbic systems. Markus Leweke will present data suggesting that the failures of these neural systems may be evident in basic measures of perceptual integration assessed with binocular depth inversion methodology. These perceptual-cognitive measures may be impaired very early in the disease process in individuals who will later

develop psychosis compared to healthy subjects and individuals with other psychiatric diagnoses. Phil McGuire will serve as discussant. These lines of research indicate the maturation of reward processing during adolescence may be essential for adult performance.

ABNORMALITIES IN REWARD PROCESSING IN OFFSPRING OF SCHIZOPHRENIA PATIENTS: FRONTO-STRIATAL ABNORMALITIES AS A HIGH-RISK PHENOTYPE

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Background: During adolescence the brain changes to prepare for the challenges of adulthood. These changes occur at different rates throughout the brain: subcortical regions such as the striatum mature early, whereas the frontal lobe is one of the last regions to fully develop. During adolescence, these regions begin to form fronto-striatal circuits, which subserve important cognitive functions such as inhibitory control and reward processing. Interestingly, adolescence is also the time of onset of most psychiatric illnesses, of which schizophrenia is the most devastating. We have shown that this disorder is characterized by dysfunctions in the fronto-striatal network: these dysfunctions are related to both the cognitive impairments such as inhibitory control and reward processing and the clinical symptoms of schizophrenia, such as psychosis and anhedonia. We hypothesized that schizophrenia is a developmental disorder, in which the fronto-striatal network fails to develop properly during adolescence. We examined the frontostriatal network with functional MRI (inhibitory control and reward processing) in 20 adolescent offspring of schizophrenia patients and 40 age and sex-matched healthy control subjects. We also included 40 children of bipolar patients to examine the specificity of the findings in schizophrenia.

Methods: Structural measures: High-resolution T1-weighted scans (on a 3T Philips Achieva scanner) of the striatum and frontal lobe, including volume, diffusion tensor (DTI) and magnetic transfer (MTR) scans. DTI and MTR scans were analyzed using fiber-tracking, based on diffusion tensor fields Functional measures: Inhibition task: This task is geared towards the cognitive aspects of the fronto-striatal network, triggering activation in the rIFG, SMA, and striatum, and deactivation in the motor cortex. Reward task: This task is geared towards the motivational aspects of the fronto-striatal network, triggering activation in the OFC, SMA, ventral striatum, and insula. Functional connectivity: The level of functional coupling between regions in the fronto-striatal network will be investigated using resting-state fMRI as well as the activations during the two tasks. Preliminary results in 14 offspring of schizophrenia patients (mean age 13.3±3 years) and 25 healthy controls (mean age 12.8±2 years). None of the participants received (medical) treatment, nor had a clinical diagnosis. Inhibitory control: Offspring of patients showed hyperactivation of the striatum and frontal cortex during proactive inhibition indicating abnormal functioning in the fronto-striatal network. Activation during reactive inhibition did not differ from healthy controls. Reward processing: Offspring of patients showed hyperactivation in the ventral striatum during reward anticipation. In contrast, activation of the ventral striatum and orbitofrontal cortex was diminished while receiving the reward.

Conclusion: Taken together, these preliminary data suggest a fundamentally different developmental trajectory in high-risk offspring of schizophrenia patients than what is seen in healthy developing adolescents, suggesting a dysfunctional fronto-striatal network is present in (unsymptomatic and unmedicated) offspring of schizophrenia patients. Thus, this phenotype is related to the (genetic) risk of developing the illness.

NEURONAL PROCESSING DIFFERENCES IN THE PREFRONTAL CORTEX OF ADOLESCENTS AND ADULTS DURING MOTIVATED BEHAVIOR

Bita Moghaddam, David Sturman
University of Pittsburgh

Introduction: Adolescence coincides with increased sensation-seeking and impulsive behavior, and is often the time of symptomatic onset for psychopathologies, such as mood disorders and schizophrenia. Little is known

about the neuronal basis of the vast behavioral changes that occurs during adolescence.

Methods: We recorded single unit and local field potential (LFP) activity from the orbitofrontal cortex of adolescent and adult rats during an instrumental associative learning task. The orbitofrontal cortex is involved in value processing and reinforcement expectation.

Results: While both groups performed the task comparably well, there were striking age-related differences in the neural encoding of salient events. At a large-scale level, adolescent LFPs had smaller increases in alpha, beta, and gamma power during reinforcement retrieval and adolescent neurons exhibited greater firing-rate variability throughout the task. Consistent with the mechanism that the coordination of spike timing and the entrainment of LFP oscillations is regulated by inhibitory activity, a smaller proportion of single units were inhibited in adolescents compared to adults during reinforcement retrieval.

Discussion: Diminished inhibitory response of orbitofrontal cortex neurons to salient events and the accompanying detrimental impact on coordinated large-scale activity may lead to reduced efficiency in the processing of cortical neural activity and related behaviors in adolescents. Understanding the neural basis of adolescent motivated behavior may give us insight into normal development and ultimately lead to clues to therapeutic strategies for schizophrenia.

DORSOLATERAL PREFRONTAL CORTEX DRIVES MESOLIMBIC DOPAMINERGIC REGIONS DURING MOTIVATED BEHAVIOR: INSIGHTS FROM DYNAMIC CAUSAL MODELING AND FMRI IN AT-RISK ADOLESCENTS

R. Alison Adcock^{1,2}, Jeffrey MacInnes¹, Vishnu Murty¹, Ian Ballard¹, Siow Ann Chong³, Mythily Subramaniam³, Richard Keefe^{3,4}, Katherine MacDuffie¹, Joann Poh⁵, Kavitha Dorairaj⁵, Jamie Thong³, Yioe Bong³

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Introduction: Motivation translates goals into action. Motivation to obtain reward is thought to depend on the midbrain [particularly the ventral tegmental area (VTA)], the nucleus accumbens (NAcc), and the dorsolateral prefrontal cortex (dLPFC), but how do the interactions among these regions relate to reward-motivated behavior? To study the influence of motivation on these reward-responsive regions and their interactions, we used functional magnetic resonance imaging (fMRI) data from healthy participants and adolescents or young adults at ultra-high risk for developing psychotic disorders (CAARMS+) as they anticipated and prepared for opportunities to obtain reward, thus allowing characterization of how information about reward changes physiology underlying motivational drive in these two populations. We modeled mesolimbic sensitivity to anticipation of reward and punishment, and used Dynamic Causal Modeling to assess the impact of external reward cues on causal relationships within this network.

Results: In healthy participants, dLPFC was the exclusive entry point of information about reward in this network: anticipated reward availability caused VTA and NAcc activation indirectly, via effects on the dLPFC. In group contrasts between at-risk participants and matched controls, there were no main effects of group during reward or loss anticipation, but both the NAcc and the VTA showed greater activation for anticipated gains than losses in controls but not the CAARMS+ participants ($p=0.02$ for VTA, $p=0.001$ for NAcc.) Furthermore, both VTA (-0.234 , $p=0.04$) and NAcc activation (-0.414 , $p=0.04$) were inversely correlated with clinical severity as indexed by PANSS positive symptom scales. Our findings of a directional prefrontal influence on dopaminergic regions during reward anticipation suggest a model in which the dLPFC integrates and transmits representations of reward to the mesolimbic and mesocortical dopamine systems, thereby initiating motivated behavior; ongoing analyses will test the hypothesis that the clinically-correlated hypoactivation in the CAARMS+ group is explained by failures in prefrontal regulation of mesolimbic systems during motivated behavior.

THE BINOCULAR DEPTH INVERSION ILLUSION TEST – A BASIC MEASURE OF PERCEPTUAL INTEGRATION

F. Markus Leweke^{1,2}, L. Kranaster³, C. Hoyer³, M.A. Neatby⁴, A. Haensel⁴, S. Gross⁴, B.M. Nolden⁴, J. Klosterkötter, H.M. Emrich⁵, D. Koethe⁶

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The binocular depth inversion illusion test (BDII) represents a sensitive measure of impaired visual information processing. It is altered in various experimental and naturally occurring psychotic states. However, it remains uncertain whether this represents a state or a trait marker and the diagnostic sensitivity and value of the BDII in early or at risk states of psychosis needs to become elucidated further. Therefore, we investigated the BDII in different major psychiatric diseases: ultra-high risk state for psychosis (UHR), first-episode, antipsychotic-naïve paranoid schizophrenia (SZ-N), short-term antipsychotically treated schizophrenia (SZ-T), major depression (MDD), bipolar disorder (BD), and dementia (D) as well as in healthy control subjects (HC). BDII scores were significantly increased in IPS, SZ-N, and SZ-T when compared to HC, indicating that visual processing is already disturbed at an early state of the disease. For MDD, BD and D no statistically significant difference was found compared to HC. The identification of individuals at high risk for developing psychosis relies on clinical examination and the use of rating scales assessing subtle, pre-psychotic psychopathology. Thus, it would be of interest to have more diagnostic tools available, testing, e.g. cognitive and perceptual impairment. We therefore analysed the receiver operating characteristic (ROC) curve, testing ultra-high risk cases versus a clinically relevant sample of non-psychotic patients and controls, including HC and patients suffering from MDD, BD or D revealing a AUC of 0.70. Thus, the BDII may be useful as an additional neuropsychological test for assessment of patients at high risk for developing psychosis.

Symposium

TRANSLATIONAL STUDIES ISOLATING COGNITIVE DYSFUNCTION AND AMOTIVATION IN SCHIZOPHRENIA AND RELATED DISORDERS

Chairpersons: Mark A. Geyer and Jared W. Young

Discussant: Athina Markou

Monday, 7 April 2014

4:15 PM – 6:15 PM

Overall Abstract: For decades, it was thought that the reduced joy reported by patients with schizophrenia affected their reduced motivation. This premise was up-ended, however, by laboratory-based findings detailing that patients experienced intact in-the-moment hedonia, despite reporting reduced hedonia in rating scales, resulting in what was referred to as the "anhedonia paradox". In an effort to resolve this paradox, many researchers began developing laboratory-based assessments of both physical and cognitive effortful behavior, as well as reward- and punishment-motivated learning. This symposium will describe the state-of-the-art science engineered to resolve this paradox and to unearth the neural mechanisms underlying amotivation in schizophrenia. These studies utilize tests with cross-species relevance that involve the use of fMRI, genetic, and pharmacological techniques to identify mechanisms and treatment targets for amotivation in schizophrenia. One of our speakers engaged in human researchers, Dr. Deanna Barch, first described this anhedonia paradox. Since then, she has been utilizing fMRI techniques with cognitive-based effortful and reward-learning tasks to determine the altered decision-making in patients alongside altered regions – including the striatum – which may underlie these abnormalities. Our next human researcher, Dr. Michael Green, will describe laboratory based tests that have been created by which amotivation can be measured in patients. He will describe how performance on these tests relates to traditional rating scale negative symptoms and how novel therapeutics could be tested in experimental animal procedures. Our first animal researcher/speaker, Dr. Eleanor Simpson, will describe efforts

to understand the neurochemistry that may affect cognitive and motivated behavior using striatal dopamine D2 and D3 over-expressing mice. Our final speaker, Dr. Jared Young, will describe a mouse model designed to elucidate the impact of SP4 modulation, that has been associated with schizophrenia, on cognitive, motivated, and reward-associative behaviors; possible mechanistic treatments will be discussed. These presentations will detail how laboratory testing in humans and experimental animals can identify patterns of behaviors in people with schizophrenia that through animal experimentation are linked to the identification of abnormal neuronal processes that mediate these behavioral changes. In summary, the cross-species approach taken by this group will provide great insights into the mechanisms underlying these cognitive and motivated behaviors, how they can be isolated, quantified and attempt to reverse these deficits. Finally, this symposium will outline a way forward for the pharmaceutical industry to re-engage in psychiatry research towards developing treatments for this often-overlooked debilitating cluster of negative and cognitive symptoms of schizophrenia.

EFFORT, MOTIVATION AND REWARD LEARNING IN SCHIZOPHRENIA: RELATIONSHIPS TO AMOTIVATION AND FUNCTIONAL IMPAIRMENT

Deanna M. Barch¹, Michael Treadway², Nathan Schoen³, Erin Dowd³

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Some of the most debilitating aspects of schizophrenia are an apparent lack of interest in or ability to exert effort for rewards and difficulties learning about future rewards. Such "negative symptoms" may prevent individuals from obtaining potentially beneficial outcomes in educational, occupational or social domains. In animal models, dopamine abnormalities decrease willingness to work for rewards and impair the ability to learn from rewards, implicating dopamine function as a candidate substrate for negative symptoms given that schizophrenia involves dysregulation of the dopamine system. Here we present data from two studies, one examining effort allocation and one examining reinforcement learning. In study 1, we used the Effort-Expenditure for Rewards Task (EEFRT) to assess the degree to which individuals with schizophrenia were willing to exert increased effort for either larger magnitude rewards or for rewards that were more probable in 59 individuals with schizophrenia and 39 demographically similar controls. In study 2, we used the Probabilistic Selection Task Developed by Frank and colleagues, along with fMRI, to examine the contribution of impairments in striatal prediction error signaling to impaired reinforcement learning in 49 individuals with schizophrenia and 41 demographically similar controls. In study 1, individuals with schizophrenia showed less of an increase in effort allocation as either reward magnitude or probability increased. In controls, the frequency of choosing the hard task in high reward magnitude and probability conditions was negatively correlated with depression severity and anhedonia. In schizophrenia, fewer hard task choices were associated with more severe negative symptoms and worse community and work function as assessed by a caretaker. In study 2, patients showed evidence of impairments in learning from positive, but not negative feedback. However, interestingly, we did not find clear evidence of reduced reinforcement learning related activity in the striatum. In contrast, during early learning, several regions involved in cognitive control demonstrated reduced overall choice-related activation in patients as compared to controls, which was consistent with a reduction in explicit learning during the early learning phase. Further, low probability choices were associated with reduced activation in schizophrenia in error- and conflict-processing regions including dorsal ACC, anterior prefrontal cortex, and thalamus, as well as OFC, medial temporal lobe, and cerebellar regions associated with executive control. Together, the results from the behavioral paradigms are consistent with patterns of disrupted dopamine functioning observed in animal models of schizophrenia. As such, these results suggest that two mechanisms contributing to impaired function and motivational drive in schizophrenia may be a reduced allocation of greater effort for higher value/probability rewards as well as impairments in learning from positive reinforcement. However, the imaging data suggest that such impairments may reflect involvement of cortical learning and control systems as well as striatally mediated subcortical systems.

ADAPTING EFFORT-BASED DECISION-MAKING PARADIGMS FOR SCHIZOPHRENIA: WHAT WORKS AND WHAT DOESN'T

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Negative symptoms are related to the daily functioning of individuals with schizophrenia. Specifically, the motivational negative symptoms (e.g., avolition) are key determinants of impaired daily functioning. Partly for this reason, there is interest in developing pharmacological treatments for the negative symptoms of schizophrenia. However, the evaluation of the negative symptoms of schizophrenia typically relies on clinical interviews, which raises concerns about their reliability and objectivity as endpoints for clinical trials. Performance-based measures of effort and motivation could yield endpoints that may be more sensitive to treatment effects. In this presentation, we will discuss: 1) recent data linking motivational negative symptoms to daily functioning, 2) our efforts to adapt an effort-based task from animal models (the progressive ratio breakpoint task, PRB), and 3) our adaptation of a cognitive effort-based task from basic behavioral science (the deck choice task). The results from our outcome modeling studies reveal a strong connection between motivational negative symptoms and outcome, but a weak association between expressive negative symptoms (e.g., affective blunting) and outcome. These results help to bolster the importance of motivational negative symptoms as a treatment target. Our initial attempt to adapt an effort-based task from animal models was the PRB task, and we had limited success. In this type of task, the motoric demands (e.g., finger tapping) increase during the testing session so that subjects need to expend more effort (e.g., tap more times) to receive the same level of reward. At some point, most subjects give up and stop responding, and this is referred to as the breakpoint. We found that patients as a group had a bimodal response: that is, some patients exerted less effort than controls and gave up easily, while others were overly persistent and kept responding for very long periods (a motoric style of inertia). Our results are more promising for the deck choice task. In this task, participants choose from one of two decks of cards, labeled as "easy" or "hard." The "hard" deck involves a more difficult cognitive demand; whereas the "easy" deck minimizes cognitive demands. The "hard" option is paired with increasingly larger financial reward (i.e., \$10, \$20, \$40) and the key dependent variable is the number of high-demand choices a person makes. Our preliminary results indicate that schizophrenia patients choose the hard option less often than controls. Further, patients with high levels of negative symptoms choose the hard option less often than those with low levels. Our results indicate that it is possible to develop valid and objective measures of motivation that can be used in schizophrenia clinical trials, although some types of paradigms will be more feasible than others.

DISSECTING MOTIVATION IN ANIMAL MODELS OF DOPAMINE DYSFUNCTION

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The negative symptoms of schizophrenia include deficits in motivation, which are currently not well treated and therefore heavily influence patient's functional outcomes. Patient studies suggest that the psychological factors underlying amotivation in schizophrenia include a reduced capacity for making effort/cost- benefit calculations as well as disrupted associative learning for positive reinforcement. Behavioural assays to further dissociate these processes, which have both motivation as well as cognitive components, are becoming available and will provide valuable information about the disorder, as well as useful outcome measures for clinical trials. To investigate the potential pathophysiological mechanisms that drive these deficits, animal models can provide powerful insights. As we shall demonstrate, such cross-species translational research benefits from the implementation of behavioural analysis that dissects the functional components of motivated behaviours that are relevant to the clinical symptoms. Altered dopamine signaling plays an important role in the pathophysiology

of schizophrenia and in animal studies dopamine signaling has been shown to be critical for incentive motivation. To assess the role of increased striatal dopamine D2 receptor (D2R) activity in the pathogenesis of schizophrenia-relevant neurobiological and behavioral phenotypes, we previously generated mice with selective overexpression of striatal D2Rs (D2R-OE mice). These mice show impairments in selected cognitive tasks relevant to the cognitive deficits observed in patients with schizophrenia as well as a deficit in incentive motivation. D2R-OE mice display a reduced willingness to work on a progressive ratio schedule of reinforcement in which the number of lever presses required for food reward increases following each reward earned. We carried out a battery of tests to identify the specific nature of this reduced motivation in D2R-OE mice. We determined that D2R-OE mice show normal hedonic reaction toward highly preferred food, but when given the choice between exerting effort to obtain a highly preferred food or consuming a less preferred reward for no effort, D2R-OE work significantly less for the preferred reward. Subsequent testing on two concurrent schedules of reinforcement determined that D2R-OE mice are less sensitive to the relative value of positive outcomes than controls. These results suggests that overexpression of striatal D2Rs results in a motivational deficit with striking similarity to that observed in patients, a decreased willingness to work that is not due to anhedonia, but to a deficit in the representation of future outcomes and/or an imbalance in the cost/benefit computation. The currently available evidence indicating an increase in D2R signaling in the striatum of patients with schizophrenia comes from PET studies using ligands which bind both D2 and D3 receptors. Therefore, to determine if an increase in D3 receptors in the striatum could also result in neurobiological and behavioral phenotypes relevant to schizophrenia, we generated a transgenic mouse model of striatal D3R overexpression (D3R-OE mice). In contrast to D2R-OE mice, D3R-OE mice did not show deficits in cognitive functions including working memory or conditional associative learning. However, like D2R-OE mice, D3R-OE mice are impaired in incentive motivation, demonstrated by a reduction in breakpoint on a progressive ratio schedule. This dissociation of the cognitive and motivational phenotypes induced by increased striatal dopamine signaling in mice provides an opportunity to further dissect the role of dopamine signaling in motivated behaviors relevant to schizophrenia.

ISOLATING POOR ATTENTION, REWARD LEARNING, AND MOTIVATION IN THE SP4 HYPMORPHIC MOUSE MODEL OF SCHIZOPHRENIA: GLYT1 INHIBITORS TREAT ONLY INATTENTION

Jared W. Young^{1,2}, Mary E. Kamenski³, Mark A. Geyer^{2,3}, Kerin Higa³, Xianjin Zhou^{2,3}

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People with schizophrenia (SZ) exhibit a myriad of behavioral abnormalities, including cognitive dysfunction and negative symptoms such as amotivation. The mechanisms underlying these behavioral deficits are often overlapping, with symptoms impacting each other. Recently, reward learning deficits have been linked with motivational deficits in patients which may both be impacted by the inattention suffered by patients. With no approved treatments for cognitive dysfunction or negative symptoms, research has focused on developing etiological model animals of SZ to better understand mechanisms impacting affected behaviors and test novel therapeutics. Polymorphisms in the developmentally important SP4 gene have been associated with SZ. In the present studies, we used Sp4 mutant mice as a model animal to understand the effects of this mutation on cross-species tests of attention, reward associative learning, and motivation. Further examination of the mechanisms contributing to altered behaviors of these mice were conducted by treating them with the glycine transporter (GLYT1) inhibitor Org 24598. We hypothesized that Sp4 hypomorphic (Hypo) mice would exhibit impaired attention, reward learning, and motivation compared with wildtype (WT) littermates due to their reduced NMDA1 receptor expression, and that the GLYT1 inhibitor would reverse these deficits. Sp4 Hypo (n=10) and WT (n=16) mice were bred from heterozygous breeders and trained in various 5-hole operant tasks, including the 5-choice continuous performance test of attention, the probabilistic learning test of reward associative learning, and the progressive ratio breakpoint schedule test of motivation. After characterization in each test, the effects of the GLYT1

inhibitor (0.3, 1, 3 mg/kg) was assessed in each test using a within-session design. Sp4 Hypo mice exhibited poorer attention, learning, and motivation compared with their WT littermate mice, similar to impairments described in patients with SZ. The inattention of the Sp4 Hypo mice was reversed by increasing synaptic glycine levels via GLYT1 inhibition treatment (3 mg/kg), which impaired attention in the WT mice. The poor reward learning and motivation of SP4 Hypo mice was not reversed by GLYT1 inhibition treatment however. Theoretically, the increased synaptic glycine reversed the 5C-CPT deficit of Sp4 Hypo mice via attenuating the effects of their reduced NMDAR1 expression. Hence, the poor learning and amotivation of the SP4 Hypo mice may not relate to their reduced NMDAR1 expression. These studies demonstrate that the developmental abnormalities resulting from mutation in the Sp4 gene have numerous behavioral consequences with various underlying mechanisms. Furthermore, because the impaired reward associative learning and poor motivation of SP4 Hypo were not attenuated by GLYT1 inhibitor treatment, these behaviors may result from overlapping affected underlying mechanisms.

Plenary Session

UPDATE ON THERAPEUTICS: IMPROVING THE CLINICAL YIELD

Chairpersons: John Kane and Richard Keefe

Tuesday, 8 April 2014

8:30 AM – 12:00 PM

Overall Abstract: New treatment development in schizophrenia remains a challenge. Despite a variety of preclinical models and translational efforts, the availability of compounds with novel mechanisms of action is limited. There are important initiatives underway to enhance our approach to diagnosis (e.g. RDoC, genomics, stem cell research) and provide a better understanding of the heterogeneity of schizophrenia in order to facilitate drug development and come closer to personalized or precision medicine. However, despite the promise that this multiyear process holds, we still face the immediate challenge of improving the lives of our current patients with better treatments. This session will allow experts from industry and academia to discuss strategies to improve the clinical yield in current drug development efforts. A number of high profile disappointments and the increasing challenge of maintaining the engagement of large pharma companies in CNS research underscore the urgency of these efforts. Daniel Umbricht will discuss strategies to assessing treatment effects in negative symptoms. Christopher Schmidt will review lessons learned from a PDE 10 development program and Bruce Kinon will do the same for a mGlu program. Richard Keefe will provide an overview of signal detection in trials involving cognitive enhancement. Jonathan Rabinowitz will discuss the power of industry academia collaboration to enhance therapeutics and John Kane will review overall challenges in the design and conduct of clinical trials in schizophrenia.

Symposium

AT RISK MENTAL STATE TREATMENT UPDATE

Chairpersons: Mark van der Gaag and Dorien H. Nieman

Discussant: Stephan Ruhrmann

Tuesday, 8 April 2014

2:00 PM – 4:00 PM

Overall Abstract: The period preceding the first psychotic episode is regarded as a promising period for intervention. Insight into optimal treatment of an at-risk mental state (ARMS) for developing a first psychotic episode has improved in the past years. In this symposium, results are presented of recent studies investigating ARMS treatment. Patrick McGorry and colleagues will present a number of recent and future clinical trials investigating whether it is possible to delay, ameliorate or even prevent psychosis. ARMS is not only a precursor of disorders in the psychotic spectrum but also of a range of other major mental disorders and suicidal behaviour. The most recently published 12 month randomized controlled trial (RCT) comparing risperidone/cognitive behavioural therapy (CBT), Placebo/CBT and Placebo/supportive therapy in 115 ARMS subjects will be discussed. All three groups improved substantially over the course of the trial on dimensional measures, particularly in terms of negative symptoms

and overall functioning. Specific treatment conditions reduced transitions to psychosis from 20% to 10% but this was a non-significant finding. The equivalent transition rate in the three groups fails to provide support for the first-line use of antipsychotics in ARMS subjects. Furthermore, Patrick McGorry et al. will give an update of an ongoing multicenter replication study of treatment with omega 3 fatty acids in 300 ARMS subjects. Tony Morrison and colleagues report on new results of research into internalised stigma in the 5-site UK-based EDIE-2 trial (n=288) investigating cognitive therapy (CT) for ARMS. ARMS subjects were assessed longitudinally using measures of psychotic experiences, depression, social anxiety and internalised stigma. Negative appraisals of unusual experiences contributed significantly to depression scores at 6 month follow up, when controlling for baseline depression and unusual psychological experiences. Furthermore, negative appraisals of experiences were significantly reduced in the group assigned to CT. The findings suggest that internalized stigma may contribute to the development of depression and that CT could be considered a non-stigmatizing intervention in ARMS subjects. Subsequently, Mark van der Gaag et al. will present a meta-analyses of CBT for ARMS subjects. A search identified 10 studies reporting 12-month follow-up data on transition to psychosis, and 5 studies with follow-ups varying from 24 to 48 months. Overall the risk reduction at 12 months was 54% with a number needed to treat of 9. Early detection and intervention in ARMS subjects can be successful to prevent or delay a first psychosis. Lastly, Dorien Nieman et al. will present a new CBT developed especially for ARMS subjects that focuses on awareness of cognitive biases and normalisation by means of psycho-education. In a Dutch RCT (n=201), 10 patients transitioned to psychosis in the treatment condition compared with 22 in the treatment as usual group ($p=0.03$). In addition, at 18-month follow-up the CBT group was significantly more often remitted from ARMS. Furthermore, Dorien Nieman et al. report on an individualized prognostic score composed of premorbid adjustment and information processing variables. In the risk class of ARMS subjects with the worst premorbid adjustment and information-processing deficits, transition rate was 74% compared to only 4% in the lowest risk class. Research into tailoring the interventions to individualized risk estimation is warranted. Stephan Ruhrmann is discussant and will integrate the results of the above mentioned studies, considering recommendations for clinical practice and further research questions.

SUBTHRESHOLD INTERVENTION TO REDUCE THE IMPACT OF EMERGING PSYCHOSIS AND RISK FOR STAGE PROGRESSION: RECENT AND FUTURE CLINICAL TRIALS

Patrick McGorry¹, Barnaby Nelson², Lisa Phillips³, Paul Amminger², Alison Yung^{2,4}

¹Orygen Youth Health Research Centre; ²Orygen Youth Health Research Centre and University of Melbourne; ³Dept of Psychology, University of Melbourne, Australia; ⁴University of Manchester

The major mental disorders are typically preceded by a subthreshold stage of emergent clinical features which result in distress, impairment and a need for care. This has been shown most convincingly for psychotic disorders but it is also the case in mood and other common disorders. In psychotic disorders a new clinical research domain has developed in many centres around the world and collectively it has been shown through meta-analysis that the Melbourne UHR criteria capture a clinical phenotype with a risk over 3 years of 36% for transition to psychosis. In addition persistence of the UHR phenotype, a range of other mental disorders and suicidal behaviour are among other disabling outcomes. While some have chosen to focus on the false positive issue and highlight the fact that most of these cases fail to progress to fully fledged psychosis, the fact is that there is a need for care and an opportunity to prevent progression across the stages of illness, not only psychosis. Hence a number of clinical trials have been conducted in recent years to determine whether it is possible to delay, ameliorate or even prevent psychosis. This has been a successful venture with ten clinical trials now revealing an average NNT of 8. We have completed and published 3 such trials using a variety of therapies including cognitive behavior therapy, needs based case management, low dose risperidone and omega 3 fatty acids. We are in the latter stages of completion of n=300 international RCT of omega 3 fatty acids with recruitment completed and follow up continuing. Data from all these projects will be presented and discussed with a special focus on the most recently published RCT com-

paring risperidone/CBT, Placebo/CBT and Placebo/supportive therapy. The 12-month transition rates were: CT+Risp, 10.7%; CT+Plac, 9.6%; Supp+Plac, 21.8%. While there were no statistically significant differences between the three groups in transition rates, all three groups improved substantially over the course of the trial on dimensional measures, particularly in terms of negative symptoms and overall functioning. Despite some methodological issues, mainly lack of power, the lower than expected and essentially equivalent transition rates in all three groups fail to provide support for the first-line use of antipsychotic medications in UHR patients. An initial psychosocial approach with supportive therapy, augmented with CBT and case management strategies is likely to be effective and carries fewer risks. Further research in broader and/or risk-enriched samples is required to guide initial treatment as well as the treatment of non-responders.

INTERNALISED STIGMA IN YOUNG PEOPLE AT HIGH RISK OF DEVELOPING PSYCHOSIS: FINDINGS FROM A COGNITIVE THERAPY TRIAL

Anthony P. Morrison^{1,2}, **Melissa Pyle**², **Suzanne L.K. Stewart**³, **Paul French**², **Rory Byrne**², **Clare Flach**¹, **Max Birchwood**⁴, **David Fowler**⁵, **Peter Jones**⁶, **Andrew Gumley**⁷

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Internalised stigma in young people meeting criteria for at risk mental states (ARMS) has been highlighted as an important issue, and it has been suggested that provision of cognitive therapy (CT) may increase such stigma. 288 participants meeting criteria for an at risk mental state were recruited as part of a multisite randomised controlled trial of cognitive behavioural therapy for people meeting criteria for ARMS (the EDIE-2 trial). Participants were assessed at baseline and at six, twelve, eighteen and twenty-four months using measures of psychotic experiences, depression, social anxiety and internalised stigma. The Personal Beliefs about Experiences Questionnaire (PBEQ) was validated for use within our ARMS sample. Correlational analyses at baseline indicated significant relationships between internalised stigma and (1) depression, (2) social anxiety (3) distress associated with unusual psychological experiences and (1) suicidal thinking. Regression analysis indicate negative appraisals of unusual experiences contributed significantly to depression scores at 6 month follow up, when controlling for baseline depression and unusual psychological experiences. Changes in internalised stigma were analysed using random effects regression (ANCOVA) adjusted for site and baseline symptoms on an intention-to-treat basis. Negative appraisals of experiences were significantly reduced in the group assigned to CT (estimated difference at 12 months was -1.36 (95% CI -2.69 to -0.02), p=0.047). There was no difference in social acceptability of experiences (estimated difference at 12 months was +0.46 (95% CI -0.05 to +0.98), p=0.079). These findings suggest that internalised stigma may contribute to the development and maintenance of depression in young people at risk of psychosis. They also suggest that, rather than increasing internalised stigma, CT decreases negative appraisals of unusual experiences in young people at risk of psychosis; as such, it is a non-stigmatising intervention for this population.

PREVENTING A FIRST EPISODE OF PSYCHOSIS: A META-ANALYSIS

Mark van der Gaag^{1,2}, **Filip Smit**^{3,4}, **Andreas Bechdolf**⁵, **Paul French**⁶, **Don H. Linszen**⁷, **Alison Yung**^{8,9}, **Patrick McGorry**⁸, **Pim Cuijpers**³

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Background: Early detection of people at risk for developing psychosis

and intervention to prevent or postpone a first psychotic episode has been performed in the last decades. Most studies were small and underpowered.

Methods: Randomized controlled trials that aimed to prevent a first episode of psychosis were searched in Ovid MEDLINE from 1996 to July 2012, EMBASE from 1996 to July 2012, PsycINFO from 1987 to July 2012, EBM Reviews - Cochrane Central Register of Controlled Trials, and EBM Reviews - Cochrane Database of Systematic Reviews, 2005 to July 2012. A search performed according PRISMA guidelines found 10 studies that reported 12-month follow-up data, and resulted in ten trials, reported in thirteen papers. Data Extraction: 12- and 24-month results on transition to psychosis were selected. The trials were assessed for quality. Random effects meta-analyses were performed.

Results: The quality of the papers varied from fair to excellent. Overall the risk reduction was 54% (RR=0.46 (95%CI: 0.33–0.64)) with a Number Needed to Treat of 8 (95%CI: 6–16). Although the interventions differed, there was no heterogeneity and publication bias was small. All sub analyses showed effectiveness. The five cognitive behavior therapy (CBT) trials showed the most robust results with a risk reduction of 48% (RR=0.52 (95%CI: 0.33–0.83)) and a NNT of 13 (95%CI: 7–83).

Conclusion: Early detection and intervention in people with an ultra-high risk of developing psychosis is effective for preventing or postponing first episode psychosis. The findings regarding CBT are robust. More trials are needed to evaluate antidepressant medication, omega-3 fatty acids and psychosocial interventions.

PREVENTIVE PSYCHOTHERAPY

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In many serious illnesses (e.g. cancer), early detection and treatment leads to improved prognosis. In light of limited treatment possibilities in late stages of major mental disorders, early detection and treatment in psychiatry is a promising topic. Clinical experience shows that it is easier to engage a patient in treatment if insight into illness is still largely intact. Our aim was to investigate the effectiveness of a cognitive behavioural therapy (CBT) especially developed for subjects with an at risk mental state (ARMS) for developing a first psychotic episode. 201 ARMS patients were recruited at 4 Dutch sites and randomized. The CBT was provided for 6 months, and the follow-up period was 18 months. The new CBT (CBTarms; 1) focuses on awareness of cognitive biases (e.g. jumping to conclusions) and normalization by means of psycho-education. In the CBTarms condition, 10 patients transitioned to psychosis compared with 22 in the treatment as usual (TAU) condition ($\chi^2(1)=5.575$, $P=0.03$). The number needed to treat (NNT) was 9 (95% confidence interval: 4.7–89.9). At 18-month follow-up the CBTarms group was significantly more often remitted from an at-risk mental state, with a NNT of 7 (95% CI: 3.7–71.2). Compared with TAU, this new CBT showed a favourable effect on the transition to psychosis and reduction of subclinical psychotic symptoms in ARMS subjects (2). Future research is warranted into individualized risk estimation with respect to tailoring the intervention to the actual needs of the patient. We recently developed an optimised prediction model of a first psychosis in ARMS subjects considering different sources of information (3). Out of a comprehensive set of predictors, the P300 event related potential (signifying information-processing deficits) and premorbid adjustment were identified as the key elements in an individualized prognostic score. The prognostic score was further stratified into three risk classes establishing a prognostic index. In

the class with the worst premorbid adjustment and information processing deficits, 74% of the subjects made a transition to psychosis whereas in the lowest risk class only 4% transitioned. Furthermore, in the highest risk class transition emerged on average 17 months earlier than in the lowest risk class. However, transferring our approach into clinical practice requires validation in an independent sample. A successful transfer would provide new opportunities for developing targeted intervention strategies based on a subjects' individual risk index.

References:

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Symposium

CHILDHOOD TRAUMA AS RISK FACTOR IN PSYCHOTIC DISORDERS – IN SEARCH OF MECHANISMS

Chairperson: Ingrid Melle

Discussant: Paola Dazzan

Tuesday, 8 April 2014

2:00 PM – 4:00 PM

Overall Abstract: Background: Large population based studies demonstrate a link between childhood trauma (CT) and increased prevalence of personality disorders, depression, bipolar disorder and schizophrenia. Existing studies rely on cross-sectional investigations and the potential mechanisms involved in the relationship between CT and the risk of developing a severe mental disorder or important core characteristics are largely unknown.

Methods: This symposium brings together recent research on the role of CT from ongoing large studies in Australia, France, the UK and Norway. The findings confirm that there are high rates of CT not only in schizophrenia but also in the ultra-high risk population and inpatients with bipolar disorder, and underlines the link between CT, disturbances in the stress-response system and potential gene x environment interactions on important clinical phenotypes.

Results: Studies of trauma in the UHR population indicate that there are high rates of CT, comparable to rates in clinical populations with established psychotic disorder, and an association between history of sexual trauma and transition to psychotic disorder when other risk factors are controlled for. In bipolar disorder, multiple traumas are more frequently reported in patients compared to controls, with emotional- and sexual abuse appearing to be associated with a more severe expression of the disorder.

Individuals exposed to high levels of CT show long term changes in their stress response system, together with cognitive and structural brain changes in regions implicated in cognitive and behavioral regulation. High levels of stress exposure are also linked to suppression of neurogenesis, possibly mediated by stress-based reductions in neurotrophic factors. Also first-episode patients and healthy controls exposed to CT have an abnormal biological stress response including high diurnal cortisol levels and increased levels of pro-inflammatory cytokines and reduced levels of brain-derived neurotrophic factor (BDNF). Additionally, carriers of the Methionine (met) allele of the BDNF Val66Met polymorphism exposed to high levels of CT demonstrate significantly poorer cognitive functioning and show structural changes in the CNS including reduced right hippocampal volumes and larger lateral ventricles.

Discussion: The presented studies confirms the high rate of CT across a broad spectrum of patient groups; underlining the importance of sexual- and emotional abuse, and add to the growing understanding of disturbances in the biological stress-response system and of gene x environment interactions as mechanisms behind the link between CT and psychosis.

HISTORY OF TRAUMA IN THE ULTRA HIGH RISK FOR PSYCHOSIS POPULATION: FINDINGS FROM THE PACE CLINIC

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Background: There is increasing evidence that childhood trauma is a risk factor for psychotic disorder and negatively impacts symptomatic and functional outcomes in people with psychotic disorders. The "ultra high risk" (UHR) for psychosis population provides a valuable population in which to study the relationship between trauma and psychosis because it allows for prospective longitudinal investigation of the relationship between the two variables in a group with a high rate of psychosis onset (about 35% over the medium-long term). This overcomes some of the methodological limitations noted with previous studies (such as the possible influence of psychotic symptoms on recall) and provides a perfectly matched control group (UHR patients who do not develop psychotic disorder).

Method: This presentation will focus on research conducted into trauma in the UHR population seen at the PACE clinic, Orygen Youth Health in Melbourne.

Results: Studies of trauma in the UHR population seen at the PACE clinic indicate: 1. High rates of trauma (present in approximately 70% of patients), substantially greater than rates in the general population and comparable to rates in clinical populations with established psychotic disorder. 2. An association between history of sexual trauma and transition to psychotic disorder when other risk factors are controlled for. 3. A thematic association between the "content" of attenuated psychotic symptoms and history of sexual trauma. A current study exploring the relationship between trauma, stress reactivity and physiological variables will also be described.

Discussion: This research indicates that childhood trauma, particularly sexual trauma, is a risk factor for onset of psychotic disorder in the UHR population, consistent with findings from other centres. Issues that need to be further explored include risk specificity (i.e., whether trauma is a general risk factor for psychiatric disorder or for psychotic disorder particularly); why sexual trauma is associated with higher levels of risk than other types of trauma; the mechanisms by which childhood trauma increases risk for disorder, including the relationship between such life events and physiological factors, as well as personality and resilience factors; and issues of how childhood trauma can best be addressed therapeutically in this population.

CHILDHOOD TRAUMA INFLUENCES THE CLINICAL EXPRESSION OF BIPOLAR DISORDERS

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Background: The pathophysiology of bipolar disorders (BD) is likely to be partly determined by environmental susceptibility factors that interact with genetic risk variants. Among them, childhood trauma has been proposed as a relevant environmental factor for BD. However, case-controls studies are lacking; most studies focus only on physical and sexual abuse (thus neglecting emotional abuse), and the influence of trauma on the clinical expression of the disorder remains to be clarified in terms of severity of the course.

Methods: First, we have assessed 206 patients with BD and 94 controls with the Childhood Trauma Questionnaire to perform a case/control study.

Second, 587 patients with BD were consecutively recruited from France and Norway, assessed using the Childhood Trauma Questionnaire, and characterized for various clinical features. Third, we studied the interaction between childhood trauma and serotonin transporter gene on the age at onset of BD in 308 patients. Finally, we used the Affective Lability Scale and the Affect Intensity Measure to correlate childhood trauma and adulthood affective instability.

Results: Multiple traumas were more frequently reported in patients as compared to controls (63% versus 33%); among trauma subtypes only emotional abuse was associated with BD with a suggestive dose-effect. We found that emotional and sexual abuses were associated with a more severe expression of the disorder, as characterized by an earlier age at onset, increased suicide attempts, more rapid cycling and greater proneness to depression. Emotional and sexual abuses were the strongest predictors of increased suicide attempts (OR=1.60 [1.07–2.39] and OR=1.80 [1.14–2.86] respectively), whilst sexual abuse was the strongest predictor for rapid cycling (OR=1.92 [1.14–3.24]). We then used Cox regression analysis to model the effects of emotional trauma and 5HTTLPR (serotonin transporter-linked polymorphism) genotypes on time to onset of BD. This model showed that there was a significant difference in the probability of developing BD between the patients with no emotional neglect and II/IIs genotype and those with emotional neglect and ss genotype ($p=0.003$). Finally, we demonstrated that the higher the exposure to trauma, the higher the level of affective instability, measured by the Affective Lability Scale and the Affect Intensity Measure.

Discussion: Our results demonstrate the importance of childhood trauma, not only as a risk factor for bipolar disorders per se, but also for a more severe clinical and dimensional profile of expression of the disorder.

HOW DOES CHILDHOOD TRAUMA CONTRIBUTE TO PSYCHOSIS ONSET? A FOCUS ON THE BIOLOGICAL STRESS RESPONSE

Valeria Mondelli

Psychological Medicine, Institute of Psychiatry, King's College London

Background: Previous studies have reported an association between childhood trauma and the onset of psychosis. However, the mechanisms underlying this association are still unclear. We have previously shown that patients at the onset of psychosis have an abnormal biological stress response, including high diurnal cortisol levels, a blunted cortisol awakening response, increased levels of pro-inflammatory cytokines (interleukin-6, IL-6; tumor-necrosis-factor alpha, TNF-alpha) and reduced levels of brain-derived neurotrophic factor (BDNF). In this presentation I will show our recent findings on the effect of childhood trauma on the biological response to stress in subjects at their first episode of psychosis and in healthy controls.

Methods: BDNF and pro-inflammatory cytokines messenger RNA levels were measured in the leukocytes of 49 first episode psychosis patients and 30 healthy controls (age mean \pm SEM 28.2 \pm 0.9 and 27.0 \pm 0.8 years respectively). In a different sample of 47 first episode psychosis patients and 35 healthy controls (age mean \pm SEM 31.0 \pm 1.5 and 32.5 \pm 2.2 years respectively), we measured salivary cortisol levels at 6 time points during the day. We calculated area under the curve for diurnal cortisol (using awakening, noon and 8pm time points) and for the cortisol awakening response (using 0, 15, 30, 60 minutes after awakening time points). In all the subjects we collected information about childhood trauma using the Childhood Experience of Care and Abuse questionnaire.

Results: Patients had reduced BDNF levels and increased levels of IL-6 and TNF-alpha when compared with controls (respectively effect size, $d=1.3$, $p<0.001$; $d=1.1$, $p<0.001$; $d=1.7$, $p<0.001$). Number of childhood trauma were negatively correlated with levels of BDNF ($p=0.006$) and TNF-alpha ($p=0.02$) at the onset of psychosis. Patients and controls with childhood sexual abuse had significantly higher diurnal cortisol levels when compared with patients and controls without sexual abuse ($p=0.02$). We found a significant interaction between status (patients/controls) and presence of childhood sexual abuse on the cortisol awakening response ($p=0.007$), with healthy controls with sexual abuse having higher cortisol awakening response than controls without abuse (727.1 \pm 112.4 vs 477.2 \pm 50.7 nmol min/l) and patients with sexual abuse having lower cortisol awakening response than patients without abuse (356.3 \pm 57.1 vs 486.2 \pm 48.0 nmol min/l).

Discussion: Childhood traumas contribute lower BDNF levels and higher

TNF-alpha levels found at the onset of psychosis. First episode psychosis patients exposed to sexual childhood abuse show different HPA axis abnormalities when compared with healthy controls exposed to sexual childhood abuse.

BDNF VAL66MET POLYMORPHISM MODULATES ASSOCIATIONS BETWEEN CHILDHOOD ABUSE–NEGLECT AND FUNCTIONAL AND STRUCTURAL ABNORMALITIES IN PSYCHOSES

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Background: Recent studies indicate cognitive function as a core phenotype of psychosis. Brain abnormalities in the direction of smaller hippocampi and larger ventricles are also reported. Brain derived neurotrophic factor (BDNF) is important for brain development and plasticity, and here we tested if the functional BDNF val66met variant modulates the association between high levels of childhood trauma (both abuse and neglect), cognitive function, and brain abnormalities in psychoses.

Methods: 249 patients with a broad DSM-IV schizophrenia spectrum disorder or bipolar disorder were consecutively recruited to the TOP research study (mean \pm age: 30.7 \pm 10.9; gender: 49% males). History of childhood trauma was obtained using the Childhood Trauma Questionnaire. Cognitive function was assessed through a standardized neuropsychological test battery. BDNF val66met was genotyped using standardized procedures. A sub-sample of n=106 Caucasians with a broad DSM-IV schizophrenia spectrum disorder or bipolar disorder (mean \pm age: 32.67 \pm 10.85; 49% males) had data on 1.5 T T1-weighted MRI scans. Free Surfer software (v 5.2.0) was used to automatically obtain measures of interest (lateral ventricles, total hippocampal formation and hippocampal subfield, and cerebrospinal fluid [CSF] volume). Regression analyses were conducted to investigate BDNF val66met, childhood trauma and brain function and structure in psychosis. All analyses presented were corrected for age, gender, diagnosis and intracranial volume. Post-hoc analysis correcting for multiple testing was also conducted.

Results: Carriers of the Methionine (met) allele exposed to high level of childhood trauma demonstrated significantly poorer cognitive functioning, specifically working memory/executive function and general cognition from the WASI, compared to homozygotic Valine (val/val) carriers. Taking in consideration multiple testing, using a more conservative p value, this was still shown for physical abuse and emotional abuse, as well as a trend level for sexual abuse. Further, met carriers exposed to high level of childhood sexual abuse showed reduced right hippocampal volume ($r^2=0.43$; $p=0.008$), and larger right and left lateral ventricles ($r^2=0.37$; $p=0.002$, and $r^2=0.27$; $p=0.009$, respectively). Moreover, carriers of the low active met allele exposed to high levels of physical neglect presented larger right and left lateral ventricles ($r^2=0.34$; $p=0.003$, and $r^2=0.26$; $p=0.043$, respectively), as well as increased CSF volume ($r^2=0.24$; $p=0.033$). When dividing into subfields of the hippocampus, the most significant findings were observed for the right CA1 ($r^2=0.38$; $p<0.001$), CA2-CA3 ($r^2=0.43$; $p=0.005$), and CA4, dentate gyrus ($r^2=0.40$; $p=0.005$), in the direction of smaller CA1, CA2-3 and CA4 volumes in met carriers with high levels of sexual abuse. No significant association was observed for the presubiculum ($p>0.5$). Furthermore, 77.4% (n=82) of the patients were taking antipsychotic medication; no significant associations were observed between antipsychotic medication and brain structures investigated. Our findings were independent of age, gender, diagnosis and intracranial volume. Lastly, a current study exploring the relationship between childhood trauma, BDNF RNA and cognitive function will also be described.

Discussion: Our data indicate gene x environmental interactions, with BDNF val66met being an important moderator between early stress and brain functional and structural abnormalities in psychosis.

Symposium

MODELING SCHIZOPHRENIA USING PATIENT DERIVED CELLS – BUT WHICH ONES?

Chairpersons: David Cotter and Alan Mackay-Sim

Discussant: Peter Falkai

Tuesday, 8 April 2014

2:00 PM – 4:00 PM

Overall Abstract: Modeling schizophrenia using patient derived cells – but which ones?

Postmortem studies have provided valuable insights into Schizophrenia (SZ) but these insights have been limited by the influence of confound such as that due postmortem delay, chronic exposure to medication and institutionalization. Models of SZ utilizing cells derived from SZ subjects are therefore particularly attractive as they are not subject to these confounds and as they offer the opportunity to assess the functionality of the living cell. One increasingly established model involves the reprogramming of fibroblasts from SZ patients into human induced pluripotent stem cells (hiPSCs) which can subsequently be differentiated into neurons. Another model involves obtaining stem cells directly from the olfactory epithelium – so called olfactory neurosphere derived stem (ONS) cells.

In the current symposium we bring together findings from recent studies using these hiPSCs and ONS cell models of schizophrenia which show how they provide the opportunities for unique and complementary insights into schizophrenia, including their potential in translational research which includes cognitive evaluations. Jane English presents data based on proteomic analysis of ONS cells from schizophrenia and control subjects. Her data implicate protein translation through the Eukaryotic Initiation Factor 2 (EIF2) pathway, a finding confirmed by gene based testing of GWAS data. Alan Mackay-Sim presents gene expression profiling data from both iPSCs and ONS cells and discusses the similarity in differential expression in these models and changes observed in cell motility and proliferation. Akira Sawa presents novel data on the confirming the utility of the ONS model and the correlation between ONS protein phosphorylation and neurocognition in SZ subjects. Finally, Kristen Brennan presents data showing that SZ derived hiPSCs exhibit diminished neuronal connectivity which is ameliorated by treatment with the antipsychotic Loxapine. Her data indicates how the model may focus more on developmental aspects of SZ and how SZ derived hiPSCs demonstrate aberrant migration and oxidative stress. Together these presentations converge to implicate early developmental processes involving connectivity, proliferation and cell migration in addition to pointing towards the translational value of these models among clinical populations.

ELUCIDATING THE MOLECULAR PATHOPHYSIOLOGY OF MENTAL ILLNESS WITH OLFACTORY NEURONAL CELLS AND INDUCED PLURIPOTENT STEM CELLS

Akira Sawa¹, Yasue Horiuchi, Nicola Casella, David Schretlen,
Koko Ishizuka

¹Johns Hopkins University School of Medicine

Due to difficulty in accessing the living brain tissue, we need surrogate cells/tissues to study neural mechanisms associated with mental illness. Induced pluripotent stem cells technology is powerful in obtaining any CNS cells, but the experimental procedures are time consuming, laborious, and expensive. To complement these weaknesses, we have used olfactory neuronal cells obtained by nasal biopsy. Our new data show that olfactory neuronal cells express key molecules that are expressed in the brain, but not in peripheral blood cells, confirming the utility of these cells. Based on the background, here we present a new study that utilizes both these two cell models: in the study we study how a specific protein phosphorylation is different between SZ and normal controls. First, we tested the level of phosphorylation in olfactory neurons from substantially large number of subjects (both SZ and controls) and confirmed that the change is significant in SZ. Of note, the phosphorylation is not observed in peripheral blood cells,

indicating that this molecular signature may be associated with neurons or neuronal cells. Then, from smaller numbers of subjects from this cohort, we generated induced pluripotent stem cells and conducted much more in-depth mechanistic analysis in neuronal development from progenitor cells to postmitotic neurons. The change of the phosphorylation observed in olfactory neurons is well correlated with alterations in specific domains of neurocognition, such as working memory. Taken together, through this presentation with unpublished data, we plan to show the translational significance of utilizing both olfactory cells and induced pluripotent stem cells prepared from the same set of subjects together with clinical and neuropsychological assessments.

MODELING PREDISPOSITION TO SZ USING HIPSCS

Kristen Brennan

Icahn School of Medicine at Mount Sinai

SZ (SZ) is a debilitating neurological disorder. Though postmortem studies have revealed reduced neuron size and spine density in SZ brain tissue, the molecular mechanisms underlying the disease state remain unclear. We directly reprogrammed fibroblasts from SZ patients into human induced pluripotent stem cells (hiPSCs) and subsequently differentiated these disorder-specific hiPSCs into neurons; SZ hiPSC neurons showed diminished neuronal connectivity, which could be ameliorated following treatment with the antipsychotic Loxapine. Gene expression comparisons of our hiPSC-derived neural progenitor cells (NPCs) and 6-week-old neurons to the Allen BrainSpan Atlas indicate that our hiPSC neural cells, from controls and patients with SZ (SZ), most resemble fetal rather than adult brain tissue, indicating that hiPSC-based models may not yet be suited for the study of the late features of this disorder. Because much of the gene signature of SZ hiPSC-derived neurons is conserved in NPCs, we used two independent discovery-based genome-wide approaches - microarray gene expression and stable isotope labeling by amino acids in cell culture (SILAC) quantitative mass spectroscopy analyses – to identify cellular phenotypes in SZ hiPSC NPCs from four SZ patients. From our findings that SZ hiPSC NPCs show abnormal gene expression and protein levels related to neural migration and oxidative stress, we predicted, and subsequently observed, aberrant migration and increased oxidative stress in SZ hiPSC NPCs. This platform, consisting of reproducible phenotypes identified through scalable assays, can be applied to expanded cohorts of SZ patients, making it a potentially valuable tool with which to study the developmental mechanisms contributing to abnormal neuronal connectivity and synaptic function seen in SZ.

SIGNIFICANT DOWN-REGULATION OF EIF2 AND ASSOCIATED RIBOSOMAL PROTEINS IN ONS CELL MODEL OF SCHIZOPHRENIA

Jane A. English¹, Melanie Focking, Lorna Lopez, Nicholas Matigian, Gerard Cagney², Alan Mackay-Sim, David R. Cotter¹

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Patient-derived cell models of SZ such as Olfactory Neurosphere-derived (ONS) cell lines can provide novel insights into our understanding of the primary neurological abnormalities associated with SZ. Patient derived cells from the human olfactory mucosa regenerate throughout life from neural stem cells and they do not require genetic reprogramming [Matigian et al. 2010]. Olfactory mucosa biopsies were obtained from patients with SZ (N=9) and healthy controls (N=9), and grown as neurospheres in defined medium [Matigian et al. 2010, Fan Y, et al. 2012]. Cells were processed for proteomic analysis and underwent quantitation using Label-free LC-MS/MS analysis on the Thermo Scientific LTQ Orbitrap. To aid interpretation of results, significant differentially expressed proteins were assessed in Ingenuity Pathway Analysis (IPA). Candidate proteins were validated by western blotting for EIF2, p-EIF2, RPL13A, and RPL18A. In addition, significant proteins underwent gene basted testing (VEGAS) for significant associations with GWAS meta-analysis data from SZ patients and controls (Ripke et al, 2013 Nature Genetics). LC-MS/MS analysis identified and quantified 826 proteins between SZ and patient derived ONS cell lines, of which 103 were significantly differentially expressed ($p < 0.05$) between groups, 16 of which

were significant following FDR. IPA indicated that protein synthesis via altered EIF2 signaling and ribosomal function (18 molecules) was the major category disturbed, with 17 ribosomal proteins significantly decreased in expression. Western blotting confirmed significant decreases in RPL13A and RPL18A, and extended our validation to include altered EIF2A and phosphorylated EIF2A in SZ ONS cells. Results of the GWAS comparisons further implicated EIF2 signaling via the implication of EIF2AK2 ($P=0.000003$), and 16 other EIF2 pathway proteins including RPL13A ($P=0.02$) and RPL18A ($P=0.04$). Our observations suggest that reduced protein synthesis via the EIF2 pathway may be a core process disturbed in SZ derived stem cells. Our novel findings are particularly important in terms of SZ neuropathology given recent findings implicating eIF2a regulation in post-mortem brain in SZ, which is required for normal synaptic plasticity and memory (Trinh, M.A. Cell Reports, 2012).

PATIENT-DERIVED STEM CELLS AND SZ: A PATH TO AETIOLOGY?

Alan Mackay-Sim¹, Nicholas Matigian, Alajendra Vitale

¹Griffith University

With large numbers of genes implicated in SZ it becomes a real challenge to understand aetiology at a molecular level. To achieve this we should move beyond the single gene level and take a systems level approach, considering that individuals may share dysfunctional signaling pathways or genetic networks, rather than a particular set of gene mutations. Patient-derived stem cells offer an appropriate level of observation to test this hypothesis with the potential for analysis of neuronal cells from patients and healthy controls. We generated 2-4 clones of induced pluripotent stem cell lines (iPSCs) from 4 SZ patients and 4 healthy controls, 18 stem cell lines in total. With these we observed significant variability in pluripotency phenotypes but were able to define criteria by which to identify optimal clones for patient versus control comparison. Gene expression profiling indicated significant patient-control differences in signaling pathways associated with cell proliferation and cell migration. Interestingly, these same pathways were implicated in gene expression differences between patient and control stem cells derived from the olfactory mucosa (olfactory neurosphere-derived, "ONS", cells). Functional analyses of these cells in vitro indicated profound changes in cell proliferation and cell motility in patient-derived ONS cells. Compared to control-derived ONS cell they have higher levels of cyclin D1 associated with faster proliferation and a shorter cell cycle. Additionally, patient-derived cells have dysregulated focal adhesion kinase signaling making them less adhesive and more motile, with fewer and smaller focal adhesions. These studies confirmed our hypothesis that appropriate patient-derived cells would demonstrate dysfunctions in neurodevelopmental signaling pathways. Notably patient-derived ONS cells and iPSCs showed similar deficits whereas fibroblasts from the same patients did not. Furthermore, the genetic reprogramming required to generate iPSCs revealed patient-control differences that were not apparent in the fibroblasts from which they were derived. These studies suggest that patient-derived stem cells are appropriate vehicles for understanding how multiple genetic risk factors come together to create cellular phenotypes that raise the risk for altered brain development. Furthermore these cellular phenotypes are demonstrated in relatively small sample sizes despite predicted genetic heterogeneity, supporting our hypothesis that such heterogeneity must focus on shared and identifiable cell functions.

Symposium

THE CANNABINOID DICHOTOMY IN SCHIZOPHRENIA: FROM RISK FACTOR TO THERAPY

Chairpersons: Andrea Giuffrida and Daniel Lodge

Discussant: David Morilak

Tuesday, 8 April 2014

2:00 PM – 4:00 PM

Overall Abstract: Cannabis intake has been long recognized to exacerbate psychosis in vulnerable individuals and as a risk factor for the development of schizophrenia. The mechanisms by which cannabinoids produce transient psychotic symptoms remain unclear. Nevertheless, recent advances in the neurobiology of the endocannabinoid system have provided an opportunity

to revisit the association between cannabinoids and schizophrenia and formulate new hypotheses. While over-activity of CB1 receptor function may contribute to the disease manifestations, other studies have shown that cannabis intake may have beneficial effects on the negative symptomatology; in addition, the observation that the endocannabinoid anandamide is elevated in the cerebrospinal fluid of drug-naïve schizophrenics and inversely correlated with schizophrenic symptoms suggests a protective role for endocannabinoids.

This symposium aims at providing a new frame to discuss and possibly reconcile some controversial findings on the neurobiology of cannabinoids and their impact on schizophrenia research. Dr. Tseng will open the session with an overview of the effects of cannabinoid exposure on prefrontal cortical network maturation and plasticity in adolescents. Dr. Giuffrida will present recent data showing that deficient endocannabinoid transmission is responsible for the social withdrawal observed in the PCP rat model of schizophrenia, and that this deficit can be reversed by systemic administration of endocannabinoid-enhancing drugs. Dr. Lodge will discuss the cross talk between endocannabinoid and dopamine systems providing evidence that dopamine dysregulation in PCP-treated rats can be normalized by enhancing endocannabinoid tone. Finally, Dr. Leweke will present recent clinical data on the therapeutic effects of modulating the endocannabinoid system in schizophrenia, and give an outlook on the potentials of such treatment strategies.

ENDOCANNABINOID-ENHANCING DRUGS REVERSE SOCIAL WITHDRAWAL IN THE PCP RAT MODEL OF SCHIZOPHRENIA

Andrea Giuffrida, Julien Matricon, Alexandre Seillier

UT Health Science Center San Antonio

Current antipsychotic therapies are ineffective against the negative symptoms of schizophrenia, which include anhedonia, reduced affect and social withdrawal. Recent studies suggest a link between these symptoms and dysfunctional endocannabinoid transmission in the brain. Increased levels of the endocannabinoid anandamide (AEA) have been reported in the cerebrospinal fluid of drug-naïve schizophrenics and were inversely correlated to the severity of negative symptoms (Giuffrida et al., 2004; Leweke and Koethe, 2008). In line with these observations, we found that administration of URB597, a drug that elevates brain AEA by blocking its degradation, reversed social withdrawal in the phencyclidine (PCP) rat model of schizophrenia via activation of CB1 receptors. The same drug, however, produced a social deficit in control rats via a CB1-independent mechanism. Administration of the selective monoacyl glycerol lipase (MAGL) inhibitor JZL184, which elevates the other major endocannabinoid, 2-arachidonoyl glycerol (2-AG), reversed the social deficit observed in PCP-treated rats, without affecting social behavior in control rats. To identify the neuronal correlates underlying the effects of endocannabinoid-enhancing drugs on social behavior, we measured c-Fos expression in several cortical, limbic and sub-cortical regions of PCP- and saline-treated rats undergoing social interaction following an injection of URB597. Social interaction increased c-Fos expression in the orbitofrontal cortex of saline-treated rats, but not in PCP-treated rats. URB597 administration prevented the activation of this brain area in control rats, whereas it restored c-Fos activation in the PCP-treated group. Interestingly, we found an opposite pattern in the central amygdala, suggesting critical contribution of the prefrontal cortex-amygdala pathway to the deficits observed in our model.

Overall, these findings indicate that PCP-induced social withdrawal results from a deficit of endocannabinoid-mediated activation of CB1 receptors, and that elevation of endocannabinoid tone can beneficially affect behaviors that mimic the negative symptoms of schizophrenia. The deleterious effects of URB597, but not JZL184, in control rats may result from a robust URB597-induced AEA elevation, which in turn may activate non-CB1 targets. Our data also show that PCP-treated rats, when engaged in social interaction, have altered patterns of neuronal activation in several cortico-limbic regions, and that URB597 can reverse these abnormalities. Thus, endocannabinoid-enhancing drugs represent a promising new class of drugs that may prove useful in the treatment of the negative symptoms of schizophrenia.

Supported by NIMH grant RO1MH91130 (AG).

INCREASING ENDOCANNABINOID LEVELS RESTORES ABERRANT DOPAMINE SYSTEM FUNCTION IN THE PCP MODEL OF SCHIZOPHRENIA

Daniel Lodge

UTHSCSA

An augmented dopamine system function is one of the oldest hypothesis of schizophrenia and suggests that mesolimbic hyperactivity underlies the positive symptoms of the disease. As there is no overt pathology within the ventral tegmental area, it is thought that the pathology of schizophrenia lies upstream of the dopamine system. Increasing evidence from clinical and preclinical studies suggests that hyperactivity within hippocampal subfields underlies the augmented dopamine system function. Indeed, here we demonstrate that sub-chronic administration of the NMDA antagonist, phencyclidine (PCP) produces an increase in VTA dopamine neuron population activity. This is attributable to an increase in ventral hippocampal (vHipp) activity as tetrodotoxin inactivation of the vHipp completely normalizes the aberrant dopamine neuron activity. Given clinical evidence of a negative correlation between central endocannabinoid levels and positive symptom severity, we examined whether enhancing endocannabinoid tone could alter dopamine neuron activity in the PCP model. Endocannabinoid tone was increased by administration of the fatty acid amide hydrolase (FAAH) blocker, URB-597 (0.3mg/kg). Here we demonstrate that the increase in dopamine neuron population activity observed in PCP-treated rats is attenuated by URB-597 suggesting that increasing endocannabinoid tone may provide a potential therapeutic approach for psychosis.

MODULATION OF THE ENDOCANNABINOID SYSTEM AS A POTENTIAL NEW TARGET IN THE TREATMENT OF SCHIZOPHRENIA

F. Markus Leweke^{1,2}, Martin Hellmich³, Franziska Pahlisch⁴,

Laura Kranaster⁴, Dagmar Koethe⁵

¹Central Institute of Mental Health; ²Heidelberg University, Germany;

³Institute of Medical Statistics, Informatics and Epidemiology, University of Cologne, Cologne, Germany; ⁴Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; ⁵Department of General Psychiatry, Medical Faculty Heidelberg, Heidelberg University, Heidelberg, Germany

Background: New pharmacological targets for the treatment of schizophrenia are urgently required. We initially identified one of the two major endocannabinoids, anandamide, as a counterbalancing if not protective factor in paranoid schizophrenia. Most recently, we reported that increasing levels of anandamide by blocking its metabolism by cannabidiol, a purified phytocannabinoid, significantly ameliorates psychotic symptoms in acute schizophrenia.

Methods: We performed a randomized, double-blind, placebo-controlled, cross-over clinical trial in acute, antipsychotic-naïve, first-break paranoid schizophrenia patients, fulfilling diagnostic criteria of DSM-IV. 29 patients were treated after written informed consent with either cannabidiol (600 mg per day) or placebo for 14 days and then switched to the corresponding cross-over condition. Additional patients to gain a total of 18 patients treated per protocol replaced dropouts.

Results: Cannabidiol significantly improved psychotic symptoms in the cannabidiol-placebo condition during the first 14 days of treatment when compared to baseline. A MMRM analysis of all randomized patients (n=29) yielded a mean improvement of 2.4 points (standard error 3.0) on PANSS total in favor of cannabidiol (vs. placebo), albeit not statistically significant. Only one patient on sequence cannabidiol-placebo terminated treatment early (last seen at visit 3) whereas 10 patients terminated early on sequence placebo- cannabidiol. The most frequent reason given was worsening of symptoms (5/11 patients). In addition, cannabidiol was detectable in serum of almost all patients in the cannabidiol-placebo group. Side-effects of cannabidiol were on the level of placebo.

Conclusions: Although limited by design issues (cross-over), duration of treatment (14 days), carry-over effects (serum levels of cannabidiol), and relevant placebo-response rates, this is the second study to provide evidence for antipsychotic properties of cannabidiol accompanied by a superior side-effect profile. Future placebo-controlled parallel-group trials studying the antipsychotic properties of cannabidiol in acute schizophrenia are nec-

essary to provide further evidence for its efficacy in the treatment of this devastating disease.

CB1 RECEPTOR SIGNALING, PREFRONTAL GABAERGIC TRANSMISSION AND ADOLESCENCE

Kuei Y. Tseng

The Chicago Medical School at RFUMS

Converging studies indicate that cannabis abuse during adolescence significantly increases the risk of developing psychosis and prefrontal cortex (PFC)-dependent cognitive impairments later in life. However, the mechanisms underlying the adolescent susceptibility to chronic cannabis exposure are poorly understood. Here I will summarize recent data showing how repeated exposure to the CB1 receptor agonist WIN during adolescence impacts the functional maturation of the PFC network. Using a non-contingent administration protocol in rats, we found conclusive evidence that exposure to a cannabinoid receptor 1 (CB1) agonist exclusively during early and mid-adolescence impairs prefrontal processing later in life. We further narrowed down this effect to a deficit in GABAergic transmission and uncovered that this prefrontal disinhibition could be normalized following single acute local infusion of the GABA-A α 1 positive allosteric modulator Indiplon. Thus, early and mid-adolescence are unique developmental periods during which the cannabinoid system predominantly interacts with the GABAergic system to regulate its proper functional maturation in the PFC. Together, these findings have direct implications in our understanding of the mechanisms that contribute to the long-term cognitive deficits observed in early adolescent onset cannabis abuse as well as the associated risk of developing psychiatric disorders such as schizophrenia.

Supported by Rosalind Franklin University, the Brain Research Foundation and NIH R01-MH086507 grants.

Symposium
UNDERSTANDING PATHWAYS TO CARE AS A MEANS OF ADVANCING EARLY INTERVENTION: FINDINGS FROM AROUND THE WORLD

Chairperson: Michael T. Compton

Discussant: John M. Kane

Tuesday, 8 April 2014

2:00 PM – 4:00 PM

Overall Abstract: Pathways to care can be defined as the contacts made during the period of time from the onset of illness until the first initiation of treatment. Although pathways to care among psychiatric patients in general have been an area of empirical examination for more than two decades, an emerging area of schizophrenia research is the examination of pathways to care in people experiencing a first episode of psychosis. The study of pathways to care represents a valuable field of inquiry for early psychosis research, especially in terms of how pathways may impact the duration of untreated psychosis (DUP) and illness outcomes. Understanding pathways to care in patients with first-episode psychosis informs efforts geared toward early recognition and intervention, thus reducing suffering and minimizing negative social consequences for those with psychosis. Concerning illness outcomes, the first contact that a first-episode patient has with psychiatric services is often essential in determining his/her subsequent adherence to treatment, and thus, outcomes of the illness. Studying when and where patients, during the course of an evolving psychotic disorder, make contacts for help can highlight where service improvements can be most effective. Understanding pathways to care may be particularly important for people's initial treatment-seeking efforts, as patients and their families often will not know how to gain access to treatment. A growing body of literature examines the various pathways to mental health care among patients with first-episode psychosis in diverse countries. Pathways to care vary across countries, based on differences in health systems, criminal justice systems, and attitudes towards mental illnesses. This Symposium will provide attendees with the most recent data on pathways to care in the United States, the United Kingdom, Canada, and Switzerland.

A COMPARATIVE STUDY OF PATHWAYS TO FIRST-EPIISODE CARE FOR PSYCHOSIS IN THREE ETHNIC GROUPS IN ONTARIO, CANADA: THE AFRICAN, CARIBBEAN, & EUROPEAN PROJECT (ACE)

Kelly K. Anderson¹, Nina Flora², Manuela Ferrari², Andrew Tuck², Suzanne Archie³, Sean Kidd^{2,4}, Taryn Tang⁴, Kwame McKenzie^{2,4}

¹Centre for Addiction and Mental Health; ²Social and Epidemiological Research, Centre for Addiction and Mental Health (CAMH) Toronto, Ontario, Canada; ³Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada; ⁴Department of Psychiatry, University of Toronto, Toronto Ontario, Canada

Differences in the pathways to care for ethnic minority groups are well documented in the international literature for chronic psychiatric disorders. Relatively less research has been done on first-episode psychosis specifically, or in a Canadian context. We recruited a sample of 171 FEP clients of Black-African, Black-Caribbean, and White-European origin from both hospital- and community-based early intervention programs in Toronto and Hamilton. We compared the three ethnic groups on duration of untreated psychosis and key indicators of the pathway to care. Compared with the White-European group, Black-Caribbean clients had an increased likelihood of referral from an inpatient unit to early intervention services ($OR=3.33$, 95% CI=1.46–7.60) and a decreased likelihood of general practitioner involvement on the pathway to care ($OR=0.17$, 95% CI=0.07–0.46), as well as fewer total contacts ($OR=0.77$, 95% CI=0.60–0.99). Black-African clients had an increased likelihood of making contact with the emergency department at first contact ($OR=3.78$, 95% CI=1.31–10.92). Differences in the duration of untreated psychosis across the ethnic groups were not statistically significant. Our findings suggest that there are significant differences in the pathways to early intervention services for psychosis for clients of African- and Caribbean-origin in our Canadian context. It is essential to gain a comprehensive understanding of the pathways that different ethnic groups take to early intervention services, and the reasons behind any observed differences, to inform the development of equitable services targeting patients in the critical early stages of psychotic disorder.

THE USE OF SOCIAL MEDIA IN EARLY PSYCHOSIS

Michael L. Birnbaum
Zucker Hillside Hospital

There have been increasing efforts to determine the factors contributing to lengthy duration of untreated psychosis and to understand the barriers to receiving timely and appropriate care. Possibly one of the greatest, and least explored, contributors to treatment delay is the initial decision to seek care. We therefore set out to elucidate the decision making process and to identify the resources used to inform this decision. We initially surveyed a sample of first episode patients in the Early Treatment Program, retrospectively exploring what changes participants noted in their thoughts and behaviors and what resources participants used to educate themselves. Given that millions of American youth are online, sharing ideas daily, we focused our attention on how social media is used as means of obtaining information, communicating distress, seeking help, expressing psychotic thought content and connecting with others. We simultaneously extracted data from participant's social media feeds from the day of inception going back two years. Our preliminary data suggests that in fact youth in the early stages of psychosis are regularly interacting with social media alongside their healthy counterparts. Additionally, as psychotic symptoms emerge, patterns, frequency and shared content change. Finally, we explored what online resources might be available to information-seeking individuals as symptoms first emerge. Using 18 hypothetical search terms developed by Early Treatment Program staff and informed by data gathered from our survey, we searched Google, Facebook and Twitter, and extracted the first 5 hits from each. An alarmingly few online resources encourage potentially psychotic youth to seek professional evaluation. Given the severity and potential destructive outcome of untreated psychosis, we must explore innovative and novel strategies of early identification and treatment including changing the online experience of youth.

REDUCING DURATION OF UNTREATED PSYCHOSIS: CARE PATHWAYS TO EARLY INTERVENTION IN PSYCHOSIS SERVICES

Max Birchwood¹, Charlotte Connor², Helen Lester², Paul Patterson², Nick Freemantle², Max Marshall², David Fowler³, Shon Lewis², Tim Amos², Linda Everard², Peter Jones⁴, Swaran P. Singh²

¹School of Psychology, University of Birmingham; ²University of Birmingham, Birmingham, UK; ³University of Sussex; ⁴Department Psychiatry, University of Cambridge

Interventions to reduce treatment delay in first-episode psychosis have met with mixed results. Systematic reviews highlight the need for greater understanding of delays within the care pathway if successful strategies are to be developed. Our objectives were to (1) document the care-pathway components of duration of untreated psychosis (DUP) and their link with delays in accessing specialised early intervention services (EIS), and (2) model the likely impact on efforts to reduce DUP of targeted changes in the care pathway. Data for 343 individuals from the Birmingham, UK, lead site of the National EDEN cohort study were analysed. A third of the cohort had a DUP exceeding 6 months. The greatest contribution to DUP for the whole cohort came from delays within mental health services, followed by help-seeking delays. It was found that delay in reaching EIS was strongly correlated with longer DUP. Community education and awareness campaigns to reduce DUP may be constrained by later delays within mental health services, especially access to EIS. Our methodology, based on analysis of care pathways, will have international application when devising strategies to reduce DUP.

HELP-SEEKING AND PATHWAYS TO CARE IN THE EARLY STAGES OF PSYCHOSIS: RESULTS FROM THE FEPsy STUDY

Anita Riecher-Rössler¹, Gertraud J. Fridgen², Jacqueline Aston³

¹University of Basel; ²Bezirkskrankenhaus Landshut, Prof. Buchner; ³University of Basel Psychiatric Clinics, Basel, Switzerland

Background: Patients with first episode psychosis (FEP) on average experience unspecific symptoms 4 to 5 years and psychotic symptoms 1 to 2 years before they seek treatment. Untreated psychosis has negative effects on the individuals' social networks, vocational and educational achievements, and duration of untreated psychosis seems to be associated with more severe symptoms, worse treatment response, and poorer overall outcome. It is therefore important to examine pathways to care to understand factors contributing to delay in access to adequate care.

Methods: We examined the help-seeking behavior of 61 individuals with an at-risk mental state for psychosis (ARMS) and 37 FEP patients in a low-threshold health care system within the FePsy (Früherkennung von Psychosen) early detection of psychoses study, using the Basel Interview for Psychoses. At the same time we examined the first signs and symptoms as perceived by the patients themselves.

Results: The mean duration of untreated illness was 3.5 years and of untreated psychosis 12 months. 86% of all individuals had sought help of some kind before reaching our specialized clinic. First help-seeking contact was usually with family members or relatives (27%), close friends (18%), office psychiatrists (14%), or general practitioners (12%). During further course most patients consulted some health professionals before reaching our specialized service. Help-seeking with non-medical institutions was rare. Women had more help-seeking contacts than men before contacting our early detection clinic. ARMS and FEP patients remembered mainly loss of energy and difficulties concentrating as their first symptoms. Also depression, social isolation, over-sensitivity and irritability, anxiety, unusual fears, and suspiciousness were reported.

Discussion: Family, close friends and medical professionals play an important role in help-seeking, leading to specialized psychiatric care. More efforts should be made to educate the public about symptoms of emerging psychosis and the help that can be offered. Also better strategies for encouraging those concerned to seek help, especially young at-risk men, should be developed.

References:

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- [2] Aston J, Bull N, Gschwandtner U, Pflueger M, Borgwardt S, Stieglitz RD, Riecher-Rössler A: First self-perceived signs and symptoms in emerging psychosis compared with depression. *Early Interv Psychiatry* 2012;6:455–459

Symposium

WHAT IS THE LONG TERM OUTCOME OF SCHIZOPHRENIA?

Chairperson: Michael Davidson

Discussant: Robin M. Murray

Tuesday, 8 April 2014

2:00 PM – 4:00 PM

Overall Abstract: During the 1970s, Ciompi and in the 1980s Harding published on the long-term outcome of schizophrenia suggesting that at least 1/3 have a reasonable to good outcome. However, there are relatively few long-term cohort studies using modern research methodologies addressing outcome in schizophrenia. This proposed symposium will present recent studies on the outcome of schizophrenia from several longitudinal cohort studies.

Dr. Jones will introduce the results of a ten year, comprehensive follow-up of AESOP-10, a ten-year follow-up of 557 subjects with a first-episode of psychosis identified in two geographically defined areas of the UK during the late 1990s. Thirty nine (7.0%) cases had died, the majority through unnatural means. Thirty (5.4%) had emigrated, and 8 (1%) were excluded; information on follow up was collated for 394 (82%) of the remaining 480. Most (270, 77%) experienced at least one period of remission but the majority (211, 71%) had been unemployed for more than 75% of the follow-up period. Overall, outcomes were worse for men and those with a non-affective diagnosis. These findings suggest the overall symptomatic course of psychoses may be better than previously thought, but social outcomes in 21st century UK are disappointing.

Dr. Kahn will present data from a naturalistic longitudinal cohort study in the Netherlands, with assessments at baseline, after three and six years of follow-up. At baseline, 1120 patients, 1057 siblings, 919 parents and 590 healthy controls were included. Results on 3 and 6-year outcome will be presented. Data on a sub-group for which MRI and cognition data are available indicate that there are dynamic changes which correlate with clinical progression.

Dr. Isohanni will present data from the Northern Finland 1966 Birth Cohort Study followed since pregnancy, and assessed at age 34 (N=73) and 43 (N=63). During the 9-year follow-up the mean annual whole brain volume reduction was 0.68% in schizophrenia vs. 0.49% in controls (adjusted p=0.015). High doses of antipsychotic medication correlated with increased brain volume loss. There was general disease progression, with relatively poor prognosis and many relapses, excess mortality and somatic comorbidity, and limited vocational achievements.

Dr. Weiser will present data on the vocational outcome of 31,333 patients using data from the Israeli Social Security Administration, linked with the Israeli Psychiatric Hospitalization Case Registry, with a mean follow-up was 11.2±5.3 years. The percent of patients working and earning the minimum wage or above was 11.3% for schizophrenia patients with a single hospitalization (30% of the cohort), and 3.6% for patients with repeated hospitalization (70% of the cohort).

Overall, these data indicate a poorer outcome than previously reported and cited in most textbooks. The social and biological implications of these findings will be discussed as well as the potential biases and cohort differences, and the possible existence of a sub-group with good prognosis will be discussed.

TEN-YEAR OUTCOMES OF PSYCHOTIC DISORDERS: THE AESOP-10 STUDY

Peter B. Jones¹, Craig Morgan², Julia Lappin², Paola Dazzan²

¹University of Cambridge; ²Division of Psychological Medicine, Institute of Psychiatry, King's College, London, UK

Background: Schizophrenia was originally conceived as a deteriorating disorder but the broader group of psychotic illnesses may have a wide range of outcomes.

Objective: To describe the ten-year outcome of a cohort with first-episode psychosis and introduce other presentations at the conference involving these data.

Method: We followed-up at ten years the AESOP cohort, 557 subjects with a first-episode of psychosis identified in two geographically defined areas of the UK during the late 1990s.

Results: Thirty nine (7.0%) cases had died, the majority through unnatural means. Thirty (5.4%) had emigrated, and 8 (1%) were excluded; information on follow up was collated for 394 (82%) of the remaining 480. Most (270, 77%) experienced at least one period of remission but the majority (211, 71%) had been unemployed for more than 75% of the follow-up period. Overall, outcomes were worse for men and those with a non-affective diagnosis.

Conclusions: The overall symptomatic course of psychoses may be better than previously thought, but social outcomes in 21st century UK are disappointing. Further presentations of these data at this conference explore this in more detail.

OUTCOMES OF SCHIZOPHRENIA FROM A LIFESPAN PERSPECTIVE. THE NORTHERN FINLAND 1966 BIRTH COHORT STUDY (NFBC 1966)

Matti Isohanni, Erika Jääskeläinen, Jouko Miettunen

Department of Psychiatry, University of Oulu, Finland

Introduction: Outcomes of schizophrenia range from recovery to chronic disability.

Objectives: To review outcomes within NFBC 1966.

Aims: To analyze outcomes in midlife: progression in brain morphometric changes, antipsychotic medication, cognition, somatic comorbidity, mortality and clinical outcomes.

Methods: NFBC 1966 (N=12058) has been followed since mid-pregnancy. Analyses of brain MRIs and cognitive and clinical characteristics were performed at ages of 34 and 43. 33 cases and 71 controls participated in both surveys.

Results: Within the NFBC 1966, during the 9-year follow-up, the mean annual whole brain volume reduction was 0.68% in schizophrenia, suggesting progressive brain abnormalities. The annual brain volume reduction for controls was 0.49% (adjusted p=0.013). High doses of antipsychotics correlated with increased brain volume loss after adjusting for measures of clinical and social functioning. Majority of the patients have marked symptoms and relapses in midlife, and are on disability pension. We also observed general disease progression: some cognitive decline, relatively poor prognosis and many relapses, excess mortality (especially suicides) and somatic comorbidity. Long DUP was associated with decreased density of the right hippocampus and a decreased rate of disability pension and a higher rate of employment.

Conclusions: Schizophrenia progresses in midlife. High doses of antipsychotics were related to accelerated brain volume loss. A deteriorating general course of schizophrenia for some individuals during midlife may reflect these brain abnormalities and reduce adult well-being and creativity typical to this epoch.

LONG TERM OUTCOME IN SCHIZOPHRENIA: A 6 YEAR FOLLOW UP IN OVER 1000 PATIENTS

René S. Kahn¹, W. Cahn², N.E. van Haren², S. Hajma², H.E. Hulshoff²

¹UMC Utrecht; ²Dept Psychiatry, Brain Center Rudolf Magnus, UMC Utrecht, The Netherlands

Objective: A longitudinal focus on gene-environment vulnerability and resilience in both patients, their unaffected family members and non-related controls offers the opportunity to elucidate etiological and pathogenetic factors influencing the onset and course of psychotic disorders. The current paper delineates the objectives, sample characteristics, recruitment and assessment procedures of the Genetic Risk and Outcome of Psychoses (GROUP) study.

Methods: A naturalistic longitudinal cohort study with assessments at baseline, after three and six years of follow-up. The study is conducted by a consortium of four university psychiatric centres, with their affiliated mental health care institutions in the Netherlands covering more than 7.5 million inhabitants. Extensive assessment of genetic factors, environmental factors, (endo)phenotypes, and outcome.

Results: At baseline, 1120 patients, 1057 siblings, 919 parents and 590

healthy controls were included. Follow-up was at 3 and 6 years. Results on 3 and 6-year outcome will be presented.

Conclusion: The GROUP study will contribute to insight in risk and protective factors in the etiology of non-affective psychotic disorders, and in the variation in their course and outcome.

NATION-WIDE EMPLOYMENT STATUS IN PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDERS

Mark Weiser¹, Michael Davidson², Ori Kapara³, Rinat Yoffe⁴, Shlomo Noy⁵

¹Psychiatric Division, Sheba Medical Center; ²Sackler School of Medicine, Tel Aviv University; ³Center for Behavioural Sciences, IDF; ⁴Ministry of Health, Israel; ⁵Sheba Medical Center, Israel

Background: The large waves of deinstitutionalization of the seventies and eighties were supposed to be followed by reintegration of the mentally ill into society, including into the working force. Effective pharmacological treatments were instrumental in deinstitutionalization and vocational training programs were expected to provide the necessary working skills. While overall, deinstitutionalization was successful, reintegration into the working force continues to be a challenge. Studies reporting on rate of work and employment of patients with severe mental illness vary widely depending on the outcome measure. However, no nation-wide survey of gainful employment of patients with severe mental disorders has ever been reported.

Methods: Data from the Israeli Psychiatric Hospitalization Case Registry were linked with data from the National Insurance Service (the equivalent of the US Social Security) which contains nation-wide data on personal income. Data were obtained on all consecutive admissions in any psychiatric hospital in the country between 1990–2008 with a diagnosis of schizophrenia, other non-affective psychotic disorders, and bipolar disorder, N=35,673. Gainful employment was considered reporting to the National Insurance Service work related income of at least 1,000 USD per month (not including disability pensions), which was the approximate minimal wage in Israel at the time of the survey.

Results: The percentages of patients earning minimum wage or above were: patients with one admission and schizophrenia 10.6%, non-affective psychotic disorders 21.6%, bipolar disorders 24.2%. Patients with multiple admissions and schizophrenia 5.8%, non-affective psychotic disorder 11.2%, bipolar disorders 19.9%. At the time of the survey >55% of the Israeli general population were employed and the rate of unemployment was 6.6%, which is not radically different from most OECD countries.

Discussion: Patients admitted for schizophrenia, non-affective psychotic disorder or bipolar disorders have a poor employment outcome, even if they are admitted only once. These results indicate that currently available vocational and pharmacological interventions might not be qualitatively and/or quantitatively appropriate to re-integrate these individuals into the working force, and more and different resources should be devoted towards this end.

Oral Presentations

ADVANCES IN IMAGING IN SCHIZOPHRENIA I

Chairperson: Sophia Vinogradov

Tuesday, 8 April 2014

4:15 PM – 6:15 PM

4:15 PM

ALTERED PATTERNS OF REWARD ACTIVATION IN A LARGE COHORT OF ANTIPSYCHOTIC NAÏVE FIRST EPISODE SCHIZOPHRENIA PATIENTS

Mette Ødegaard Nielsen^{1,2}, Egill Rostrup³, Sanne Wullf²,
Henrik Nørbaek-Emig², Jayachandra Raghava³, Birte Glenthøj²
¹Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research;
²CINS & CNSR; ³FIU

Background: Disturbances of the brain reward system are suggested to play an important role in the development of central psychopathological symptoms in schizophrenia, and several studies have shown dysfunctions of the reward system. Often these studies are driven by specific hypotheses

trying to link a certain aspect of reward processing to specific symptoms. However, reward processing is a complex mechanism, as it entails the interaction of several brain regions over time. Thus, a deficit found in one part of the reward process might be secondary to other mechanisms, which might not have been caught by the focused analyses. By using a multivariate approach we want to confirm previous findings in a smaller group of patients (Nielsen et al. Biol Psychiatry 2012;71), and further we expect this method to reveal other important alterations in reward processing.

Methods: 53 antipsychotic-naïve first-episode patients with schizophrenia and 48 healthy controls were included as part of a large multimodal first episode study. The participants went, among others through a functional Magnetic Resonance Imaging (fMRI) study while playing a monetary reward task.

The functional images were pre-processed by performing motion correction and transforming all subjects into standard space (MNI 2mm). The pre-processed data has been analyzed using the multivariate approach called partial least squares (PLS – McIntosh lab, Baycrest). This method was used in order to find functionally connected patterns in a whole brain context. PLS has the benefit that it does not analyze specific contrasts or compare groups. Instead the PLS analysis identifies latent variables (LV) which explain the covariance of conditions and brain activity. The significance of each LV is determined by a permutation test (n=5000) and bootstrap estimate (n=50). For the analyses a total of 17 conditions were defined; 2 conditions related to group and 15 conditions related to the reward paradigm (6 describing anticipation phase, 2 describing the action phase, and 7 describing the outcome phase)

Results: The analysis revealed 30 LV's of which 7 were highly significant ($p<0.001$). LV 1 and LV2 were primarily describing covariance of the brain activity explained by the different conditions of the paradigm, and there were no group differences. LV 3, 4 and 5 were describing covariance with group specificity.

LV 3 described areas in the brain related to group differences during the anticipation evoked by salient cues, and during outcome evaluation of certain gain, certain loss and uncertain loss. Among these areas were parts of striatum and medial and dorso-lateral prefrontal cortex.

LV 4 described a widespread network with group difference related to the anticipation of outcome of salient trials.

LV 5 defined among others small areas in medial prefrontal and anterior cingulated cortex which were related to group differences during outcome evaluation of unexpected gain and unexpected loss but also related to neutral outcome.

Discussion: The results of these analyses can be divided in two parts. Firstly, the present findings confirm our previous more hypothesis specific results from a smaller group, where we demonstrated pronounced group differences in the ventral striatal area during anticipation of salient events. Secondly, the results provide new information about reward processing, by demonstrating a changed pattern of deactivation just after the action related to salient events. Additionally, several changes during outcome evaluation, particularly in relation to unexpected outcome, were observed. This is in accordance with the idea of an altered prediction error response. Finally our analyses suggest that even the response to a neutral outcome may be altered in schizophrenia.

4:30 PM

DYNAMIC SUSCEPTIBILITY CONTRAST (DSC) MRI CAN BE USEFUL TO AUTOMATICALLY CLASSIFY PATIENTS WITH PSYCHOSIS

Letizia Squarcina¹, Cinzia Perlini², Denis Peruzzo³, Umberto Castellani³, Veronica Marinelli², Marcella Bellani¹, Gianluca Rambaldelli², Antonio Lasalvia¹, Sarah Tosato¹, Katia de Santis¹, Mirella Ruggeri¹, Paolo Brambilla⁴

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Background: Hemodynamic changes have previously been reported in major psychoses, and machine learning has successfully been applied to automatically classify these disorders, aiming at being of support in diagnostic decisions. Vascular abnormalities could represent the hemodynamic basis of structural brain modifications happening in patients with psychosis.

However, none of the prior studies has combined machine learning and perfusion imaging. To our best knowledge, this is the first study trying to classify psychosis based on brain perfusion imaging. First Episode Psychosis (FEP) patients were selected so to avoid the confounding role of chronicity and medication.

Methods: 35 healthy controls (HC, 44.6±9.9 years old, 16 males) and 35 first episode psychosis patients (FEP, 41.7±7.8 years old) underwent a MRI session with a 1.5T Siemens Symphony scanner. T1 and Dynamic Susceptibility Contrast (DSC) images were acquired, skull stripped and aligned to the MNI template using FSL, with the aim of obtaining data from all subjects in the same space. On the registered images, ROIs corresponding to left and right frontal, parietal, temporal and occipital lobes, insula, caudate and cerebellum were obtained. Cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT) were obtained fitting the data to the DSC model using block-circulant SVD, after quantification of the Arterial Input Function estimated from arterial voxels in the image. The distribution of values of CBF, CBV and MTT in the ROIs were represented with an histogram calculated over 100 discrete bins and used as feature vectors to classify subjects into the two distinct groups of HC and FEP, after correction for age differences. We used both linear support vector machine (SVM) and group-lasso multiple kernel learning (GL-MKL). We also analyzed the vector w, normal to the hyperplane separating the two classes, to identify how relevant changes in perfusion parameters between the classes happen.

Results: Mean values of CBV and CBF for patients resulted slightly lower than in HCs, up to 13%, being significant for CBV in right caudate and right frontal lobe, and in left frontal lobe and left cerebellum. Linear SVM reached an accuracy of 83% on the histogram of CBV in right frontal lobe, 80% on left parietal lobe CBV and 79% on right occipital lobe CBV. The shape of vector w suggests that the values of CBV that lead to the best discrimination of FEP from HC are those near the peak of the histogram, characterized by relatively low CBV. GL-MKL reached an accuracy of 87% with the highest weights associated to right frontal CBV, left frontal CBV and right cerebellum CBV. The two group did not result significantly different for age or gender (t-test, p=0.05)

Discussion: With the combined use of perfusion imaging and machine learning, we were able to distinguish HC and FEP patients with an accuracy of over 80%, showing that perfusion can be used as a potential marker to classify patients with psychosis, who show reduced blood volume and flow in the brain. Both SVM and MKL found that differences are located especially in frontal lobes and in cerebellum, which are brain areas known to be involved in psychosis. The use of both techniques allows us to identify the most affected areas, then to consider all areas simultaneously, achieving a better distinction between classes, and to infer, from the shape of the vector w, that the brain areas which are discriminating between HC and FEP are those where the CBV is relatively low, meaning that patients have more voxels with a small blood volume when compared with healthy.

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EXPLORING THE SENSORY COMPLEXITY OF HALLUCINATORY EXPERIENCES USING MULTIMODAL CONNECTIVITY ANALYSIS

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Background: Hallucinations constitute one of the most representative and disabling symptoms of schizophrenia. Even if auditory hallucinations (AH) and visual hallucinations (VH) may both occur in schizophrenia, the impact of the presence of one vs. two sensory modalities (A+VH) have been poorly explored in this disorder. This study aimed at deciphering the distinct patterns of connectivity that could be associated with different hallucinatory modalities. We focused on the hippocampal complex (HC) connectivity network and the mesolimbic pathway, which consists of the ventral tegmental area (VTA) and nucleus accumbens (NAcc), all previously shown involved in the hallucinatory pathophysiology.

Methods: Two carefully selected subgroups of schizophrenia patients with only auditory hallucinations (AH, n=16) or with audio-visual hallucinations (A+VH, n=17), matched for sex, gender, PANSS scores and antipsychotic dosages, were compared using multimodal connectivity analysis, including resting state functional MRI and diffusion MRI. Resting-state functional

connectivity analyses (rsFC) were seeded on the HC and the NAcc. Between-group comparisons were performed using random-effects ANCOVA with rs-FC as the dependent variable, the AH and V+AH groups as the between-subjects factor, and age as the covariate ($\text{qFDR} < 0.05$). Tract-Based Spatial Statistics (TBSS) completed the analysis to explore between-group differences in structural white-matter connectivity.

Results: Sb-FC was significantly higher in A+VH patients compared with the AH group in the HC, the medial prefrontal cortex (mPFC) and the caudate nuclei. V+AH patients also exhibited greater rs-FC between the NAcc and a large-scale network encompassing the VTA, the mPFC, the HC and the anterior insula. Finally, TBSS showed specific higher white matter connectivity in the A+VH group than in the AH group in the pathways connecting the HC with visual areas, such as the forceps major and the inferior-fronto-occipital fasciculus.

Discussion: The level of activity within the HC network and the mesolimbic pathway appeared to be positively associated with the sensory complexity of hallucinatory experiences (e.g., one vs. two sensory modalities), which may support the aberrant salience hypothesis of schizophrenia. Crucially, the current design allowed a high degree of control between the two groups as the observed between-group differences cannot be attributed to schizophrenia per se or to antipsychotic medications, known to potentially affect connectivity data. These findings suggest that there are distinct multimodal connectivity patterns in patients with hallucinations that depend on the sensory-modality. Future clinical and neurobiological studies of hallucinations should evaluate not only the global severity of symptoms but also their level of sensorial complexity.

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FUNCTIONAL OUTCOME IN PEOPLE AT HIGH RISK FOR PSYCHOSIS PREDICTED BY THALAMIC GLUTAMATE LEVELS AND PREFRONTAL-STRIATAL ACTIVATION

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Background: Recent studies have shown that baseline neuropsychological measures can predict subsequent functional outcomes in people at ultra high-risk for psychosis. However, little is known about the neurobiological factors that determine functional outcome in people at high risk for psychosis. Using multimodal neuroimaging, we investigated whether cortical responses during a cognitive task and thalamic glutamate levels were associated with subsequent functional outcome.

Methods: Sixty subjects participated: 33 at Ultra High Risk (UHR) for psychosis subjects, who met Comprehensive Assessment of At Risk Mental State (CAARMS) criteria, and 27 age matched healthy controls (CTRL). At baseline, cortical responses during a verbal fluency task were measured using functional Magnetic Resonance Imaging (fMRI) and proton Magnetic Resonance Spectroscopy (1H-MRS) was used to measure thalamic glutamate levels. The UHR subjects were then followed clinically for a mean duration of 18 months, and subdivided into "good" and "poor" functional outcome subgroups according to their Global Assessment of Function (GAF) score at follow-up. Group and interaction effects were examined using ANCOVA in SPM-8 software.

Results: UHR subjects with a poor functional outcome at follow-up (mean GAF score=48) showed greater activation in the left inferior frontal and superior temporal gyri, the insula bilaterally, and the right parahippocampal gyrus relative to UHR subjects with a good functional outcome (mean GAF score = 76) and the CTRL group. The poor functional outcome group also had lower levels of thalamic glutamate relative to the good functional outcome group ($t(31)=2.57$, $p=0.01$). ANCOVA showed a significant group x thalamic glutamate level interaction, revealing an alteration in the relationship between thalamic glutamate levels and prefrontal-striatal activation in poor functional outcome UHR subjects relative to the other two groups.

Discussion: In people at high risk for psychosis, their subsequent level of functioning may depend on the extent to which neurophysiological and neurochemical function is perturbed when they first present to clinical services. The involvement of the glutamate system also raises the possibility that treatments that act on glutamate function may be useful in the management of the early phase of psychosis.

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GENETIC AND ENVIRONMENTAL INFLUENCES ON BRAIN FUNCTION IN SCHIZOPHRENIA. AN FMRI STUDY OF THE MAUDSLEY TWIN AND FAMILY COHORTS

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Background: Schizophrenia is a heritable but aetiologically complex disorder. Intermediate phenotypes as quantitative traits pathophysiological closer to the underlying genetic risks represent an experimental strategy to help address this complexity. Verbal fluency performance satisfies many criteria for an intermediate phenotype for schizophrenia. Our aim was to assess the influence of genetic and environmental factors on this executive function task in schizophrenia.

Methods: We used a twin-sibling study of 206 subjects; 163 twins, varying in their zygosity and concordance for schizophrenia, and 43 singletons from siblings varying in their concordance for schizophrenia. We assessed performance and regional brain activation using functional magnetic resonance imaging, during a phonological verbal fluency task. After between group testing, we conducted full genetic modelling.

Results: Across groups there was a differential pattern of activation in fronto-temporal areas. Patients and their unaffected relatives developed greater activation in the left inferior frontal gyrus, and greater deactivation in the left hippocampal and middle temporal gyri bilaterally. These features were maximally evident in subjects with schizophrenia, and least in controls. When the analysis was restricted to the unaffected relatives and healthy controls, a similar pattern was evident, with the unaffected relatives showing greater inferior frontal and left superior temporal activation, and greater right parahippocampal and right superior/middle temporal deactivation than healthy controls. Genetic modelling indicated a phenotypic correlation between schizophrenia and increased activity in the inferior frontal gyrus and reduced activity in the left middle temporal gyrus and left hippocampus, which was principally due to shared genetic effects.

Discussion: Both schizophrenia and its familial vulnerability were associated altered frontal, parahippocampal and temporal activation during verbal fluency. The altered left inferior frontal activity was particularly associated with schizophrenia, while altered right middle/superior temporal and right medial temporal activity were more heritable and more intimately linked to the genetic risk for schizophrenia.

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IN VIVO EVIDENCE OF REDUCED BRAIN CANNABINOID RECEPTORS IN SCHIZOPHRENIA

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Background: Converging lines of evidence suggest several relationships between cannabinoids and psychosis. According to the exogenous hypothesis, exposure to cannabinoids is associated with psychosis outcomes. Beyond the exogenous hypothesis, there is some evidence suggesting endocannabinoid dysfunction in schizophrenia. Post-mortem studies comparing schizophrenic patients with healthy controls have shown either increased density of cannabinoid receptor 1 (CB1Rs) in specific cortical layers of a number of brain areas, or no difference in the expression of CB1R in cortical areas strongly related to psychosis. In addition, post-mortem studies have shown that CB1R expression can be modulated by cannabis use and antipsychotic medication (dopamine [DA] D2 receptor antagonists).

Methods: To characterize CB1R availability in schizophrenia, we recruited 19 male schizophrenia patients and 19 age-matched male healthy controls

to participate in a resting state High Resolution Research Tomography (HRRT) study using the ¹¹C-OMAR CB1R tracer. In a subset of subjects we measured CB1R availability before and after treatment with DA D2 receptor antagonists to determine the effects of antipsychotic treatment on CB1R availability.

Results: Relative to controls, schizophrenia patients showed statistically significant reductions in CB1R density in the posterior cingulate cortex (PCC) ($p=0.043$) and trend level reductions in the amygdala ($p=0.09$), hypothalamus ($p=0.095$) and caudate ($p=0.1$); these group differences were small (partial eta² 0.044 to 0.048). In addition, treatment with DA D2 receptor antagonists decreased CB1R availability. Furthermore, CB1R density in the PCC showed a positive correlation with the PANSS (5-factor) Excitation dimension ($r=0.507$, $p=0.038$).

Discussion: These results suggest alterations in CB1R availability in schizophrenia and provide some support for the endogenous hypothesis. These results are in contrast with other PET studies that found increased CB1R availability in schizophrenia patients. Whether the reductions in CB1R availability are primary or secondary to the course of the illness is not clear. Furthermore, since PET measures available receptors, it is not clear whether the reductions in CB1R are caused by elevations in endocannabinoid levels as reported elsewhere.

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INTEGRATING PHARMACOLOGY AND COMPUTATION: TOWARDS UNDERSTANDING MECHANISMS OF COGNITIVE AND CONNECTIVITY DEFICITS IN SCHIZOPHRENIA

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Background: Schizophrenia is associated with distributed neural network dysfunction, which in turn profoundly impacts behavior and cognition. Such disturbances are reliably detected using either task-based or resting-state neuroimaging. Neuroimaging, however, does not allow measurement at the level of neurons, which is where pharmacological treatments ultimately exert their effects. Therefore, there is still a gap between understandings of psychiatric illness across levels of analysis. One leading cellular hypothesis in schizophrenia postulates a disruption in cortical excitation/inhibition (E/I) balance due to dysfunction of the NMDA glutamate receptor, which may profoundly affect cognitive function such as working memory (WM). To test this hypothesis in relation to disrupted WM function we present novel results from two complementary approaches: First, we present targeted behavioral and neural hypotheses derived from computational models of spatial WM developed with biophysical level of detail. Second we test the hypothesis of disrupted E/I balance using causal pharmacological manipulations in healthy volunteers and independent clinical findings in early course schizophrenia patients.

Methods: We generated specific behavioral and neural predictions of disrupted E/I balance via biophysically-based computational modeling of spatial WM, implemented with spiking neurons and realistic synaptic conductances. We incorporated a hypothesized ketamine-induced synaptic disinhibition mechanism into our model. We tested model predictions via behavioral and neuroimaging findings using an NMDA receptor antagonist – ketamine – that has been shown to transiently induce cardinal schizophrenia symptoms. We directly compare these findings to clinical results from patients with early course schizophrenia.

Results: Our findings largely follow model predictions. Using BOLD imaging, we show that ketamine disrupted task-dependent activation and connectivity during WM as previously found in schizophrenia and in line with computational modeling simulations. We offer a parsimonious hypothesis for these effects via our computational modeling, namely cortical disinhibition, suggesting the importance of E/I balance for cortical microcircuit function and cognition. We also show that compared to controls, patients exhibit specific WM deficits consistent with model predictions. A similar pattern of results emerges with ketamine whereby controls display results similar to patient findings.

Discussion: Our initial findings show promising support for disinhibition as a neural model of WM deficits in early course schizophrenia and ketamine

as a suitable pharmacological model of these deficits. We argue for the ongoing need to bridge mechanistic understanding of cellular dysfunction, systems-level disturbances and, ultimately, psychiatric symptoms. We suggest that clinical neuroscience studies should aim to harness the synergistic combination of these tools to move towards developing effective hypothesis-driven treatments for schizophrenia.

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STRESS-INDUCED CHANGES IN PREFRONTAL CORTEX DOPAMINE D2/3 RECEPTOR AVAILABILITY IN PSYCHOSIS

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Background: Recent studies show that the mesolimbic dopaminergic response to psychosocial stress is increased in psychosis. Stress-induced dopamine activity in the prefrontal cortex (PFC) in the context of psychosis has been less well investigated, partly due to methodological constraints. Investigating the role of stress-induced dopamine activity in PFC is essential, as studies in healthy controls, those at increased risk for psychosis and rodents have demonstrated a key regulatory role for the PFC in the stress response. Changes in this regulatory role potentially drive increased stress-sensitivity in psychosis. Using a common variant of the simplified reference tissue model, we investigated for the first time stress-induced PFC dopamine activity in psychosis. Subjective stress and psychotic symptoms were also assessed.

Methods: 12 healthy controls, 12 patients currently not on medication (Med-) and 12 patients currently on medication (Med+) matched on age and gender were subjected to an [18F]fallypride positron emission tomography psychosocial stress paradigm using the Montreal Imaging Stress Task. Total scan duration was 180 minutes.

Results: Regression analyses revealed large differences in stress-induced changes in [18F]fallypride binding in ventromedial (vm) PFC and dorsolateral (dl) PFC with differences across the three groups ($p < 0.01$). Med+ and Med- demonstrated little change in D2/D3 availability in response to stress, whereas controls showed large changes in receptor availability. There were subtle differences between Med+ and Med-. Associations with current symptoms and subjective stress revealed group differences.

Discussion: We show for the first time that D2/3 receptor availability in VMPFC/DLPFC following stress is dependent on group status. Med+ showed a low stress-induced dopaminergic response, Med- slightly higher and controls highest, whilst the subjective stress response demonstrated the opposite. Differences in stress-induced changes in D2/3 receptor occupancy between Med+ and Med- could suggest that the stress response depends on medication or illness-phase. The strong association between stress-induced dopaminergic PFC activity and subjective stress/symptoms indicates that changes in the regulatory dopaminergic role of the PFC play an essential role in stress-sensitivity and symptom levels in psychosis.

Oral Presentations

ADVANCES IN IMAGING IN SCHIZOPHRENIA II

Chairperson: Alessandro Bertolino

Tuesday, 8 April 2014

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CORTICAL THICKNESS IN INDIVIDUALS WITH NONCLINICAL AND CLINICAL PSYCHOSIS

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Background: Symptoms that are linked to schizophrenia and other psychotic disorders, such as auditory verbal hallucinations, are also commonly reported by individuals who function well in society. These individuals are not in need for care, do not suffer from schizotypal personality disorder or other psychotic disorders, and provide the opportunity to investigate the relationship between nonclinical psychotic symptoms and brain morphology. The purpose of this study was to compare cortical thickness in individuals with nonclinical auditory verbal hallucinations (AVH) to patients with a psychotic disorder and AVH on one hand and to healthy controls on the other hand.

Methods: Fifty individuals with nonclinical AVH (most of them also experienced other nonclinical psychotic symptoms), 50 patients with a psychotic disorder and AVH, and 50 healthy controls participated in this study and underwent structural magnetic resonance imaging. The three groups were matched for age, gender, handedness and years of parental education. Cortical thickness was assessed for 68 distinct cortical regions using the FreeSurfer software suite. Data were analyzed with analysis of covariance with age and gender as covariates. In additional analysis, cortical thickness of each cortical region was ranked across groups. Prevalence of each order was then assessed across all regions.

Results: Analysis of covariance revealed that for the left pars orbitalis, left paracentral gyrus, right fusiform gyrus and right inferior temporal gyrus cortical thickness was lowest in patients, intermediate in the nonclinical AVH group, and highest in controls. The patients also showed additional cortical thinning in widespread frontal, temporal and parietal areas compared to both other groups. Ranking the levels of cortical thickness per brain region revealed that for a large majority of brain regions (88%), the patients had the lowest cortical thickness, the nonclinical individuals with AVH were in between, and the control subjects had the highest cortical thickness.

Discussion: These findings show that individuals with nonclinical psychotic symptoms show a similar but less pronounced pattern of cortical thinning as patients with a psychotic disorder, which is suggestive of a similar, but milder underlying pathophysiology in the nonclinical hallucinating group compared to the psychosis group.

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DIFFERENTIAL DIAGNOSTIC CLASSIFICATION OF FUNCTIONAL PSYCHOSES USING MRI-BASED PATTERN RECOGNITION

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Background: Research into the neurobiology of schizophrenic and affective psychoses yielded cross-nosological overlaps ranging from genes to brain structural alterations. Furthermore, the reliable clinical differentiation of both disorders is frequently challenged by the co-occurrence of affective and psychotic features. These observations have fueled the long-standing debate whether these two disease groups share a common etiopathological basis or, alternatively are subserved by two distinct neurobiological surrogates. Thus, the detection of biomarkers enabling the single-subject differentiation of functional psychoses could (1) validate existing nosological constructs, and (2) facilitate clinical decision making in unclear/ambiguous cases.

Methods: We evaluated whether the individualized differential diagnostic classification of schizophrenia (SZ) and major depression (MD) could be facilitated by the multivariate pattern classification of structural MRI (sMRI) data. Therefore, the T1-weighted scans of 158 SZ (mean \pm SD age: 30.8 \pm 10.0 yrs.; 39% female) and 104 MD patients (mean \pm SD age: 42.3 \pm 12.0 yrs.; 50% female) patients were processed using high-dimensional voxel-based morphometry, which produced gray matter (GM) volume maps normalized to MNI space. These maps were residualized for age and gender effects using the sMRI data of 432 healthy volunteers. The adjusted GM maps entered a machine learning pipeline that extracted diagnostic features using principal component analysis and linear support vector machines. Generalization of

diagnostic performance was measured in terms of accuracy, sensitivity and specificity using repeated nested cross-validation. Additionally, a misclassification analysis was carried out to identify possible subgroups of SZ and MD patients, which showed a high neuroanatomical overlap and thus were difficult to separate at the individual level.

Results: The overall cross-validated classification accuracy was 76% (correct SZ/MD classifications: 72%/80%). The discriminative pattern involved GM volume reductions in SZ vs. MD, which were predominantly located in the perisylvian, limbic, medial prefrontal and precuneal cortices. GM volume reductions in MD vs. SZ patients were primarily detected in the premotor, sensorimotor, parietal, cerebellar and brainstem structures. Further analyses revealed that the "SZ-likehood" of MD patients was highly correlated with the age of disease onset, leading to a significantly higher misclassification rate among MD patients with an age of onset between 15 and 30 yrs. Finally, an additional within-disease MRI classification analysis revealed that early-onset MD patients could be separated from late-onset patients (median split: 36 yrs) with an accuracy of 84%, while in the similarly stratified SZ groups (median split: 24 yrs) classification accuracy measured only 64%.

Discussion: The findings suggest that schizophrenia and major depression could be reliably identified at the single subject level using neuroanatomical pattern recognition. The decreased diagnostic separability of MD patients with an early disease onset may challenge the traditional nosological boundaries between schizophrenic and mood disorders and may relate to higher levels of chronicity and unfavorable disease outcomes previously found in this patient population.

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ELEVATED ANTERIOR CINGULATE CORTEX GLUTAMATE LEVELS ARE ASSOCIATED WITH ANTIPSYCHOTIC TREATMENT RESISTANCE AND CLINICAL SEVERITY IN SCHIZOPHRENIA

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Background: Approximately one third of schizophrenia patients do not respond adequately to dopaminergic antipsychotic medication. Such patients have seemingly normal striatal presynaptic dopamine synthesis (Demjaha et al, 2012), however they show elevated anterior cingulate cortex compared to healthy controls (Demjaha et al, 2013) as measured by proton magnetic resonance spectroscopy (1H-MRS). It is thus suggested that glutamatergic abnormality is an additional non-dopaminergic neurochemical dysfunction in schizophrenia and could be a potential biomarker for the stratification of resistant and responsive patients. To date, there no studies that report glutamatergic differences between resistant and responsive patients.

Methods: We acquired 1H-MRS spectra at 3 Tesla in the anterior cingulate cortex from 21 treatment-resistant and 20 responsive schizophrenia patients. LC-Model was used to estimate metabolite levels in ratio to creatine (Cr). Only metabolite spectra that showed Cramer-Rao lower bounds (CRLB) <20% were included in the analysis. Additionally signal-to-noise ratio (S/N) ≥5 was required for inclusion. Based on those criteria two patients from each group were excluded, hence data from 19 treatment-resistant and 18 responders were analysed. No differences were found between the two groups in CRLB and S/N.

Results: Glutamate/Cr levels were increased by 11% for resistant patients compared to responsive patients ($t(35)=2.34$, $P=0.025$, two-tailed; representing a large effect size $d=0.76$). Significance was increased after removal of 4 outlier values (above and below three standard deviations from mean), $t(31)=2.91$, $P=0.006$, two-tailed, reflecting a large effect size $d=1.05$. Collapsing across both groups, higher glutamate/Cr levels were associated with greater severity in general psychopathology ($r=0.5$, $P=0.006$), total symptoms ($r=0.47$, $P=0.013$), and at trend level with positive symptoms ($r=0.36$, $P=0.0503$) measured by the Positive and Negative Syndrome Scale.

Discussion: Our findings show for the first time that schizophrenia treat-

ment-resistant patients show increased anterior cingulate cortex glutamate levels. This finding can potentially be used to stratify treatment-resistant and responsive patients, while glutamatergic dysfunction is associated with greater severity in symptomatology. This suggests further consideration for the use of glutamatergic compounds in the treatment of schizophrenia, with likely greater benefit to patients that show resistance to antidopaminergic treatments.

5:00 PM

EMERGING EVIDENCE OF Affected ANATOMICAL RICH CLUB HUB STRUCTURE IN SCHIZOPHRENIA PATIENTS, THEIR HEALTHY SIBLINGS AND THEIR NON-AFFECTED YOUNG OFFSPRING

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Background: Healthy brain function depends on effective processing and efficient integration of information within a network of neural interactions. In the past years, several studies examining the topological architecture of the human (and animal) brain network (known as the 'connectome') have revealed distinct properties of efficient processing and communication attributes, including pronounced formation of functional and structural communities, short communication pathways, as well as the formation of a small set of centrally placed communication "brain hubs" that form a central "core" or "rich club" in the brain. As a collective of hubs, the rich club has been suggested to form a crucial infrastructure for global interactions and integration of information between the different functional and cognitive domains of the human brain (Van den Heuvel and Sporns, TICS, 2013). Being crucial for brain communication, the central embedding of these brain hubs also renders them points of vulnerability in diseases that heavily affect cognitive processing, in particular schizophrenia.

Methods: Examining the brain's anatomical and functional connectivity architecture, combining diffusion weighted imaging (DWI) with resting-state fMRI measurements of 3T and 1.5T MR imaging, we examined hub and rich club structure of the brain networks of patients with schizophrenia (2 groups of >40 patients), a group of healthy siblings of patients (>40) and a group of young not affected offspring of patients (16 children, age <16 years), all compared to a group of age-matched healthy controls (>100 controls in total). Connectome reconstruction and functional interactions between brain regions was established for each of the individual subjects (Van den Heuvel and Sporns J Neuroscience 2011), after which the organization of the obtained brain networks was examined by means of network science.

Results: Anatomical white matter connectome organization of brain hubs (rich club density) was found to be significantly affected in patients as compared to the group of healthy controls ($p<0.05$, Van den Heuvel et al. JAMA Psychiatry 2013), having an important effect on the communication capacity and functional dynamics of the brain networks of patients ($p<0.05$, permutation testing, 10,000 permutations). Furthermore, suggesting a familiar, possible genetic, background of this effect, rich club structure was observed to be significantly reduced in the group of healthy siblings ($p<0.05$, 10,000 permutations), as well as in the group of not affected offspring of patients ($p<0.05$, 10,000 permutations), with rich club densities of these groups being in between the control and patient populations. Furthermore, commonly reported connectome alterations (e.g. affected clustering, longer communication paths etc) were found to centralized around frontal rich club nodes, further underscoring a strong involvement of these frontal hubs in the disease.

Discussion: Our findings provide several lines of evidence for a reduced hub connectivity and rich club structure to play an important role in the etiology of schizophrenia. Affected anatomical connectivity was found to be most prominent for connections linking central brain nodes, suggesting a strong effect on brain communication and global integration of information. Importantly, the observation of a reduced rich club structure in healthy siblings and healthy offspring suggest a familiar, likely genetic, background of this effect. This suggests an important role for altered rich club formation in the development of schizophrenia.

5:15 PM**GABA AND GLUTAMATE IN SCHIZOPHRENIA: A 7T 1H-MRS STUDY**

Anouk Marsman¹, Rene Mandl², Dennis Klomp³, Marc Bohlken², Vincent Boer³, Anna Andreychenko³, Wiepke Cahn², René Kahn², Peter Luijten³, Hilleke Hulshoff Pol²

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Background: Schizophrenia is characterized by a loss of brain tissue, which may represent an ongoing pathophysiological process. Mechanisms that may be involved are the glutamatergic and GABAergic systems (Marsman et al., 2013). In this study, alterations in GABA (gamma-aminobutyric acid) and glutamate (Glu) levels in patients with schizophrenia as compared to healthy control subjects were examined. Performing 1H-MRS at an ultra-high magnetic field strength of 7T results in increased sensitivity and spectral resolution, which are particularly important when measuring Glu and GABA.

Methods: 18 schizophrenia patients (age 27.6±6.1, M/F=13/4) and 23 matched healthy control subjects (age 27.7±5.3, M/F 16/7) participated in this study. All participants underwent a general cognitive assessment using the full Wechsler Adult Intelligence Scale (WAIS)-III (Wechsler, 1997). Healthy control subjects did not have a history of psychiatric or neurological disorders, and did not have first-degree family members with psychiatric or neurological disorders.

1H-MRS experiments were performed on a 7T whole body MR scanner (Philips, Cleveland, OH, US). A birdcage transmit head coil was used in dual transmit driven by 2x4 kW amplifiers, in combination with a 32-channel receive coil (both Nova Medical Inc., Burlington, MA, US). For the assessment of Glu an sLASER sequence (Boer et al., 2011) was used. Non-water-suppressed spectra were obtained for quantification. GABA-edited experiments were conducted using a MEGA-sLASER sequence (Andreychenko et al., 2012). Voxels were located in the medial prefrontal and medial occipital lobe.

Fitting of the sLASER spectra was performed with LCModel-based software implemented in Matlab (De Graaf, 1999), which uses a priori knowledge of spectral components to fit metabolite resonances (Govindaraju et al., 2000). To correct for the contribution of gray matter, white matter and cerebrospinal fluid in each voxel, segmentation was performed using the SPM8 software package. Fitting of the MEGA-sLASER spectra was performed by frequency-domain fitting of the GABA and Cr resonances to a Lorentzian line-shape function in Matlab. GABA levels were expressed as the ratios of their peak areas relative to the peak areas of the Cr resonance. Spectra with a CRLB of 20% or more were excluded from the study. Statistical analyses were performed using SPSS 21.0 (2012, Chicago, IL). To evaluate differences in metabolite levels between patients and controls multiple univariate analyses of variance were done.

Results: There was significant main effect of group on GABA/Cr ratio in the prefrontal cortex ($p=0.0012$), due to patients having lower GABA/Cr ratios as compared to healthy controls. There was no significant main effect of group on GABA/Cr ratios in the occipital cortex. There were no significant main effects of group on Glu concentrations. There was a significant interaction of intelligence-by-group on GABA/Cr ratio in the prefrontal cortex ($p=0.04$), due to patients with a higher intelligence having lower GABA/Cr ratios ($p<0.001$).

Discussion: The main finding of this study is that prefrontal GABA/Cr ratios in patients were significantly lower as compared to healthy controls. Moreover, the lower prefrontal GABA/Cr ratios in patients were strongly correlated with their level of general cognitive functioning, with high functioning patients showing lower GABA/Cr ratios. Considering the relatively young age of the sample, this may suggest a role for GABA in the earlier stages of schizophrenia.

5:30 PM**PREFRONTAL ABNORMALITIES IN NAA AND GLUTAMATE LEVELS IN PERSONS WITH A PSYCHOTIC DISORDER OR AT RISK FOR A PSYCHOSIS: A LARGE H-MRS STUDY**

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Background: It has been shown that persons people with a psychotic disorder or who are at risk for psychosis may have an aberrant functioning of the prefrontal cortex. These prefrontal abnormalities have been related to negative symptoms and cognitive impairments. A decreased quality of prefrontal neurons and abnormal glutamate levels may cause the prefrontal abnormalities and concurrent symptoms. In this study we investigated the levels of N-Acetyl Aspartate (NAA, measure for neuronal integrity) and glutamate in a large sample of persons with a psychotic disorder or at risk for psychosis.

Methods: We included 106 patients with a diagnosis of schizophrenia spectrum disorder. In addition, 16 persons with an At Risk Mental State (ARMS) for psychosis and 36 healthy controls underwent a H-MRS single voxel spectroscopy scan in the white matter of their left lateral prefrontal cortex. We used a 2 cm³ voxel with standard PRESS sequence of Philips. Absolute levels of glutamate (GLU) and NAA were determined in LCModel by using the water peak as a reference. The concentrations were corrected for gray matter and CSF content of the voxel. Patients and ARMS subjects were compared to their matched healthy control subjects. Moreover, the relations with age, duration of illness, negative symptoms, and cognitive performance on a planning task were investigated.

Results: We found that NAA and GLU levels were higher in young persons with a psychosis, but that the levels decreased stronger with increasing age than in healthy controls. A longer duration of illness was also weakly associated with lower NAA and GLU levels. In the ARMS subjects, NAA and GLU levels were lower at a young age, but higher in older subjects, while there was no effect of age on NAA in the healthy control group and a negative association with GLU. Moreover, both patients and ARMS subjects showed a negative association between GLU levels and negative symptoms, but not for NAA, neither an effect for cognitive performance.

Discussion: In conclusion, patients with a psychosis, levels of NAA and glutamate may decrease to a stronger extend with increasing age than in healthy controls. Contrary, patients with a developing psychosis may show excessive levels of GLU and NAA, though this hypothesis needs further investigation. Notably, negative symptoms are related to lower prefrontal levels of glutamate, which is an excitatory neurotransmitter.

5:45 PM**REDUCED MICROSTRUCTURAL WHITE MATTER ALTERATIONS IN PSYCHOTIC DISORDER: STABLE OR PROGRESSIVE?**

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Maastricht University

Background: A consistent finding in cross-sectional DTI studies in schizophrenia is reduced white matter integrity. To what extent structural white matter brain alterations remain stable or progress over times has not been well investigated. Longitudinal DTI studies in the early stages of schizophrenia are lacking, with the exception of two ultra-high risk (UHR) studies that showed predominantly FA decreases in the transition phase from UHR to first-episode psychosis [1]. In the present longitudinal, whole brain, voxel-based, family study we examined the hypothesis that fractional anisotropy (FA), as a measure of white matter integrity, decreases more in patients than in siblings and healthy controls.

Methods: At two time points with an average scan interval of 3 years, DTI scans were acquired from 258 participants at baseline (80 healthy controls, 93 non-psychotic siblings, 85 patients with a psychotic disorder; mean illness duration: 5 years) and from 180 participants at follow up (58 controls, 61 siblings, 61 patients).

Processing of DTI data was effectuated using tract-based spatial statistics (TBSS) v1.2 in FSL. Skeleton mean FA values were extracted from 38 JHU la-

beled white matter tracts and exported to Stata version 12 [2]. Main effects of group and group × time interactions in the model of FA were examined with multilevel random regression procedures. Analyses were adjusted for the a priori hypothesized confounding variables age, sex, handedness and educational level.

Results: There was a significant association between group (linear trend) and FA at both time points (baseline and follow-up: B = -0.006, P=0.001). Patients showed significantly lower mean FA than controls and siblings at baseline (B = -0.006, P=0.001) and at follow-up (B = -0.007, P=0.001). Siblings were different from controls only at the second measurement point (B=-0.009, p=0.02). There was also a significant effect of time (linear trend) on FA (B = -.001, P=0.002) and a significant group × time interaction ($\chi^2=16.8$, P=0.00) in the model of FA. Stratified analyses showed a significant effect of time on FA in siblings (B = -0.003, P=0.00), but not in controls and patients.

Discussion: At baseline and at follow-up, patients with psychotic disorder showed reduced white matter integrity in comparison to healthy controls. Results contradict a progressive brain disease, as reductions remained stable over an average time period of 3 years. Analysis provided evidence for a differential effect of time in the siblings that requires further investigation.

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TOPOLOGICAL FEATURES OF STRUCTURAL BRAIN NETWORKS IN SUB-CLINICAL PSYCHOSIS REVEALED BY GRAPH THEORETICAL ANALYSIS OF TRACTOGRAPHY DATA

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Background: Schizophrenia has long been conceptualised as a 'disconnection syndrome'. Understanding disconnectivity in schizophrenia can benefit greatly from graph theory (GT), a powerful mathematical framework that quantifies topological features of networks. Previous studies have reported several structural network related changes in schizophrenia by applying GT to tractography data. Here we elucidate structural network changes that manifest in early prodromal stages of the disease by examining network topology in a large homogeneous birth cohort who have had psychotic experiences (PEs) without a clinical diagnosis of psychosis.

Methods: 248 subjects were selected from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, where psychotic experiences were assessed using the PLIKS interview at age 17. Those whose PEs were verified by trained researchers as suspected or definite (cases), and subjects with no such experiences (controls) were invited to undergo MRI scanning (124 cases, 126 controls). At the time of scanning all subjects were 18 years old. All data were acquired on a 3T GE HDx MRI system. HARDI data were acquired with cardiac-gated EPI sequence with 60 gradient orientations. Data were analysed in ExploreDTI and corrected for motion, eddy current distortions and field inhomogeneities. Whole-brain tractography was then performed. Tract termination points were registered to the AAL atlas, creating a 116×116 connectivity matrix. The matrices were binarised at a range of thresholds (0-20 streamlines). A range of GT metrics was computed. Network-level: Global and mean efficiency, density, mean betweenness, mean strength, global and mean clustering coefficient and smallworldness. Node-level: Strength, degree, betweenness centrality, local efficiency, local clustering coefficient, modularity and path length. Unpaired t-tests were computed for all GT metrics between cases and controls. Multiple comparisons were corrected using permutation tests. Additional correction for statistical bias was carried out across thresholds. Only significant effects spanning more than 6 thresholds were retained.

Results: Network-level metrics: density and mean efficiency were significantly lower in cases compared to controls at $p_{corr}<0.05$. All other network-level metrics showed no significant differences. Node-level metrics: efficiency, betweenness centrality, degree and clustering coefficient all showed significant regional differences. Controls showed higher effi-

ciency in several regions including inferior frontal, temporopolar, cingulate and occipitoparietal cortices. Increased degree was found in occipital and cerebellar regions. Cases showed increased betweenness centrality and clustering coefficient in supplementary motor area and orbitofrontal cortex, but the opposite effect was seen in the caudate. Cases also showed higher clustering coefficients in the insula.

Discussion: The results show subtle, but topologically significant changes in white matter occur in individuals with psychotic experiences, which can lead to functional changes at the network-level. These conform to similar results in schizophrenia: Zalesky et al (2010) also showed density and mean efficiency is reduced in schizophrenia. Regions showing reduced node-level efficiency overlap with many regions previously implicated by Van den Heuvel et al (2010). Results for betweenness and clustering coefficient are less consistent. It is likely that these measurements will fluctuate as different network components become impaired at different stages of psychotic illness. Future identification of those who transition to full psychosis will help to differentiate more specific graph theoretical predictors of psychosis.

Oral Presentations

BIMARKERS

Chairperson: Cynthia Shannon-Weickert

Tuesday, 8 April 2014

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CONTINUITY OF EXTERNALISING AND INTERNALISING PSYCHOPATHOLOGY AS PREDICTORS OF PSYCHOTIC-LIKE EXPERIENCES IN A LONGITUDINAL GENERAL POPULATION COHORT OF TEENAGERS

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Background: Prospective, longitudinal studies of high risk samples or population cohorts have consistently demonstrated that, by middle childhood, individuals who subsequently develop schizophrenia display difficulties across multiple domains of functioning, including internalising and externalising problems. To date, few studies have examined the association between changes in externalising and internalising problems throughout childhood and early adolescence and psychotic-like experiences (PLEs). The primary contribution of this study is investigating these associations in a general population sample of early teens.

Methods: Longitudinal data were collected at two assessments. In the first assessment, 8099 children aged 9-11 years (mean 10.4 years, SD 0.8 years; 95% of eligible children) completed questionnaires independently in class at school, with corresponding questionnaires completed by the child's primary caregiver (n=1504; 19%) at home. The second assessment was conducted approximately 2 years later, with follow up data provided by 561 children and their primary caregivers, representing 7% of the initial community cohort. Internalising and externalising psychopathology were assessed via the Strengths and Difficulties Questionnaire (Goodman, 1997), and PLEs via the 9-item Psychotic-Like Experiences Questionnaire for Children (Laurens et al. 2012). A selection bias (Heckman correction) was computed to examine the effect of sample attrition between waves 1 and 2 on the representativeness of the sample.

Results: A series of logistic regression analyses were used to examine the extent of the associations between patterns of continuity/discontinuity in child externalising and internalising problems between assessments 1 and 2 (i.e., remitting, incident, and persistent) and the presence of at least one psychotic-like experience at assessment 2. Statistically significant associations were observed between persistent and incident patterns of internalising and externalising problems and later PLEs. No association was present for those presenting remitting psychopathology. Statistical control for the effects of confounding factors (gender, age at each assessment, PLEs at assessment 1) had no impact, with associations remaining statistically significant after adjustment. Results before and after adjustment for sample selection hazard scores (selection bias) indicated that the conclusions drawn

from both sets of findings were similar, implying that sample selection bias was unlikely to have influenced study findings.

Discussion: Persistent and incident internalising and externalising problems from mid-childhood into adolescence are associated with later PLEs in the general population, whereas childhood-limited psychopathology (remitting problems) are not. Interventions that target the persistence or incidence of internalising or externalising psychopathology from childhood to adolescence may impact on the expression of PLEs. Further research is needed to elucidate whether common or distinct mechanisms influence the associations of internalising and externalising psychopathology with PLEs.

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INFLAMMATORY RESPONSE IN FIRST-EPIISODE PSYCHOSIS

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Background: Cytokines, and chemokines as their subgroup, are a large group of proteins that regulate all aspects of innate and adaptive immunity. Several first-episode psychosis studies have observed elevations in proinflammatory cytokines in first-episode psychosis, while chemokines have received much less attention. Therefore, we set out to investigate changes in cyto- and chemokines in patients with first-episode psychosis and matched general population controls.

Methods: First episode psychosis patients with a median of 27 days of antipsychotic medication and matched controls were recruited from the capital area of Finland. Serum levels of 38 cytokines and chemokines were analyzed using the Milliplex MAP Kit (HCYTMAG-60K-PX38, Millipore Corp., Billerica, MA). In addition, cardiovascular risk markers were measured. The analyses were done at baseline and for patients also 2 months later.

Results: The study group consisted of 37 (21 males) first-episode patients and 19 (10 males) controls, with a mean age of 26.1 and 28.6 years, respectively. At baseline, patients and controls did not differ significantly in terms of BMI or waist circumference. FEP patients as compared to healthy controls had higher CCL22 and lower TGF α , CXCL1, CCL7, IFN α 2, ApoA-I and HDL-C levels. The findings remained significant after adjusting for BMI, age and sex. Duration of antipsychotic treatment did not correlate significantly with cytokine levels. CCL22 level had decreased significantly at 2 month follow-up, but was still higher than in controls.

Discussion: Inflammatory response is dynamic, and our findings reflect the situation in a subacute phase of first-episode psychosis. The observed profile of systemic chemokines in first-episode psychosis, such as increased CCL22 and decreased CXCL1, CCL7 and IFN- α , could reflect up-regulation of STAT6 signaling. The classical proinflammatory state characterized by elevated IL-1, IL-6 and TNF- α may be a relatively short-lived phenomenon associated with acute psychosis, and was not observed in this study. The earliest metabolic alteration in first-episode psychosis was decreased HDL-C and ApoA-I, suggesting a vulnerability to metabolic syndrome from the onset of psychosis.

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PREMORBID AND CURRENT COGNITIVE FUNCTION IN SCHIZOPHRENIA ASSOCIATE WITH TREATMENT RESISTANCE AND EGF 61 AA GENOTYPE

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Background: Disaggregating clinical clusters within schizophrenia (SCZ) such as cognitive impairment (CI) and treatment resistance will assist in identifying pathological mechanisms and possible biomarkers. Others' and our data have elucidated involvement of the epidermal growth factor (EGF) system in both these clinical processes in SCZ and other neuropsychiatric disorders. We have proposed that deficient EGF signalling is ameliorated by clozapine through EGF receptor transactivation in treatment resistant SCZ (TRS) and low EGF function is associated with cognitive impairment

in Parkinson's disorder, dementias and mouse models of psychosis. A functional single nucleotide polymorphism in the EGF gene (61A>G) provides a model where the 61AA homozygote produces less EGF than the AG heterozygote and GG homozygote. We therefore, postulated that cognitive impairment is associated with TRS and that the EGF 61A>G SNP is associated with impaired cognitive processes.

Methods: Clinical and cognitive data and DNA from participants with a diagnosis of SCZ (n=664) were accessed from the Australian Schizophrenia Research Bank. TRS was defined as current or past treatment with clozapine. Cognitive data were the Wechsler Test of Adult Reading (WTAR) standard score as a measure of premorbid cognitive ability and Letter Number Sequencing (LNS), Controlled Oral Word Association Test (COWAT) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) as measures of current cognitive ability. These scores were z transformed (based on a cohort including healthy controls n=634) and composite scores were computed for the domains of Executive Functioning, Memory and Attention. Genotyping for EGF 61 A>G SNP (rs4444903) was performed using a TaqMan® assay and allele frequencies for AA, AG and GG genotypes were obtained. The groups were compared using standard statistical tests.

Results: TRS patients had significantly lower premorbid intellectual function when compared to non-TRS patients (WTAR score – TRS=-0.55±1.2, non TRS=-0.23±1.1, mean \pm s; p=0.004). TRS patients had significantly lower current performance when compared to non-TRS patients in working memory and executive functioning tests (LNS score – TRS=-0.72±0.86, non-TRS=-0.33±0.92; p<0.001; RBANS Memory composite score – TRS=-1.11±0.91, non-TRS=-0.43±0.90; p<0.001; RBANS Attention composite score – TRS=-0.83±0.80, non-TRS=-0.46±0.87; p<0.001; but not COWAT score; p=0.79, and RBANS Language composite score; p=0.17).

The EGF genotypes were in Hardy-Weinberg Equilibrium. Patients with the 61AA genotype had significantly lower premorbid cognitive ability (WTAR score – AA participant s=-0.40±1.12), than non-AA participants (-0.21±1.1; p=0.031). AA patients had significantly lower current cognitive abilities characterised by working memory (LNS; AA=-0.55±0.84, non AA=-0.38±0.93; p=0.018), Executive Functioning (COWAT; AA=-0.50±0.91, non AA=-0.31±0.96; p=0.014) and RBANS Attention domain composite score (AA=-0.64±0.82, non AA=-0.49±0.89; p=0.033) but not RBANS Language composite score (p=0.21) and Memory composite score (p=0.19).

Discussion: These data demonstrate in a large cohort that people with TRS have significantly poorer pre-morbid intellectual function than people with treatment responsive schizophrenia and that impairment persists through the illness. Moreover, cognitive impairment is associated with the 61AA genotype suggesting that lower EGF levels may contribute to this symptom domain. Together these data support a model where a hypofunctioning EGF system may predispose and link to both treatment resistance and cognitive impairment in schizophrenia. This provides genetic and molecular targets to investigate as plausible biomarkers for treatment planning and early intervention in schizophrenia.

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REAL-TIME DETECTION OF COGNITIVE DECLINE IN CHILDREN AT HIGH GENETIC RISK OF SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: There is an emerging consensus that schizophrenia is a neurodevelopmental disorder characterized by a cognitive deterioration beginning in childhood (1-3). We have already reported severe cognitive impairments in children and adolescents (HR) descending from multi-affected families of Eastern Quebec (4). We now report in a longitudinal study of 40 high-risk offspring aged 6 to 26 that 10 of them presented a global IQ decline of 10 points suggesting that they are going through a developmental transition toward the disease.

Methods: We already reported that the phenotypic, endophenotypic and genetic findings in the children, the non-affected adults and the patients of this familial sample were strongly resembling the findings reported in general or sporadic samples (5). In this high-risk sample, we used a step by step sampling approach to narrow-down the early disease mechanisms. Upstream, we started with a 20-year follow-up of 48 densely

affected multigenerational kindreds, including 1500 clinically characterized adult members. We then identified 400 members affected by a DSM-IV schizophrenia or bipolar disorder. Downstream, we finally focused on HRs aged 6 to 26. Forty of them were administered a neuropsychological battery (Wechsler scale and 9 cognitive domains), at two different times at an average interval of 5 years, and at different developmental periods from age 6 to age 26.

Results: Whereas 30 HRs showed a stable IQ (mean global IQ of 95), as many as 10 of these youths underwent a notable decrease of their cognitive functioning over a period of around 5 years, as expressed by a decline of 9 to 18 points. Such declines did not occur at particular developmental periods but were apparent in preadolescence for some HRs or later for others. The declines ended up in more severe disorders for some offspring but not for all, or not yet, since some of the declining HRs were still adolescents. Interestingly, the decrease in IQ happened as much in children having a high initial IQ as in those having initial average or lower IQ. The longitudinal cognitive profile of the declining children and adolescents will be presented, as well as the relationship with social functioning and attenuated symptoms of psychosis.

Discussion: Our data suggest that a considerable number of the children and adolescents at high genetic risk descending from densely affected families exhibit a significant cognitive deterioration that can occur either in preadolescence or later in adolescence up to young adulthood. The findings also suggest that i) the timing of measurements is crucial for future research, ii) the form of the trajectory matters as much as the presence of any cognitive deficit measured at a specific time and iii) at least two measures of cognitive functioning at a few years of interval should be taken to detect the risk trajectory. The results motivate intervention research aiming to normalize the trajectory.

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RISK OF DIABETES IN PEDIATRIC PATIENTS EXPOSED TO ANTIPSYCHOTICS: A NATIONWIDE 12-YEAR CASE-CONTROL STUDY

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Background: Antipsychotics are associated with weight gain and increased diabetes risk. However, the risk and rate of diabetes in antipsychotic-treated youth is unclear.

Methods: Longitudinal register linkage case control study of diabetes in all psychiatric patients aged <18 years in Denmark from 01.01.1999–31.06.2010. Patients with and without antipsychotic exposure were compared regarding the occurrence of diabetes, defined by prescription of ≥1 oral antidiabetic medication.

Results: We compared the risk of diabetes in 48,311 psychiatrically ill youth. Of 7,256 antipsychotic-exposed youth, 35 (0.48% (95% confidence interval (CI) = 0.33%–0.67%); males = 0.21% (95%CI = 0.10%–0.40%), females = 0.86% (95%CI = 0.56%–1.26%), $P < 0.001$) developed diabetes. Of 41,055 youth un-exposed to antipsychotics, 139 (0.34% (95%CI = 0.28%–0.40%); males = 0.08% (95%CI = 0.05%–0.13%), females = 0.74% (95%CI = 0.61%–0.88%), $P < 0.001$) developed diabetes. In a logistic regression analysis, adjusting for sex, age and diagnoses, diabetes development was associated with antipsychotic drug exposure (odds ratio (OR)=1.60; 95%CI = 1.03–2.45, $P < 0.05$, female sex (OR=4.39; 95%CI = 2.88–6.68, $P < 0.0001$), and older age at first psychiatric diagnosis (OR=1.19; 95%CI = 1.12–1.27, $P < 0.0001$), but not with psychiatric diagnosis or drug dosage. In a Cox-regression analysis, adjusting for sex, age and diagnoses, shorter time to diabetes onset was associated with antipsychotic exposure (Hazard Ratio (HR)=2.01; 95%CI = 1.23–3.24), $P < 0.005$, female sex (HR=4.83; 95%CI = 3.12–7.48, $P < 0.0001$), and older

age at first psychiatric diagnosis ($HR=1.22$; 95%CI = 1.14–1.30, $P < 0.0001$), but not with psychiatric diagnosis or drug dosage.

Discussion: Antipsychotic treatment, female sex and older age at psychiatric diagnosis were associated with a significantly more frequent as well as earlier diabetes onset in pediatric patients. Strict indications for antipsychotic treatment and routine cardiometabolic monitoring are crucial.

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RNA SEQUENCING OF CHOROID PLEXUS IN SCHIZOPHRENIA AND UNAFFECTED CONTROL SUBJECTS

Maree J. Webster, Sanghyeon Kim
Stanley Medical Research Institute

Background: There is accumulating evidence that an increase in markers of inflammation occurs in both the blood and CSF of patients with schizophrenia. Our recent RNA sequencing study of hippocampus also showed elevated expression of markers of inflammation, however many of these markers were expressed in cells at the blood-brain barrier and thus implicated this structure in the pathophysiology of schizophrenia¹. The homeostatic environment of the brain is primarily maintained and protected by two barriers. The endothelial blood-brain barrier (BBB) comprised of the cerebral vasculature and by the epithelial blood-cerebrospinal fluid barrier (BCSF) comprised primarily of the choroid plexus (CP).

Methods: We began a more detailed investigation of possible abnormalities in these barriers by performing RNA-sequencing of the choroid plexus of 34 schizophrenia and 34 normal control subjects. Forty million 100-bp paired end sequence reads were generated on the Illumina HiSeq2000. Sequence reads were mapped to the human reference genome (hg18) using the TopHat v2.0.0 and then aligned reads per genes were counted by htseq-count (subprogram of HTseq). The differential expression analysis was performed using edgeR.

Results: We found 53 abnormally expressed genes in schizophrenia as compared to controls and only 7 of these were down-regulated. Gene Ontology pathway analysis revealed many of the genes clustered in immune, inflammation and defense response pathways. Genes involved in regulation of cell proliferation and ion homeostasis were also significantly represented. Pentraxin (PTX3) which is a serum protein rapidly produced and released in response to primary inflammatory signals (e.g. TNF α , IL1 β , LPS) was one of the most significantly up-regulated genes in the CP. The chemokines CCL2 and CCL20 were also significantly up-regulated in the CP of schizophrenia. To further determine which biological processes were altered in the choroid plexus of schizophrenia we conducted an unsupervised co-expression network analysis using the normalized RNA-seq data of all genes in the choroid plexus of both schizophrenia and controls. A total of 20 co-expression modules were generated but only one showed a trend level of significance associated with schizophrenia ($p=0.06$). This was a large module containing 256 genes. Cell motion, angiogenesis and blood vessel morphogenesis were the most significantly enriched genes in this module and suggest a possible abnormality in the integrity of the endothelial barrier. Interestingly a second module was highly significantly associated with estimated lifetime use of antipsychotics ($p=4 \times 10^{-5}$). This module contained 201 co-expressed genes with defense, immune and inflammation response as the most significantly enriched. Six of our differentially expressed genes were also in this co-expression module including CCL2, CCL20, CSF3, SERPINA3A, HMOX1, and SLC11A1 and were all positively correlated with antipsychotic dose.

Discussion: While it is possible that the medication is causing the increase in expression of these genes in the CP, serum levels of cytokines tend to be decreased in patients after taking antipsychotic medication² and our analysis of gene expression in the CP of patients with bipolar disorder do not show a positive correlation between antipsychotic dose and markers of inflammation. Further studies to validate and replicate the findings are ongoing in a larger cohort of subjects with more varied diagnostic categories and medication histories.

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5:45 PM**THE NEUROBIOLOGY OF NEGATIVE SYMPTOMS AND THE EFFECT OF GLYCINE REUPTAKE INHIBITORS****Daniela Alberati***F. Hoffmann-La Roche AG, pRED, Pharma Research & Early Development, DTA Neuroscience*

Background: Negative symptoms can affect up to 60% of patients with schizophrenia. Their severity is predictive of poor outcomes. Avolition (reduced motivation to initiate or persist in goal-directed behaviour) is a critical component of negative symptoms in schizophrenia and has been hypothesised to drive clinical features of apathy, asociality, and alogia. Recently, four major components have been identified that transform reward information into behavioural responses: 1) hedonics; 2) reward prediction and wanting combined with reinforcement learning; 3) cost-benefit analysis; and 4) ability to generate and execute goal-directed action plans necessary to achieve the valued outcome.

Methods: Animal models were used to investigate the *in vitro* and *in vivo* effects of bitoperatin (a glycine reuptake inhibitor [GRI] under phase 3 investigation for the treatment of predominantly negative and suboptimally controlled positive symptoms of schizophrenia) and a close analogue of bitoperatin on different components of motivation typically dysfunctional in schizophrenia, particularly in patients with negative symptoms.

Results: Bitoperatin modulated rat ventral tegmental area dopaminergic neuronal firing (a crucial process for reward prediction and reinforcement learning) and attenuated deficit in motivated behaviour induced by decreased dopaminergic neurotransmission in rats. In non-human primates, bitoperatin enhanced accuracy in the delayed match-to-sample task, a dorsolateral prefrontal cortex paradigm, implying a positive effect on working memory (a crucial component of executive function). Furthermore, GRIs alleviated deficits in attentional-set shifting (an index of cognitive flexibility) in rats induced by subchronic phencyclidine (PCP) treatment. GRIs also alleviated social interaction deficits in rats induced by subchronic PCP treatment or by isolation rearing in combination with early post-natal PCP treatment.

Discussion: These results support the hypothesis that improved NMDA receptor function may be a valuable strategy for the treatment of avolition in patients with negative symptoms.

6:00 PM**THE ROLE OF OLIGOPEPTIDASES IN SCHIZOPHRENIA – TRANSLATIONAL EVIDENCE FROM HUMAN TO ANIMAL RESEARCH**

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Background: Oligopeptidases are a class of enzymes that cleaves peptides but not proteins. The first two oligopeptidases described were Nuclear-Distribution protein nudE-like 1 (Ndel1) and Prolyl-oligopeptidase (POP), besides the Angiotensin-I Converting Enzyme (ACE). Later, Ndel1 was showed to be the binding partner of DISC1, a gene associated to schizophrenia (SCZ) susceptibility. In the first study to evaluate the Ndel1 enzyme activity in human, we found a significantly lower Ndel1 activity in SCZ patients compared to healthy controls (HC) plasma (Gadelha et al., J Psych Res 2013). To extend the investigation of oligopeptidases in SCZ, we also examined the POP and ACE activities in human plasma, as these enzymes also share the same natural substrates with Ndel1. Cognitive enhancing properties of POP inhibitors and the ACE involvement in cognition and behavior were demonstrated by others using animal models. Few studies have suggested altered ACE levels in cerebrospinal fluid of SCZ patients. However, we are the first to validate the correlation of the enzymatic activity with SCZ in both human patients and animal models.

Methods: 92 SCZ patients were compared to 105 HC. POP and ACE activity

in human plasma samples were measured by fluorimetric assays, using FRET specific peptide substrate. ACE transgenic mice were evaluated in cognitive tasks.

Results: POP activity in human plasma was null for all samples. The ACE enzymatic activity was significantly higher in SCZ patients compared to HCs ($F=0.16$, $p<0.001$) and, among patients, this higher activity was correlated with the PANSS disorganized/cognitive dimension (Spearman's rho=-0.224 $p=0.037$). No correlation of ACE enzymatic activity to gender and age in the whole sample, and of duration of illness and dose of antipsychotics among SCZ patients were observed. Titration of ACE gene using transgenic mice allowed demonstrating a significant cognitive impairment due to higher ACE activity.

Discussion: Our results show convergent evidence suggesting that higher ACE enzymatic activity levels could be associated to cognitive/disorganization symptoms in SCZ. Furthermore, ACE inhibitors have been shown to improve cognitive measures in animal models and to delay dementia progression in humans. Previous results with Ndel1 showed a lower enzymatic activity levels among hebephrenic and treatment-resistant SCZ patients, which usually present more prominent cognitive disturbances and disorganization symptoms, pointing towards the same direction of ACE results. Final validation of the full range of behavioral characteristics of ACE transgenic mice and genetic and cognitive evaluation of our patients and controls samples is being conducted. Overall, these results support a potential involvement of oligopeptidases in SCZ.

Oral Presentations**GENETICS AND EPIDEMIOLOGY****Chairperson: Dan Rujescu****Tuesday, 8 April 2014****4:15 PM – 6:15 PM****4:15 PM****A POPULATION-BASED LONGITUDINAL STUDY OF SERUM INTERLEUKIN-6 AND C-REACTIVE PROTEIN IN CHILDHOOD AS PREDICTORS OF PSYCHOSIS AND DEPRESSION IN YOUNG ADULT LIFE**

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Background: A potential role of early-life infection and inflammation in the aetiology of schizophrenia is supported by clinical epidemiological, experimental healthy volunteer and animal model research. Recently, cytokine mediated communication between the immune system and the brain has been implicated in the pathophysiology of both schizophrenia and depression. This is supported by meta-analyses reporting increased serum interleukin (IL) 6 and C-reactive protein (CRP) in first episode psychosis, acute psychotic relapse and depression. However, due to their cross-sectional design these studies cannot ascertain whether increased IL-6/CRP is a cause or consequence of illness. Longitudinal studies of systemic inflammatory markers and subsequent risk of psychosis are lacking, and those of depression are limited in number with inconsistent results. In a longitudinal design we predicted that higher levels of systemic inflammatory markers (IL-6 and CRP) in childhood would increase the risks of developing psychosis and depression in the future.

Methods: We used data from approximately 4500 individuals from the general population-based Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. IL-6 and CRP was measured in non-fasting serum samples obtained at age 9 years. The outcomes of psychotic experiences and psychotic disorder were measured by the face-to-face semi-structured psychotic-like symptoms interview (PLIKSi) at age 18 years. Depression was measured in two ways: a clinical interview and a questionnaire so as to allow internal replication. The sample was divided into thirds according to tertiles of the IL-6 and CRP distributions in all individuals with these measures at age 9 years (irrespective of their status at the end of follow-up). We used logistic regression to calculate the odds ratios (ORs) and 95% confidence intervals (CI) for developing psychiatric outcomes at age 18 years among individuals in the middle and top, compared with the bottom third of inflammatory marker distribution at age 9 years. Linearity

of association was tested by inspection of the OR over the thirds of the inflammatory marker distribution. Regression models were adjusted for age, sex, body mass index, ethnicity, social class, past psychological and behavioural problem, and maternal post-natal depression.

Results: At age 18 years, 101 participants reported psychotic experiences (4.0%), 35 met the criteria for psychotic disorder (1.4%), and 423 met the criteria for depression (17.2%) (all based on clinical interviews). Participants in the top third of IL-6 values compared with the bottom third at age 9 years were more likely to develop psychotic experiences at age 18 years (adjusted OR 1.81 (95% CI 1.01 to 3.28)). The risks of psychotic disorder and of depression at age 18 years were also increased with higher IL-6 at baseline; adjusted OR 2.40 (95% CI 0.87 to 6.62) and 1.55 (95% CI 1.13 to 2.14), respectively. In addition, the associations between serum IL-6 at age 9 years and the risks of psychotic experiences and depression at age 18 years were consistent with a dose-response relationship. The results remained virtually unchanged using the questionnaire measure of depression.

Discussion: Higher levels of the systemic inflammatory marker IL-6 in childhood is associated with the risk of subsequent psychosis and depression. Processes in the inflammatory pathway may be therapeutic targets for these disorders. Inflammation might explain the high comorbidity between cardiovascular disease, diabetes, schizophrenia and depression.

4:30 PM

ANTICIPATING AND EXPERIENCING PLEASURE IN SCHIZOPHRENIA: A NEW PARADIGM

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Background: Anhedonia in schizophrenia is generally defined as "a loss of the ability to feel pleasure". Anhedonia predicts transition to diagnosis in an ultra-high risk group and poor functional outcomes in schizophrenia. Debate surrounding conflicting results in the literature has held back the development of targeted interventions. Despite reporting low levels of pleasure in questionnaires, individuals with schizophrenia seem to experience similar levels of pleasure as controls when asked "in the moment". One explanation may be a specific deficit in anticipating pleasure whilst the experience of pleasure in direct response to a positive stimulus (consummatory) is intact. The aim of the study was to develop a new computer task which measured both anticipatory and consummatory pleasure using the same methodology and stimuli.

Methods: A healthy control group (n=16) and a group of individuals with schizophrenia (n=39) completed a newly developed computer task. The participants firstly give consummatory ratings of valence and arousal for positive social, positive physical and neutral images. The participants learn associations between 4 images and cues as part of a learning paradigm. The participants then produce anticipatory pleasure ratings of these 4 images in response to the cues alone. Participants also completed measures of mood, pleasure and symptoms. To assess consistency the computer task was repeated within two weeks.

Results: The consummatory ratings in the computer task were highly consistent in the clinical (average r=0.85, p<0.001) and the control (average r=0.91, p<0.001) groups. Anticipatory ratings were consistent only in the control group (average r=0.67, p<0.06) with the clinical group showing larger discrepancies while anticipating the same stimuli at different time points. In the clinical group mood and symptoms correlated with anticipatory ratings (p<0.1).

As expected, there were no significant differences in the consummatory ratings between the groups. In contrast to the hypothesis there was also no difference found in anticipatory ratings. A within-groups analysis revealed a pattern in both groups of participants under-anticipating pleasure to high pleasure images and over-anticipating pleasure to low pleasure images from the consummatory phase. This pattern appears in more ratings in the clinical group.

Discussion: The consummatory ratings made during the computer task are consistent. The anticipatory ratings are consistent only in the control group. Anticipatory fluctuations in the clinical group are influenced by mood and symptoms. There is no "in the moment" pleasure deficit in schizophrenia. No difference in anticipatory pleasure was seen in contrast to the hypothesis. However, a pattern of emotional blunting is observed

which is particularly pronounced in the clinical group. A reduced ability to distinguish high pleasure from low pleasure when anticipating could be linked to the low motivation and apathy reported in schizophrenia. A targeted intervention which heightened emotional experience and awareness when anticipating events may be beneficial.

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COMMON AND RARE RISK VARIANTS IMPLICATE PAK SIGNALING IN THE MOLECULAR ETIOLOGY OF SCHIZOPHRENIA

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Background: The emerging genetic architecture of schizophrenia includes a spectrum of risk variation from rare mutations of large effect, to many common risk variants of small effect. Highly penetrant risk mutations, although rare, may be particularly important in facilitating dissection of molecular etiology to gain biological insight in model systems.

Methods: We conducted a gene-based analysis of large (>100kb), rare copy number variants (CNVs) in the Wellcome Trust Case Control Consortium 2 (WTCCC2) schizophrenia sample of 1,564 cases and 1,748 controls all from Ireland, and further extended the analysis to include an additional 5,196 UK controls. We performed a replication analysis in a European dataset including 3,111 cases and 2,267 controls and in a further UK bipolar dataset of 2,243 cases and 10,259 independent controls. We confirmed this finding in an extended sample including 11,707 psychosis cases and 21,000 controls. CNV calls were validated across arrays, through haplotype analysis and by sequencing of CNV breakpoints. We tested this family by common variant analysis in the Psychiatric Genomics Consortium 2 (PGC2) Schizophrenia Dataset (>38,000 cases and >110,000 controls).

Results: We found association with duplications at chr20p12.2 (P=0.007) and some evidence of replication in large independent European schizophrenia (P=0.052) and UK bipolar disorder case-control cohorts (P=0.047). A combined analysis of Irish/UK subjects including additional psychosis cases (schizophrenia and bipolar disorder) identified 22 carriers in 11,707 cases and 10 carriers in 21,204 controls (meta-analysis CMH P value = 2×10^{-4} (odds ratio (OR)=11.3, 95% CI=3.7, ∞). Nineteen of 22 cases and 8 of 10 controls carried duplications starting at 9.68Mb with similar breakpoints across samples. By haplotype analysis and sequencing we identified a tandem ~149kb duplication overlapping the gene p21 Protein-Activated Kinase 7 (also called PAK5) indicative of a single ancestral duplication event. We confirmed the breakpoints in 8/8 carriers tested and found co-segregation of the duplication with illness in two additional family members of one of the affected probands.

P21-activated kinases (PAKs) are a family of serine/threonine protein kinases, regulated by the Rho family of small G proteins and involved in multiple intracellular signaling pathways. Six PAK genes are expressed in human and based on their regulatory functions are classified into Group I (PAK 1-3) and Group II (PAK4-6) members. Group I PAKs are activated by RAC-PAK signaling to promote axon connectivity, and synapse formation, in the developing brain in a pathway regulated by another schizophrenia risk gene DISC1. Group II members are less investigated, but PAK7 knockout mice are viable with no obvious developmental abnormalities. PAK6/PAK7 double knockout mice show behavioral and learning deficits suggesting functional redundancy between these isoforms. PAK6 maps to one of the common risk loci identified in the PGC2 dataset ($p=4.9 \times 10^{-8}$). Finally, in a co-immunoprecipitation experiment we confirmed interaction between PAK7 and DISC1 in synaptoneuroosomal preparations from full mouse brain at post-natal day 8-10.

Discussion: We identified a rare, inherited mutation with a common founder contribute to psychosis risk in the European population. This implicates PAK7 a gene from a family of 6 p-21-activated kinases involved in the development/regulation of synaptic networks and regulated by DISC1. We report provisional evidence confirming interaction between PAK7 and DISC1 suggesting a potential signalling mechanism in the molecular etiology of psychosis.

5:00 PM

DOPAMINE OR GLUTAMATE: USING GENETIC COPY NUMBER VARIANT PATHWAY ANALYSIS AND TREATMENT RESISTANCE TO ADJUDICATE SCHIZOPHRENIA HYPOTHESES

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Background: The dopamine and glutamate hypotheses are the major competing theories of the pathophysiology of schizophrenia (Sz). The dopamine hypothesis arises chiefly from the observation that all licensed antipsychotics act via dopamine receptors. However around 30% of patients with Sz fail to respond to initial antipsychotic therapy – so-called treatment resistant schizophrenia (TRS). This raises the prospect that those who respond to initial antipsychotics may have predominant dopamine-based pathophysiology whereas those with TRS do not. Conversely it is feasible that those with TRS instead display glutamate-based pathophysiology. Initial evidence supporting these hypotheses is emerging from molecular imaging studies. In this study we set out to test these hypotheses using copy number variant (CNV) pathway analysis in large treatment resistant and generic Sz populations.

Methods: TRS cases were from the CLOZUK sample (n=6558). CLOZUK consists of patients with a clinical diagnosis of TRS taking the antipsychotic clozapine. The control samples for the TRS analysis consisted of four publicly available, non-psychiatric datasets, totaling 11 255 samples.

There are no available treatment-responsive samples of sufficient size so we decided to use generic schizophrenia samples as non-treatment resistant samples. A proportion of these samples (around 30%) will have TRS but this will serve to decrease power and is thus conservative. The generic Sz samples were the International Schizophrenia Consortium (ISC; 3045 cases and 3185 controls) and Molecular Genetics of Schizophrenia (MGS; 2215 cases and 2556 controls).

All discovery cases were genotyped at the Broad Institute on either Illumina OmniExpress or OmniCombo arrays.

The control datasets were genotyped on Illumina arrays similar to those used for the cases.

The ISC dataset was typed on the Affy 5.0 and 6.0 array and the MGS sample on the Affy 6.0 array.

CNVs were called using standard procedures and quality control filtering following methods described in Kirov et al. (Molecular Psychiatry, 2012). We included in the analysis rare CNVs (<1%), at least 15kb in size and with coverage of at least 15 probes.

For both the TRS and generic schizophrenia analyses enrichment across gene sets was sought using logistic regression methods (see Kirov et al (2012)). The principle pathway analyses focused on (i) dopamine pathways (from the Mouse Genome Informatics) and (ii) NMDA receptor pathways (experimentally defined proteome datasets (Kirov et al, 2012)). CNV pathway analyses for the ISC and MGS were performed within the individual samples and meta-analysed.

Results: In the TRS CLOZUK dataset the CNV pathway analysis revealed significant enrichment in NMDA receptor gene sets ($p=1.07 \times 10^{-6}$) but no such enrichment in dopamine pathways ($p=0.561$). In contrast the generic schizophrenia samples demonstrated significant enrichment in dopamine pathways ($p=0.006$) and in NMDA receptor gene sets ($p=0.0011$), although this association was significantly weaker than in the TRS sample.

Discussion: In large datasets of those with Sz we have demonstrated that TRS may be associated with distinct molecular pathways. Using hypothesis-driven CNV pathway analysis we show that those with TRS display enrichment in NMDA receptor gene sets but no such enrichment in dopamine-based pathways in contrast to those with schizophrenia not selected for treatment-resistance. These results represent a double dissociation and provide evidence that treatment resistance may be useful in defining those with distinct pathophysiology and in adjudicating between the dopamine and glutamate hypotheses of schizophrenia.

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INTERACTION OF MATERNAL INFECTION AND ADOLESCENT CANNABINOID EXPOSURE ON miRNA REGULATION OF GENE EXPRESSION IN THE ADULT ENTORHINAL CORTEX

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Background: The cortical neuropathology of schizophrenia (SZ) has been shown to display postmortem epigenetic changes that reflect early life experience. These affect the regulation of gene expression at the level of transcription, through changes in chromatin structure; and post-transcriptionally through non-coding RNAs, such as microRNA (miRNA). The aim of the current study was to investigate the role of miRNA in the brains' response to maternal immune activation and adolescent cannabis exposure, alone and in combination, as both have been identified as environmental risk factors for SZ.

Methods: Pregnant Wistar rats received an intravenous injection of polyribosinic-polyribocytidilic acid (poly I:C) or vehicle on embryonic day 15. Beginning post-natal day (PND) 35, male offspring were treated daily with the synthetic cannabinoid HU210, or vehicle, for 14 days and euthanized on PND 55. Whole genome miRNA microarrays were performed on the left and right entorhinal cortex (EC) and whole genome mRNA microarrays on the left EC as this region has been shown to display altered volumes and other anatomical abnormalities in SZ.

Results: Offspring of poly I:C treated rats exposed to HU210 during adolescence (two-hit group) exhibited significant differences in miRNA expression, compared to either treatment alone, where only a small effect was observed for each treatment with respect to untreated controls. This effect occurred predominantly in the left hemisphere and was dominated by a large subgroup of miRNA differentially transcribed from a single imprinted locus on chromosome 6q32. In humans, the syntenic locus (14q32) encodes a large proportion of miRNAs found to be differentially expressed in white blood cells from patients with SZ. Similarly, alterations in gene expression occurred primarily in the two-hit group, with genes highly enriched in pathways including: axon guidance, ErbB signalling and T cell receptor signalling. Differentially expressed genes identified as potentially regulated by differentially expressed miRNA in the same treatment group were identified as highly enriched in the gamma-aminobutyric acid signalling pathway, synaptic transmission, transmission of nerve impulse and cell-cell signalling, processes repeatedly implicated in the pathophysiology of SZ. These genes encode proteins with prominent functions in neuronal growth and differentiation; development of specific cortical layers; synaptic plasticity and transmission; axonogenesis; GABA neurotransmitter system; and learning and memory formation.

Discussion: These results support the two-hit hypothesis of SZ in which an early first insult leads to a deficient neuronal network and is followed by a late second insult that modulates gene activity leading to an ongoing psychotic illness. As afferent connections from the EC enter the hippocampus in a layer specific manner during development, changes in the expression of genes with important roles in neuronal growth and differentiation and development of specific cortical layers could have deleterious effects on learning and memory pathways. These findings indicate that the interaction of both an early and late environmental insult can enhance changes in offspring miRNA expression in the EC with possible outcomes relevant to schizophrenia in adulthood.

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PREMATURE DEATH IS HIGHER IN PERSONS WITH PSYCHOTIC DISORDERS BUT NOT WITH PSYCHOTIC EXPERIENCES: A POPULATION-BASED LONGITUDINAL STUDY

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Background: Psychotic disorders are associated with higher rates of mor-

tality than those observed in the general population. Mortality in patients with schizophrenia is 2 to 4 times higher and life expectancy is 20% shorter. Previous studies have suggested that the mechanisms explaining the association between psychosis and death may include the cumulative effects of unhealthy lifestyle factors following disease onset, delay in diagnosis of medical comorbidities, lower quality of medical care, and treatment with antipsychotic medication. Psychotic experiences in the general population are far more prevalent than psychotic disorders and are associated with risk for later psychotic disorders, but mortality rates in persons with psychotic experiences have not been explored.

Methods: We utilized data from a two-stage epidemiological study of mental disorders among 4,914 young adults aged 25–34 in a population-based 10-year birth cohort (1949–1958) conducted in Israel in the 1980's. Twenty five years later, the epidemiological data (including assessment of psychotic experiences) was linked with the Israeli Psychiatric Hospitalization Case Registry and the National Death Registry. Cox Proportional Hazards regression was used to assess the association between psychotic disorders and experiences, and all-cause-mortality. The data were weighted to estimate rates in the original population from which the cohort sample was drawn.

Results: The prevalence of psychotic disorders in the current cohort was 1.5% (n=821) and the prevalence of psychotic experiences in the general population was 14.2% (n=83). One hundred and seventy four persons (3.6%) died during the follow-up period. Premature death (prior to the age of 57, the end of follow-up) was significantly more prevalent in persons with psychotic disorders (23.1%) but not psychotic experiences (3.4%) compared to the general population (3.3%) ($\chi^2=85.6$, $p<0.001$). Persons with psychotic disorders were 9 times more likely to die by the age of 57 than persons from the general population (95% CI: 3.32–23.30). Excess mortality in persons with psychotic disorders appears to be caused both by external causes of death and natural causes (namely, infectious and parasitic diseases, circulatory system diseases, digestive system diseases and respiratory diseases).

Discussion: Persons with psychotic disorders, but not those with psychotic experiences, are at increased risk of premature death. Although persons with psychotic experiences share some demographic and clinical characteristics as those with psychotic disorders, premature death appears to be unique to patients with clinically diagnosed disorders.

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THE GENETIC ARCHITECTURE OF SCHIZOPHRENIA: HOW DO CNVs AND POLYGENIC SCORES CONTRIBUTE TO DISEASE RISK?

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Background: Both rare CNVs and common SNPs contribute to the genetic risk for schizophrenia. Several specific CNV regions and an increased burden of large deletion CNVs have demonstrated associations with schizophrenia. A significantly higher polygenic risk score in subjects with schizophrenia has also been established, confirming that many common SNPs confer risk for this disorder as well. The relationships between these rare and common genetic risk factors have not been thoroughly investigated, and we sought to address the following questions: 1) Do cases with CNVs have lower polygenic risk scores compared to cases without CNVs? 2) Do cases with CNVs have higher polygenic risk scores compared to controls with CNVs? 3) Do controls with CNVs have lower polygenic risk scores than controls without CNVs?

Methods: We investigated the polygenic risk score differences within and between case and control groups by CNV carrier status using the Swedish Schizophrenia Consortium (N=4646) as the discovery sample to score the International Schizophrenia Consortium (ISC) (N=4921) subjects. Analyses will be extended to CNV and GWAS data from the Psychiatric Genomics Consortium. CNV carriers were defined by the two classes of CNVs conferring the greatest disease risks: 1) having one of 12 specific CNVs previously associated with schizophrenia or 2) carrying any large CNV deletion greater than 500kb.

Results: 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. Control subjects with specific associated CNVs had lower polygenic scores than other control subjects, but controls with and without large deletions had similar scores.

Discussion: These initial results are partly inconsistent with an additive model of CNV and polygenic risk. The presence of an associated CNV alone is not sufficient to result in schizophrenia, but also requires a context of increased risk from common variants.

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THE ROLE OF IMAGING GENETICS IN UNANTICIPATED SCHIZOPHRENIA RISK GENE DISCOVERY: TNIK AND MICRORNA-137

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Background: Brain imaging has been important in understanding the effects of psychiatric risk genes on brain function. Brain imaging can also be used as a tool for discovery of unanticipated risk genes for serious mental disorders such as schizophrenia. Working memory deficits have been established in schizophrenia. Dorsolateral prefrontal cortex (DLPFC) activation during a working memory task has been considered a measure of cortical inefficiency, and is commonly observed in schizophrenia patients.

Methods: DLPFC fMRI BOLD activation during a working memory task was used as a quantitative trait in the context of two GWAS studies in schizophrenia patients. The association of DLPFC BOLD activation was calculated for each SNP that met standard QC criteria using permutation statistics to control for false positives. Top SNPs were further considered for their potential biological significance including use of gene set enrichment analysis (GSEA) to test for common networks and pathways in the two independent studies.

Results: Several SNPs surviving Type 1 error corrections have potential biological significance. TNIK physically interacts with DISC1 and co-regulates AMPA and NMDA glutamate receptors (Potkin et al, 2010). The GSEA of the two imaging genetics GWAS SNPs identified several statistically significant miRNAs including miRNA-137 10–7.6. The miR-137 rs1625579 risk allele (T) is associated with DLPFC hyperactivation, an established schizophrenia risk phenotype and considered a measure of brain inefficiency. MiRNA 137 is involved in neural stem cell proliferation and differentiation, neurogenesis, and neuronal maturation.

Discussion: The International Schizophrenia Consortium case control study of 51,695 subjects in a two-stage analysis identified miRNA137 at 10-13 as a new etiological mechanism for schizophrenia (Ripke et al, 2011; 2013). Subsequent studies found this risk allele to be associated with an earlier onset of schizophrenia, smaller hippocampi, and decreased FA (Lett et al, 2013), as well as cortical inefficiency (van Erp et al., 2013). MicroRNAs (miRNAs) are small, noncoding, regulatory RNAs that control the expression of about 60% of protein coding genes by inducing mRNA cleavage or translational inhibition in the miRNA target sites in their 3' untranslated (UTR) regions. A single miRNA can bind to and regulate many different mRNA targets, and therefore, influence complex regulatory networks. miRNA silencing occurs at both protein and mRNA levels, especially when considering temporal regulation.

Both TNIK and targets of microRNA-137 such as TCF4 are components of the translational convergent functional genomics genetic risk prediction score for schizophrenia proposed by Ayalew and colleagues (2012). These confirmatory studies highlight the value of using brain imaging as a quantitative phenotype for discovering novel risk genes in schizophrenia.

Oral Presentations**HIGH RISK RESEARCH****Chairperson: Nina Schoeler****Tuesday, 8 April 2014****4:15 PM – 6:15 PM****4:15 PM****ALTERED RELATIONSHIP BETWEEN MEDIAL TEMPORAL LOBE RESTING CEREBRAL BLOOD FLOW AND STRIATAL DOPAMINE SYNTHESIS CAPACITY IN PEOPLE AT RISK OF PSYCHOSIS**

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Background: Pre-clinical models propose that increased excitatory activity in the medial temporal lobe (MTL) drives elevated striatal dopamine function (via reciprocal MTL-striatal pathways) in psychosis. Using Magnetic Resonance Imaging (MRI) and 18F-DOPA Positron Emission Tomography (PET) we examined resting cerebral blood flow (rCBF) in the MTL and presynaptic dopamine synthesis capacity (18F-DOPA Ki) in the striatum in subjects with an Ultra High Risk (UHR) for psychosis and healthy controls (CTRL). We predicted that, relative to CTRL, UHR subjects would show increased MTL rCBF and a perturbed association between MTL rCBF and striatal 18F-DOPA Ki.

Methods: Fifty UHR and 28 CTRL subjects matched for age and gender underwent continuous Arterial Spin Labelling (cASL) to measure rCBF. In 34 of the same subjects (22 UHR, 12 CTRL subjects), 18F-DOPA PET Ki values were also available. ANCOVA in Statistical Parametric Mapping (SPM) software examined rCBF group effects with age, gender and whole brain rCBF included as nuisance covariates. The association between rCBF and striatal presynaptic dopamine synthesis capacity was investigated using one-way ANCOVA. rCBF analyses were restricted to the bilateral MTL and striatal regions of interest defined using WFUpickatlas. Results are reported using corrected threshold ($p < 0.05$).

Results: Relative to CTRL, UHR subjects showed increased rCBF in the right parahippocampal gyrus and caudate head. In both these regions, there was a significant interaction between group, rCBF and dopamine function. In CTRL subjects there was a negative association between rCBF and striatal 18F-DOPA Ki, whereas in UHR subjects this association was positive.

Discussion: The altered relationship between MTL perfusion and presynaptic striatal dopamine capacity in UHR compared CTRL subjects is consistent with the hypothesis that increased hippocampal activity may drive elevated striatal dopamine activity in those at risk for psychosis. While these correlational methods cannot determine causality, this may arise from altered activity in reciprocal MTL-striatal pathways.

4:30 PM**CHILDHOOD SLEEP DISTURBANCE AND RISK OF PSYCHOTIC EXPERIENCES IN A LARGE UK BIRTH COHORT**

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Background: Sleep disturbances are commonly reported in the psychosis "prodrome" but rarely explored in relation to psychotic experiences or as a risk indicator for these experiences. We investigated the relationship between specific early sleep disturbances in childhood, specific parasomnias (nightmares, night terrors and sleepwalking) and later adolescent psychotic experiences in a birth cohort.

Methods: The data was from a large UK Birth cohort study (Avon Longitudinal Study of Parents and Children - ALSPAC). The presence of frequent nightmares and other sleep disturbances in children was obtained prospectively from mothers during multiple assessments conducted when children were aged between 2.5 and 9 years. Experience of nightmares, night terrors and sleepwalking (specific parasomnias) was assessed using a semi-structured clinical interview at age 12. Psychotic experiences were assessed at age 12 and 18 years using a semi-structured clinical interview. 6796 children completed this interview at 12 and 4720 at aged 18. Both inter-

views had a good inter-rater reliability (average kappa value for inter-rater reliability was 0.72 at 12 and 0.83 at 18).

Results: Children who were reported by their mothers as experiencing frequent nightmares between 2.5 and 9 years of age were more likely to report psychotic experiences at age 12, regardless of sex, family adversity, emotional or behavioral problems, IQ and potential neurological problems (OR=1.16, 95% CI=1.00–1.35, $P=0.049$). Difficulty getting to sleep and night waking were not found to be associated with age 12 psychotic experiences when controlling for confounders. Children reporting any of the specific parasomnias at age 12 had higher rates of concurrent psychotic experiences than those without such sleeping problems, when adjusting for all confounders (OR=3.62, 95% CI=2.57 – 5.11, $P<0.001$). There was a significant association between the presence of nightmares at 12 and psychotic experiences at 18 when adjusted for possible confounders and psychotic experiences at 12 (OR 2.14, 95% CI 1.59 – 2.87, $P<0.001$) but not the other specific parasomnias. The odds ratios for this particular association were larger for those who reported psychotic experiences at both 12 and 18.

Discussion: Nightmares and night terrors, but not other sleeping problems, in childhood were associated with psychotic experiences at 12 years of age, whilst only nightmares in childhood were strongly related to psychotic experiences at 18. These findings tentatively suggest that arousal and Rapid Eye Movement (REM) forms of sleep disorder, especially nightmares, might be early indicators of susceptibility to psychotic experiences.

4:45 PM**DIFFICULTY IN MAKING CONTACT WITH OTHERS AND SOCIAL WITHDRAWAL AS EARLY SIGNS OF PSYCHOSIS IN ADOLESCENTS – THE NORTHERN FINLAND BIRTH COHORT 1986**

Juha Veijola¹, Satu Koskela¹, Graham Murray², Tanja Nordström¹, Jouko Miettunen¹, Erika Jääskeläinen¹, Pirjo H. Mäki^{1,3}

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Background: Social withdrawal is among the first signs of the prodromal state of psychosis seen in clinical samples. The aim of this prospective study was to find out whether difficulty in making contact with others and social withdrawal precede first episode psychosis in young general population.

Methods: The members of the Northern Finland Birth Cohort 1986 (N=6,274) completed the PROD-screen questionnaire in 2001–2002. The Finnish Hospital Discharge Register was used to detect both new psychotic and non-psychotic disorders requiring hospitalisation during 2003–2008.

Results: 23 subjects developed psychosis and 89 developed a non-psychotic mental disorder requiring hospitalisation during the follow-up. Of those who developed psychosis, 35% had reported difficulty or uncertainty in making contact with others and 30% social withdrawal in adolescence. In hospitalised non-psychotic disorder the corresponding percentages were 10% and 13% and in the control group without hospital-treated mental disorder 9% and 11%. The differences between psychotic and non-psychotic hospitalised subjects ($p<0.01$) as well as controls ($p<0.001$) were statistically significant regarding difficulty or uncertainty in making contact with others.

Discussion: In this general population-based sample self-reported difficulty or uncertainty in making contact with others in adolescence preceded psychosis specifically compared to hospitalised non-psychotic mental disorders and controls.

5:00 PM**HIGH BLOOD CYTOKINE LEVELS ARE RELATED TO DECREASED VERBAL FLUENCY AND BROCA'S AREA VOLUME REDUCTION IN SCHIZOPHRENIA**

Thomas Weickert¹, Stu G. Fillman^{2,1}, Rhoshel Lenroot¹, Jason Bruggemann², Maryanne O'Donnell³, Stanley Catts⁴, Cynthia Shannon-Weickert¹

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Background: There is increasing evidence for the role of the immune system in the pathogenesis of schizophrenia. We predicted a subset of people with schizophrenia would display increased immune activity which would be related to more severe cognitive and structural brain abnormalities.

Methods: In 42 patients with schizophrenia and 42 age and sex matched controls we assayed cytokine mRNA (IL1 β , IL8, IL6, IL18 and IL2) from white blood cells, cognition and structural MRI.

Results: Applying a two-step clustering algorithm, we identified two subgroups characterized by either high (n=35) or low (n=49) cytokine levels. The high inflammatory group contained significantly more people with schizophrenia (n=22/35) than controls (n=13/35, $\chi^2=3.97$, p<0.05). There was no IQ difference between high and low inflammatory groups; however, verbal fluency was significantly lower in the high inflammation group, t(40)=−2.32, p<0.05. A forward stepwise linear regression showed that IL1 β mRNA had a significant inverse relationship with verbal fluency in schizophrenia, $\beta=-0.35$, F(1,40)=5.51, p=0.02. The schizophrenia high/low inflammatory groups (n=36) differed significantly across language region volumes in the left hemisphere, F(4,26)=3.38, p=0.02. Post-hoc analysis showed only the left pars opercularis volume was significantly (15%) smaller in the high inflammatory group, F(1,29)=5.31, p<0.03.

Discussion: These results show that increased levels of peripheral immune mRNAs are significantly related to both poorer verbal fluency and reduced Broca's area brain volume in schizophrenia. These results raise the possibility of administering anti-inflammatory treatments that may reverse language deficits and associated brain abnormalities in subgroups of people with schizophrenia identified by immune related biomarkers.

5:15 PM

IS TREATMENT RESISTANT SCHIZOPHRENIA A “TYPE” OR A “STAGE” OF PSYCHOTIC ILLNESS?

Arsime Demjaha¹, Julia Lappin¹, Maxine X. Patel¹, James H. MacCabe¹, Kevin Morgan², Ulrich Reininghaus¹, Oliver Howes¹, Peter B. Jones³, Robin M. Murray¹, Craig Morgan¹, Paola Dazzan¹

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Background: It is unclear whether antipsychotic treatment resistance in schizophrenia manifests at the outset of illness, or evolves over time with illness chronicity. We examined this issue in a large cohort of first episode psychosis (FEP) patients followed up for 10-years. We hypothesised that treatment resistance would already be apparent at illness outset, and thus represents a distinct subtype of illness. Furthermore, we examined whether neurodevelopmental factors would predict future treatment resistance to antipsychotic medication.

Methods: The analytical cohort comprised 323 FEP patients who were studied at first contact (baseline) and again at 10-year follow up. Rigorous examination of clinical information, including information on presence and severity of symptoms, and medication data, during the follow up period was performed to determine the course of treatment resistance. Logistic regression analyses were conducted to assess the predictive power of neurodevelopmental factors for treatment resistance.

Results: Seventy-four (13% of the total sample) FEP patients were found to be resistant to antipsychotic treatment. The majority of these patients (84%) were unresponsive from the outset and remained resistant throughout the illness. Negative symptoms and a younger age of onset were significant predictors of subsequent treatment resistance (OR=1.2, p=0.01 and OR=0.9, p=0.04 respectively).

Discussion: The findings indicate that treatment resistant schizophrenia, in a majority of patients, may be a distinct subtype of schizophrenic illness of a probable neurodevelopmental origin.

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REWARD PROCESSING IN UNAFFECTED SIBLINGS OF SCHIZOPHRENIA PATIENTS: AN FMRI STUDY

Max de Leeuw, René Kahn, Matthijs Vink
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Background: Schizophrenia is characterized by impaired functioning of the fronto-striatal network: hyperdopaminergic activation in the striatum and hypodopaminergic activation in the frontal cortex. These network dysfunctions result in cognitive deficits such as impaired reward processing. Reward processing can be divided into two sub-processes: anticipation

and the outcome of reward. Functional MRI studies in patients have shown hypo-activation of the ventral striatum during reward anticipation. Whether this impaired reward processing is related to the genetic risk of schizophrenia is not known. To answer this question, we investigated reward processing using fMRI in siblings of schizophrenia patients who share on average 50% of their ill siblings' genes.

Methods: Twenty-eight unaffected siblings and 29 matched controls performed a Monetary Delayed Incentive task during fMRI scanning. All subjects were rewarded in 50% of the reward trials.

Results: Despite equal performance, during reward anticipation siblings showed hypoactivation in the ventral striatum compared with controls. During the outcome of reward, hyperactivation in the ventral striatum and in the orbital frontal cortex was found in siblings compared to controls.

Discussion: These findings are consistent with the notion of impaired dopaminergic functioning in the fronto-striatal network typically associated with schizophrenia. Impaired reward processing may constitute a vulnerability factor for schizophrenia. Twin studies should clarify whether these phenotypic abnormalities are a full genetic risk factor of schizophrenia.

5:45 PM

SALIENCE MATTERS: BRAIN POTENTIALS DISTINGUISH PREMORBID ATTENTION PROBLEMS AMONG CHILDREN AT-RISK FOR SCHIZOPHRENIA

Kristin R. Laurens^{1,2}, Sheilagh Hodgins³, Robin M. Murray²

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Background: A robust marker of brain dysfunction in schizophrenia (Cohen's d=0.89) is reduction in amplitude of the P3 (or P300) event-related potential (ERP) that indexes attention and working memory processes. It is elicited typically using a two-tone auditory oddball paradigm that presents infrequent task-relevant target stimuli (which require a behavioural response) within a train of frequent task-irrelevant non-target (or standard) stimuli. The P3 amplitude reduction to target stimuli is present at the chronic and first-episode phases of schizophrenia, and may predict transition to psychosis among at-risk adolescents/young adults. We sought to characterise potential premorbid brain function abnormalities among at-risk children aged 9–12 years in detail, using an auditory novelty oddball task variant that dissociates an earlier, automatic frontocentral P3a sub-component elicited by infrequent task-irrelevant salient novel stimuli from a later parietal P3b sub-component elicited by the infrequent task-relevant target stimuli.

Methods: We examined brain function in two at-risk groups, including a group with family history of schizophrenia (FHx; n=20) and a group of children presenting a triad of replicated antecedents of schizophrenia (ASz; n=20), namely (i) psychotic-like experiences; (ii) a social, emotional, or behavioural problem; and (iii) a speech-and/or-motor developmental delay or abnormality. At-risk groups were compared with a group of typically-developing (TD; n=28) peers who had no family history or antecedents of schizophrenia. Groups did not differ significantly on age, sex, ethnicity, socio-economic status, or handedness. Three group (FHx, ASz, TD) x three stimulus (targets, novelties, non-targets) x five site (Fz, FCz, Cz, CPz, Pz) repeated-measures ANOVAs on peak P3 amplitude and latency data were conducted, and were repeated as ANCOVAs to control for poorer intellectual function (IQ) among the at-risk groups relative to TD children.

Results: A significant group-by-condition interaction indicated reduced novelty P3a amplitude, but not target P3b or non-target P3 amplitudes, in both at-risk groups relative to TD children. This result remained after correcting for IQ differences between groups. No latency differences were observed.

Discussion: At-risk children aged 9–12 years, both those with family history and those presenting multiple childhood antecedents, display disturbances in frontal mechanisms supporting involuntary attention orienting to salient stimuli, while more conscious parietal mechanisms supporting stimulus evaluation and context updating are, as yet, unaffected in these children. The latter may emerge more proximally to transition to psychosis; 48-month follow-up assessments are underway to ascertain the evolution of these components as participants mature through adolescence.

6:00 PM**THE EXCESS OF NON-RIGHT-HANDEDNESS IN SCHIZOPHRENIA IS NOT THE RESULT OF METHODOLOGICAL ARTIFACTS AND BIASES – A META-ANALYSIS**Marco Hirnstein, Kenneth Hugdahl
University of Bergen**Background:** The notion that schizophrenia is characterised by increased non-right-handedness is a cornerstone of the theory that schizophrenia arises from, and is genetically linked to, abnormal brain lateralisation. Reviews and meta-analyses have reported higher rates of non-right-handers in schizophrenia patients. However, this was suggested to be the result of a sex artefact or a hidden bias in self-report handedness questionnaires. The present study therefore investigated in a meta-analytical approach whether the excess of non-right-handedness is seen in both females and males and also when handedness is assessed behaviourally.**Methods:** Electronic databases were searched for studies that reported (1) the rate of female and male non-right-handers in schizophrenia compared to controls and (2) the rate of non-right-handers in schizophrenia (regardless of sex) based on behavioural handedness assessment.**Results:** The odds ratios (OR) for both females OR=1.63 (based on 621 patients, 3747 controls) and males OR=1.50 (based on 1213 patients, 3800 controls) differed significantly from 1.0, indicating both female and male schizophrenia patients were more often non-right-handed than controls. Moreover, there was an excess of non-right-handedness in schizophrenia patients when handedness was assessed behaviourally: OR=1.84 (1255 patients, 6260 controls). Even when both sex and behavioural handedness assessment were controlled for simultaneously, the excess of nonrighthandedness persisted.**Discussion:** The findings clearly demonstrate that the excess of non-right-handedness in schizophrenia does not result from a sex artefact or from biased handedness questionnaires. It is a true empirical effect and may indeed reflect a genetic link between schizophrenia and brain lateralisation.

Oral Presentations**THERAPEUTICS****Chairperson: Robert Zipursky****Tuesday, 8 April 2014****4:15 PM – 6:15 PM**

4:15 PM**ANTIPSYCHOTIC MEDICATION AND REMISSION OF PSYCHOTIC SYMPTOMS. LONG TERM DEVELOPMENT AND CHARACTERISTICS**Ditte R. Gotfredsen, Regitze Soelling Hansen, Carsten Hjorthøj,
Stephen Austin, Merete Nordentoft
Mental Health Centre Copenhagen**Background:** Randomised clinical trials on discontinuation of antipsychotic medication after a psychotic episode indicate that there is a risk of relapse when medication is discontinued. Therefore several national guidelines recommend continuous use of antipsychotic medication after a psychotic episode, in order to minimize the risk of relapse. However all antipsychotic medication have adverse effects such as extrapyramidal symptoms, weight gain and increased risk of metabolic syndrome. Some studies have identified a subgroup of patients who can obtain remission of psychotic symptoms without using antipsychotic medication on a long term basis. This study investigated the long term development and outcome of first episode psychotic patients and whether patients in remission of psychotic symptoms display certain characteristics.**Methods:** The study is based on the Danish Opus Trial which is a cohort study including 496 patients diagnosed with schizophrenia spectrum disorders. The patients were followed over a time period of 10 years and data regarding socio-demographic factors, psychopathology, level of functioning and medication was collected at 4 different follow-ups. Based on this data different characteristics and patient trajectories was identified.**Results:** At all follow-ups a proportion of patients who obtained stable remission without a use of antipsychotic medication was found. This proportion of remissioners increased at each follow-up and reached its'

maximum at the 10 year follow-up, where it accounted for 30% of the patient population. A favourable outcome at the 10-year follow-up was associated with female gender, shorter duration of untreated psychosis and no substance. The results also revealed that patients tend to follow certain trajectories over time. From the 5 to 10-year follow-up 87% of the patients in remission, without antipsychotic medication, remained in remission. The tendency for stabilization was also found for the other patient groups.

Discussion: A substantial proportion of patients with schizophrenia spectrum disorders were in remission without the use of antipsychotic medication at all follow-ups peaking at year 10 with 30%. These patients seem to differ from the rest in terms of different characteristics. Furthermore the majority of this subgroup remains in remission at each consecutive follow-up, indicating stability in the disease course especially on the long term basis. The results suggest that guidelines on antipsychotic medication do not pay sufficient attention to the patient subgroup in long term remission without a use of antipsychotic medication. These findings call for further trials on discontinuation.

4:30 PM**CHILDHOOD TRAUMA AND PSYCHOSIS IN A PROSPECTIVE COHORT STUDY: CAUSE, EFFECT, AND DIRECTIONALITY**Ian Kelleher¹, Helen Keeley², Paul Corcoran², Hugh Ramsay³,
Camilla Wasserman⁴, Vladimir Carli⁵, Marco Sarchiapone⁶,
Christina Hoven⁴, Danuta Wasserman⁵, Mary Cannon³¹Karolinska Institutet, National Centre for Suicide Research and Prevention of Mental Ill-Health; ²National Suicide Research Foundation, Cork, Ireland;³Royal College of Surgeons in Ireland; ⁴Columbia University; ⁵Karolinska Institutet; ⁶University of Molise**Background:** A relationship between childhood trauma, psychotic experiences and psychotic disorder is well established. There is still much debate, however, as to whether the relationship is causal. A number of prospective cohort studies have addressed this issue but key epidemiological questions remain unanswered, including: 1. Is the relationship between childhood trauma and psychotic experiences uni- or bi-directional? 2. Does trauma predict newly incident psychotic experiences? 3. Does cessation of trauma predict cessation of psychotic experiences?**Methods:** Prospective cohort study of 1,112 school-based adolescents aged 13 to 16 years, assessed at baseline, 3-months, and 12 months for childhood trauma (physical assault and bullying) and psychotic experiences.**Results:** There was a bi-directional relationship between childhood trauma and psychotic experiences, with trauma predicting psychotic experiences over time and vice versa. However, even after accounting for this bi-directional relationship with a number of strict adjustments, looking only at newly incident psychotic experiences occurring over the course of the study following exposure to traumatic experiences, we found that trauma was strongly predictive of psychotic experiences. There was a dose-response relationship between severity of bullying and risk for psychotic experiences. What is more, cessation of trauma predicted cessation of psychotic experiences, with the incidence of psychotic experiences decreasing significantly in individuals whose exposure to trauma ceased over the course of the study.**Discussion:** After a series of conservative adjustments, we found that exposure to childhood trauma predicted newly incident psychotic experiences. We also report the first direct evidence that cessation of traumatic experiences in the population leads to a reduction in the incidence of psychotic experiences.

4:45 PM**INTENTION-TO-HARM IS THE KEY COMPONENT LINKING CHILDHOOD TRAUMATIC EXPERIENCES TO PSYCHOSIS**Martine M. van Nierop¹, Tineke Lataster¹, Feikje Smeets¹, Catherine van Zelst¹, Ron de Graaf², Margreet ten Have², Maarten Bak^{1,3},
Inez Myin-Germeys¹, Wolfgang Viechtbauer¹, Jim van Os¹, Ruud van Winkel¹¹Maastricht University; ²Trimbos; ³Mondriaan Mental Hospital**Background:** A large number of studies have reported a link between

childhood trauma and psychosis, however the exact mechanism underlying this association remains elusive. Several psychological models have been postulated, but data from large, representative samples specifically investigating possible pathways are scarce.

Methods: In two longitudinal population-based studies (NEMESIS-1, N=7076 and NEMESIS-2, N=6646) and one longitudinal cohort study (G.R.O.U.P., including psychotic disorder patients [N=1119], their unaffected siblings [N=1057] and healthy controls [N=589]), childhood trauma, psychotic symptoms and other psychopathology were assessed. In all three studies, differences of effects of trauma with or without intent associated with psychosis were investigated. In NEMESIS-1 and NEMESIS-2, other theories were tested involving specificity of associations of particular trauma types (i.e. physical, sexual or psychological abuse, emotional neglect, growing up in foster care or death of a loved one) and particular psychotic symptoms (i.e. hallucinations in general, auditory-verbal hallucinations, delusions in general or paranoia). In NEMESIS-2, it was investigated whether exposure to childhood trauma was associated with a number of affective symptoms indicative of hopelessness for the future and low self-esteem (based on the 'social defeat' hypothesis of psychosis), and whether these symptoms in turn were mediators in the association with psychosis.

Results: In NEMESIS-1 and NEMESIS-2, trauma with an intention to harm (psychological, sexual or physical abuse) showed a stronger association with psychotic experiences than trauma without intent (death of a loved one) ($\chi^2=58.62$, df=1, $p<0.001$). Similar results for psychotic disorder patients were found in the GROUP study: physical, emotional and sexual abuse was associated more strongly with psychotic symptoms than physical or emotional neglect (B 0.24, CI 0.09–0.40, $p=0.002$). In NEMESIS-2, symptoms indicative of social defeat (e.g. hopelessness about future and loss of self-confidence) were strong and separate mediators in the association between childhood trauma and psychotic experiences (proportion of mediating effect 31%) as well as between childhood trauma and the narrower phenotype of psychotic disorder (proportion of mediating effect 87%). No evidence was found indicating that any of the trauma types showed stronger associations with either hallucinations in general, auditory-verbal hallucinations, delusions in general or paranoia.

Discussion: Intention-to-harm, possibly through a mechanism of "social defeat", is the key component which links childhood trauma to psychotic experiences in adulthood. No evidence was found to support psychological theories regarding specific associations between particular types of trauma and particular psychotic symptoms.

5:00 PM

NEGATIVE MODULATION OF THE SYNAPTIC VESICLE PROTEIN (SV2A): A NEW PHARMACOLOGICAL TARGET FOR COGNITIVE DEFICIT ASSOCIATED WITH SCHIZOPHRENIA

Marc Laruelle, Eric Detrait, Yves Lamberty, Karine Leclercq, Eric Jnoff, Martin Wood, Michel Gillard, Emilie Jigorel, Henrik Klitgaard, Laurent Provins
UCB

Background: The cognitive deficits associated with schizophrenia are thought to be related to hypofunction of glutamate transmission at NMDA receptors. SV2A is a family member of synaptic vesicle proteins, widely distributed throughout the brain, and involved in the control of exocytosis of glutamate and other neurotransmitters. SV2A knock down triggers spontaneous seizures which suggests that anticonvulsant SV2A ligands like levetiracetam, reduce excessive release of glutamate and thereby act as positive SV2A modulators. We report here a new class of drugs that act as negative SV2A modulators and therefore are expected to increase deficient release of glutamate and might constitute a new class of medications for cognitive deficits related to NMDA hypofunction in schizophrenia. Among these, UCB0255 was identified as a preclinical candidate for further development. UCB0255 displays high selectivity and affinity ($pKi=7.9$) for SV2A.

Methods: The pro-cognitive activity of UCB0255 was tested in normal rats, as well as in the subchronic phencyclidine (PCP) rat model (5 mg/kg ip bid for 7 days followed by 7 days washout). The subchronic PCP model recapitulates several key features of schizophrenia, such as enduring cognitive deficits, low prefrontal dopamine, and low prefrontal metabolism.

Results: UCB0255 increased memory performance in normal rats. UCB0255

alleviated 24h delay-dependent forgetting of a familiar object, raising the recognition index by 20% compared to rats forgetting the familiar object. In the latter test, efficacy was observed when UCB0255 was administered before as well as shortly after the acquisition trial, indicating that the drug candidate acts on both memory acquisition and consolidation.

UCB0255 (0.01–3 mg/kg, ip) was found to counteract object recognition memory deficit in the subchronic PCP model. It raised the recognition index of PCP-treated rats by 30% and thereby normalized it to the level of non-PCP treated rats.

At these pharmacologically active doses UCB0255 was found to occupy 5 to 70% of SV2A sites as determined by *in vivo* binding experiments. No pro-seizure activities were observed in the dose range associated with pro-cognitive effects.

Discussion and conclusion: UCB0255 is a selective and high affinity SV2A negative modulator, revealing a promising pro-cognitive profile, particularly in an animal model of prefrontal hypofunction relevant for schizophrenia. The present project was supported by a grant from the Walloon Region (Belgium) – (Conventions N°6368 & 6827).

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NOVEL GENETIC RISK VARIANTS FOR CLOZAPINE-ASSOCIATED NEUTROPENIA

Sophie Legge¹, Marian Hamshere¹, Stephan Ripke², Alexander Richards¹, Jennifer Moran³, Kimberly Chambert², Steven A. McCarroll², Dan Rujescu⁴, Michael O'Donovan¹, Michael Owen¹, James T.R. Walters¹

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Background: Clozapine has been demonstrated to be more effective than other antipsychotics in patients with treatment resistant schizophrenia (TRS). Nevertheless, clozapine is widely under prescribed. A contributing factor is the rare hematological side effect of agranulocytosis, a rapid reduction of neutrophils to below 500 cells/mm³. Neutropenia is a less severe form when the neutrophil count is decreased to below 1500 cells/mm³. If undetected, agranulocytosis can be fatal because the defence offered by white blood cells is decreased. Clozapine treatment is accompanied by mandatory blood monitoring in the UK and if neutropenia is detected, a "red alert" is given and clozapine treatment discontinued. The current prevalence of agranulocytosis in those taking clozapine is 0.8% and neutropenia 2.9%. The aim of the present study was to investigate genetic causes of these "red alert" cases of clozapine-associated neutropenia in two genome wide association analyses.

Methods: 5469 patients who took clozapine for at least a year without developing this rare side effect were compared to (i) patients who had developed neutropenia and received a "red alert" (N=64) and (ii) in a more stringent analysis, those with a neutrophil count below 1000 cells/mm³ (N=18), referred to as severe neutropenia. Samples were obtained either anonymously from the CLOZUK sample in partnership with Novartis or from the Cardiff COGS (Cognition in Schizophrenia) sample. The samples were typed on either Illumina Omni or Illumina Combo and SNP imputation conducted using BEAGLE as part of a joint project with the Stanley Centre at the Broad Institute. Quality control and logistic regression using PLINK was performed separately for each chip and results meta-analysed using fixed effects. After quality control, 7,166,715 SNPs were included in the neutropenia analysis and 4,960,983 SNPs were included in the severe neutropenia analysis.

Results: Two variants were associated with clozapine-associated neutropenia at the genome wide significance level: rs116019360 (OR=4.03, $P=3.35 \times 10^{-8}$, 17.2% vs. 4.7%) upstream of LOC284661 and rs112478317 (OR=7.25, $P=4.46 \times 10^{-8}$, 7% vs. 1.1%) downstream of MSRB3. The second analysis of severe neutropenia identified a genome wide significant intronic variant, rs75062547 (OR=15.45, $P=2.46 \times 10^{-8}$, 22.2% vs. 2.3%) in SLX4IP. The gene SLX4IP interacts with SLX4 which has been found to cause a form of Fanconi Anemia, a rare recessive disorder characterised by bone marrow failure.

Discussion: We have identified several novel genetic risk variants for clozapine-associated neutropenia and severe neutropenia from two genome wide association studies. Of particular note was the finding in severe neutropenia that identified genome wide significant association in SLX4IP, a gene that interacts with SLX4. Mutations in SLX4 have been found

to cause a form of Fanconi Anemia. We are currently following up on these results and seeking replication. Identifying genetic associations with clozapine-associated neutropenia is important because a sensitive and specific predictive test would be an invaluable tool for clinicians and could conceivably lift the burden of blood monitoring.

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RECOVERY IN REMITTED FIRST-EPIISODE PSYCHOSIS AT 7 YEARS OF FOLLOW-UP OF AN EARLY DOSE REDUCTION/DISCONTINUATION OR MAINTENANCE TREATMENT STRATEGY

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Background: Short-term outcome studies of antipsychotic dose-reduction/discontinuation strategies in patients with remitted first-episode psychosis (FEP) showed higher relapse rates but no other disadvantages compared with maintenance treatment; however, long-term effects on recovery have not been studied before. Aim of the study was to compare rates of recovery in patients with remitted FEP after 7 years of follow-up of a dose reduction/discontinuation (DR) vs. maintenance treatment (MT) trial.

Methods: The present study is a seven-year follow-up of a 2-year open randomized clinical trial comparing MT and DR. One hundred twenty-eight patients participating in the original trial were recruited from 257 patients with FEP referred from October 2001 to December 2002 to 7 mental health care services in a 3.2 million-population catchment area. Of these, 111 patients refused to participate and 18 patients did not experience remission. After 7 years, 103 patients (80.5%) of 128 patients who were included in the original trial were located and consented to follow-up assessment. After 6 months of remission, patients were randomly assigned to DR strategy or MT for 18 months. After the trial, treatment was at the discretion of the clinician.

Primary outcome was rate of recovery, defined as meeting the criteria of symptomatic and functional remission. Determinants of recovery were examined using logistic regression analysis; the treatment strategy (MT or DR) was controlled for baseline parameters.

Results: The DR patients experienced twice the recovery rate of the MT patients (40.4% vs. 17.6%). Logistic regression showed an odds ratio of 3.49 ($P=0.01$). Better DR recovery rates were related to higher functional remission rates in the DR group but were not related to symptomatic remission rates. The mean antipsychotic dose (daily dose in haloperidol equivalent milligrams) in patients originally receiving DR (2.20 [2.27] mg) remained significantly lower during the last 2 years of follow-up compared with the dose in patients who were receiving MT (mean, 3.60 [4.01] mg; $t_{101}=-2.18$; $P=0.03$). Though relapse rates in DR after the original 2-year trial were twice those in MT, after three years relapse rates came on par and did not significantly differ on the long term. The mean (SD) number of relapses in the sample was 1.24 (1.37). Categorized by group, the mean numbers were DR, 1.13 (1.22) and MT, 1.35 (1.51); this difference was nonsignificant ($t_{101}=-0.81$, $P=0.42$).

Discussion: Dose reduction/discontinuation of antipsychotics during the early stages of remitted FEP shows superior long-term recovery rates compared with the rates achieved with MT. Relapse rates were initially higher in DR but came on par from 3 years to end of follow-up. To our knowledge, this is the first study showing long-term gains of an early-course DR strategy in patients with remitted FEP. Additional studies are necessary before these results are incorporated into general practice.

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RISK OF MORTALITY IN OFFSPRING OF MOTHERS WITH PSYCHOSIS: A WESTERN AUSTRALIAN WHOLE-OF-POPULATION COHORT STUDY

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Background: Offspring of mothers with severe mental illness are known to have higher mortality rates. Our aims were (i) to estimate the risk of stillbirth, neonatal and post-neonatal death including sudden infant death syndrome (SIDS), and childhood mortality (ages 1-9) in offspring of mothers with psychosis compared to offspring of mothers with no known mental illness and (ii) to examine the contribution of maternal physical morbidity and reproductive pathology (obstetric complications) to mortality outcomes.

Methods: This is a whole-of-population record linkage study comparing outcomes for 15,486 offspring born between 1980-2001 to mothers with a history of psychosis recorded on the psychiatric case register with 452,459 offspring born in the same period to mothers with no history of mental illness. The study database includes data from the following registers: midwives, psychiatric (inpatient/outpatient), hospital morbidity and mortality.

Results: There were 7124 offspring deaths recorded on the mortality register. Using unadjusted logistic regression, compared to offspring of mothers with no mental illness, offspring of mothers with psychosis were at significantly greater risk of: any death (odds ratio 1.6, 95% CI 1.5-1.8), stillbirth (odds ratio 1.2, 95% CI 1.0-1.5), neonatal death (odds ratio 1.7, 95% CI 1.4-2.1), post-neonatal death (odds ratio 2.1, 95% CI 1.7-2.7), SIDS (odds ratio 3.0, 95% CI 2.3-4.0) and death in childhood (odds ratio 2.3, 95% CI 1.8-3.0).

When we looked at maternal morbidity and reproductive pathology, compared to mothers with no mental illness, mothers with psychosis were significantly more likely: to have physical health conditions including chronic renal dysfunction (odds ratio 2.0, 95% CI 1.5-2.5), asthma (odds ratio 1.8, 95% CI 1.7-1.9), thyroid dysfunction (odds ratio 1.5, 95% CI 1.2-1.9), diabetes (odds ratio 1.2, 95% CI 1.02-1.3), essential hypertension (odds ratio 1.2, 95% CI 1.1-1.3), circulatory disease (odds ratio 1.2, 95% CI 1.1-1.4) and to experience obstetric complications at the time of the index birth/pregnancy including pregnancy complications (odds ratio 1.1, 95% CI 1.1-1.2), labor and delivery complications (odds ratio 1.1, 95% CI 1.0-1.1) and neonatal complications (odds ratio 1.3, 95% CI 1.2-1.4).

In terms of socioeconomic status and race, they were also significantly more likely: to be in the most disadvantaged quintile of socio-economic disadvantage (odds ratio 2.4, 95% CI 2.2-2.5) and to be indigenous (odds ratio 2.3, 95% CI 2.1-2.5).

Our next steps are to examine cause of death and to undertake multivariate analysis to assess the relative contribution of potential predictors to mortality outcomes.

Discussion: At least some part of the higher risk of mortality in the offspring of mothers with psychosis may be linked to other factors associated with maternal psychiatric illness including poor physical health, poor obstetric outcomes and socio-economic disadvantage. Better antenatal care and support for mothers during the birth of their child may help reduce infant mortality.

6:00 PM

SOCIAL SUPPORT AS AN EFFECT MODIFIER OR MEDIATOR IN THE RELATIONSHIP BETWEEN CHILDHOOD ADVERSITY AND PSYCHOSIS?

Charlotte Gayer-Anderson¹, Stephanie Beards², Kathryn Hubbard², Adanna Onyejajka², Grant McQueen², Ulrich Reininghaus², Paola Dazzan¹, Carmine Pariante⁴, Valeria Mondelli¹, Robin M. Murray¹, Craig Morgan¹

¹Institute of Psychiatry, King's College London; ²Centre for Epidemiology and Public Mental Health, Health Service and Population Research Department, Institute of Psychiatry, King's College London

Background: Previous studies have reported an association between various indicators of adversity, including abuse, in childhood and psychosis. However, the majority of exposed individuals do not develop psychosis. Given that support from caregivers and peers following childhood trauma has been found to be one of the strongest protective factors associated with resilience to other mental health outcomes, e.g. PTSD and depression, this study aimed to explore whether social support modifies the association

between childhood trauma and psychosis, or if childhood abuse impacts on psychosis risk indirectly by increasing the individuals' social isolation.

Methods: Data on 227 first-presentation psychosis cases and 199 unaffected population-based controls was drawn from the Childhood Adversity and Psychosis (CAPsy) Study. Using the Childhood Experience of Care and Abuse Interview (CECA), information was obtained on early adversity before the age of 17 (psychological abuse, physical abuse, bullying victimisation) and perceived social support in childhood (from adults, from peers, and perceived loneliness). Data was analysed using mediational analyses and logistic regression (and tested for interaction on an additive scale using Interaction Contrast Ratios).

Results: Compared with controls, cases more commonly reported experiences of severe bullying victimisation (adjusted odds ratio [aOR] 2.69, 95% Confidence Interval [CI] 0.96–7.51), and severe psychological (aOR 6.27, 95% CI 2.48–15.84) and physical (aOR 1.69, 95% CI 0.91–3.11) abuse. In addition, cases were approximately two times more likely than controls to report feeling lonely (aOR 2.36, 95% CI 1.41–3.97), and to having low support from adults (aOR 2.17, 95% CI 1.31–3.59) and peers (aOR 2.15, 95% CI 1.31–3.53). There was no strong evidence that social support modified these relationships, which may be due to limited power to test interaction effects at this point. There was, however, strong evidence that around 35–40% of the total effect of severe psychological abuse, and 50–58% of the total effect of severe physical abuse, on psychosis was via pathways through low perceived support from adults (indirect effects: psychological abuse – aOR 2.75, 95% CI 1.07–7.09; physical abuse – aOR 1.91, 95% CI 1.08–3.37), low perceived support from peers (indirect effects: psychological abuse – aOR 2.96, 95% CI 0.98–8.94; physical abuse – aOR 1.67, 95% CI 1.02–2.75), and perceived loneliness (indirect effects: psychological abuse – aOR 2.47, 95% CI 1.07–5.69; physical abuse – aOR 1.79, 95% CI 1.04–3.08). In addition, 69% of the total effect of severe bullying victimisation on psychosis was via pathways through feelings of loneliness in childhood (indirect effect: aOR 7.01, 95% CI 1.51–32.52).

Discussion: This is the first study to show that the effects of abuse in childhood on psychosis appear to be mainly mediated through low levels of perceived childhood support. Additionally, high levels of support from adults or peers may be protective in those who experience severe bullying victimisation. These findings have significant implications for the intervention of psychosis.

Workshop

BIOLOGICAL AND PSYCHOPATHOLOGICAL DIMENSIONS OF PSYCHOTIC DISORDERS: THE ROAD FORWARD TO DECONSTRUCTION?

Chairpersons: Tilo Kircher and Werner Strik

Discussant: Wolfgang Gaebel

Tuesday, 8 April 2014

6:30 PM – 8:30 PM

Overall Abstract: Dimensional concepts are (again) gaining attention in the pursuit of understanding the pathophysiology of psychotic disorders. In particular, patterns of clinical features linked to specific brain systems may allow to disentangle classical diagnostic categories, and to identify specific neurobiological dysfunctions on a neurobiological dimensional level. In this symposium, research projects are presented which have related psychotic symptom clusters to structure and function of particular brain systems. Specifically results will be presented which support a relationship of thought and verbal hallucinations with the language system, catatonic and other movement disorders with the motor system, and of paranoid symptoms of abnormal salience and emotion processing with the limbic system. In the symposium an overview of the current state of the field and an outlook will be given about past and current studies.

THOUGHT AND LANGUAGE DISORDERS AND THEIR NEURAL PATHOPHYSIOLOGY

Tilo Kircher

¹Department of Psychiatry and Psychotherapy, Philipps-University Marburg, Marburg, Germany

Speech and language disorders, such as concreteness and formal thought disorder (FTD) are core symptoms of Schizophrenia, but do occur to a similar extent in other diagnoses such as bipolar disorder and major depression. We will review clinical rating scales of FTD and introduce a new, validated scale, the TALD. Further, structural and functional brain imaging data will be reviewed and own novel findings presented, relating speech and language dysfunctions to neural networks, within schizophrenia and across the "functional psychoses". The impact of genetic variance and NMDA receptor blockage on brain function will be addressed with a particular focus on speech and language (dys-)function. We demonstrate, from the genetic to the brain structural and functional level, that particular aspects of the neural language system is disrupted in patients with FTD across traditional diagnoses.

THE BRAIN SYSTEMS UNDERLYING HALLUCINATIONS AND CATATONIA

Werner Strik

University Hospital of Psychiatry

Dissociation of higher psychic functions is a central feature of schizophrenia, and was the rationale for Eugen Bleuler to create its name. At the best of his knowledge, Bleuler grouped these functions in the symptom domains of thinking-feeling-acting (Denken-Fühlen-Handeln). In recent studies, auditory hallucinations, thought and motor disorders were linked to brain disorders at the systems level. Based on the Bern Psychopathology Scale for Psychoses, BPS; Strik et al, 2010), psychotic patients were stratified based on the severity of symptom dimensions related to language, emotional or movement dysregulations. Significant changes of gray matter density were found in meaningful brain regions, namely left Broca's region, right ventral striatum, and right SMA, respectively. Furthermore, in the case of auditory verbal hallucinations, a pathophysiological mechanism was described involving a hyperexcitation of the language system including the primary auditory cortex. The results support a dimensional view on symptom clusters which can be mapped on the respective brain systems.

ALTERED TRANSFER OF MOMENTARY MENTAL STATES (ATOMS) AS THE BASIC UNIT OF PSYCHOSIS LIABILITY IN INTERACTION WITH ENVIRONMENT AND EMOTIONS

Jim van Os

Maastricht University Medical Centre/King's College London

Psychotic disorders are thought to represent altered neural function. However, research has failed to map diagnostic categories to alterations in neural networks. It is proposed that the basic unit of psychotic psychopathology is the moment-to-moment expression of subtle anomalous experiences of subclinical psychosis, and particularly its tendency to persist from moment-to-moment in daily life, under the influence of familial, environmental, emotional and cognitive factors. In a general population twin sample (n=579) and in a study of patients with psychotic disorder (n=57), their non-psychotic siblings (n=59) and unrelated controls (n=75), the experience sampling paradigm (ESM; repetitive, random sampling of momentary mental states and context) was applied. We analysed, in a within-person prospective design, (i) transfer of momentary anomalous experience at time point (t-1) to time point (t) in daily life, and (ii) moderating effects of negative affect, positive affect, daily stressors, IQ and childhood trauma. Additionally, (iii) familial associations between persistence of momentary anomalous experience and psychotic symptomatology were investigated. Higher level of schizotypy in the twins (but not higher level of psychotic symptoms in patients) predicted more persistence of momentary anomalous experience in daily life, both within subjects and across relatives. Persistence of momentary anomalous experience was highest in patients, intermediate in their siblings and lowest in controls. In both studies, persistence of momentary anomalous experience was moderated by higher levels of negative affect, daily stressors and childhood trauma (only in twins), and by lower levels of positive affect. The study of alterations in the moment-to-moment transfer of subtle anomalous experience of psychosis, resulting in their persistence, helps to explain why psychotic and emotional dysregulation tend to cluster in a single phenotype such as schizophrenia, and how familial and environmental risks increase the

risk of expression of psychosis from, first, subtle momentary anomalous experience to, second, observable clinical symptoms.

NEURAL NETWORK MODEL DECONSTRUCTION OF PSYCHOSIS

Sophia Frangou

Icahn School of Medicine at Mount Sinai

Functional magnetic resonance imaging (fMRI) has proved a powerful tool in examining disorder-related neural circuitry alterations in psychosis. Available evidence indicates abnormal recruitment and connectivity in circuits encompassing primary and associative perceptual regions, medial prefrontal (ACC) and temporal regions (amygdala/hippocampus), parietal (PAR) and prefrontal (PFC) cortical areas. These observations imply the involvement of large scale brain networks but do not provide any evidence of mechanisms relating these findings to clinical features of the disorder. This study combined Statistical Parametric Mapping (SPM) with Dynamic Causal Modelling (DCM) to compare all plausible models of effective connectivity generated by fMRI data obtained during the 2-back working memory task euthymic patients with bipolar disorder (n=47), patients with schizophrenia (n=40) and matched healthy individuals (n=50). There are two main findings. First, all diagnostic groups comprised heterogeneous populations of subjects whose data could be explained by a number of different neural network models. Therefore disease expression in psychosis may involve some mechanisms that deviate significantly from and others that are nested within the normal variation. Second, some connectivity models had unique clinical relevance and were associated with psychosis burden and mood instability. We have shown that models of effective connectivity during working memory capture the diversity in patients with psychosis. This approach allows us to delineate the clinical relevance of the different connectivity models seen in psychosis in terms of their associated clinical features.

Workshop

NEUROADAPTATIONS TO CHRONIC ANTIPSYCHOTIC TREATMENT IN PRECLINICAL MODELS

Chairperson: Shitij Kapur

Discussant: Shitij Kapur

Tuesday, 8 April 2014

6:30 PM – 8:30 PM

Overall Abstract: Using a pharmacological animal model of antipsychotic drug treatment, in which a strict adherence to clinically relevant dosing is observed, we propose three talks highlighting the effects of antipsychotic drug treatment on (1) neurotransmitter release, (Dr Davide Amato), with implications for antipsychotic treatment non-response, (2) effects on brain morphology (Dr Anthony Vernon), with implications for the impact of antipsychotics on negative symptoms and cognition and (3) metabolic effects of antipsychotics (Dr Margaret Hahn), with implications for mechanisms of antipsychotic-associated weight gain and glucose dysregulation. Such pharmacological models, although useful are however limited by their non-specificity. Therefore, complementary studies in genetic knock out or overexpression models, particularly of the dopamine D2 receptor (the primary target of antipsychotic drugs) are essential to understand the behavioural consequences, and associated cellular and molecular brain adaptations due to alterations in D2 receptor function. We therefore propose a final talk to address this issue (4) (Dr Kellendonk) on a translational genetic mouse model in which expression of the dopamine D2 receptor is increased in the striatum, a known consequence of chronic antipsychotic drug treatment, and the utility of this as a translational model to understand not only the pathophysiology of schizophrenia, but also how this may provide insights into the effects of antipsychotic drugs, particularly on motivation and cognition. Antipsychotic drugs are given to patients chronically to treat psychosis. Neuropsychological adaptations take place during antipsychotic treatment, but it is not clear how these are related to beneficial clinical outcomes (the control of positive symptoms), nor to detrimental clinical outcomes (adverse effects such as tardive dyskinesia, antipsychotic-induced weight gain) and treatment non-response. Addressing these issues in humans remains problematic. Controlled studies using

appropriate animal models including clinically relevant antipsychotic drug dosing is therefore vital to understand the neural adaptations that take place during the course of antipsychotic treatment. In organising this symposium, our aim is to stimulate a critical discussion on this highly clinically relevant topic. In particular, we aim to stimulate debate on how we might use current and evolving knowledge and new methodologies in the field of neuropharmacology and neuroscience to advance our understanding of the long-term impact of antipsychotic treatment, which ultimately, may inform the clinical use of these drugs. Given the current fervent debate concerning antipsychotic use in light of the lack of any new emerging drugs to treat psychosis, we believe this topic is both timely and relevant to the structure of the scientific program. Indeed the content of this symposium is relevant to parallel congress tracks discussing the clinical use of antipsychotics in not only schizophrenia, but other psychiatric disorders such as Bipolar disorder, efforts to develop novel antipsychotics and the development of adjunctive treatments to increase antipsychotic drug efficacy and/or mitigate adverse effects and the clinical use.

MECHANISMS OF ANTIPSYCHOTIC TREATMENT FAILURE

Davide Amato¹, Christian P. Müller², Fabio Canneva², Paul Cumming², Simone Maschauer², Benedict Quinger², Olaf Prante², Stephan von Hösten², Johannes Kornhuber²

¹Department of Psychiatry and Psychotherapy, Friedrich-Alexander University of Erlangen-Nürnberg, Erlangen, Germany; ²Section of Addiction Medicine, Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University, Erlangen, Germany

Antipsychotic treatment failure is a common consequence of chronic treatment in schizophrenia. Clinical as well as preclinical studies reported that the initial treatment efficacy is soon followed by decreased therapeutic effects. Despite these empirical evidences, the mechanisms of treatment failure are unknown. We have characterized an animal model that has captured the time course of antipsychotic treatment failure using clinically relevant antipsychotic doses. Our model will propose a neurobiological mechanism which goes behind the traditional view of D2 receptor supersensitivity as interpretative platform of several antipsychotic treatment side effects.

IMPACT OF CHRONIC ANTIPSYCHOTIC DRUG TREATMENT ON BRAIN MORPHOLOGY: A CAUSE FOR CONCERN?

Anthony C. Vernon¹, Sridhar Natesan², Winfred Chege², William R. Crum³, Michel Modo¹, Jonathan D. Cooper¹, Steven C.R. Williams³, Shitij Kapur⁴

¹King's College London, Institute of Psychiatry, Dept. of Neuroscience; ²King's College London, Institute of Psychiatry, Dept. of Psychosis Studies; ³King's College London, Institute of Psychiatry, Dept. of Neuroimaging; ⁴Institute of Psychiatry, Kings College, London, UK

Progressive loss of grey and white matter has been linked to the pathogenesis and lack of clinical improvement in schizophrenia (SCZ) and related psychoses. Increasing evidence from neuroimaging and neuropathology studies however, suggests that chronic antipsychotic treatment may contribute to the trajectory of brain volume decreases. Therefore it is critical to differentiate "disease" from "medication"-related brain volume changes and determine the underlying biological mechanisms. Addressing these questions in clinical populations is challenging. Ethical issues preclude a definitive study of placebo-treated SCZ patients and healthy individuals chronically treated with antipsychotics. Furthermore, neuroimaging findings in humans cannot easily be confirmed by neuropathology. Rodent models offer an effective means to address some of these issues, affording precise control over drug exposure, age, and linking *in vivo* neuroimaging with *ex vivo* neuropathology. Therefore, we have implemented a model in laboratory rats combining serial *in vivo* MRI (clinically comparable technology) and clinically relevant antipsychotic doses with post-mortem analysis, to link *in vivo* neuroimaging findings with neuropathology. This work has demonstrated that in normal animals, chronic antipsychotic treatment decreases total neocortical volume (1), an effect seen across different antipsychotics (Haloperidol and olanzapine) (1), distinct from what is seen with chronic lithium (2) and is reversible on drug withdrawal (2). Our most

recent work has demonstrated that antipsychotics specifically reduce the volume and thickness of the anterior cingulate cortex (ACC) but not that of the primary visual (V1) cortex. Decreased ACC volume is associated with no significant loss of either neurons or astrocytes, but rather, an increase in the density of these cells suggesting the drug-induced changes are likely to reflect alterations in synaptic or dendritic architecture. This work has translational relevance to human neuroimaging studies of psychiatric illness treated with antipsychotics, including SCZ. In particular, this approach facilitates "reverse-translation", potentially informing the neurobiological mechanisms underlying antipsychotic drug-induced volumetric abnormalities reported from neuroimaging studies in SCZ patients. Furthermore, this work may ultimately, may inform the clinical use of these drugs.

References:

- [1] Vernon et al., Biol Psychiatry. 2011; 69(10): 936-44.
- [2] Vernon et al., Biol Psychiatry. 2012; 71(10): 855-63.

CLINICAL INSIGHTS DERIVED FROM RODENT MODELS OF ANTIPSYCHOTIC-INDUCED METABOLIC PERTURBATIONS

Margaret K. Hahn^{1,2}, Gary Remington^{3,4}, Araba Chintoh^{4,6}, Celine Teo⁴, Paul Fletcher⁴, Jose Norbrega⁴, Melanie Guenette^{4,5}, Tony Cohn^{1,4}, Adria Giacca⁶

¹University of Toronto, Department of Psychiatry; ²Center for Addiction and Mental Health, Complex Mental Illness; ³Department of Psychiatry, University of Toronto; ⁴Centre for Addiction and Mental Health, Toronto, ON, Canada;

⁵Institute of Medical Sciences, University of Toronto, Canada; ⁶Department of Physiology, University of Toronto, Canada

Antipsychotic medications, currently the cornerstone of treatment for schizophrenia, have been associated with significant metabolic side effects, including dyslipidemia, weight gain and glucose dysregulation. In turn, these factors are understood to contribute to increased cardiovascular (CV) morbidity and premature mortality observed in serious mental illness. Understanding underlying mechanisms of these adverse effects, and also how they may overlap with therapeutic efficacy, is imperative to developing targeted interventions to attenuate cardiometabolic risk factors, and effective anti-psychotic treatments devoid of these side-effects. In this respect, the field has turned to *in vivo* work in animals to model what is observed clinically and elucidate possible underlying mechanisms of antipsychotic-induced metabolic disturbances. As will be discussed, rodents serve as useful models for some, but not all aspects of metabolic side-effects. Glucose dysregulation, which can occur through both adiposity-dependent, and adiposity-independent pathways, may arguably offer the strongest translational value from rodents to humans. This talk will review what we have learned from preclinical models of antipsychotic-induced metabolic dysregulation, focusing on glucose dysregulation, plausible underlying mechanisms, including our group's recent work elucidating the role of receptor binding profiles of antipsychotic medications, and contributions of the central nervous system (CNS) to these perturbations. Discussion will also turn to preclinical investigations of plausible interlinks between CNS control of glucose metabolism and therapeutic pathways of antipsychotic medications.

DOPAMINE D2 RECEPTORS REGULATE THE ANATOMICAL BALANCE OF BASAL GANGLIA CIRCUITRY

Christoph Kellendonk, Maxime Cazorla, Fernanda Delmondes de Carvalho, Muhammad O. Choha, Mariya Shegda, Nao Chuhma, Steve Rayport, Susanne Ahmari, Holly Moore
Columbia University, New York State Psychiatric Institute, New York, NY

In the classical model of basal ganglia, striatal output projections are organized into two distinct pathways: the direct pathway – which directly projects to the substantia nigra (SNr) – and the indirect pathway – which projects to the external globus pallidus (GPe) and then relays through intermediate neurons to the SNr. Both pathways are thought to be anatomically segregated and to exert opposing effects on locomotor activity, motivational behavior and cognition. Single-cell tracing studies have challenged the strict dichotomy between these pathways revealing that the vast majority of "direct" neurons possess collaterals to the GPe. Here, we show that

these collaterals, which bridge between the direct and indirect pathway are highly plastic in the adult animal and are bi-directionally regulated by striatal dopamine D2 receptors (D2R). Overexpression of D2Rs in the striatum of the mouse selectively increases the extent of GPe collaterals of the direct pathway via its effects on neuronal excitability of the indirect pathway. In contrast, genetic downregulation of D2Rs selectively decreases the density of striatonigral GPe collaterals. Increased direct pathway collaterals are associated with stronger inhibition of pallidal neurons *in vivo* and with disrupted behavioral activation after optogenetic stimulation of the direct pathway. Remarkably, we found that chronic blockade with haloperidol, an antipsychotic medication used to treat schizophrenia, decreases the extent of bridging collaterals and rescues the locomotor imbalance. These findings suggest a role for bridging collaterals in regulating the concerted balance of striatal output connectivity and may have important implications for the understanding of schizophrenia, a disease that involves excessive activation of striatal D2Rs and that is traditionally treated with D2R blockers.

Workshop

NEUROSTIMULATION FOR PSYCHOTIC SYMPTOMS

Chairpersons: Remko van Luterveld and Bob Oranje

Discussant: Renaud Jardri

Tuesday, 8 April 2014

6:30 PM – 8:30 PM

Overall Abstract: In recent years, there is increasing interest in neurostimulation as a treatment option for psychotic symptoms. These include 1-Hz repetitive magnetic stimulation (rTMS), with which brain activity is modulated using magnetic pulses at a 1-Hz frequency, theta-burst magnetic stimulation (TBS), which is a similar technique using intermittent short trains of magnetic pulses, transcranial direct current stimulation (tDCS), which uses electrical current to alter brain activity and magnetic seizure therapy (MST), which induces seizures through magnetic fields. In the current symposium we present data from four research groups investigating the efficacy and neural mechanisms of these promising neurostimulation techniques. Dr. Jerome Brunelin will present data on the first double blind sham-controlled randomized clinical trial of tDCS in the treatment of psychotic symptoms as well as unpublished results concerning the neural correlates of this technique. Dr. Philipp Homan will present new findings regarding neuroimaging markers predicting response to rTMS and tDCS neurostimulation therapy. Dr. Remko van Luterveld will present new findings concerning a large TBS double blind sham-controlled randomized clinical trial on severity of auditory verbal hallucinations and Dr. Daniel Blumberger will present new data regarding the first clinical trial using MST to treat psychotic symptoms. Dr. Renaud Jardri will lead the discussion, with a special focus on future direction to advance this research.

EFFECTS OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON TREATMENT-RESISTANT PSYCHOTIC SYMPTOMS AND BRAIN FUNCTIONAL-CONNECTIVITY IN PATIENTS WITH SCHIZOPHRENIA

Jerome Brunelin¹, Marine Mondino², Renaud Jardri³, Emmanuel Poulet²

¹CH le Vinatier; ²University of Lyon, UCB Lyon 1, CH Le Vinatier, Lyon, France;

³CHRU Lille, Université de Lille, France

Objective: Even if mechanisms of action remain unclear, non invasive brain stimulation techniques are thought to be useful to alleviate treatment-resistant auditory hallucinations and negative symptoms in patients with schizophrenia. Our objective was to test whether transcranial Direct current Stimulation (tDCS) applied over the left temporoparietal junction (assumed "inhibitory" – cathode) and the left prefrontal cortex (assumed "excitatory" – anode) can impact clinical symptoms and functional connectivity of targeted regions in patients with schizophrenia presenting treatment-resistant auditory verbal hallucinations. We hypothesized that tDCS alleviates symptoms by modulating functional connectivity of a distributed brain network involving language-related and self-recognition areas.

Method: In a double blind sham-controlled randomized clinical trial, thirty patients with schizophrenia and treatment-resistant auditory verbal hallucinations were randomly allocated to receive either 20 minutes of active 2mA tDCS or sham stimulation twice a day during 5 consecutive working

days. The anode was placed over the left prefrontal cortex according to 10/20 EEG international system (PFC - F3FP1) and the cathode over the left temporoparietal junciton (TPJ - T3P3). Seed-based functional connectivity maps were compared before and after stimulation sessions (5 minutes resting state fMRI). Seed were placed in regards of the electrode locations. Analyses were done using Brain Voyager QX on resting state fMRI maps.

Results: Clinical impact of tDCS was investigated in the initial sample of 30 patients. tDCS results in an improvement of global symptoms: hallucination (~31%, measured by Auditory Hallucination Rating Scale – AHRS) and general symptomatology (~12% measured by Positive and Negative Syndrome Scale – PANSS) especially negative (~12%), positive (~15%) and depressive (~17%) symptoms. The effect on auditory verbal hallucination had an at least 3 months duration. The impact of tDCS on seed-based functional connectivity was investigated in a subsample of 21 patients (10 new participants). We reported a significant decrease of functional connectivity in fronto-temporal network (language-related brain areas) after active tDCS compared to sham treatment. After active and compared to sham, we reported a decrease of functional connectivity between the TPJ and the PFC and the Inferior Frontal Gyrus (including Broca's area) as well as a decreased connectivity between the PFC and the TPJ and the Inferior Frontal Gyrus.

Conclusion: tDCS seems to be a promising tool to modulate brain networks underlying clinical symptoms in schizophrenia.

FROM THE NEUROBIOLOGY OF ORIGIN AND TREATMENT OF AUDITORY VERBAL HALLUCINATIONS

Philipp Homan, J. Kindler, Y. Morishima, T. Dierks, D. Hubl

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One of the most intriguing phenomena in psychopathology is auditory verbal hallucinations (AVH). With the advent of the computerized neuroimaging techniques we got the potentiality to investigate brain processes directly in those who experience hallucinations. The results of resting perfusion and functional imaging studies have implied that AVH are associated with altered neuronal activity in cerebral areas that are responsible for language production and perception. This seems to be pronounced in the dominant hemisphere, but with sometimes unexpected lateralities most probably due to compensatory mechanisms. 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. However, in schizophrenia, therapy of AVH comprises a critical domain. The one-month prevalence of these hallucinations exceeds 70% and, in 25–30% of patients, these perceptions are resistant to medication, resulting in functional disability and a low quality of life. The development of new therapeutic strategies additional to the standard of pharmacological antipsychotic treatment is urgent. Non-invasive brain stimulation expands the therapeutic regimens. Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have been recently shown to be potential and safe methods to relieve the hallucinatory burden in those, who did not respond to conventional approaches. In about 50% of pharmaco-resistant patients AVH could be significantly diminished or cured. With our TMS and tDCS treatment study we further improved the understanding of the neurobiological mechanisms responsible for basic hallucinatory mechanisms as well as responsiveness to the brain stimulation treatment approaches. Brain perfusion measurements before and after successful TMS treatment indicated significant reduced brain activity as measured by regional cerebral blood flow in the auditory cortex and Broca's areas, two of the main players in the generation of AVH. Regarding the identification of responders we demonstrated an involvement of the language system in the generation of AVH. Especially 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. First results indicate that an increased spontaneous neuronal activity in this region may be marker for response to TMS therapy. To further elucidate the circuit associated with AVH we investigated regions implied in the generation of AVH in terms of effective connectivity. Therefore, we used fMRI data measured before TMS and extracted the time series of regions that showed a decrease in neuronal activity after TMS. We tested how these regions exert influence over another using dynamic causal modelling.

Corresponding model structure of AVH patients were compared with that of healthy subjects and influence of TMS was tested.

A PILOT CASE SERIES OF MAGNETIC SEIZURE THERAPY IN REFRACTORY SCHIZOPHRENIA

Daniel M. Blumberger^{1,2}, Jonathan Downar^{3,4}, Zafiris J. Daskalakis^{5,6}

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Schizophrenia (SCZ) is a debilitating disorder that exerts enormous personal, social and economic costs. Despite recent advances in psychopharmacological treatments nearly 40% of patients achieve only a partial response and 10% experience no response at all. To date, only a few alternatives have been available: these generally include clozapine and electroconvulsive therapy (ECT). Both, however, are associated with significant side effects. ECT is associated with significant cognitive impairment and the stigma associated with ECT limits its broader use as a refractory treatment. More recently, rTMS has demonstrated some efficacy in attenuating auditory hallucinations, however replication of the initial positive findings has not been consistent. Together, these limitations highlight the need for additional treatments aimed at ameliorating the sequelae of SCZ. Magnetic seizure therapy (MST) is a newer form of convulsive therapy that utilizes high frequency and intensity repetitive transcranial magnetic stimulation to induce therapeutic seizures. Magnetic fields penetrate through tissues unimpeded and thus a lower amount of energy is required to induce a seizure. Preliminary animal and human studies have focused on the application of the treatment in depression. To date, no studies have reported the use of magnetic seizure therapy (MST) in a population of patients with refractory SCZ. This presentation will present data on the efficacy and tolerability of MST in a series of patients with refractory SCZ treated in the context of an ongoing open-label pilot study. Patients with schizophrenia, age 18–85 were eligible to participate if they had a BPRS score > 37 and were capable to consent to treatment. Patients had to be fit for anaesthesia and were cleared medically by anaesthesia. Anticonvulsants, lithium and benzodiazepines greater than 2 mg of lorazepam equivalent were not allowed. Patients were allowed to remain on antipsychotic medication during the trial. Response was defined as an 18-item BPRS < 25, for consistency with recent large studies of ECT in treatment-resistant schizophrenia. The cognitive battery included assessments of anterograde and retrograde memory, specifically looking at learning, retention and retrieval in both the verbal and non verbal domains. This will include assessments such as the Autobiographical Memory Interview Short Form, MATRICS Consensus Cognitive Battery (MCCB), Stroop and Verbal Fluency using the COWAT. Cognitive function during the treatment phase of the study will be assessed with the Montreal Cognitive Assessment (MoCA). Additionally, time to reorientation will also be measured after each MST session using previously published standardized methods that evaluate orientation to name, date of birth, age, place and day of the week. Cognition was assessed with the Montreal Cognitive Assessment prior to treatment after every 6 treatments and after the last treatment. Patients received treatment twice or three times per week up to a maximum of 24 treatments.

THETA-BURST REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION AS TREATMENT FOR AUDITORY VERBAL HALLUCINATIONS

Remko van Luterveld¹, Sanne Koops², Iris Sommer²

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Objective: Auditory verbal hallucinations (AVH) are a characteristic symptom of schizophrenia. In 25% of patients, these hallucinations are resistant to antipsychotic medication. Previous studies have investigated 1-Hz repetitive transcranial magnetic stimulation (rTMS) to the left temporoparietal region as a non-invasive treatment option for treatment-resistant patients,

with several studies with large sample sizes not demonstrating efficacy of rTMS compared to sham stimulation. A new stimulation protocol using continuous theta-burst rTMS could provide a more effective therapeutic option.

Methods: In a double-blind study, forty-one patients with AVH were randomly allocated to either continuous theta-burst rTMS (a burst of 3 stimuli at 50 Hz, which was repeated at intervals of 200 ms; 900 pulses total at 80% motor threshold) or sham treatment. The theta-burst TMS group received 10 treatments over left temporoparietal cortex distributed over five consecutive days. The placebo group received 10 treatments of sham stimulation following the same procedures as the theta-burst group. Severity of AVH was assessed using the psychotic symptom rating scales (PSYRATS), the auditory hallucinations rating scale (AHRS) and item P3 of the positive and negative syndrome scale (PANSS) before treatment, after five days of treatment, and during follow-up one month later. Data were analyzed using repeated measures ANOVA.

Results: Significant main effects of treatment were observed for the PSYRATS ($p=0.017$) and a trend was observed for the AHRS ($p=0.053$), indicating 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.

Conclusion: These results suggest a placebo effect of continuous theta-burst rTMS on the left temporoparietal region.

Workshop

NEXT STEPS WITH GWAS AND GENE SEQUENCING: FUNCTIONAL MUTATIONS, GENE BY GENE INTERACTIONS AND PATHWAY ANALYSIS

Chairperson: Dick McCombie

Discussant: To Be Announced

Tuesday, 8 April 2014

6:30 PM – 8:30 PM

Overall Abstract: GWAS has made significant progress towards identifying robust genomic associations for schizophrenia and demonstrated genetic overlap with other psychiatric disorders. These studies show that common variants can capture a sizeable fraction of the genetic variance, but the associated SNPs are rarely functional and often map some distance from the nearest plausible gene. The relative risk of any one associated SNP is typically low and the biological inference is indirect. Nevertheless, the statistical evidence for a polygenic risk score that accounts for a sizeable fraction of the variance is strong and bioinformatics approaches that seek evidence for gene set or pathway enrichment are showing promise and for gene-by-gene interaction are showing promise. At the other end of the genetic spectrum, structural and copy number variant analysis has identified a growing number of loci which when disrupted are highly penetrant and thus identify putatively causal mechanisms. These are typically rare events, or indeed sometimes unique, but collectively do account for a significant fraction of all cases. They do however pose a problem to statistical genetic validation. Nevertheless, they may provide informative start points through which to ask specific questions about biological pathways and mechanisms thus linking with our growing knowledge obtained by GWAS to enable the understanding of the biological processes contributing to schizophrenia. Another major challenge is understanding gene - by - gene interactions; for example how a rare variant interacts with one of more common variants. With the advent of next generation sequencing, it is now possible at reasonable cost to obtain whole exome or whole genome sequence on individual cases and relatives to ask more precise questions about the genetic architecture and origins of schizophrenia. However, there are significant challenges to the interpretation of the observed sequence variation as each genome carries a substantial number of common, rare and de novo mutations. It is possible to interpret coding variants that introduce frame shift mutations, splice variants, non-synonymous amino acid substitution and stop mutations with confidence, but these are just the tip of the iceberg of observed genetic variation. The questions which this symposium seeks to address are how to bridge the gap between the GWAS and the structural variant/copy number variant approach. Using well-worked examples, by leaders in the field, we will present and discuss: 1) new evidence for functional genetic variants through next generation sequencing; 2) novel bioinformatics approaches towards assessing the functionality of non-coding sequence variation; and 3) evidence for gene-by-gene interaction, or epistasis.

MULTIGENE ANALYSES AND EXOME SEQUENCING IN SCHIZOPHRENIA

Shaun Purcell

Mount Sinai Hospital

I will describe two recent large-scale applications of exome sequencing to schizophrenia, considering both family-based (focused on de novo mutation) and population-based designs, in total generating exome sequences on almost 7,000 individuals. Single-variant and gene-based association approaches did not yield significant results after correction. Rather, a significant enrichment of rare coding mutations was only observed when considering sets of functionally related genes, in particular pointing to an increased burden of ultra-rare gene-disruptive mutations in cases, across many genes. We discuss implications for the genetic architecture of schizophrenia and the current necessity for gene-set and network-based analytic approaches.

PAK SIGNALING AS A MOLECULAR RISK MECHANISM FOR PSYCHOSIS

Aiden Corvin

Trinity College Dublin, Dublin, Ireland

Understanding the molecular etiology of schizophrenia is likely to be an important step in guiding future treatments. The emerging genetic architecture involves a spectrum of risk variation from rare mutations of large effect, to common risk variants of small effect which collectively account for at least 25% of genetic risk. This risk also crosses existing diagnostic boundaries, particularly with other adult onset disorders including bipolar disorder. We have recently identified a rare duplication at the P21 Protein-activated kinase (PAK7) gene, which is inherited within the European population and increases risk of psychosis substantially (meta-analysis CMH P value=2x10⁻⁴ (odds ratio (OR)=11.3, 95% CI=3.7, ∞)). PAK7 is developmentally co-expressed with another psychosis risk gene (DISC1) and is involved in the development and maintenance of synaptic networks. In this presentation we discuss evidence of involvement of other PAK family members in schizophrenia risk, based on the largest assessment of common risk variation to date, the Psychiatric Genomics Consortium 2 (PGC2) schizophrenia analysis. This dataset includes genome-wide association study (GWAS) data on more than 35,000 cases. Finally we discuss future directions in investigation of PAK signaling as a potential risk mechanism for psychosis susceptibility.

USING HIGH THROUGH-PUT SEQUENCING OF THE DISC1 LOCUS TO UNDERSTAND THE GENETIC COMPLEXITY OF PSYCHIATRIC ILLNESS

Pippa A. Thomson^{1,2}, Jennifer S. Parla³, Allan F. McRae⁴, Melissa Kramer³, Kamna Ramakrishnan², Jai Yao³, Dinesh C. Soares², Shane McCarthy³, Stewart W. Morris², Lorna Cardone³, Steve Cass², Fumiaki Ogawa², Niamh Ryan², Elise Malavasi², Elena Ghibani³, William Hennah⁵, Kathy L. Evans², Daniella Rebolini³, David J. Porteous²

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A balanced t(1;11) translocation that transects the Disrupted in schizophrenia 1 (DISC1) gene shows genome-wide significant linkage for schizophrenia and recurrent major depressive disorder (rMDD) in a single large Scottish family, but genome-wide and exome sequencing-based association studies have not supported a role for DISC1 in psychiatric illness. We sought to understand the genetic complexity of common and rare variation at the DISC1 locus by next generation sequencing in over 1,500 individuals including 653 individuals with psychiatric illness and 889 controls. Rare

DISC1 coding variants identified exclusively in patients were found in likely functional protein domains and functional analyses have confirmed effects on protein-protein interactions and mitochondrial function. Sequence validation confirmed that the majority of single nucleotide polymorphisms had a minor allele frequencies of <1% and have not been reported in the 1000 Genomes Project. Analysis suggests that many variants remain undiscovered and are essentially private. Such high levels of rare variation requires multi-marker analyses and better understanding of the putative function of non-coding variants. We will present the results of analyses from both sequencing of the DISC1 locus and the DISC1 interactome that consists of over 260 genes implicated in downstream signalling of the DISC1 pathway. The results identify association between DISC1 and recurrent major depression from both single marker and burden analyses, as well as evidence for epistatic interactions between regions of DISC1, and nominal association for burden of coding and non-coding variants with measures of mood and cognition. These results indicate that variants that alter gene expression will be as important as those that alter protein sequence. We will describe our bioinformatic pipelines for prioritisation of both coding and non-coding variants utilising the growing publically available genome annotation.

INTERPRETING GENE NETWORKS FOR SCHIZOPHRENIA RESEARCH: BIASES, HEURISTICS, AND CONTROLS

Jesse Gillis

Cold Spring Harbor Laboratory, Cold Spring Harbor, USA

A central challenge to understanding neuropsychiatric disorders is determining how candidate variants interact with one another and the environment to produce a disease phenotype. In response to this challenge, gene networks have become a common resource for integrating potentially diffuse functional effects into a single common framework. Ideally, candidate variants not only converge on consistent pathways or interact within a network, but also do so in a way that is perturbed in response to disease or factors relevant to disease. The interpretation of gene networks related to the brain is particularly important not just because the biology of the brain is complex, but also because the number of genes involved appears to be so high. This has the effect of making methods for interpreting systemic properties of the brain particularly likely to rely on computational means, and many of the problems that seem endemic to network analysis are actually properties specific to the interpretation of brain related networks. For example, how should we interpret a cluster of genes numbering in the thousands that seems to be involved in disease? While network analyses can be extremely opaque (even to their developers), they are grounded in a few straightforward principles. Understanding those principles gives us a basis for interpreting the results of network studies. The central top-down principle in the interpretation of gene networks is "Guilt by Association" (GBA) and it simply states that genes which share functions are more likely to be associated. 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. A good network is taken to be one which exhibits this property strongly, and networks are frequently optimized to ensure this property holds. Many, perhaps most, analyses of "novel" sets of candidate disease genes rely on GBA to claim that the genes have some known shared function determinable through their associations. In a recent series of papers, we laid out grounds for treating previous gene network analyses related to function with scepticism. We showed that gene networks (protein interactions, genetic interactions and co-expression) tend to encode very generic information about gene function without learnable specificity, leading to highly multifunctional genes dominating analyses to the point that details of network structure have a surprisingly small impact. We suggest that this property plays a dominant role in most previously reported network analyses. We focus on replicating published reports on schizophrenia gene networks in demonstrating the important role of this confound. We consider approaches for addressing this problem using co-expression networks. Multifunctionality bias can creep into co-expression analyses in subtle ways (e.g., gene representation across microarray platforms). We will present our findings as to "best practises" surveyed across a large collection of public microarray data sets and focusing on meta-analysis of matched schizophrenia/control data across 306 post-mortem samples from the pre-frontal cortex. Because co-expression networks built in this way are not so generically swamped by enrichment of

multifunctional/prevalent/promiscuous/hub genes, they exhibit specificity to the data from which they were constructed (e.g., disease state). We provide concrete steps necessary to control for functional specificity when attempting to characterize schizophrenia candidate genes in network data.

Workshop

RECENT ADVANCES IN COGNITIVE BEHAVIOUR THERAPY FOR PSYCHOSIS (CBTp) FOR COMPLEX AND TREATMENT RESISTANT GROUPS

Chairperson: Emmanuelle Peters

Discussant: Til Wykes

Tuesday, 8 April 2014

6:30 PM – 8:30 PM

Overall Abstract: CBTp is recommended by national UK (NICE 02; 09) and US (PORT; 10) treatment guidelines. However, it is not without controversy. Some have claimed that the CBTp movement has gone too far, with claims for its efficacy being unfounded (McKenna, 03), while others have claimed it has not gone far enough, and should be offered as an equal choice to medication (Morrison, 12). Recent advances have focused on theoretically-informed, targeted interventions, rather than branding CBTp as a quasi-neuroleptic (Birchwood & Trower, 06). This symposium will present the latest findings in CBTp trials for complex and treatment resistant populations by the leaders in the field. The discussant, Til Wykes (Institute of Psychiatry), who has published the most highly quoted CBTp meta-analysis (Wykes et al, 08), will cast a critical eye on the findings and lead a discussion on their clinical implications. Max Birchwood (Warwick University) will present the results of a multicentre RCT comparing CBT for Command Hallucinations with treatment-as-usual (TAU). In a sample of 197 individuals, CBT significantly reduced the perceived power of the voice to do harm, which was linked to a halving of the rate of serious compliance 18 months post randomisation. This trial demonstrates one of the largest effect size of CBTp to date, and marks a significant breakthrough in the evidence base for this most severe group. Tom Craig (Institute of Psychiatry) will describe the development of AVATAR therapy, an adaptation of "voices dialogue" therapy in which patients enter into a dialogue with their voices. Patients create a representation of their voice using computerised face animation software, and select a speech sample matching the quality of their voice. The therapist speaks either as the avatar or in their own voice. The pilot study (Leff et al, 13) showed striking results, with patients who received AVATAR therapy reporting significant reductions in hallucinations compared to TAU; some patients stopped hearing voices entirely. The larger RCT is underway, comparing 7 sessions of AVATAR therapy with a supportive counselling control condition for 142 patients with treatment-resistant voices. Basic descriptive data and illustrative cases will be presented, and the updated AVATAR system will be demonstrated. Traditionally therapists have been wary of treating trauma in psychosis patients, for fear that it may worsen the psychosis. Mark van der Gaag (Vrije Universiteit Amsterdam) will report the findings from a group of 155 patients with psychosis and post-traumatic stress disorder (PTSD) who were randomised to Eye Movement Desensitisation and Reprocessing (EMDR); Prolonged Exposure (PE), or TAU. Both therapies were effective with large effect sizes (EMDR: 0.76; PE: 0.83) on PTSD scale scores, with 66% of the treated patients no longer fulfilling criteria for PTSD, and fewer adverse events than the TAU group. This trial demonstrates that reducing trauma symptoms in psychosis through exposure is a safe and effective psychological intervention. To date, CBTp has mostly been implemented as an adjunct to medication. Tony Morrison (University of Manchester), however, showed in a pilot trial that CBTp could be effective in individuals who have chosen to not take medication (Morrison et al, 12). These results have been replicated in a larger RCT, which recruited 74 unmedicated patients who were followed up for a minimum of 9 and a maximum of 18 months. Psychiatric symptoms were significantly reduced in the CBTp group, compared to TAU, with an estimated between-group effect size of -6.52 (95% CI -10.79 to -2.25, p=0.003). The results have important implications for the provision of mental health services for people with schizophrenia spectrum disorders.

THE MRC COMMAND TRIAL: RESULTS OF A MULTI-CENTRE, RANDOMISED CONTROLLED TRIAL OF COGNITIVE THERAPY TO PREVENT HARMFUL COMPLIANCE WITH COMMAND HALLUCINATIONS

Max Birchwood¹, Maria Michail², Alan Meaden³, Shon Lewis⁴, Linda Davies⁵, Graham Dunn⁵, Til Wykes⁶, Nick Tarrier⁶, Emmanuelle Peters⁶

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Background: Acting on command hallucinations in psychosis can have serious consequences for self and others and is a major source of clinical and public concern. There are no evidence-based treatment options to reduce this risk behaviour. Our new treatment uses cognitive therapy to challenge the perceived power of voices to inflict harm on the voice hearer if commands are not followed, thereby motivating compliance.

Methods: COMMAND is a pragmatic, single blind, intention-to-treat, randomized controlled trial comparing Cognitive Therapy for Command Hallucinations (CTCH) + Treatment as Usual (TAU) with TAU alone. Eligible participants were from UK mental health services reporting command hallucinations for at least 6 months leading to major episodes of harm to self or others. The primary outcome was harmful compliance and secondary outcomes: beliefs about voices' power and related distress; psychotic and depression symptoms. Outcome was assessed at 9 and 18 months. The trial was registered under controlled-trials.com (ISRCTN62304114).

Findings: 197 participants were randomly assigned (98 to CTCH+TAU and 99 to TAU), representing 81.4% of eligible individuals. At 18 months, 46% of the TAU participants fully complied compared to 28% of those receiving CTCH+TAU (odds ratio = 0.45, 95% confidence interval 0.23 to 0.88, p=0.021). The estimate of the treatment effect common to both follow-up points was 0.57 (95% confidence interval 0.33 to 0.98, p=0.042). The total estimated treatment effect for voice power common to both time points was -1.819 (95% confidence interval, -3.457 to -0.181, p=0.03). Treatment effects for secondary outcomes were not significant.

Interpretation: The trial demonstrated a large and significant reduction in harmful compliance, in parallel with the singular target of treatment, the perceived power of the voice. We believe this marks a significant breakthrough in this high risk group which consumes much clinical and public concern. Funding: Medical Research Council UK and the National Institute for Health Research.

COMPUTER ASSISTED THERAPY FOR AUDITORY HALLUCINATIONS: THE AVATAR CLINICAL TRIAL

Tom Craig¹, Philippa Garety², Thomas Ward², Mar Rus-Calafell³, Geoffrey Williams⁴, Mark Huckvale⁴, Julian Leff⁵

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Background: About 25% of people with schizophrenia continue to suffer with persecutory auditory hallucinations (AH) despite adequate treatment. Existing psychological therapies such as cognitive behaviour therapy are lengthy and costly. An adaptation of "voices dialogue" therapy in which patients are encouraged to enter into a dialogue with their voices appears to be helpful (Romme et al 2009) and informed the development of AVATAR therapy.

Methods: Patients create a representation of the entity they imagine as the source of their AH using computerised face animation software. Using a further programme, they then select and modify a speech sample (actually the voice of the therapist) tweaking this until they are satisfied that it matches the quality of the AH that they experience. Therapy proceeds with patient and therapist at linked computers in separate rooms. The therapist is able to speak either as the avatar (which the patient perceives as appropriately lip and facially synced), or in his/her own voice when giving advice and coping instructions. Therapy is provided over 7 weekly sessions

each of which lasts half an hour. The character of the "avatar" becomes gradually more supportive and less threatening as therapy proceeds. Each session is recorded and given to the patient on a portable MP3 player with instructions to listen to the recording between sessions to reinforce progress. The system was evaluated in a pilot study comparing AVATAR therapy with treatment as usual (Leff et al 2013). We are now moving on to a larger randomised controlled trial comparing 7 sessions of AVATAR therapy with a supportive counselling control condition for 142 patients with treatment-resistant auditory hallucinations.

Results: In the pilot study that included 26 patients, 14 were randomised to AVATAR. Compared to the 12 who received TAU, patients who received AVATAR therapy reported statistically and clinically significant reductions in total PSYRATS score (average reduction of -8.75 points, p<0.002) and total BAVQ-R (average reduction -5.9 points, p<0.004). Three patients stopped hearing voices entirely. The 12 patients who were in the control arm were subsequently offered AVATAR therapy and 8 accepted the offer. A secondary analysis looking at within-group change across all patients who received AVATAR therapy confirmed the results of the first analysis. The larger replication RCT is just underway. We will present some basic descriptive data, illustrative cases and demonstrate the revised AVATAR system which is more sophisticated in the graphics and voice synchronisation.

Discussion: Results of the first pilot study were striking but the sample was small, proved difficult to recruit and had a substantial drop-out. It was delivered by a single highly experienced therapist. The new study will be delivered by several therapists and will attempt to provide a control for therapist time and attention. Outcome data will be collected by independent research team so that we can test for the adequacy of masking of the assessments.

References:

- [1] Romme et al. 2009. Living with voices: 50 stories of recovery. PCCS Books.
- [2] Leff et al. 2013. Computer assisted therapy for medication-resistant auditory hallucinations: proof of concept study. British J Psychiatry 202, 428–33.

THE RESULTS OF EYE MOVEMENT DESENSITISATION AND REPROCESSING AND PROLONGED EXPOSURE IN PATIENTS WITH POSTTRAUMATIC STRESS DISORDER AND CHRONIC PSYCHOTIC DISORDER

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⁷Behavioural Science Institute, NijCare, Radboud University, Nijmegen & MHO 'Pro Persona', Centre for Anxiety Disorders Overwaal, Lent, The Netherlands

Background: Many patients with schizophrenia also suffer from post-traumatic stress disorder (PTSD). This condition is underdiagnosed and undertreated. Hardly any evidence is available on the efficacy and safety of trauma treatment in psychotic patients.

Methods: 155 patients with a chronic psychotic disorder and PTSD were randomised into three arms: Eye Movement Desensitisation and Reprocessing (EMDR; Shapiro protocol); Prolonged Exposure (PE; Foa protocol); or treatment as usual (TAU). Randomisation was performed stratified by research site by an independent randomisation agency. Both treatment conditions consisted of maximum eight 90-minute sessions. Therapists were trained in both interventions and supervised during the trial and treated patients in both treatment conditions. All sessions were recorded on video and treatment fidelity was checked. Assessments were performed by blind research assistants.

Results: Both treatments were effective and hard large effect-sizes (EMDR: d=0.76 and PE d=0.83) on total Clinician-Administered PTSD Scale scores (CAPS) at the end of treatment. Also 66% of the treated patients no longer fulfilled the criteria for a PTSD diagnosis (DSM-IV) at the end of treatment. The Number Needed to Treat for EMDR was 2.4 and for PE the NNT was 3.4. Most adverse events took place in the TAU condition.

Discussion: Both PTSD and PE are effective in reducing trauma symptoms on the CAPS and bring patients into remission of no longer fulfilling the

criteria of PTSD. The treatments are safe to perform. Follow-up data will be presented also.

COGNITIVE THERAPY FOR PEOPLE WITH SCHIZOPHRENIA SPECTRUM DISORDERS NOT TAKING ANTIPSYCHOTIC MEDICATION: A RANDOMISED CONTROLLED TRIAL

Anthony P. Morrison^{1,2}, Douglas Turkington³, Melissa Pyle², Helen Spencer⁴, Alison Brabban⁵, Graham Dunn⁶, Tom Christodoulides⁴, Rob Dudley⁴, Nicola Chapman², Paul Hutton²

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Our trial aimed to determine whether cognitive therapy (CT) is effective in reducing psychiatric symptoms experienced by people with schizophrenia spectrum disorders that have chosen not to take antipsychotic medication. We conducted a two-site single-blind randomised controlled trial comparing CT plus treatment as usual (TAU) with TAU only. Participants were followed-up for a minimum of 9 and a maximum of 18 months. 74 participants with schizophrenia spectrum disorders who had chosen not to take antipsychotic medication psychosis (aged 16–65 years; mean 31.47; SD 12.27) were recruited. 37 were assigned to CT and 37 to TAU. Our primary outcome was the Positive and Negative Syndrome Scale (PANSS) total score, which provides a continuous measure of psychiatric symptoms associated with schizophrenia spectrum disorders on the basis of a commonly used structured psychiatric interview. Changes in outcomes were analysed following the intention-to-treat principle, using random effects regression (a repeated-measures ANCOVA) adjusted for site, age, gender and baseline symptoms. Psychiatric symptoms were significantly reduced in the group assigned to CT, in comparison with TAU, with an estimated between-group effect size of -6.52 (95% CI -10.79 to -2.25, p=0.003). CT significantly reduced psychiatric symptoms and appears safe and acceptable in people with schizophrenia spectrum disorders who have chosen not to take antipsychotic medication. The results have important implications for the provision of mental health services for people with schizophrenia spectrum disorders.

Workshop

TWENTY YEARS OF RESEARCH ON THE 22Q11.2 DELETION SYNDROME AND SCHIZOPHRENIA: WHAT HAVE WE LEARNED SO FAR?

Chairperson: Jacob A.S. Vorstman

Discussant: René Kahn

Tuesday, 8 April 2014

6:30 PM – 8:30 PM

Overall Abstract: The 22q11.2 deletion syndrome (22q11DS) is caused by a well-described genetic lesion. Approximately 25% of patients with 22q11DS develop schizophrenia, making it the strongest known single genetic risk factor for schizophrenia. Since the first report of increased prevalence of schizophrenia in 22q11DS individuals in 1994, there has been an increasing research effort across the globe, aiming to elucidate the mechanisms behind this association. The progress over the past 20 years goes well beyond enhancing our understanding of schizophrenia in patients with 22q11DS. The 22q11.2 deletion should also be considered as a truly unique model to study schizophrenia. In the words of Thomas Insel, Director of the National Institute of Mental Health: "Important insights into the trajectory from risk to disorder [schizophrenia] may be gained from ongoing longitudinal studies of these children, comparing cognitive, affective and neural development in those who do and do not develop psychosis ..." (Insel, Nature, 2010). What is it that makes the 22q11DS-model so special for schizophrenia research? In essence, its strength lies in the fact that it tackles two major obstacles in the field. First, it can overcome some of the difficulties inherent in studying the very early (pre-psychosis) manifestations of schizophrenia. In the general population, extremely large samples are required to provide sufficient power for the prospective study of the earliest developmental stages of the disease. In contrast, a relatively small cohort of young indi-

viduals with 22q11DS can be sufficiently powered, given that about 1 in 4 subjects will develop schizophrenia. Second, it is now widely acknowledged that schizophrenia is highly heterogeneous with respect to genetic etiology. Although patients may present with a similar constellation of symptoms, each individual may have a different set of genetic variants involved in causation. This genetic heterogeneity presents a challenge for the identification of disease-relevant biomarkers. In contrast, the common genetic etiology of 22q11DS patients provides an opportunity for translational studies, including those using animal models. In the present symposium, we will review, from 5 different angles, the most important findings from the past 20 years of schizophrenia research using the 22q11.2 deletion as a model. Our objective is to provide participants with a comprehensive state-of-the-art update on our current understanding of developmental risk factors for psychosis in patients with 22q11DS as well as the implications for the broader understanding of the pathophysiology of schizophrenia. The following aspects will be included in our presentations: 1) genetic mechanisms of schizophrenia in 22q11DS, 2) neurocognitive development in 22q11DS and 3) structural and functional brain characteristics predictive of psychotic symptom expression in 22q11DS; 4) neuropsychiatric symptoms preceding the first psychosis in 22q11DS, and 5) biological insights derived from 22q11DS mouse models.

THE 22Q11.2 DELETION SYNDROME AS A MODEL FOR DEMENTIA PRAECOX

Jacob A.S. Vorstman¹, Elemi Breetvelt, Saska Duijff, René Kahn

¹Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, The Netherlands

Kraepelin proposed the term "Dementia Praecox" – i.e. early dementia – emphasizing the cognitive deterioration in addition – and prior – to the onset of psychotic symptoms in schizophrenia. Since then, several studies have replicated Kraepelin's initial observation this cognitive deterioration. Of particular relevance are the findings indicating that a loss of cognitive skills often precedes the first psychotic episode by several years. Consequently, psychosis is likely a manifestation of an advanced stage of schizophrenia, even though the first psychotic episode most often marks the beginning of medical attention and treatment. Studying the schizophrenia's earliest manifestations is highly relevant. This may be likened to the fact that it was only after it had been established that myocardial infarction was not the starting point of cardiovascular disease, that the importance of its early manifestations such as hypertension and cholesterol abnormalities was understood. This turned out to be a crucial shift in thinking, allowing for entirely novel strategies to reduce the risk of myocardial infarction. Similarly, to further our insight into schizophrenia, research efforts should not only be directed on its advanced stage (i.e. psychosis) but also on its earliest manifestation; changes in cognitive and behavioral function occurring early in childhood and preceding the first psychosis. Examining the early trajectory is extremely challenging because it requires very large prospective longitudinal cohorts given the % rate of the schizophrenia. Against this background, the 22q11.2 deletion syndrome (22q11DS) can be considered as a highly appealing model to study schizophrenia, including its early manifestations. Approximately 25% of 22q11DS individuals develop schizophrenia, making it the strongest single genetic risk factor known for schizophrenia. Importantly, the core phenotype of schizophrenia in 22q11DS patients is similar to schizophrenia in patients without 22q11DS. Therefore, it is not surprising that several research groups have endeavored longitudinal studies where children with 22q11DS are followed into adulthood. The goal of this presentation is to provide an update on the results of these studies. Results from four important clinical studies (ongoing and recently completed) focusing on the early cognitive or behavioral characteristics of 22q11DS will be presented. In the first study childhood social functioning was retrospectively assessed in 22q11DS adults and compared between those with and without schizophrenia. In a second (ongoing) prospective study the predictive strength of social dysfunction with regard to the later emergence of psychotic symptoms in 22q11DS patients is examined. Finally, we will present findings from a longitudinal IQ study in a cohort of children with 22q11DS as well as from a recently initiated large international 22q11DS research consortium including prospectively collected serial IQ measurements in 22q11DS youth. The results from this analysis, -by far the largest cohort reported thus far -, demonstrate a clear

loss of cognitive abilities in those (later) diagnosed with a psychotic disorder, starting at an early age. Taken together these findings indicate that a clinically relevant deterioration in certain domains of cognitive/psychiatric function precedes the onset of psychosis in 22q11DS patients. This is consistent with Kraepelin's dementia praecox concept of schizophrenia. These observations not only have direct relevance to our understanding of the neuropsychiatric phenotype of the 22q11.2 deletion but also underline the value of using 22q11DS as a model to study the early trajectory of schizophrenia.

22Q11.2 DELETION SYNDROME AS A GENETIC MODEL FOR SCHIZOPHRENIA

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There is now 20 years of research available on the most common of all microdeletions in humans, the 22q11.2 deletion, and its association with schizophrenia. The evidence is overwhelming that this copy number variation on the long arm of chromosome 22 is a major cause of schizophrenia in the general population. The 22q11.2 deletion syndrome represents the first of several molecular genetic subtypes of schizophrenia involving rare, recurrent copy number variants. Individually rare, collectively these account for a significant minority of patients with schizophrenia. The 22q11.2 deletion syndrome associated with the hemizygous (on one chromosome only) 22q11.2 deletion is, like all genetic conditions, variable in its expression from person to person. The alleles on the intact chromosome 22q11.2 region and variants in the rest of the genome may hold the key as to why it is that about one in four individuals with the 22q11.2 deletion develop a psychotic illness and three in four do not. In Toronto, our large cohort of adults with 22q11.2 deletion syndrome has allowed us to compare those with schizophrenia and those with no history of psychotic illness. In a study of copy number variants, we have found no evidence that additional structural variants at the resolution of microarrays contribute to risk for schizophrenia. Like others, we have shown that the functional variant of the COMT gene on the intact chromosome 22 does not act as a contributing risk factor for schizophrenia in 22q11.2 deletion syndrome. Other genes in the region, such as PIK4CA and DGCR8, show more evidence for an effect. The latter gene encodes a key microRNA processing protein and we have intriguing initial data implicating a possible role of microRNAs and their target genes throughout the genome modulating risk for schizophrenia. Importantly, we also have evidence that the variable neuropsychiatric expression of the 22q11.2 deletion represents true pleiotropy, in other words, that one psychiatric disease is not merely developing into another later in life. As a naturally occurring genetic model for schizophrenia, 22q11.2 deletion syndrome is common enough in the general population to represent a substantial pool of at risk individuals. Retrospective, cross-sectional and prospective studies of individuals with 22q11.2 deletions demonstrate that the characteristics of schizophrenia most familiar to clinicians and researchers are similar to those of schizophrenia in the general population. The extraordinary advantage of 22q11.2 deletion syndrome is that it offers the ability to study a more genetically homogeneous group of individuals from the risk conveyed by a major genetic variant to expression as a disorder. This may assist greatly in coming to an improved understanding of the complex genetics of schizophrenia and its neurodevelopmental pathogenesis.

NEUROCOGNITIVE FUNCTIONING IN 22Q11.2 DELETION SYNDROME

Raquel E. Gur¹, Beverly S. Emanuel, James J. Yi, Donna

M. McDonald-McGinn, Sunny X. Tang, Elaine H.J. Zackai, Daneen Whinna, Margaret C. Souders, Monica E. Calkins, Christian G. Kohler², Adam Savitt, Ruben C. Gur³

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The 22q11.2 deletion syndrome (22q11DS) is characterized by heterogeneous medical and neuropsychiatric presentations. Neuropsychiatric features consist of developmental delay with mild and borderline intellectual disability and at least one psychiatric disorder diagnosed in most indi-

viduals. Neuropsychological measures, applied in the study of brain and behavior, utilize healthy comparators to gauge performance deficits. Reduced intellectual abilities, nonverbal more than verbal, was reported in youths with 22q11DS. The neuropsychological profile indicates impaired executive functions such as attention and working memory, as well as verbal and nonverbal episodic memory, visuospatial processing and visuomotor functioning. Given the complexity of 22q11DS, the choice of an appropriate comparison group is important when examining neurocognitive functioning. Few studies have compared performance of 22q11DS youths to other neurodevelopmental disorders, including individuals with psychosis spectrum (PS) features. The implementation of a comprehensive examination of brain and behavior in 22q11DS as a window to understanding schizophrenia vulnerability, requires a systematic approach in large well-characterized samples. Such an effort can dissect potential contributors to impaired neurocognitive functioning, a hallmark of non-deleted patients with PS features and 22q11DS individuals with and without PS. The strategy will be illustrated with data from a computerized neurocognitive battery (CNB) that measures accuracy and speed of performance in several neurobehavioral domains implicated in PS and in 22q11DS. The neurobehavioral domains include: Executive (Abstraction & Mental Flexibility, Attention, Working Memory), Episodic Memory (Words, Faces, Shapes), Complex Cognition (Verbal Reasoning, Non-Verbal Reasoning, Spatial Processing), Social Cognition (Emotion Identification, Emotion Intensity Differentiation, Age Differentiation), and Sensorimotor Speed (Motor, Sensorimotor). The presentation will examine the neurocognitive profile in 22q11DS, with and without PS, relative to non-deleted youths with PS, developmental delay and medical comorbidities, and typically developing participants. We found that 22q11DS is associated with impaired performance in accuracy across neurocognitive domains, compared to all other groups. As in PS, face memory and emotion identification are differentially impaired in 22q11DS, both for accuracy and speed. Patients with 22q11DS also demonstrate delayed neurocognitive age compared to the other groups. Similar to individuals with PS, complex cognition and social cognition show the greatest developmental delay. These findings buttress neuroimaging studies on emotion processing circuitry that is impacted in schizophrenia. Therefore, avenues for intervention that benefit people with PS could also be of potential benefit to youth with 22q11DS.

STRUCTURAL AND FUNCTIONAL NEURAL CONNECTIVITY AS A PREDICTOR OF PSYCHOTIC SYMPTOM EXPRESSION IN 22Q11.2 DELETION SYNDROME

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OBJECTIVE: 22q11.2 Deletion Syndrome (22q11DS) is a genetic mutation associated with disorders of cortical connectivity and social dysfunction. However, little is known about the functional connectivity (FC) of the resting brain in 22q11DS, nor its relationship with social behavior and psychotic symptom development. Additionally, structural alterations in white matter fiber tracts that underlie functional changes have not been investigated.

METHOD: A seed-based-analysis of resting-state functional MRI data was used to investigate FC within the default mode network (DMN) in 31 youth with 22qDS and 56 demographically-matched controls. Subsequently, the relationship between DMN connectivity, Social Responsiveness Scale (SRS) scores and positive psychotic-like symptoms was examined in 22q11DS participants. Using diffusion tensor imaging, we investigated the relationship between white matter integrity, indexed via fractional anisotropy (FA) values, in key long-range fiber tracts. **RESULTS:** Relative to 22q11DS participants, controls showed significantly stronger FC between the posterior cingulate cortex (PCC) and other DMN nodes, including the precuneus and left frontal pole. 22q11DS patients did not show age-associated connectivity changes observed in typically-developing controls. Increased connectivity between PCC and medial prefrontal regions was associated with better social competence and less severe positive symptoms in 22q11DS. 22q11DS patients showed concomitant alterations in white matter microstructure, as indicated by reduced FA in tracts connecting frontal and limbic regions (uncinate fasciculus), as well as occipito-temporal tracts (inferior longitudinal fasciculus). Reduced FA in the uncinate was associated with increased positive symptom severity in 22q11DS participants. **CONCLUSIONS:** DMN

integrity may play a key role in social information-processing. We observed disrupted DMN connectivity in 22q11DS consistent with patterns observed in idiopathic schizophrenia, as well as autism spectrum disorder. Increased strength of long-range DMN connectivity was associated with better social functioning and decreased symptom severity in 22q11DS. Alterations in structural connectivity in long-range white matter fiber tracts appeared to underlie these functional alterations. Together, these findings support a "developmental-disconnection" hypothesis of symptom development in this disorder.

INSIGHTS INTO SCHIZOPHRENIA FROM 22Q11DS MOUSE MODELS

Laurie R. Earls¹, Stanislav Zakharenko²

¹Department of Developmental Neurobiology; ²St Jude Children's Research Hospital

Due to the poor association between individual gene mutations and schizophrenia in humans, modeling this disease in mice has been difficult. The lack of mouse models for schizophrenia has limited its study in several ways. For example, studies of brain function that are highly invasive can be performed in mice, but not in humans. Also, human genetics and environment are highly variable, introducing myriad confounding factors into human studies. Finally, compliance with antipsychotic treatment in human patients is often inconsistent, generating yet another source of variability in the study of patient populations. By comparison, mouse models have low genetic and environmental variability, and pharmacologic intervention can be controlled by the researcher. Furthermore, mouse models allow studies of brain circuit function that are too invasive to be performed in patients. High conservation of the 22q11 region on mouse chromosome 16 has allowed for the development of mouse models for 22q11DS over the last 2 decades. Because of the high association between 22q11DS and schizophrenia in humans, 22q11DS mouse models are increasingly becoming the preferred genetic model for studying schizophrenia. However, the psychiatry of 22q11DS is complex, assigning us the difficult task of separating mouse phenotypes that are schizophrenia related from those that are symptomatic of the deletion but unrelated to schizophrenia. One way to do this is to focus study on later ages, as schizophrenia onset occurs late in human development, whereas 22q11DS symptoms are often present early in life. Additionally, follow-up on mouse model findings in patient populations may assist in distinguishing schizophrenia-related phenotypes identified in the mouse. While caution should be exercised in treating 22q11 models as synonymous with schizophrenia models, some novel findings suggest that study of models of 22q11DS may indeed provide new insights into schizophrenia etiology. In the last few years, a novel pathway of age-dependent hippocampal dysfunction has been described in mouse models of 22q11DS. Dgcr8 is a microRNA biosynthesis gene contained in the 22q11 deletion region. In mice, depletion of the Dgcr8 gene results in a reduction in miRNAs, some of which are affected in an age-specific manner. In mature adults (~16 weeks), but not in adolescent mice (~8 weeks), loss of 2 miRNAs, miR-25 and miR-185, results in aberrant up-regulation of the Sarco/endo plasmic reticular ATPase, Serca2. This increase occurs at the protein, but not transcript level. Serca2 is a Ca²⁺ pump that maintains ER Ca²⁺ stores. Its elevation results in increased Ca²⁺ release from ER stores during synaptic plasticity induction and synaptic plasticity abnormalities in the hippocampus of 22q11DS mouse models. We have further shown SERCA2 protein to be elevated in postmortem brain tissue samples from patients with schizophrenia. We hypothesize that the age-dependent elevation of SERCA2 may be a mechanism for cognitive dysfunction in schizophrenia patients in general, and that miRNA loss predisposes 22q11 Deletion patients to these cognitive deficits through SERCA2 misregulation.

Plenary Session

THE CLINICAL CHALLENGES OF COMORBIDITY WITH ADDICTION AND SOMATIC DISEASE

Chairpersons: Nick Stefanis and Mary Cannon (Substance Abuse), Robin Murray and John McGrath (Physical Disease)

Wednesday, 9 April 2014

8:30 AM – 12:00 PM

Overall Abstract: In this Plenary Session, four international experts on the field will present evidence from neuroimaging, neuropharmacology and population epidemiology perspectives highlighting how substance abuse/dependence may moderate the expression of psychosis. While neuroimaging studies have indicated that the major locus of dopaminergic dysfunction in schizophrenia is presynaptic, characterized by elevated dopamine synthesis and release capacity, Prof. Abi-Dargham (Columbia University, USA) and Prof. R. Murray (Institute of Psychiatry, UK) will tackle the apparent inconsistency that arises from recent studies showing that dopamine release in patients with schizophrenia and comorbid substance use is considerably blunted, comparable in magnitude to substance users, suggesting that oversensitivity of the D2 receptor or abnormality of the post-D2 signaling pathway may also be involved in substance use psychosis. Prof. Callaghan (University of Northern British Columbia, Canada) will present evidence from a large population-based cohort study in California that patients with methamphetamine-related conditions and cannabis use have a significantly higher risk of schizophrenia than matched control population or indeed than other substance use disorders. Finally Prof. van Os (Maastricht University, The Netherlands) will present evidence from a large family based cohort including patients, their siblings and parents, that familiar correlation of psychosis varies considerably as a function of selective environmental exposures such as cannabis (but interestingly not childhood trauma) indicating the importance of selective gene-environment interactions in psychosis susceptibility.

Symposium

CLINICAL STAGING IN SEVERE MENTAL DISORDERS: TOWARDS STAGE SPECIFIC TREATMENTS IN PSYCHOSIS

Chairpersons: Marta Rapado-Castro and Seetal Dodd

Discussant: Patrick McGorry

Wednesday, 9 April 2014

1:30 PM – 3:30 PM

Overall Abstract: Many mental disorders follow a progressive course from early stages with vague symptoms to a chronic deteriorative state, suggesting a deleterious neuropathologic progression of damage to key brain circuits. These appear mediated by oxidative stress regulation, inflammation, decreased neurotropic growth factors, apoptosis, mitochondrial dysfunction and impaired neuroplasticity. Supporting clinical observations, neuroimaging studies have shown the existence of brain abnormalities which are apparent from the onset and progressively change over the course of the illness, including during the progression from the ultra high-risk to the first episode phase. This symposium aims to provide a comprehensive overview of those mechanisms and present evidence of staging in major psychiatric disorders, particularly in psychosis. Evidence of stage specific treatments will be presented and potential neuroprotective agents will be discussed within the clinical staging framework allied to the early intervention paradigm.

BRAIN IMAGING MARKERS OF PSYCHOSIS RELAPSE. IS THERE EVIDENCE FOR A PSYCHOSIS RELAPSE SIGNATURE?

Christos Pantelis

University of Melbourne, South Carlton, Australia

Schizophrenia is a debilitating illness that is often associated with progressive clinical deterioration following repeated episodes of illness. Despite the clinical evidence for clinical attrition, the nature of any associated neurobiological pathology has not been examined systematically. I will review the neurobiological imaging markers associated with psychosis onset and

relapse and consider whether these may be potential state markers of acute psychosis. I will consider a number of markers of neurobiological changes associated with acute psychosis. These include dynamic changes in brain structure in the frontal and temporal regions, neurochemical alterations in dopamine and glutamate and evidence for neuroinflammation through microglial activation. We propose that with the use of repeat longitudinal assessments of brain imaging markers over the course of a psychosis relapse, the neurobiological trajectory indicative of a "relapse signature" for psychosis will be identified (Copley et al, *Int Clin Psychopharmacol*, 2013, doi: 10.1097/YIC.0b013e32835ab37c).

FATTY ACID MARKERS OF PSYCHOSIS PROGRESSION AND TREATMENT RESPONSE

Paul Amminger

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Long-chain omega-3 polyunsaturated fatty acids (PUFAs) may play a role in the pathogenesis of psychotic and major affective disorders. Alterations in fatty acids include a decrease in omega-3 PUFAs and increased omega-6/omega-3 PUFA ratios in plasma, erythrocytes, adipose tissue and post mortem brain tissue. The patterns of these fatty acid alterations are not specific to psychotic or major mood disorders, but are also found in other conditions accompanied by increased oxidative stress such as Alzheimer's disease, and during normal ageing. We have now first evidence that these alterations can be observed early in the course of a psychiatric condition. I will show that cell membrane fatty acids in individuals at ultra high-risk (UHR) for psychosis (Stage 1b) differ from healthy comparisons; show that cognitive impairment in UHR individuals correlates with cell membrane fatty acids; show that membrane fatty acids predict both transition to psychotic disorder but also response to treatment; and address if a brief period of supplementation with omega-3 PUFAs can prevent transition to psychotic disorder over the longer-term. In summary, our findings imply that membrane fatty acid abnormalities are present before the manifestation of schizophrenia, and may serve as markers to guide early interventions. As omega-3 PUFAs are potent anti-inflammatory agents, our findings also suggests that neuroinflammation could be a stage-specific phenomenon in UHR individuals that may precede the dopamine over-activity associated with a first psychotic episode.

STAGING AND NEUROPROTECTION

Seetal Dodd^{1,2}

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Staging models have been proposed in schizophrenia and bipolar disorder, and discussed for unipolar depression, panic disorder, substance use disorders, anorexia and bulimia nervosa. Illness staging offers a way of conceptualizing mental disorder where prevention of illness onset and neuroprogression is as important for consideration as symptom control and relapse prevention. The staging model in mental health follows similar models in physical health, commencing with stage 0, an asymptomatic stage where risk factors are present, stage 1, prodrome where symptoms are less severe than required for diagnostic thresholds, stage 2, a first episode of illness, stage 3, recurrence and stage 4, treatment resistance. Consequent from the staging model are the concepts of stage specific treatments and neuroprotection. There is evidence that some standard treatments for BD may impede the neuroprogression of the illness and some novel treatments may have neuroprotective properties. Molecular mechanisms implicated in neuroprogression include the dysregulation of neurotrophins, neurogenesis and apoptosis, neurotransmitters, inflammatory, oxidative and nitrosative stress, mitochondrial dysfunction, cortisol and the hypothalamic-pituitary-adrenal axis, and epigenetic influences. The staging model will be presented for various psychiatric disorders, and discrepancies for supporting evidence between various disorders will be demonstrated. Strong evidence is available for schizophrenia and bipolar disorder, whereas the evidence in major depression is less clear. Putative neuroprotective agents will be discussed, focusing on their mechanisms of action, efficacy and safety. Advantages and

limitations of considering stage of illness and neuroprotective strategies in clinical practice will be discussed.

DURATION OF THE ILLNESS AND RESPONSE TO TREATMENT

Marta Rapado-Castro

Hospital General Universitario Gregorio Marañón, CIBERSAM, Madrid, Spain

Schizophrenia is a chronic and often debilitating disorder in which stage of illness appears to influence course, outcome, prognosis and treatment response. Those people with chronic schizophrenia are characterized by non-remitting symptoms and functional decline over time suggestive of neuroprogression. Current evidence suggests roles for oxidative, neuroinflammatory, neurotrophic, apoptotic, mitochondrial and glutamatergic systems in the disorder. Conventionally higher dose medications and a combination of treatments are required to diminish consequences of long duration of the illness. While current therapies have some effectiveness, there are shortfalls in recovery. The staging model provides a clinical framework on which particular interventions may counteract the progression of the illness at a particular point of time. This approach could potentially guide treatment and assist in predicting outcome by improving the timing of interventions according to specific markers of progression over time. Conventional treatments of late stage illness would be reviewed and novel therapies with a benign adverse effect profile such as N-acetyl cysteine (NAC) would be presented as well as supportive evidence for its effectiveness in late stage illness.

Symposium

DRUG REPURPOSING AND EMERGING ADJUNCTIVE TREATMENTS FOR SCHIZOPHRENIA

Chairpersons: Vicki L. Ellingrod and Joshua Roffman

Discussant: Peter Buckley

Wednesday, 9 April 2014

1:30 PM – 3:30 PM

Overall Abstract: Despite a growing armamentarium for the treatment of schizophrenia, many patients are left with residual positive, negative and cognitive symptoms. This clinical conundrum has resulted in numerous, diverse lines of research focusing on the use of adjunctive treatments. Despite the vast differences in the pharmacology of these agents, each has the potential to effectively treat residual symptoms and affect patient outcomes in a positive manner. With recent declines in the industrial pipeline of innovative schizophrenia medications, the notion of medication repurposing, defined as the practice of using old drugs in new ways, is garnering much attention from researchers worldwide. This emerging treatment tactic may prove beneficial for not only the treatment of schizophrenia, but for advancing our understanding of the pathophysiology of this complex disorder. The overall goals of this symposium are to highlight different innovative lines of research involving repurposed treatments for schizophrenia, and to discuss ongoing and future research efforts in this area. To do this, we will focus on four divergent repurposed pharmacologic interventions. First, we will focus on the role of one carbon metabolism and the use of folate and B-vitamins in the reduction of negative symptoms. We will include recent clinical trial results and new MRI data on folate-related changes in brain structure and function. Second, we will discuss the use of minocycline for the treatment of schizophrenia, including new data that relates symptom improvement to reduced inflammation and related biomarkers. Next, we will extend our discussion of the role of inflammation within schizophrenia by describing the utility of aspirin on positive symptoms in patients with high levels of serum CRP, indicating potentially greater inflammation. Lastly, this symposium will discuss the place of nitroprusside in schizophrenia treatment as results from a recent trial shows immediate and sustained improvements in positive and negative symptoms. Thus, despite the current thought that our new medication pipeline for schizophrenia is currently waning, new lines of innovative research centering on medication repurposing schizophrenia provide reasons for optimism. In addition to shedding new light onto the pathophysiology of this illness, the findings presented here suggest new treatments that can potentially be rapidly translated into practice and into improved outcomes for those with schizophrenia.

POSITIVE SYMPTOMS RESPOND TO ADD-ON ASPIRIN IN SCHIZOPHRENIA PATIENTS WITH HIGH SERA CRP LEVELS: A POST-HOC ANALYSIS OF AN RCT

Mark Weiser¹, Shimon Burstein², Liliana Fodoreanu³, Roxana Chirita⁴, Ghiorghie Talau⁵, Diana Cirjaliu⁶, Naama Fund⁷, Robert Yolken⁸, John Davis⁹, Michael Davidson¹⁰

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Introduction: This is a post hoc analysis of data from a previously performed RCT which administered add-on aspirin or placebo to patients with schizophrenia receiving anti-psychotics. We hypothesized that patients with high levels of CRP, perhaps reflecting high levels of inflammation, would have a better response to aspirin compared to patients with lower levels of CRP.

Methods: The original study was a multi-center, N=400 trial was designed with one placebo arm to be employed as a comparator for 3 active arms. Inclusion criteria were 4 (moderate) or above on CGI-S and 34 (moderate) score on two of the following four PANSS items: delusions, hallucinatory behaviors, conceptual disorganization or suspiciousness/persecution, and/or a total PANSS negative symptoms score above 18. Before entering the trial and throughout the trial all subjects received anti-psychotics at doses within PORT recommendations. Upon entering the trial they were randomized to aspirin 1000 mg/d + pantoprazole 40 mg/d, minocycline 200 mg/d, pramipexole 1.5 mg, or placebo. Duration of the study was 16 weeks. Primary outcome measure was changes in total PANSS scores, secondary outcome measures included PANSS subscales.

Results: Mean age of patients was 42, 50% were females, mean duration of illness was 13 years, mean PANSS total score at baseline was 92. The ANOVA for overall change for all comparison of 3 drugs and placebo for the primary outcome of the total PANSS scores was significant, p=0.03. Individual comparisons between each drug and placebo showed trends for significance (Effect size, ES=0.28, p=0.056) for aspirin, and were non-significant for minocycline (ES=0.14, p=0.33) and for pramipexole (ES=0.01, p=0.95). For positive symptoms the overall ANOVA was not significant, p=0.084. Individual comparisons between each drug and placebo showed a trend for significance for aspirin (ES=0.24, p=0.08), and were non-significant for minocycline (ES=0.04, p=0.77) and pramipexole (ES=0.11, p=0.45). The sample was then divided into thirds according to CRP level at baseline. Patients with high (CRP>3850 ng/ml) were significantly more likely to have improvements in their mean PANSS positive scores (ES=0.61, p=0.03), whereas patients with intermediate CRP scores 1300<CRP≤3850 ng/ml, ES=0.07, p=0.78) or low CRP scores (CRP≤1300 ng/ml, ES=-0.35, p=0.19) did not. These results were not observed on the effects of aspirin on negative symptoms, general psychopathology or total PANSS, nor were they observed in the patients receiving minocycline or pramipexole.

Discussion: The results of this post-hoc analysis might cautiously be interpreted as indicating that a subgroup of patients with relatively high levels of CRP, a non-specific marker of inflammation, have significant improvements in positive symptoms upon inhibition of COX-1 or COX-2, or other biological effects, both inflammatory and non-inflammatory of aspirin. The effect of aspirin on this small subgroup of responders might be the reason that previous studies found a small, consistently replicated over-all effect of aspirin in schizophrenia which was too small to be of clinical significance. This issue should be further tested by 1) performing similar post-hoc analyses on previous RCTs which administered aspirin or other anti-inflammatory agents in schizophrenia. Future studies might screen patients for CRP and randomize those with high CRP levels to add-on treatment with aspirin or placebo.

ADJUNCTIVE MINOCYCLINE IN CLOZAPINE TREATED SCHIZOPHRENIA PATIENTS

Deanna L. Kelly^{1,2}, Kelli M. Sullivan³, Heidi J. Wehring³, Joseph P. McEvoy⁴, Richard Keefe^{5,6}, Robert P. McMahon³, James M. Gold³, Stephanie Feldman³, Chip Warfel³, Ann Marie Kearns³, Jennifer Osing³, Jessica Russ⁴, Gopal Vyas³, Charles M. Richardson³, Sharon August³, Robert W. Buchanan³

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Background: Schizophrenia is a devastating and costly illness. 33-50% of people with schizophrenia do not respond to first line agents leaving clozapine as the best alternative for treatment. Over 60% of people treated with clozapine continue to have persistent symptoms and cognitive impairments. Preliminary data has suggested that adjunct treatment with minocycline may offer robust symptom improvement in patients with schizophrenia, including those taking clozapine. Minocycline has novel and interesting molecular effects, including AMPA receptor modulation and anti-inflammatory and neuroprotective effects, which suggest it may have a significant role in treatment of neurologic and psychiatric disorders.

Methods: We conducted a 10-week double-blind, placebo controlled study of adjunctive minocycline vs. placebo in clozapine treated patients to assess the benefit of minocycline in the treatment of persistent positive symptoms and cognitive impairments (N=50). Inclusion criteria were a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, ages 18 to 65 years, at least 6 months of clozapine treatment and a current dose of 200 mg/day for at least 3 months and a documented total clozapine level of 350 ng/ml. In addition they were required to have a total BPRS score of ≥ 45 or CGI of ≥ 4, and a positive symptom score of ≥ 8 (≥ 4 on at least one item). Participants were excluded with Lyme disease and other active infections, treatment with lamotrigine and current significant medical conditions. Upon entering the trial participants were randomized to 100 mg BID or placebo following a one week titration of 50 mg BID. The primary outcome measure was change in the Brief Psychiatric Rating Scale (BPRS) positive symptom subfactor and the composite score of the MATRICS Consensus Cognitive Battery (MCCB). We also examined negative symptoms using the SANS and changes in peripheral inflammatory markers.

Results: 52 participants were enrolled in the trial and 2 discontinued in the first weeks of treatment (one with diagnosis of cancer and one with high triglycerides). There were 46 participants from MPRC and 6 from Duke University. Thus, 50 participants will have completed the trial. The mean age of the group was 34.0±10.3 years, 60% were Caucasian and 74% were males. The mean duration of illness was 14.6±10.2 years. The study will be unblinded at the end of 2013 and full results will be presented at the symposium. This is the first study to examine the adjunctive use of minocycline in chronic patients treated with clozapine.

THE USE OF SODIUM NITROPRUSSIDE FOR THE TREATMENT OF SCHIZOPHRENIA

Jaime Hallak^{1,2}, Serdar Dursun³, Glen Baker³, Joao P. de Oliveira⁴, Joao Abrao¹, Paulo Abreu⁵, Paulo R. Evora¹, Jose Crippa¹, Antonio W. Zuardi¹

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Despite decades of study, the etiology and physiopathology of schizophrenia remain unknown. Recent evidence suggests that nitric oxide (NO) may be implicated in schizophrenia. NO is a gas that mediates the release of neurotransmitters, learning, memory, and neurodevelopment. Studies investigating the role of NO in patients with schizophrenia found evidence that points to a disruption in NO-mediated neurotransmission. Therefore, we investigated the effects of sodium nitroprusside, an NO donor, as an add-on treatment for patients with schizophrenia. Twenty adult schizophrenia

patients treated with stable doses of antipsychotics were randomly assigned to two groups that received an infusion of either sodium nitroprusside or placebo for four hours. Psychiatric symptoms were assessed at baseline and every hour during the infusion with the Brief Psychiatric Rating Scale (BPRS) and the negative subscale of the Positive and Negative Syndromes Scale (PANNS-n). Additional assessments were made 12 hours after the infusion, daily for seven days, and weekly for four weeks. Cognitive tests (Stroop Color Word Test, N-back, and FAS) were administered at baseline and 12 hours after the end of the infusion. No side effects were reported by the participants. All the clinical and demographic characteristics of the sample including age, education, duration of disease, gender, diagnostic subtype, and type of antipsychotic in use were matched across groups. Symptom ratings were significantly reduced in the group treated with sodium nitroprusside, but not in the placebo group. Cognitive performance was also significantly improved in the nitroprusside group compared to placebo. There were no significant differences between the two groups regarding the physiological parameters analyzed (systolic and diastolic blood pressure, cardiac rhythm, and oxygen saturation). The strategy of treating schizophrenia patients for four hours with 0.5 mcg/kg/min sodium nitroprusside improved psychopathology and cognitive function. Our findings support the hypothesis that the NMDA-NO-GMPc pathway is affected in schizophrenia and that nitric oxide donors such as sodium nitroprusside could thus be a promising approach in the management of the disorder. Although exciting, these results are preliminary and must be replicated by future studies.

EFFECTS OF FOLIC ACID AND VITAMIN B12 SUPPLEMENTATION ON NEGATIVE SYMPTOMS AND RELATED MRI INDICES

Joshua Roffman¹, Steven J. Lamberti², Eric Achtyes³, Eric A. Macklin⁴, Gail C. Galendez⁵, Lisa H. Raeke⁵, Alexandra S. Tanner⁵, Noah J. Silverstein⁵, New Fei Ho⁵, Jordan W. Smoller⁵, Michele Hill⁵, Donald C. Goff⁶

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Background: Among patients with schizophrenia, considerable disability is associated with negative symptoms and cognitive deficits. Converging evidence from genetic, epidemiologic, and brain imaging studies implicates abnormal folate metabolism in schizophrenia risk, and specifically in negative symptoms. We undertook a randomized, multi-center clinical trial of folic acid and vitamin B12 (a cofactor in the folate metabolic pathway) to determine whether this intervention improved negative symptoms of schizophrenia, and whether such improvement was influenced by functional genetic variants in the folate metabolic pathway. We also determined whether folate and B12 changed cortical thickness or working memory-related brain activation, which are consistently altered in schizophrenia.

Methods: A parallel-group, randomized, double-blind, placebo-controlled clinical trial of 16 weeks of treatment with 2 mg folic acid and 400 mcg B12 randomized 140 outpatients with chronic schizophrenia, recruited from three community mental health centers. Participants were genotyped for four common, functional variants in FOLH1, MTHFR, MTR, and COMT that had previously been associated with alterations in folate metabolism and negative symptom severity. A subset of 22 patients also received MRI scans (Siemens TIM Trio) just prior to and after the 16 week treatment period.

Results: Folate plus B12 improved negative symptoms significantly compared to placebo when all four genotypes were taken into account, but not when genotypes were excluded. In post hoc tests, a specific interaction of the 484T>C variant of FOLH1 (rs202676) with treatment was observed, wherein only patients homozygous for the 484T allele demonstrated significantly greater benefit with active treatment. In parallel we observed an inverse relationship between red blood cell folate concentration at baseline and 484C allele load, which persisted until 8 weeks of treatment. Change in positive and total symptoms did not differ between treatment groups. Among patients receiving MRI scans, those in the folate plus B12 group demonstrated increased cortical thickness and working memory-related activation within the frontoparietal control network following treatment. Increase in mid-cingulate cortex thickness correlated with decrease in

negative symptom scores. MRI changes were not evident in the placebo group.

Conclusions: Folate plus B12 supplementation improved negative symptoms of schizophrenia, but only when accounting for functional genetic variants in the folate metabolic pathway. The strongest genetic effect was observed for a coding variant in FOLH1, which facilitates translocation of dietary folates across the intestinal lumen. The 484T>C variant influenced both blood folate levels and negative symptom change in the present study. Folate and B12 also improved structural and functional brain imaging measures within the frontoparietal control network, which is dysfunctional in schizophrenia. These findings suggest a personalized medicine approach involving genetic and brain imaging markers that can be followed up in additional studies of folate-based interventions in schizophrenia.

Symposium

LIFESPAN EVOLUTION OF NEUROCOGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

Chairperson: Larry J. Seidman
Discussant: Abraham Reichenberg

Wednesday, 9 April 2014

1:30 PM – 3:30 PM

Overall Abstract: Neurocognitive impairment in schizophrenia compared to controls has been robustly demonstrated at all phases of the illness, including premorbid, prodromal, first episode, and chronic phases. Neurocognitive decline has been commonly accepted, but not reliably documented, in schizophrenia. This is now changing, particularly with data emerging from long-term birth cohort studies beginning in early childhood and following individuals into illness, as well as from ongoing follow-up studies of first episode schizophrenia with substantial follow up periods. The goal of this symposium is to provide a state of the art summary of current findings on longitudinal studies of neurocognition in schizophrenia. Experts from 6 separate studies around the world will present new work or discuss it (Dr. Reichenberg): Dr. Seidman (Chair) will briefly discuss neurocognitive findings from the United States Collaborative Perinatal Project following children from age 7 to 39, which demonstrates significant decline in IQ specific to schizophrenia compared to affective psychosis. However, that study cannot identify when such declines occur given the 30 year gap in testing. Dr. MacCabe will begin to fill in some of the missing information by demonstrating in the Swedish Cohort Study that relative declines take place in spatial, inductive and verbal reasoning from age 10 to 13 to 18 although the pattern was different in verbal reasoning whereby an improvement between age 10 and 13 was followed by steep decline between 13 and 18. Decline between ages 13 to 18 was the key factor predicting later psychosis. Dr. Joyce will discuss her 4 year follow-up study of first episode psychosis examined in the West London First Episode Study. She reports that cognitive impairment is generalised and present at the time of psychosis onset. However, despite progressive changes in cortical pathology following the first episode, measured by MRI measures of cortical thickness and area, cognitive impairment does not progress further. This raises the question as to whether the changes observed prior to psychosis continue after the first episode. Dr. Rund, using data from the Scandinavian TIPS first episode study consistent with Dr. Joyce's findings, demonstrates relative stability of neurocognitive functioning over 10 years for most measures, other than verbal learning, which demonstrates decline. He also demonstrates that decline in some aspects of IQ in schizophrenia is associated with relapse during the first year of illness. This raises the important question of clinical moderators of stability or decline, and begins to address issues of heterogeneity. Dr. Murray presents data from the Northern Finland 1966 Birth Cohort Study on testing at ages 34 and 43 indicating that the schizophrenia group showed greater deterioration in abstraction with memory than controls, but there were no differences between schizophrenia and controls in rate of change of other cognitive measures. Interestingly, results showed that age of learning to stand in infancy predicted later deterioration of abstraction with memory in adult schizophrenia. These data suggest that deterioration may occur later than previously documented, but may also be linked to neurodevelopmental features. Dr. Reichenberg, will discuss these studies, comparing and contrasting them. Comparisons between the longitudinal course of neurocognition in schizophrenia and affective psychoses, and their implications to etiological models and nosology will be highlighted.

COGNITIVE TRAJECTORY BETWEEN AGES 10, 13 AND 18 AND RISK FOR PSYCHOSIS IN ADULTHOOD: A SWEDISH LONGITUDINAL COHORT STUDY

James H. MacCabe¹, Mizanur Khondoker², Susanne Wicks³, Sofia Löfväng³, Anthony Sion David², Åsa Berndtsson⁴, Jan-Eric Gustafsson⁴, Peter Allebeck³, Christina Dalman³

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Background: There is now clear evidence that patients with schizophrenia suffer from a variety of cognitive deficits during childhood and adolescence. However, very little is known about the course of premorbid cognition over the premorbid period. AIMS: To assess the impact of cognitive developmental trajectory in adolescence on risk for schizophrenia in adulthood.

Method: Longitudinal cohort study using four population-based cohorts of males born in Sweden in 1953, 1967, 1972 and 1977, totaling 13,910 individuals, and followed to 31 December 2006. Scores in tests of verbal, spatial and inductive ability at age 10 and 13 and in equivalent tests at army conscription (age 18) were the exposures. Hospital admission for schizophrenia in adulthood was the outcome.

Results: Spatial and inductive reasoning showed the expected pattern approximately linear decline over time in pre-psychotic children relative to the population. However verbal reasoning showed a different pattern, whereby there was improvement between age 10 and 13 followed by steep decline between 13 and 18. Relative decline in verbal ability between age 13 and 18 was strongly associated with increased risk of schizophrenia (adjusted hazard ratio for an increase of one standard deviation in verbal ability = 0.59 (95% confidence interval = 0.40, 0.88; p=0.009)). Decline between age 13 and 18 was a stronger predictor of schizophrenia than absolute score at age 18. The association was not confounded by parental educational level, family history of psychosis or urbanicity, and was present in late-onset cases, indicating that this was not a prodromal effect.

Discussion: Spatial and inductive reasoning show a pattern of gradual decline during adolescence in pre-psychotic individuals. However verbal ability shows a modest improvement between ages 10 and 13 followed by a sharp relative decline between 13 and 18 that is strongly predictive of schizophrenia and other psychoses. This suggests an impairment of late neurodevelopment affecting the acquisition of verbal skills.

NEUROCOGNITIVE FUNCTIONING IN SCHIZOPHRENIA AT FIRST EPISODE AND OVER THE FIRST FOUR YEARS OF ILLNESS

Eileen M. Joyce¹, Thoman Barnes², Verity Leeson², Maria Ron³, Leticia Gutierrez-Galves³, Jon Roiser³

¹UCL Institute of Neurology; ²Imperial College, London; ³University College London

Background: Neurocognitive impairment is a core feature of schizophrenia which can both precede the onset of psychosis and predict the degree of later functional impairment. Understanding the course of neurocognitive impairment is important to understand how this relates to other neurobiological markers of illness and whether interventions should be targeted at specific time points. This was examined in the West London First Episode Study.

Methods: Patients were recruited if aged 16–55 years and had no more than 12 weeks antipsychotic exposure. Only patients with a diagnosis of schizophrenia or schizoaffective disorder, ascertained 1 year after psychosis onset, were included. They were assessed at presentation and at two further points over the first 4 years of illness on tests of cognitive function which included: IQ, working memory span and manipulation, learning and memory, rule learning, set shifting, planning and thinking time. To investigate the relationship between changes in neurocognitive function and cortical changes, a subset of participants underwent a structural MRI twice over the same period. Healthy controls were assessed at similar time points. In addition, to investigate the relationship between neurocognition and cortical connectivity, a subset underwent magnetoencephalography (MEG) while performing a simple task of detecting stimulus change requiring minimal decision making.

Results: In two separate cohorts, cognitive function showed no evidence of deterioration following psychosis onset. This was true for IQ and specific cognitive domains. There was improvement in several domains but, when compared to changes in the control group over time, these were attributable to practice effects. A substantial subgroup showed evidence of cognitive decline already present at the time of psychosis onset. For both cohorts, cognition at onset predicted functional outcome 3–4 years later. In a subgroup of patients, MRI measures of cortical thickness and area at psychosis onset showed reduced fronto-temporal cortical area compared to controls and the degree of area reduction was related to current and premorbid IQ. When patients and controls were examined a mean of 2 years later there was a reduction in the thickness of the frontal cortex and, to a lesser extent, the parietal cortex, but no change in area. Although there was no concomitant deterioration in cognitive function over this period, IQ and working memory at psychosis onset predicted the degree of thinning of frontal and parietal cortex in patients two years later. MEG analysis was consistent with the hypothesis that functional disconnection in the frontoparietal network may mediate the generalised cognitive impairment in schizophrenia.

Conclusion: Cognitive impairment is generalised and present at the time of psychosis onset. Despite progressive changes in cortical pathology following the first episode, cognitive impairment does not progress further. This suggests that cognitive impairment may be longstanding in some and, in others, deteriorate around the time of psychosis onset. Generalised cognitive impairment is related to structural and functional abnormalities of fronto-temporal-parietal association cortex supporting the dysconnectivity hypothesis of schizophrenia.

A 10 YEAR LONGITUDINAL FOLLOW-UP OF FIRST EPISODE PATIENTS (FEP) IN THE SCANDINAVIAN TIPS STUDY

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¹Department of Psychology, University of Oslo; ²Vestre Viken Hospital Trust;

³NORMENT Centre, Institute of Clinical Medicine and Department of Psychology, University of Oslo, Oslo, Norway; ⁴Department of Psychiatry, University of Oslo

A substantial proportion of patients suffering from schizophrenia exhibit a general cognitive and intellectual impairment at illness onset. However, the long-term course of neurocognition continues to be a topic of controversy. In the TIPS project, a prospective longitudinal study of the relationship between duration of untreated psychosis (DUP) and outcome in FEP, 301 patients were included. The patients were 15–65 years of age, and met the DSM-IV criteria for non-organic psychosis. Patients were tested neuropsychologically (NP) for the first time after remission of psychotic symptoms (1). They were reassessed 1, 2, 5 and 10 years after baseline. IQ-measures (3 WAIS-R subtests) were obtained at baseline and 10-year follow-up assessment. Eight NP tests were used. A subset of measures was selected from each test to be entered as variables in a principal component analysis. Five factors were identified, explaining 72% of the variance (2). The NP battery at baseline was completed by 207 patients, 138 at 1 year, 111 at 2 years, and 62 at 5 years (3) and, 43 subjects were assessed at 5 assessments spanning 10 years. In addition, 90 patients were investigated on IQ at baseline and 10 year follow-up. In addition to the examination of the longitudinal course of cognitive functioning, a central aim of the TIPS study has been to study neurocognition in relation to clinical characteristics such as symptoms, premorbid function, and relapses. DUP was of special interest in order to investigate the neurotoxicity hypothesis, which postulates that being psychotic has a toxic effect to the brain. In general, a relatively stable course of neurocognition was found during the 10 years follow-up period. No major changes were found in the level of neurocognitive functioning from baseline to the 1-year and 2-year follow-ups. Further, 3 of the 5 indices did not change from 2 to 5 years follow-up. However, a significant decline in verbal learning, refines the picture of average neurocognitive stability. At 10-year follow-up all of the 4 indices showed overall stability.

INFANT MOTOR DEVELOPMENT PREDICTS DECLINE IN EXECUTIVE FUNCTION IN ADULT SCHIZOPHRENIA IN THE NORTHERN FINLAND 1966 BIRTH COHORT STUDY

Graham Murray¹, Hiroyuki Kobayashi^{2,3}, Matti Isohanni⁴, Erika Jääskeläinen⁴, Jouko Miettunen⁴, Marjo Riitta Järvelin^{5,6}, Marianne Haapea⁴, Peter Jones², Jouko Miettunen⁴

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Neurodevelopmental and neurodegenerative theories are traditionally viewed as incompatible accounts that compete to explain the pathogenesis of schizophrenia. However, it is possible that neurodevelopmental and neurodegenerative processes could both reflect common underlying causal mechanisms. We hypothesized that cognitive dysfunction would gradually deteriorate over time in schizophrenia and the degree of this deterioration in adulthood would be predicted by an infant measure of neurodevelopment (age of learning to stand without support). We aimed to examine the association between age of learning to stand in infancy and deterioration of cognitive function in adulthood. Participants were non-psychotic control subjects (n=71) and participants with schizophrenia (n=34) drawn from the Northern Finland 1966 Birth Cohort study. Participants were assessed at age 34 and 43 on the following cognitive measures: verbal learning with the California Verbal Learning Test, visual learning with the Visual Object Learning Test, and abstraction and abstraction with memory from the Abstraction, Inhibition and Working Memory Test. The schizophrenia group showed greater deterioration in abstraction with memory than controls, but there were no differences between schizophrenia and controls in rate of change of other cognitive measures. Age of learning to stand in infancy significantly inversely predicted later deterioration of abstraction with memory in adult schizophrenia (later infant development linked to greater subsequent cognitive deterioration during adulthood), possibly suggesting a link between abnormal neurodevelopmental and neurodegenerative processes in schizophrenia.

**Symposium
OXYTOCIN, SOCIAL COGNITION, AND SCHIZOPHRENIA**

Chairperson: Robert W. Buchanan

Discussant: Shitij Kapur

Wednesday, 9 April 2014

1:30 PM – 3:30 PM

Overall Abstract: People with schizophrenia are characterized by marked impairments in social function. These impairments may reflect disturbances in basic social cognitive processes, including emotion recognition and perception (i.e., the ability to infer emotional information from facial and other non-verbal and verbal expressions); social perception (i.e., the ability perceive social cues from the context of the observed behavior); theory of mind (i.e., the ability to make inferences about the intentions and beliefs of others, and attributional style (i.e., how a person tends to explain the causes of events in their lives). The development of therapeutic approaches to enhance social cognition is a major area of treatment development. In this regard, a potentially promising approach is the use of oxytocin to improve social cognitive processes, which would be hypothesized to lead to improved social function. Oxytocin has been shown in animals to play a critical role in the regulation of social and emotional behaviors, including social affiliation, pair bonding, maternal behavior, and social memory. In normal healthy controls, studies have demonstrated that intranasal oxytocin: 1) increases the amount of time spent gazing at the eye region; 2) improves the ability to infer the internal mental state of another person through processing affective eye expressions, with this effect potentially more pronounced in those who have difficulty in identifying their own emotions; 3) enhances the ability to recognize facial expressions, with a differential effect observed for rapidly presented happy facial expressions; 4) increases the perception of attractiveness and trustworthiness in the

faces of others; 5) reduces arousal ratings to negative or threatening human visual stimuli; and 6) decreases the likelihood that positive or neutral facial emotions will be misclassified as negative emotions. In the past 5 years, there have been several challenge studies and clinical trials of oxytocin in people with schizophrenia, which suggest that oxytocin may have mixed effects on social cognition and symptoms. The proposed Symposium is designed to provide an update from preclinical to clinical studies on the relationship among oxytocin, social cognition, and schizophrenia. James Koenig, Ph.D. will present preclinical findings on the relationship between oxytocin and social function from the subchronic phencyclidine (PCP) and prenatal stress animal models of schizophrenia. Gregory Strauss, Ph.D. will present data from a cross-sectional study, which examines the relationship between oxytocin levels and various aspects of facial and emotion processing in healthy controls and people with schizophrenia; Andrea Meyer-Lindenberg, M.D. will present data on the effect of acute oxytocin and vasopressin challenge studies on neural circuits involved in emotion processing and the impact of genetic variations of vasopressin and oxytocin receptors on these effects; and Stephen Marder, M.D. will present results from a recently completed 6-week, placebo-controlled, randomized clinical trial designed to examine the effect of oxytocin administration on social cognition and function in people with schizophrenia. Shitij Kapur, M.D., Ph.D. will serve as the Discussant.

PRECLINICAL ASSESSMENT OF OXYTOCIN'S ABILITY TO MODULATE SOCIAL BEHAVIOR

James Koenig

National Institute of Neurological Diseases and Stroke, Rockville, USA

The hypothalamic peptide, oxytocin, was originally found to be an essential regulator of female reproductive behaviors, including maternal behavior and lactation. However, in the late 1980's and early 1990's publications from a number of laboratories began to reveal a role for oxytocin in non-reproductive social behaviors in male rodents. Seminal reports by Witt, Insel, Popik and vanRee, to name a few, sparked great interest in the biology of oxytocin beyond its role in reproductive functions. The importance of oxytocin in social behaviors was further confirmed through the use of genetically manipulated mouse models around 2000. Several neuropsychiatric disorders, including schizophrenia and autism, share the symptom of asociality and an argument has been made for oxytocin as a novel target for further prosocial drug development. However, current understanding of how and where oxytocin acts in the brain to elicit improved social functioning is still somewhat obscure. To that end, gaining further insights into the ability of oxytocin to modulate social behavior relevant to schizophrenia has been an important focus of research. In a series of studies, we have demonstrated that brain oxytocin levels in both the subchronic phencyclidine (PCP) and prenatal stress animal models of schizophrenia were reduced in animals showing increased social withdrawal. Moreover, our studies demonstrated that administration of the peptide could improve social liabilities present in both models. Interestingly, the ability of oxytocin to improve social functioning resulted when the peptide was administered directly into the central nucleus of the amygdala, which has been shown to receive a direct oxytocinergic neural projection from the paraventricular nucleus of the hypothalamus (PVN), the home of the brain's oxytocin cell bodies. Furthermore, we showed that gestational environmental insults, such as stress, compromise the expression of a key transcriptional regulator for oxytocin in the PVN of animals with social deficits. However, because oxytocin is a small peptide, it has a restricted ability to penetrate the brain after systemic administration, which potentially limits the use of this peptide as a therapeutic agent. An alternative pathway that overcomes this obstacle is to identify mechanisms to pharmacologically activate brain neurons that produce oxytocin and bolster the release of the endogenous peptide in brain centers regulating social function. Recent findings from my laboratory demonstrated the feasibility of using this approach in a neurodevelopmental animal model of schizophrenia. Together evidence from preclinical and clinical studies identified oxytocin as an important component of the neurocircuit engaged during social activity and that oxytocin-related mechanisms are impaired in psychiatric disorders having a social withdrawal component. The ability to use oxytocin as a prosocial therapeutic will require further investigation but the appropriate groundwork now appears to be in place to justify studies with this goal.

ASSOCIATIONS BETWEEN PERIPHERAL OXYTOCIN LEVELS AND IMPAIRED SOCIAL COGNITION IN SCHIZOPHRENIA

Gregory Strauss

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Background: In healthy individuals, intranasal administration of oxytocin has been found to enhance several aspects of social cognition. Given evidence for impairments in both lower-level (e.g., social cue perception) and higher-level (e.g., inferring social meaning) social cognition in schizophrenia, there has been increased interest in evaluating the efficacy of oxytocin as a treatment for social cognition deficits. However, the results of these trials have been inconsistent. To identify new potential treatment targets for clinical trials, the current study examined the association between endogenous peripheral oxytocin levels and multiple lower-level and higher-level tests of social cognition.

Methods: Participants included 46 outpatients diagnosed with schizophrenia and 24 demographically matched healthy controls. A battery of eye-tracking and behavioral tasks was administered to assess lower- and higher-level social cognition, including: facial affect recognition, facial trustworthiness and attractiveness judgments, biological motion perception, body emotion identification, social cue recognition, and higher-level social inference. Serum concentrations of oxytocin were analyzed using a radioimmunoassay.

Results: Participants with schizophrenia and controls did not significantly differ in serum oxytocin levels. However, in both groups, lower peripheral oxytocin levels were associated with poorer performance on tests of facial affect recognition, biological motion, identifying emotion in body gestures, social cue recognition, and social inference. Eye-tracking data revealed that restricted visual scanning of faces mediated the relationship between peripheral oxytocin levels and several types of evaluative social judgments (facial affect recognition, trustworthiness, attractiveness).

Conclusions: Endogenous oxytocin levels are meaningfully associated with lower-level and higher-level social cognition impairments in people with schizophrenia. These domains of social cognition may be valid targets for acute-challenge or repeated dosing intranasal oxytocin trials designed to enhance social cognition in people with schizophrenia.

IMPACT OF PROSOCIAL NEUROPEPTIDES ON HUMAN BRAIN FUNCTION AND STRUCTURE: IMPLICATIONS FOR SCHIZOPHRENIA

Andreas Meyer-Lindenberg

Central Institute of Mental Health, Mannheim, Germany

In animals, oxytocin and vasopressin are key mediators of complex emotional and social behaviors, reduce anxiety, and impact fear conditioning and extinction. We report on functional neuroimaging studies in healthy human subjects. In males receiving oxytocin or placebo, oxytocin potently reduced activation of the amygdala and reduced coupling of the amygdala to brainstem regions implicated in autonomic and behavioral manifestations of fear [1]. In males receiving arginine-vasopressin, an impact on the perigenual cingulate cortex (pACC) is found [2]. We also report on imaging genetic studies characterizing the effects of genetic variation in the vasopressin receptor (AVPR1A) [3] and the oxytocin receptor gene (OXTR) [4,5], implicated in risk for autism, on brain structure and function related to emotional regulation and social behaviour, which show an effect on the amygdala-pACC circuit. Recent studies on environmental risk factors for schizophrenia (urbanicity, migration) again implicate this circuit [6]. Changes in pACC were also among the most reliable in a recent meta-analysis of structural and functional findings in early psychosis [7]. Taken together, the results suggest neural mechanisms for neuropeptide approaches to modulate and treat core brain phenotypes for schizophrenia linked to environmental risk and social cognition.

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OXYTOCIN AND SOCIAL COGNITION TRAINING

Stephen R. Marder¹, Michael C. Davis, Junghhee Lee, William P. Horan, Jonathan K. Wynn, Michael F. Green

¹UCLA Semel Inst. for Neuroscience and Human Behavior, VA VISN 22 MIRECC

Single doses of Oxytocin (OT) can enhance the salience of social information. We evaluated whether this property of OT would enhance learning during social cognitive skills training exercises in individuals with schizophrenia. Subjects were 27 male schizophrenia outpatients who met DSM-IV-TR criteria for schizophrenia and were taking antipsychotic medications.

Methods: Subjects participated in a 6-week (12-session) course of Social Cognitive Skills Training (SCST) that focused on 3 areas: 1. Facial Affect Recognition; 2. Recognizing non-verbal gestures and vocal cues; and 3. Empathy. SCST was provided within a group setting. Subjects were randomly assigned by group to receive either intranasal OT (40 IU) or placebo 30 minutes prior to each session. Hence, each session included subjects randomized to OT and placebo. We evaluated scores on social cognition measures including Eckman Facial Recognition, The Profile of Nonverbal Sensitivity (PONS) and the Empathic Awareness Test; clinical symptoms (Brief Psychiatric Rating Scale; BPRS) and Clinical Assessment Interview for Negative Symptoms; CAINS), neurocognition (MATRICS Consensus Cognitive Battery; MCCB), and event-related potentials during a face processing paradigm (N170 and N250). Participants only received OT immediately prior to each training session; they did not receive OT between sessions or on the day of assessments. Subjects were assessed at baseline, one week following the final training session and one month later. Generalized linear mixed models were used to evaluate time effects (across the three assessments) and time X treatment group (OT, placebo) effects.

Results: 13 patients were randomized to receive OT and 14 to placebo; there were no significant demographic differences between the groups. On the social cognitive tests, subjects receiving OT demonstrated significantly greater improvements on the Empathic Accuracy Test than those receiving placebo ($p=0.03$, $d=0.92$ post-treatment and $p=0.03$, $d=0.98$ at 1 month follow-up). There were no OT-related effects for the other tests, but there was a main effect of time on the Eckman Facial Recognition Test ($p<0.0001$ post-treatment and $p<0.0001$ at 1 month follow-up). There were no significant changes in clinical symptoms and cognition, though a main effect of time for the MCCB neurocognitive composite score indicated improvement across both groups ($p<0.01$ at 1-month follow-up). In addition, there was a significant increase in left-hemisphere N170 amplitude for emotion identification in participants who received OT ($p<0.05$ at 1 month follow-up), but not in those receiving placebo.

Discussion: This study demonstrates possible therapeutic benefits of administering OT prior to training sessions that target social cognition. The effects of OT were most pronounced for empathic accuracy, a high-level social cognitive process, which has been shown to be more difficult to modify with current social cognition remediation programs. The benefits of OT can be attributed to enhancement of learning from training sessions rather than acute effects on testing ability since all assessments were scheduled at least 1 week apart from treatment administration. These initial results support further investigation of this novel use of intranasal OT in schizophrenia.

Symposium
RESEARCH IN UNMEDICATED PATIENT POPULATIONS: INSIGHTS INTO THE NEUROBIOLOGY OF SCHIZOPHRENIA
Chairperson: Peter Uhlhaas

Discussant: William T. Carpenter

Wednesday, 9 April 2014
1:30 PM – 3:30 PM

Overall Abstract: The large majority of schizophrenia (ScZ) research is performed in patient populations who have been treated with anti-psychotic medication for considerable periods of time which could potentially represent a major confound because of possible effects on brain activity and anatomy. The current symposium provides an interdisciplinary overview on studies that have performed neuroimaging experiments in unmedicated ScZ patients using anatomical, functional and electrophysiological approaches which are compared to patterns of brain activity following antipsychotic medication or with chronically medicated cohorts. This evidence is complemented by work that tested systematically the effects of antipsychotics on brain anatomy in non-human primates. Birthe Glenthøj (Copenhagen University) will present longitudinal fMRI-data on reward abnormalities in a cohort of n=64 medication-naïve, first-episode (FE)-patients. At baseline, FE-ScZ patients demonstrated an attenuation of brain activation during reward anticipation which was normalized following the antipsychotic medication treatment (AGJ, 2012). Moreover, SPECT-measurements in striatum predicted treatment response of positive symptoms. Recent work by Lawrence Kegeles (AGP 2012) (Columbia University) demonstrated elevated MRS-measured glutamate and GABA-levels in unmedicated ScZ-patients while normal levels were demonstrated in a medicated cohort. The pattern in unmedicated ScZ-patients is consistent with the effects of acute ketamine administration in healthy participants on glutamate and GABA concentrations, suggesting a possible role of NMDA receptor hypofunction in ScZ. The correlation of these levels with positive symptoms raises the possibility that patients least responsive to antipsychotic medications may benefit the most from potential glutamatergic or GABAergic pharmacotherapy. Consistent with altered excitation/inhibition (E/I) balance-parameters, MEG-data in medication-naïve FE-patients by Peter Uhlhaas (Neuron, 2012, ScZ-Res. 2013) (Univ. of Glasgow) reveals increased gamma-band power and connectivity in resting-state recordings as well as increased excitability of cortical networks during visual processing which is not present in chronically medicated ScZ-patients. The pattern of brain activity in FE-ScZ agrees with the effects of Ketamine on neural oscillations in healthy volunteers providing further support for the role of aberrant glutamatergic neurotransmission at illness onset. Finally, Karl-Anton Dorph-Petersen (Aarhus Univ.) will summarize evidence from several studies which examined the effects of antipsychotics on anatomical variables in monkeys (Biol. Psych. 2008) These results show an association between chronic haloperidol or olanzapine exposure and a ~10% reduction in brain weight and volume with preserved total neuron number but reduced glia-cell number. Together, these findings suggest important differences between physiological and anatomical variables in unmedicated vs. medicated patient populations as well as potentially detrimental effects of antipsychotics on brain structure. Thus, the symposium highlight the necessity for further work in this area as well as raises practical and ethics issues in regards to research in unmedicated ScZ-patient populations (Discussant: William Carpenter, Univ. of Maryland).

MEDICATION-NAÏVE, FIRST-EPISTODE SCHIZOPHRENIA PATIENTS SHOW INCREASED EXCITABILITY OF NEURAL CIRCUITS: INSIGHTS FROM MAGNETOENCEPHALOGRAPHY (MEG)
Peter Uhlhaas¹, Wolf Singer², Michael Wibral³, Marcus F. Leweke⁴
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In this study, we assessed Magnetoencephalographic (MEG) responses in a sample of medication-naïve first-episode (FE-patients) patients with schizophrenia (ScZ) (n=17) during resting-state recordings and visual processing to examine potential differences in neural oscillations and event-

related fields (ERFs) compared to 1) a sample of chronically medicated ScZ patients and 2) a group of healthy volunteers who were administered a subanesthetic dose of Ketamine. The latter group was included to examine the potential compatibility of findings in FE-ScZ patients with the NMDA-R hypofunctioning model of ScZ. MEG signals were analyzed with Morlet-wavelets and a dynamical imaging of coherent sources (DICS) beamformer and transfer-entropy values were computed between sources as an index of effective connectivity. Resting-State Data: FE-ScZ patients revealed an increase in resting-state neural oscillations and connectivity in the gamma-frequency range in a network including hippocampus, temporal gyrus and cerebellum which correlated with the strength of positive symptoms. This upregulation was not present in chronic ScZ-patients. Task-Related MEG-Responses: MEG-data were analysed for ERF-responses and oscillatory power at sensor and source-level during the presentation of Mooney faces, a visual stimulus which requires the grouping of stimulus elements into coherent object representations. Similar to chronic ScZ-patients, the amplitude of 60–120 Hz power was significantly reduced at illness-onset although the impairment was less pronounced. In addition, the analysis of M100, M170 and M250 components revealed increased responses in FE-ScZ patients while in chronic patients reductions in all components were observed. MEG-data during Ketamine: Neural oscillations were recorded in a group of 15 healthy volunteers during the administration of a subanesthetic dose of ketamine (0.006 mg/Kg) and a placebo saline solution in a within-subject design. MEG-data were recorded during the presentation of a sinusoidal grating and at rest. The acute administration of ketamine lead to an upregulated gamma-band activity both at rest and during visual processing in health controls. This is possibly mediated by a shift in the excitation/inhibition balance in favour of excitation of pyramidal cells due to hypofunctioning NMDA-receptors. Summary: The analysis of MEG-data reveals distinct pattern of neural responses in FE-ScZ patients which is supported by elevated, spontaneous gamma-band activity as well as increased amplitude of ERF-responses which were not observed in chronically medicated ScZ-samples. This pattern of MEG-activity at illness onset is consistent with the effects of the NMDA-R antagonist Ketamine on MEG-parameters in healthy volunteers, suggesting that aberrant glutamatergic neurotransmission may underlie the increased excitability of neural circuits.

REWARD PROCESSING, DOPAMINE D2/3 RECEPTOR BINDING, AND TREATMENT OUTCOME: A LONGITUDINAL STUDY OF ABNORMALITIES IN THE REWARD CIRCUIT IN INITIALLY ANTIPSYCHOTIC-NAÏVE FIRST-EPISTODE SCHIZOPHRENIA PATIENTS
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Background: Some of the best validated findings in schizophrenia are an association between increased striatal dopamine activity and positive schizophrenic symptoms and the relationship between striatal dopamine D2 blockade and the resolution of the positive symptoms. Likewise well-established is an association between striatal dopamine release and reward processing. In line with this, it has been suggested that the positive symptoms are linked to a dysfunction of the brain reward system. We have recently demonstrated alterations of the brain reward system in 31 antipsychotic-naïve first-episode schizophrenia patients [1]. Improvement of the positive symptoms after treatment of 23 of the patients was linked to a normalization of the reward system [2]. These subjects were the first included in a cohort of 64 patients. The purpose of the present study was to validate our previous findings in the total cohort of patients and relate them to striatal dopamine D2/3 binding potentials (BP) at baseline and blockade at follow-up. In secondary analyses, we further wanted to relate the reward abnormalities to structural connectivity in the reward system. Additionally, we wanted to explore if baseline D2/3 BP could serve as predictors for outcome.

Methods: 64 antipsychotic-naïve first-episode schizophrenia patients and 64 controls matched for age, gender, and parental socio-economic status went through an examination program including functional magnetic resonance imaging (fMRI) with a variant of the monetary incentive delay task, structural MRI (including DTI), and Single Photon Emission Computed Tomography (SPECT) using 123I-labeled iodbenzamid (IBZM) as the radioligand. The Positive and Negative Syndrome Scale (PANSS) was used to assess psychopathology. 47 of the patients were re-examined after 6 weeks of treatment with the relatively selective D2/3 receptor antagonist, amisulpride. Healthy controls were examined at the same time points. Not all patients and controls went through all examinations.

Results: The preliminary analyses of data from the total cohort of patients support the above mentioned data from our group showing: 1) that patients during reward anticipation demonstrate attenuation of brain activation in the ventral striatum, ventral tegmentum, and the anterior cingulated cortex during presentation of salient cues; and 2) that the positive symptoms are linked to the reward abnormalities as is treatment outcome. As expected, we found no significant differences in striatal D2/3 BP between patients and controls at baseline, whereas our preliminary data demonstrated a significant correlation between low BP at baseline and improvement of PANSS total (all patients) ($p < 0.002$) and PANSS positive symptoms (males only) ($p < 0.015$). The latter finding is in agreement with an association between high dopamine release and low D2 receptor availability in striatum. At the presentation reward processing will further be related to striatal D2/3 BP and structural connectivity in the reward system in the antipsychotic-naïve state and after 6 weeks of medication, and to recent data from the literature.

Conclusion: The present longitudinal data from a large cohort of never previously treated patients stress the significance of abnormalities in reward processing for the development as well as treatment of positive psychotic symptoms. The data further suggest that treatment outcome can be predicted based on D2/3 BP in antipsychotic-naïve patients. The gender differences are in line with previous findings from our group [3].

References:

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GABA AND GLUTAMATE AS POTENTIAL THERAPEUTIC TARGETS IN SCHIZOPHRENIA

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Background: The GABA and glutamate (Glu) systems have been implicated in the pathophysiology of schizophrenia (ScZ). Multiple markers have been found in postmortem studies that suggest deficient GABAergic function in fast-spiking, parvalbumin-positive interneurons. NMDA receptor hypofunction (NRH) has been hypothesized in the illness and has been shown in preclinical studies to stimulate Glu release when induced acutely. The status of the GABA and Glu systems in the illness and in NRH have become amenable to *in vivo* study using magnetic resonance spectroscopy (MRS). Here we focus on three recent studies suggesting that abnormalities in these systems in ScZ may be related to NRH and are markedly changed by antipsychotic medication.

Methods and results: A study comparing 16 unmedicated patients to 16 medicated patients and 22 healthy controls found 30% elevations in GABA and Glu in the medial prefrontal cortex in the unmedicated but not in the medicated patients (Kegeles et al., AGP 2012). In this study, both GABA and Glu were related to the PANSS positive symptom subscale across the patient groups. A longitudinal study of Glu in 24 first-episode patients reported elevated Glu in the associative striatum that decreased to normal levels following 4 weeks of antipsychotic medication treatment (de la Fuente Sandoval et al., JAMA Psychiatry online 2013). Glu levels at 4 weeks were related to positive symptoms at the same time point. In a study of the time course of GABA and Glu levels following NRH induced by acute ketamine administration (0.5 mg/kg i.v. over 40 minutes) in 12 healthy subjects, both neurochemicals showed acute ketamine-induced surges (Kegeles et al. Sch

Bull 2013;39 Suppl 1, S140). The MRS acquisitions consisted of 6 time points for each subject acquired at baseline and at 5 successive 15-minute intervals during and following ketamine administration. The data showed a significant 17% surge in Glu and 11% in GABA, which followed a time course similar to the extracellular Glu surge reported in rodents with acute ketamine challenge.

Discussion: These data suggest that GABA and Glu levels are abnormally elevated in first-episode as well as unmedicated patients with ScZ, and that second-generation antipsychotic medication treatment lowers these levels to the normal range. The surges in both neurochemicals following ketamine suggest that the Glu surge may drive the surge in GABA. Elevations in both GABA and Glu in ScZ suggest that the Glu elevation may be more primary in the pathophysiology of the illness, and the similarity to the changes induced in healthy subjects by ketamine are consistent with a role for NRH in ScZ. The relationship of positive symptoms to GABA and Glu levels, particularly in medicated patients, suggests that subjects whose positive symptoms are the least treatment-responsive may be those whose GABA and Glu levels respond the least. Future study is needed to investigate whether these nonresponders may be the best candidates for potential glutamatergic or GABAergic pharmacotherapy.

CHRONIC ANTIPSYCHOTIC MEDICATION EXPOSURE CHANGES THE BRAIN STRUCTURE IN MACAQUE MONKEYS

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A large body of literature based upon postmortem or *in vivo* imaging techniques has described the presence of subtle structural brain changes in subjects with schizophrenia. Obviously, most studied subjects have a history of antipsychotic medication – the exception being imaging studies of newly diagnosed cases. In order to robustly interpret most of these findings it is therefore essential to determine if prolonged treatment with antipsychotic medications to some degree contributes to these brain changes. This is important both for gaining insight into the disease process of schizophrenia and for elucidation of the mechanisms underlying the effects of antipsychotic medications – these effects being both therapeutic and adverse. One way to examine this effect of antipsychotic medication on brain structure is the experimental study of non-human primates. Thus, we exposed three groups each consisting of six experimentally-naïve, young adult, male macaque monkeys to twice-daily oral doses of haloperidol, olanzapine or placebo treatment, respectively, for approximately two years. By analysis of repeated blood samples from the animals, we confirmed that the steady state, trough plasma levels of haloperidol and olanzapine were in the therapeutic range corresponding to the current treatment of schizophrenia. After the period of medication exposure, the monkeys were euthanized and subsequently the total brain weight as well as weight and volume of the left hemisphere were obtained – the latter by a high-precision implementation of the principle of Archimedes. Importantly, we observed a significantly ~10% smaller total brain weights and volumes in both the haloperidol and olanzapine exposed groups. Searching for the structural correlate of the observed volume reduction we performed histological studies of the cerebral cortex of the parietal lobe using methods based upon unbiased stereological principles. In these studies we found a lower total glial cell number and a higher neuron density, without a difference in total neuron number, in the antipsychotic-exposed monkeys. This was followed by an immunocytochemical stereology study of the parietal brain tissue in which we found a significant 21% lower astrocyte number and a non-significant 13% lower oligodendrocyte number in the antipsychotic-exposed monkeys. Similar effects were observed in both the haloperidol and olanzapine groups. Clearly, it is important to consider the differences between male, healthy macaque monkeys and human subjects with schizophrenia. However, our findings indicate that chronic antipsychotic medications might cause some of the structural changes identified in schizophrenia.

Symposium**SCHIZOPHRENIA RESEARCH: THE CHALLENGE OF MEASUREMENT VARIABILITY****Chairpersons: Janet B.W. Williams and John M. Kane****Discussant: René S. Kahn****Wednesday, 9 April 2014****1:30 PM – 3:30 PM**

Overall Abstract: Research techniques in psychobiology of schizophrenia have become highly sophisticated in recent years. Wider availability of MRI and PET imaging, for example, has greatly expanded neuroimaging as a strategy to identify, delineate and track putative brain abnormalities. These and other technological advances are increasingly susceptible to measurement variability which makes it difficult to combine data from different sites in a study, or make comparisons across studies. Growing complexity creates a demand for more and more standardization, including calibration of instruments, testing procedures and interpretation of results. The need for standardization cuts across many areas of medicine from radiology to psychiatry, and centralizing key functions often enables standardization. This symposium will focus on four areas of special interest to schizophrenia researchers: MRI, PET, assessment of sleep dysfunction, and clinician-based assessment of psychiatric diagnosis and symptom severity. The FDA acknowledged inadequate quality control of standardization procedures for imaging equipment used to explore brain structure and function, recommending that “blinded image evaluations by multiple independent readers be performed in the phase 3 efficacy studies”. The EMA also recognized the need for standardization, and provided guidance in one area that “the definition of progression must be based on a combination of standardised clinical and biological data and centralised blinded review is needed in order to establish progression”. Alterations in sleep architecture are common in psychotic disorders, but the literature is limited to inconsistent replications and lack of diagnostic specificity, issues common to other electrophysiological assessments such as ERP and eye tracking studies. At least in part these limitations are related to variations among studies, patient populations, instrumentation, data processing approaches and scoring procedures, making centralized, blinded processing of data and standardized calibration of equipment critical. In psychiatric clinical trials, attempts to achieve true standardization of raters in clinical trials are few and far between. Various forms of bias, driven by enrollment pressure, financial burdens, expectation and recall contribute significantly to failure of clinical trials in schizophrenia, as does variability due to decentralized diagnosis and assessment procedures. Speakers in each content area will offer perspective on traditional administration and interpretation of tests in their field and the need for standardization. What processes have been adopted? How did the pros and cons of that approach impede or facilitate the process? What was the reaction to change? Is there consensus and acceptance? What issues remain to be resolved? The goal of the symposium is to facilitate the sharing of learning across fields as we standardize and, in many cases, centralize quality control.

MULTI-SITE PET IMAGING: CONSIDERATIONS FOR APPROPRIATE STANDARDIZATION**Ilan Rabiner^{1,2}**¹*Imanova;* ²*Institute of Psychiatry, King's College*

Positron emission tomography (PET) has become over the last 20 years an indispensable tool for psychiatric research. The sensitivity and specificity of PET allows an accurate quantification of the regional distribution of molecular targets in the living human brain, an outcome unachievable by other methods. When discussing standardization of PET methods across multiple sites, a distinction should be made between quantitative methods and clinical rating assessments. The outcome parameters derived from quantitative methods (such as BPND, VT or Ki) are strongly correlated to meaningful physiological parameters (such as target density, or enzyme activity), and in principle, absolute quantification is feasible. However, differences in scanner sensitivities, spatial resolution, reconstruction algorithms and attenuation correction methods mean that differences in quantification between different sites, and even different scanners on the same site, are inevitable. The differences between scanning sites, due to the factors

above, will be of greater concern when the outcome parameter is a single parameter, derived from a single scan per subject, rather than a change in parameter within subject in response to a challenge paradigm (such as target occupancy by a drug, or change in target availability due to an endogenous neurotransmitter release). Studies looking for a within-subject change will be more robust for across site comparisons, and may thus require significantly less cross-standardisation. The sources of variability inherent in quantitative PET methods are sufficiently well understood to allow appropriate modeling of these factors, which should enable the estimation of the potential variability across sites. An adequate estimation of such variability will allow the investigators to place it in context of the general study variability (e.g. due to biological differences in the subject population) and guide the researchers as to the optimal standardisation effort required. In contrast to quantitative PET, studies which rely on clinical rating of PET data are inherently more difficult to standardize, as the sources of variability are less transparent, and less amenable to modelling. Therefore considerably more effort will have to be undertaken to standardize both the acquisition, image reconstruction and rater training procedures to enable cross-centre comparison. It should be remembered that appropriate standardization across sites is a procedure that should take into account the potential variability due to imaging methods and both the biologically relevant effect size, as well as the general study variability. Hence, the amount of standardization required will differ across different studies and should always be appropriate to the task at hand, rather than chasing an ideal.

STANDARDIZATION OF MAGNETIC RESONANCE IMAGING APPROACHES IN NEUROPSYCHIATRIC ILLNESS: CHALLENGES AND OPPORTUNITIES**Alan Anticevic***Department of Psychiatry, Yale University, New Haven, USA*

Over the past 20 years non-invasive neuroimaging has become an increasingly productive and viable tool to develop markers of large-scale neural system alterations in neuropsychiatric illness. For instance, the terms “MRI” and “schizophrenia”, are associated with over 4500 PubMed results, illustrating the explosion of neuroimaging studies of schizophrenia. This technology has undoubtedly advanced our understanding of neural network dysfunction in schizophrenia using structural, cognitive task and resting-state approaches to name a few. However, a major challenge facing the field of clinical neuroimaging is to standardize and merge the wealth of information that will continue to become available across sites and studies. This objective is especially important for allowing discovery science to maximize the available information during a continued search for neural markers of psychiatric illness. This goal, however, is faced with a number of challenges. The focus is placed on standardization of neuroimaging data acquisition, neuroinformatics and database challenges, as well as differences in analytic approaches and techniques across studies. A key area of standardization relates to task-based activation studies, where differences in analyses and modeling approaches are still vast. This is contrasted somewhat with resting-state neuroimaging experiments, where the field is converging on a set of best practices that may facilitate biomarker development through discovery science. Next, the presentation focuses on possible ways across laboratories as well as large-scale neuroimaging initiatives in which clinical neuroimaging studies can achieve standardization. Indeed, despite challenges, emerging opportunities exist. For instance, the Human Connectome Project (HCP) offers a path forward. HCP is an ongoing international effort to map the macro-conneomics of the human brain using the combination of cutting-edge functional, structural and diffusion-weighted approaches. In doing so, the HCP has brought forward to key advances: i) innovation in neuroimaging data acquisition that allow unprecedented spatial and temporal resolution in clinical neuroimaging; ii) development of algorithms used to process and analyze the wealth of data made available via these novel acquisition approaches. Advantages of this framework are discussed from the perspective of data standardization, ease of use, and comparisons across studies and sites. Specific ongoing challenges will be presented that may guide continued development of best practices when implementing this technology for clinical neuroimaging. In summary, clinical neuroimaging has provided a wealth of information regarding the patterns of neural system alterations in schizophrenia across modalities. The challenge facing the field is to continue to refine and standardize neuroimaging approaches, from data acquisition to publication, in ways that can allow ongoing discovery science to take place.

SLEEP EEG STUDIES IN SCHIZOPHRENIA: METHODOLOGICAL CONSIDERATIONS**Matcheri Keshavan***Beth Israel Deaconess Medical Center and Massachusetts Mental Health Center, Harvard University, Boston, MA, Boston, USA*

Alterations in electroencephalographic (EEG) sleep architecture are common in psychotic disorders, but the literature is limited to inconsistent replications and lack of diagnostic specificity, issues common to other electrophysiological assessments such as ERP and eye tracking studies. This presentation will review potential methodological reasons for the lack of consistency in the literature. A review of the literature on EEG biomarkers in psychotic disorders was done with the following questions in mind: how robustly do these measures differ between patients and controls, and how diagnostically specific are they? How are these tests traditionally administered and standardized, and what are their advantages and limitations? What are the issues that need to be addressed? What are the best ways to maximize reliability and validity, while keeping costs and subject burden to a minimum? We focused on sleep biomarkers, but also considered other EEG biomarkers (evoked response potentials, resting EEG) in the review. While there are robust differences between patients and controls on several sleep EEG measures such as slow wave sleep and REM proportions and densities, few show effects that discriminate between DSM diagnostic categories. At least in part these limitations are related to variations between studies, patient populations, small sample sizes and small effect sizes, labor intensive procedures and patient burden, factors affecting physiological states such as smoking and activity levels, differences in instrumentation, data processing approaches and scoring procedures. Establishing group differences will require reduction of both instrumentation and biological noise. Automated detection algorithms (e.g. delta counts, spindle density, etc.) and artifact rejection procedures are likely to increase sensitivity and specificity. Ambulatory studies might help cost and subject burden. Making centralized, blinded processing of data, clear quality control procedures and standardized calibration of equipment are critical.

CLINICIAN-BASED ASSESSMENT OF PSYCHIATRIC DIAGNOSIS AND SYMPTOM SEVERITY**Janet B.W. Williams***MedAvante, Hamilton, USA*

FDA puts the estimate of failed trials in schizophrenia at 25%, with placebo response growing steadily. In psychiatric clinical trials, most procedures

are conducted by site-based clinicians whose diagnoses and assessments may be influenced by various forms of bias, and whose individual findings may contribute to variability of results when combined with those of other raters and sites. Bias and variability are two key contributors to trial failure and a number of strategies have attempted to address them. On a systems level, dramatically increasing the sample size of a study has been attempted as a way to improve signal detection, but larger samples require more raters, sites and countries which adds to the problem of variability and signal noise and may decrease effect size. Others have tried to be more selective in choosing sites; however, personnel turnover can affect success rates if a site does not have consistent training, and good performance in one trial may have a very low correlation with good performance in the next study at that same site. Finally, despite efforts to conduct trials in certain countries that demonstrated good signal detection in previous studies, placebo response seems to be increasing nonetheless. At the rater level, strategies to avoid bias and reduce variability have included limiting participation to very experienced raters, and increasing rater training. Unfortunately, clinical experience alone does not result in good interrater reliability within a cohort of raters; experienced raters must be carefully calibrated with each other to achieve this. In addition, studies have shown that even intensive group rater training at the beginning of a study does not improve interrater reliability significantly, even in the short term. Thus, the variability that results from combining ratings from many different sites remains. Recent methodological approaches to improving trial failure rates include supplementing site ratings with patients' self-reports of symptoms, dual assessments by site-based and independent raters, and providing feedback to site raters based on reviews of their recorded interviews. Each of these methods has advantages and disadvantages, which will be reviewed. Another particularly powerful method replaces a large number of site-based raters with a much smaller cohort of remote centralized raters who are geographically and financially independent from the sites. These experienced raters can be trained and calibrated to a single standard, continuously monitored to avoid rater drift, and blinded to protocol details (e.g., inclusion criteria) and visit number (e.g., baseline vs. endpoint) to avoid expectation bias. This method has met considerable resistance from site-based clinicians who believe they can yield the most informed ratings based on strong relationships with study subjects. However, a growing body of evidence indicates that centralization to ensure blinding and independence of raters improves signal detection or lowers placebo response.

POSTER SESSIONS

Poster Session SUNDAY POSTER SESSION

Poster #S1

FURTHER EVIDENCE OF THE EFFECTS OF CHILDHOOD ABUSE IN FIRST-EPIISODE PSYCHOSIS AND SUBCLINICAL PSYCHOSIS

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Background: Examining the role of childhood traumatic experiences in first episode of psychosis (FEP) is relevant for interventions since a history of childhood trauma is predictive of a worsened course of psychotic disorders (Ramsay et al 2011; Üçok & Bikmaz 2007) and poorer social outcomes (Cusak et al 2004). However, research on the role of childhood trauma in FEP is still relatively scarce. The present study aimed to extend the literature on childhood trauma and psychosis examining the impact of child abuse across the continuum of psychosis, from subclinical psychosis to first episode of psychosis. Specifically, we seek to evaluate whether childhood abuse is more frequently reported among individuals at FEP and/or individuals at high risk for psychosis compared to nonclinical control individuals.

Methods: The study included a total of 198 individuals divided in three groups: i) 48 patients (mean age = 29.1; SE=8.4; 47% males) with a FEP drawn from an ongoing epidemiological and longitudinal intervention program of first-episode psychosis (PAFIP) conducted at the University Hospital Marqués de Valdecilla (Spain); ii) a sample consisting of 77 individuals (mean age = 22.7; SE=5.4; 40% males) at (psychometric) risk for psychosis (scoring above the 75th percentile for both positive and negative dimensions of subclinical psychosis; "High CAPE" group) and iii) a control group (scoring below the 25th positive and negative dimensions of subclinical psychosis; "Low CAPE" group) consisting of 73 individuals (mean age = 22.5; SE=3.7; 36% males). The last two samples were drawn from a larger sample of individuals from the general population characterized for subclinical psychosis by means of the positive and negative dimensions of the Community Assessment of Psychic Experiences (CAPE; Stefanis et al 2002). Self-reported instruments [Stressful life events screening questionnaire-Revised (Goodman et al 1998) in the FEP sample and the Childhood Trauma Questionnaire (Bernstein & Fink 1998) in the High and Low CAPE groups] were used to assess childhood abuse including physical and sexual abuse. Fisher's exact tests were performed to compare the frequency of exposed and no-exposed to child abuse individuals between the groups since one of the cells has a frequency of less than five cases. Three comparisons were performed: i) FEP vs. Low CAPE; ii) FEP vs. High CAPE and iii) High CAPE vs. Low CAPE.

Results: FEP group presented the highest frequency of child abuse (52% exposed) followed by High CAPE group (26% exposed) while Low CAPE group presented the lowest frequency (1% exposed). FEP group significantly presented a higher rate of individuals exposed to child abuse compared to Low CAPE group ($p<0.000$) and also compared to High CAPE group ($p=0.004$). High CAPE individuals also presented significantly more cases of individuals exposed to child abuse compared to the Low CAPE group ($p<0.000$).

Discussion: We found that the frequency of child abuse in both patients and risk subjects for psychosis, two different groups of individuals within the psychotic spectrum, was higher than in the control group. These results are in line with previous studies (Sahin et al 2013; Üçok & Bikmaz 2007) and provide support for the existence of an etiological continuum with increasing presence of the risk factor, child trauma in this case, underlying a phenotypic continuum of severity from low subclinical psychosis to FEP.

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Poster #S2

CARDIOMETABOLIC ADVERSE EFFECTS OF SECOND-GENERATION ANTIPSYCHOTICS IN DRUG NAÏVE CHILDREN AND ADOLESCENTS IN ACUTE CARE

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Background: Cardiometabolic effects of second-generation antipsychotic medications are concerning but have not been sufficiently studied in pediatric and adolescent patients naive to antipsychotic medication, especially in acute care. The aim of our study is to evaluate the association of second-generation antipsychotic medications with cardiometabolic parameters in patients without prior antipsychotic medication exposure after seven days of treatment in acute care.

Methods: Weight, Body mass index (BMI), blood pressure, serum total cholesterol, high density lipoproteins, low density lipoproteins, triglycerides, glycaemia, aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), white blood cells count, creatinine, prolactin, free thyroxine (FT4), thyroid stimulating hormone (TSH), electrocardiogram, were measured at baseline and after 7 days of follow up in a population of drug-naïve children and adolescents taking second generation antipsychotics in a naturalistic observational setting.

Results: In the overall population we found a significant increase of triglycerides and prolactin and reduction of LDH and CPK. Interestingly, when the antipsychotics were analyzed separately, it appeared that risperidone induced significant increase of prolactin levels, aripiprazole induced a significant reduction in all cholesterol values (total, HDL, LDL), olanzapine induced a significant reduction of CPK, quetiapine induced a significant increase of triglycerides and a significant decrease of glycaemia.

Discussion: Second generation antipsychotics had significant effects on various cardiometabolic parameters in drug-naïve children and adolescents also after only the first seven days of treatment. The relevance and the meaning of these effects need further evaluations.

Poster #S3

ANTIPSYCHOTIC-INDUCED MOVEMENT DISORDERS IN LONG-STAY PSYCHIATRIC PATIENTS: A PROSPECTIVE STUDY

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Background: The purpose of this study was to assess the frequency and the risk factors of drug-induced movement disorders namely, tardive dyskinesia (TD), parkinsonism, akathisia and tardive dystonia, in a representative sample of long-stay patients with chronic severe mental illness.

Methods: Naturalistic study of 209 long-stay patients with chronic mental illness requiring long-term antipsychotic treatment, examined by the same rater at least two times over a 4-year period, with a mean follow-up time of 1.1 years, with validated scales for TD, parkinsonism, akathisia, and tardive dystonia. Prospective assessment of both persistent and fluctuating (repeated) movement disorders measures the phenotype more specifically and that increases the validity of the associations between movement disorders and risk factors.

Results: The frequencies of persistent movement disorders in the sample were 28.4% for TD, 56.2% for parkinsonism, 4.6% for akathisia and 5.7%

for tardive dystonia. Two-thirds of the participants displayed at least one type of persistent movement disorder. Yearly incidence rates of persistent movement disorders were 19.6% for TD, 21.6% for parkinsonism, 3.5% for akathisia and 0% for tardive dystonia. Fluctuating TD was positively associated with age (hazard ratio (HR) per year exposure=1.04, 95% CI=1.02-1.06). Fluctuating parkinsonism was positively associated with age (HR=1.03, 95% CI=1.02-1.04) and the total antipsychotic defined daily dose (DDD) (HR=1.07, 95% CI=1.03-1.11). Risk factors did not predict akathisia and tardive dystonia.

Discussion: The findings were that (i) having persistent drug-induced movement disorders seems to be the norm for long-stay patients with chronic mental illness and long-term antipsychotic treatment; (ii) these patients have a high risk of incident movement disorder, in particular TD and parkinsonism; (iii) higher age is an important predictor of TD and parkinsonism; and (iv) total antipsychotic defined daily dose (DDD) is an important predictor of parkinsonism. Measures are required to remedy this situation.

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Poster #S4

TWO CANDIDATE GENE-BASED ASSOCIATION STUDIES OF ANTIPSYCHOTIC-INDUCED MOVEMENT DISORDERS IN LONG-STAY PSYCHIATRIC PATIENTS: PROSPECTIVE STUDIES

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Background: Four types of antipsychotic-induced movement disorders: tardive dyskinesia (TD), parkinsonism, akathisia and tardive dystonia, subtypes of TD (orofacial and limb truncal dyskinesia), subtypes of parkinsonism (rest tremor, rigidity, and bradykinesia), as well as a principal-factor of the movement disorders and their subtypes, were examined for association with variations (SNPs) in 2 studies; one in 10 candidate genes (PPP1R1B, BDNF, DRD3, DRD2, HTR2A, HTR2C, COMT, MnSOD, CYP1A2, and RGS2) and another one in 7 candidate genes (GRIN2B, GRIN2A, HSPG2, DRD3, DRD4, HTR2C, and NQO1).

Methods: Naturalistic study of 168 white long-stay patients with chronic mental illness requiring long-term antipsychotic treatment, examined by the same rater at least twice over a 4-year period, with a mean follow-up time of 1.1 years, with validated scales for TD, parkinsonism, akathisia, and tardive dystonia. The authors genotyped 31 SNPs in 10 candidate genes and 45 tag SNPs in 7 candidate genes, associated with movement disorders or schizophrenia in previous studies. In both studies genotype and allele frequency comparisons were performed with multiple regression methods for continuous movement disorders.

Results: In the first study, various SNPs reached nominal significance: TD and orofacial dyskinesia with rs6265 and rs988748; limb truncal dyskinesia with rs6314; rest tremor with rs6275; rigidity with rs6265 and rs4680; bradykinesia with rs4795390; akathisia with rs4680; tardive dystonia with rs1799732, rs4880 and rs1152746. In the second study, various tag SNPs reached nominal significance: TD with rs1345423, rs7192557, rs1650420, and rs11644461; orofacial dyskinesia with rs7192557, rs1650420, and rs4911871; limb truncal dyskinesia with rs1345423, rs7192557, rs1650420, and rs11866328; bradykinesia with rs2192970; akathisia with rs324035; and the principal-factor with rs10772715. After controlling for multiple testing, all of the found association lost their statistical significance.

Discussion: The findings suggest that selected SNPs are not associated with a susceptibility to movement disorders. However, as the sample size was small and previous studies show inconsistent results, definite conclusions cannot be made. Replication is needed in larger study samples, preferably in longitudinal studies which take the fluctuating course of movement disorders and gene-environment interactions into account.

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Poster #S5

GENDER DIFFERENCES IN THE EFFECT OF CHILDHOOD TRAUMA EXPERIENCES ON PRODROMAL SYMPTOMS AND PERSONALITY DISORDER TRAITS IN YOUNG ADULTS AT HIGH-RISK FOR PSYCHOSIS

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Background: Childhood trauma experiences (CTE) represent a socio-environmental risk factor for the development of schizophrenia spectrum disorders and have a negative impact on the course and outcome of psychotic disorders (Bendall et al., 2008). Few studies have addressed trauma in people at ultra-high-risk (UHR) of psychosis (e.g. Addington et al., 2013; Velthorst et al., 2013). Their findings suggested that CTE are highly prevalent in populations at UHR of psychosis and related to attenuated positive symptoms. Moreover, it has been found that a history of sexual abuse increases the rates of conversion to psychosis (Bechdolf et al., 2010; Thompson et al., 2009) and that females are more likely to report CTE than males (Addington et al., 2013). This study aimed to explore: 1) the presence of CTE in At-Risk Mental State (ARMS) patients and whether it differed according to gender, and 2) the association of CTE with prodromal symptoms and personality disorder traits and the possible moderating role of gender on these associations.

Methods: 35 ARMS patients (91.4% met criteria for Attenuated Psychotic Symptoms group according to UHR criteria; Yung et al., 2005) were assessed for psychopathology, personality disorder traits, and history of CTE as assessed by the CTQ-B (Berstein et al., 1994). The mean age of patients was 20.9 years and 60% were male.

Results: Overall, ARMS patients reported low-moderate scores ($5 \geq 12$) on emotional abuse (EA), sexual abuse (SA), and emotional neglect (EN), according to CTQ norms. 48.6% reported having experienced a separation or loss of a parent before the age of 17 (41.2% separation of parents, the father of 2 patients died and one patient was abandoned). Females showed significantly higher levels of SA (moderate-severe) and parental separation/loss but lower levels of EN than males. EA predicted negative and general symptoms, behavioral and motor/physical changes, and borderline personality disorder traits. Physical abuse (PA) predicted positive and negative symptoms, cognitive and motor/physical changes, and schizotypal personality traits. SA predicted positive, negative, and general symptoms as well as cognitive changes. Physical neglect (PN) predicted behavioral changes, whereas parental separation/loss predicted motor/physical change. EN did not predict prodromal symptoms or personality disorder traits. Furthermore, gender moderated the effects of PA and SA on prodromal symptoms, showing a greater impact in females than in males. The associations of EA, PN, and parental separation with symptoms and personality disorder traits were not moderated by gender.

Discussion: Findings showed strong associations between CTE and several symptom dimensions of ARMS patients despite the small sample size of this preliminary report. Consistent with previous studies, SA was related with positive attenuated psychotic symptoms (Velthorst et al., 2013) and females showed higher levels of SA than males (Addington et al., 2013). The results suggest that different experiences of childhood abuse (EA, PA and SA) have an effect on symptom severity even before the onset of the first psychosis episode, and that they exert a stronger effect in females than in males. This study supports the importance of CTE as a relevant psychosocial factor at the early stages of psychosis. Even if trauma was self-reported and assessed concurrently with prodromal symptoms, the association of

patients' subjective appraisal of CTE and symptoms is in itself a critical issue to understand and highly relevant for its potential impact on the outcome of the at-risk status.

Poster #S6

CHILDHOOD TRAUMA MEDIATES THE ASSOCIATION BETWEEN ETHNIC MINORITY STATUS AND MORE SEVERE HALLUCINATIONS IN PSYCHOTIC DISORDER

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Background: Both ethnic minority status and childhood trauma are established risk factors for psychotic disorders. Both are also found to be associated with increased level of positive symptoms, in particular auditory hallucinations. Our main aim was to investigate the experience and effect of childhood trauma among ethnic minorities with psychosis, hypothesizing that they would report more childhood trauma than the majority and that this would be associated with more current and lifetime hallucinations. We also hypothesized that childhood trauma would mediate a possible association between ethnic minorities and hallucinations.

Methods: In this cross-sectional study 454 patients with a SCID-I DSM-IV diagnosis of non-affective or affective psychotic disorders were included. Current hallucinations were measured with the Positive and Negative Syndrome Scale (item P3; Hallucinatory Behavior). Lifetime hallucinations were assessed with the Structured Clinical Interview for DSM-IV (SCID-I) items auditory hallucinations (B16), voices commenting (B17) and two or more voices conversing (B18). Childhood trauma was assessed with the Childhood Trauma Questionnaire, self-report version. The ethnic minority group (n=69) consisted of non-Caucasian first- and second-generation immigrants who were primarily from Asia (n=39, 57%) and Africa (n=27, 39%).

Results: The ethnic minority group reported significantly more childhood trauma (T -test = -3.866, df 405, $p < 0.001$), specifically physical abuse (Mann Whitney U = 8.170, $p < 0.001$), physical neglect (Mann Whitney U = 9.427, $p < 0.001$), and sexual abuse (Mann Whitney U = 10.156, $p < 0.003$) than the majority group. They also had significantly more current hallucinatory behavior (Mann Whitney U = 10.942, $p < 0.013$). Over 30% of the ethnic minority group reported auditory hallucinations of two or more voices conversing, which was significantly higher than the 19% seen in the majority group ($\chi^2 = 4.692$, df 1, $p < 0.03$). Multivariate regression analyses indicated that childhood trauma mediated the association between ethnic minority status and more severe current hallucinations, and lifetime hallucinations of two or more voices conversing.

Discussion: More childhood trauma among ethnic minorities with psychosis partially explains findings of more current and lifetime hallucinations in this group. The association between childhood trauma and first rank symptoms may in part explain the heightened risk of being diagnosed with a schizophrenia-spectrum diagnosis in certain ethnic minorities. The present findings show the importance of childhood trauma not only as a risk factor for schizophrenia but also as experiences that influence specific psychotic symptoms directly. Further of clinical relevance we are reminded to assess and treat the effects of childhood trauma in ethnic minority groups presenting with psychotic disorders.

Poster #S7

META-ANALYSIS OF CHANGES IN BRAIN STRUCTURE IN HEALTHY INDIVIDUALS WITH A HISTORY OF CHILDHOOD ADVERSITY

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Background: Childhood adversity is a risk factor for psychosis with an estimated population attributable risk of 33% (Varese et al, 2012). The main biological system thought to underlie this association is the Hypothalamic-Pituitary-Adrenal (HPA) axis, which moderates the stress response in humans. This is supported by findings that HPA-axis-related structures

such as the hippocampus and amygdala are altered in psychosis, and particularly in people with psychosis who have experienced childhood adversity. Research comparing healthy people with and without a history of childhood adversity allows for the disentangling of the effect of psychiatric conditions from the effect of childhood adversity itself. The traumagenic neurodevelopmental model suggests that childhood adversity increases vulnerability to psychosis by creating hypersensitivity to stress. By extension, people that experienced childhood adversity and did not develop a psychiatric condition represent a particularly stress-resilient population. Unlike in psychiatric populations, experiencing childhood adversity may not have led to significant overactivation of the HPA-axis and subsequent abnormal volumetric development. The aim of this meta-analysis was to investigate associations between childhood adversity and hippocampal and amygdala volume in psychiatrically healthy adults.

Methods: The MEDLINE database was searched for studies using magnetic resonance imaging that had measured brain structure in healthy adults with and without childhood adversity. We identified seven eligible papers (1,322 participants) reporting hippocampal volumes and three eligible papers (803 participants) reporting amygdala volumes. Effect sizes were calculated from each study and pooled using a random effects meta-analysis.

Results: No significant differences in hippocampal (effect size = -0.116; 95% confidence interval -0.375 to 0.043; $p=0.119$) or amygdala volume (effect size = -0.002; 95% confidence interval -0.168 to 0.165; $p=0.984$) were found between healthy participants with and without childhood adversity. A study determining hippocampal volume in elderly participants was then excluded. In the remaining six studies participants with a history of childhood adversity were found to have a significantly greater hippocampal volume than those without such a history (effect size = -0.028; 95% confidence interval -0.436 to -0.019; $p < 0.05$).

Discussion: The lack of association between childhood adversity and amygdala volume supports the notion that healthy controls that experienced adversity in childhood and did not develop a psychiatric illness have a greater resilience to stress than people who went on to develop a psychiatric illness. However, when we excluded a study including only elderly participants, the overall association between childhood adversity and hippocampal volume was significant, suggesting some vulnerability to the effects of childhood traumatic experiences. Apfel et al (2011) found that associations between trauma and hippocampal volume only in people currently experiencing PTSD, and not in those with only a past history of PTSD. This suggests that volumetric abnormalities associated with exposure to traumatic experiences may lessen over the lifespan.

Poster #S8

GLUCOMETABOLIC HORMONES AND CARDIOVASCULAR RISK MARKERS IN ANTIPSYCHOTIC-TREATED PATIENTS

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Background: Treatment with antipsychotic drugs is widely associated with metabolic side-effects such as overweight and disturbed glucose metabolism, but the pathophysiological mechanisms are unclear.

Methods: Fifty-one non-diabetic, antipsychotic-treated male patients ((mean±standard deviation) age: 33.1±6.7 years; body mass index (BMI) 26.0±4.7 kg/m²; waist circumference: 95.8±13.2 cm; glycated hemoglobin (HbA1c): 5.7±0.3%) and 93 age and waist circumference-matched healthy male controls (age: 33±7.3 years; BMI: 26.1±3.9 kg/m²; waist circumference: 94.6±11.9 cm; HbA1c: 5.7±0.3%) participated in this cross-sectional

study. Blood was sampled in the fasting state and 90 min after ingestion of a standardized liquid meal (2,268 kJ).

Results: Compared to healthy controls, patients were characterized by elevated fasting levels of glucose, proinsulin, C-peptide and glucose-dependent insulinotropic polypeptide (GIP) and higher postprandial levels of insulin, proinsulin, C-peptide and GIP. Also, patients exhibited elevated plasma levels of C-reactive protein and signs of dyslipidemia. Fasting plasma levels of insulin, glucagon, glucagon-like peptide-1 (GLP-1), ghrelin, leptin, adiponectin, tumor necrosis factor-alpha, plasminogen activator inhibitor 1, interleukin 6 and postprandial levels of glucagon, GLP-1, ghrelin, leptin and adiponectin did not differ between groups.

Discussion: Presenting with an insulin resistant-like pattern, including beta cell hypersecretion and elevated GIP levels, non-diabetic antipsychotic-treated patients display emerging signs of dysmetabolism and a compromised cardiovascular risk profile. The appetite regulating hormones, GLP-1 and ghrelin appear not to be influenced by antipsychotic treatment. Our findings provide new clinical insight into the pathophysiology behind metabolic side-effects of antipsychotics, and put emphasis on the importance of implementing metabolic screening into psychiatric practice.

Poster #S9

ELECTRONIC MEASUREMENT OF MOVEMENT DISORDERS: VALIDITY AND RELIABILITY

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Background: When treating psychotic disorders it is important to determine the optimal antipsychotic dose for a patient. An optimal dose can improve medication compliance and reduce the discomfort and stigmatization associated with movement disorders (Caliguri et al., 2006). Subclinical bradykinesia could be a valid measure for the optimal antipsychotic dose. This idea is based on the findings that antipsychotics are effective at a D2 receptor occupancy above 65%, and that up until a D2 receptor occupancy of 80%, bradykinesia does not occur or merely in a very subtle form (Seeman, 2002). Rating scales are the conventional method of assessing bradykinesia in a clinical setting, for example the Unified Parkinson Disease Rating scale (UPDRS). However, due to their limited sensitivity rating scales are not well suited to measure subtle forms of bradykinesia, furthermore, to achieve a good inter-rater reliability intensive training is required. Electronic movement registration might offer a solution for measuring subtle forms of bradykinesia, because it is potentially more sensitive, more reliable and less subjective than observer based rating scales. The aim of this study is to determine the validity and reliability of an electronic device that measures bradykinesia.

Methods: 75 patients treated at GGz centraal (Amersfoort, The Netherlands) will be included. Included are patients treated for psychotic symptoms with antipsychotic medication. The validity is determined by comparing the rating on the UPDRS with the score based on the electronic measurement. The reliability is determined by comparing the scores of the electronic device in 25 randomly selected patients with the scores on a second electronic measurement administered a day later. The electronic measurement consists of four tasks; walking, elbow flexion/extension, lower arm pronation/supination and a leg agility task. The selection of tasks is based on a pilot study we performed (Mentzel et al., 2013). Movements are captured using six inertial sensors (XSENS, Enschede, The Netherlands) attached to the upper and lower arm, the upper and lower leg and the lower back using velcro straps.

Results: At the time of submission 66 of the 75 patients are included. The final results on the validity and reliability of this electronic device that measures bradykinesia will be presented at the conference.

Discussion: The discussion and conclusion will be presented at the conference.

Poster #S10

POLYPHARMACY TO COUNTERACT ANTIPSYCHOTIC-INDUCED WEIGHT GAIN AND METABOLIC ADVERSE EFFECTS IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Data regarding effective strategies to manage antipsychotic-induced metabolic adverse effects are limited. Using concomitant medications to counteract these adverse effects may be a rational option. We performed a systematic review and meta-analysis regarding the effectiveness of medications to counteract antipsychotic-induced metabolic adverse effects in patients with schizophrenia.

Methods: Published articles from 1950 to September 2013 were searched using EMBASE, MEDLINE, PsycINFO, PubMed, and the Cochrane Library. Clinical trial registries were searched for unpublished trials. Double-blind randomized placebo-controlled trials focusing on patients with schizophrenia were included if they reported on changes in antipsychotic-induced metabolic adverse effects using concomitant medications as a primary outcome. Two independent authors extracted variables related to participants, interventions, comparisons, outcomes and study design. For continuous outcomes, the inverse variance statistical method and random effects model were used to calculate mean differences. For dichotomous outcomes, the Mantel-Haenszel statistical method and random effects model were used to determine odds ratios. The primary outcome was change in body weight. Secondary outcomes included clinically relevant weight change, fasting glucose, hemoglobin A1c, fasting insulin, insulin resistance, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides.

Results: From the initial list of 1092 records, 40 published and 7 unpublished studies were identified; of these, 39 trials representing 19 unique interventions were included in this meta-analysis. Concomitant metformin was the most extensively studied drug in regards to body weight, with a mean difference of -3.17kg (95% confidence interval: -4.44 to -1.90kg) compared to placebo; however, results were highly heterogeneous ($I^2=88\%$). Synthesized effects for topiramate, sibutramine, aripiprazole and reboxetine were also significant. Metformin was the only drug with evidence of clinically relevant weight change in both prevention and treatment studies. Taking together the limited data in regards to glucose metabolism and blood lipids, metformin and rosiglitazone improved insulin resistance, while aripiprazole, metformin and sibutramine decreased blood lipids.

Discussion: Although additional drug costs, side effects of concomitant drugs themselves, possibility of drug interactions, and paucity of data regarding certain interventions need to be taken into account, polypharmacy in this context may warrant a prudent individualized consideration. The current evidence points to a possible use of adjunctive metformin in order to counteract weight gain and other metabolic adversities with ongoing antipsychotic treatment in schizophrenia.

Poster #S11

THE JOINT EFFECT OF SOCIAL ADVERSITY IN CHILDHOOD AND IN ADULTHOOD ON PREDICTING PSYCHOSIS

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Background: There is robust evidence that social adversity in childhood and in adulthood are separately associated with an increased risk of psychosis (Agid O et al. 1999, Morgan C et al. 2008, Stilo S. et al. 2012). We moved beyond the study of each exposure separately by looking at synergistic

effects. We sought to clarify whether social adversity in childhood (defined as presence of separation and/or loss from one or both parents before age of 17) and in adulthood (defined as presence of social disadvantage) combined in the onset of psychosis.

Methods: As part of the GAP, Wellcome, and EU-GEI studies, we collected information on social adversity from a sample of first episode psychosis patients (n=507) and in a control sample (n=425) recruited from the areas in South-East London covered by the South London and Maudsley NHS Foundation Trust. To assess interaction on an additive scale we used Interaction Contrast Ratio [ICR] to assess the combined effect of social adversity in childhood (no/yes) and social adversity in adulthood (no/yes), on outcome status (case/control). Confidence intervals and p-values for Interaction Contrast Ratio [ICR] were calculated using the nlcom procedure in STATA 11.

Results: We found evidence that adversity in childhood and adulthood combined synergistically to increase odds of psychosis. In those exposed to childhood adversity alone the OR was 1.80 (95% CI 1.20–2.70); in those exposed to adult adversity alone the OR was 7.03 (95% CI 4.67–10.59); and in those exposed to both it was 13.26 (95% CI 8.59–20.47). The combined effect was greater than the sum of the individual effects (Interaction Contrast Ratio [ICR] 5.42, 95%CI 0.10–10.73, p=0.04).

Discussion: There was strong evidence that childhood adversity and adulthood adversity combined synergistically to increase odds of psychosis beyond the effect of each individually. Essentially, there were some people who developed psychosis who would not have developed it if either social adversity in childhood or adversity in adulthood had been absent.

Poster #S12

INCREASED PRE-SYNAPTIC STRIATAL UPTAKE OF DOPAMINE AS A POTENTIAL MECHANISM OF ANTIPSYCHOTIC FAILURE

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Background: Antipsychotic failure is a common consequence of chronic treatment in schizophrenia [1]. The neurobiology of treatment failure is unknown. Animal models have captured antipsychotic failure after 14 days continuous treatment with osmotic pumps [2,3]. Although dopamine D2 receptor supersensitivity accompanied antipsychotic failure in those models, it was not sufficiently explicative of treatment failure [2]. Numerous pre-clinical studies unambiguously report that 2–3 weeks antipsychotic treatment leads to a decrease of extracellular dopamine basal levels in the striatum. We found this to occur specifically during treatment failure, but not during treatment efficacy, in an animal model [3]. Decreased extracellular dopamine basal levels lead to a decreased homeostatic negative feedback. It may potentiate dopamine signalling by keeping the release of dopamine constant, which might overwhelm antipsychotic inhibition and eventually causes treatment failure. We enquired whether antipsychotic induced-decrease of dopamine basal levels might be due to an increased dopamine transporter activity, decreased release capacity or decreased dopamine synthesis. We measured the monoamine transporters and tyrosine hydroxylase (TH) concentrations at different intervals of haloperidol treatment as an index of dopamine uptake and synthesis changes, respectively. Then, we measured dopamine release after local potassium (K⁺) infusion in target brain areas during treatment failure.

Methods: Microdialysis: Extracellular dopamine was sampled from nucleus accumbens, caudate-putamen and medial prefrontal cortex in vehicle and haloperidol treated (0.5 mg/kg/d, 14 days) rats before and after an infusion (via reversed dialysis) of 100 mM K⁺. HPLC was used for dopamine quantification. We also measured the extracellular concentrations of haloperidol before and after potassium infusion with GC-MS. Western-blotting: dopamine, serotonin, noradrenalin transporters (DAT, SERT, NET) and TH expressions were measured in nucleus accumbens, caudate-putamen and medial prefrontal cortex specimens from control and haloperidol treated rats, after 2, 6 and 14 days treatment. Protein levels were measured in the synaptosomal fractions as well as in total extracts.

Results: Fourteen days haloperidol treatment reduced basal dopamine (P<0.05). Potassium infusion induced dopamine release in control and haloperidol treated rats (P<0.05), with no between-group differences (P>0.05). Surprisingly, we found that also haloperidol was released after

local K⁺ challenge (P<0.05). DAT expression was increased in a subgroup of rats after 14 days treatment compared to control group in the caudate-putamen (P<0.05). TH levels were increased as a function of DAT levels after 14 days haloperidol treatment.

Discussion: In animal models, haloperidol effects on behaviour might decay after 14 days treatment because of an increased striatal DAT activity which decreases extracellular dopamine basal levels. This effect is accompanied by increased TH levels, which may potentiate the availability of ready-to-release dopamine. DAT activity was significantly increased only in a subgroup of rats resembling the clinical phenomena where only a percentage of subjects face treatment failure. Finally, it was unexpected that haloperidol was co-released with dopamine when locally stimulated with K⁺. We suggest that the adaptations observed here, together with the well known D2 supersensitivity, might offer the ground to better understand the neurobiological mechanisms of antipsychotic action and failure.

Poster #S13

DNA METHYLATION AND GABAERGIC PATHOLOGY OF SCHIZOPHRENIA

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Background: Schizophrenia is a severe mental illness with its origins in disturbances of neuronal development and a subtle brainpathology in which deficits in specific GABAergic neuronal subtypes areapparent. This is demonstrated by decreases in markers of GABAergic neuronal functions, such as expression of thesynthesising enzyme glutamic acid decarboxylase (GAD) and parvalbumin, aprotein present in a subgroup of GABA-containing interneurons. Several animal paradigms, such as isolationrearing, sub-chronic PCP administration and neonatal inflammatory challenge, that model aspects of schizophrenia also result in deficits of parvalbumin,indicative of GABAergic pathology underlying the abnormal behaviors in these models. Recent studies have demonstrated abnormalities in DNA methylation invarious indicators of GABAergic function in schizophrenia. These abnormalities include both indicators of a general hypermethylation in brain regions important in the pathology of the disease, and effects on specific components of GABAergic neurons. These findings suggest that a hyperfunctional DNAmethylation may be responsible for deficiencies in GABAergicneurotransmission. There is also evidence suggesting that such effects may be ameliorated by antipsychotic drug treatment. Asyet, however, these effects have not been investigated in the animal models that mimic aspects of schizophrenia. The main of this work was to evaluate if there is a hypermethylation the parvalbumin gene in brain tissue from different areas from subjects with schizophrenia that relates to the parvalbumin deficit seen in the disease and if there is a hypermethylation the parvalbumin gene in brain tissue from chronic animal models associated with parvalbumin deficits.

Methods: For this we used brain tissue from Nottinghamseries of post-mortem samples of patients with schizophrenia and control subjects. Methylation levels (as a percentage for each subject) at each CpGsite within the sequence chosen were determined following bisulphite reactionand pyrosequencing. We investigated DNA methylation in brain tissue (different areas) of animals undergoing chronic PCP administration, which we find to induce a long-lasting decrease in parvalbumin-positive cells, and behavioral effects reminiscent of some symptoms of schizophrenia.

Results: Our results showed an high increase in the levels of DNA methylation in the third CpG site of the promoter region for parva lbumin gene at hippocampus of rat brains undergoing chronic PCP administration when compared with control animals (130%; p<0.05), while any alteration was found in prefrontalcortex (PFC). The results from human brain samples showed any alterations in PFC or hippocampus.

Discussion: These results indicate a possible alteration in DNA methylation associate with the decrease in the parvalbumin levels in schizophrenia in the rat models, probably associated with the drug effect and could help us to understand the mechanism that underlie the suppression of parvalbumin expression in both the disease and rat models.

Poster #S14**PRENATAL IMMUNE ACTIVATION IMPAIRS SYNAPTIC DEVELOPMENT IN THE ABSENCE OF OVERT GLIAL PATHOLOGY**Sandra Giovanoli¹, Urs Meyer²¹*Physiology and Behaviour Laboratory, ETH Zürich;* ²*Physiology and Behavior Laboratory, ETH Zurich*

Background: Impairments in synaptic development and functioning have been strongly implicated in the etiopathology of schizophrenia and related disorders. Such deficits appear to be caused, at least in part, by genetic predisposition factors affecting the development of synaptic circuits. Such genetic risk is likely complemented by the negative consequences of exposure to environmental adversities operating at critical stages of brain development. Maternal infection during pregnancy is one such environmental factor that has attained increasing recognition in this context. However, the effects of prenatal infection on synaptic development are only marginally explored.

Methods: We used a mouse model of maternal administration of the viral mimetic poly(I:C) (5 mg/kg, i.v., gestation day 9) to explore the consequences of prenatal viral-like immune activation on synaptic development. Offspring were first tested in a Y-maze working memory paradigm and the prepulse inhibition (PPI) test of sensorimotor gating to confirm the long-term behavioral impact of prenatal poly(I:C) exposure. Post-mortem immunohistochemical analyses of pre- and post-synaptic markers (synaptophysin, synaptosomal-associated protein 25 [SNAP-25], Bassoon, post-synaptic density protein 95 [PSD-95]) were then performed to study the effects of prenatal immune activation on the expression of synaptic proteins in distinct layers of the hippocampus. In addition, we quantified the total (Iba1-positive) and activated (CD68-positive) microglia and astrocytes (GFAP-positive) to explore whether the anticipated alterations in synaptic markers would be associated with overt glial pathology. All investigations were performed in peri-puberty and adulthood so as to assess possible maturation-dependent effects of prenatal immune activation.

Results: Prenatal poly(I:C)-induced immune activation led to impaired working memory in peri-pubertal and adult offspring, whereas the poly(I:C)-induced PPI deficiency showed a post-pubertal delay and only emerged in adult offspring. Protein levels of the pre-synaptic markers synaptophysin, SNAP-25, and Bassoon were significantly reduced in the hippocampus of adult (but not in peri-pubertal) poly(I:C) offspring, indicating altered maturation of hippocampal active zone proteins involved in pre-synaptic vesicle exocytosis. On the other hand, prenatal poly(I:C) exposure led to an age-independent reduction in the hippocampal levels of the post-synaptic density protein PSD-95. These synaptic changes occurred in the absence of overt glial pathology: Neither markers of total (Iba1) or activated (CD68) microglia, nor astrocytes (GFAP) were significantly altered in the hippocampus of poly(I:C) offspring relative to controls.

Discussion: Our findings demonstrate that prenatal immune activation disrupts normal synaptic development of the hippocampus. Pre-synaptic abnormalities appear to be dependent on post-pubertal maturational processes and may therefore be relevant especially for those behavioral pathologies with adult onsets. In contrast, changes in the post-synaptic density proteins PSD-95 are manifested already during peri-pubertal maturation and may be linked to age-independent cognitive deficits such as working memory impairment. Our study further highlights that prenatal immune change can significantly disrupt behavioral/cognitive functions and synaptic development without being associated with persistent glial pathology.

Poster #S15**A MOUSE MODEL OF 22Q11 DELETION SYNDROME EXHIBITS DEFICITS IN BEHAVIORS RELEVANT TO THE CORE DOMAINS OF SCHIZOPHRENIA**Zoe A. Hughes, Radka Graf, Ashley Hanks, Susan Lotarski, Alexander I. More, Stacey Sukoff Rizzo, Liam Scott, Polina Stolyar
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Background: Approximately 20–25% of individuals with a chromosome 22q11.2 microdeletion develop schizophrenia. Mouse models have been engineered to delete the 23 syntenic genes of mouse chromosome 16 [Df1(16)1+] and serve as tools for investigating the range of domains

affected in schizophrenia. In the present studies we characterized 22q11 mice in assays aligned with the positive, negative and cognitive symptoms of schizophrenia.

Methods: Multiple cohorts of adult male 22q11 HET mice and their wild-type (WT) littermates (Df(16)1+; Paylor et al., 2001) were characterized in a range of assays. To assess “positive symptom-like” behaviors: prepulse inhibition (PPI) of acoustic startle was assessed using 3 prepulse intensities (3, 7, 9 dB) and stimulant-induced locomotor activity after amphetamine administration (0.56–3.2 mg/kg) was measured. To assess potential deficits in motivation (akin to negative symptoms), mice were tested in the progressive ratio assay where mice were food restricted and trained to nose poke for a food reward. To determine whether the mutation caused a cognitive phenotype, mice were tested for their ability to distinguish between a familiar and novel arms of a Y-maze. To assess spatial working memory, mice were trained in the touchscreen location discrimination reversal task and their performance assessed using stimulus locations with varying degrees of separation. The final cohort of mice was implanted with electrodes in the medial prefrontal cortex and CA1 to measure hippocampal-prefrontal network activity during a spatial working memory task using the T-maze.

Results: PPI was significantly reduced in HET mice at all prepulse intensities ($F(1,56)=12.59$; $P=0.001$). No genotype dependent differences were observed in habituated or amphetamine-stimulated locomotor activity ($P>0.05$). In progressive ratio, HET mice performed less nose pokes for rewards than WT mice ($F(1,22)=11.63$; $P=0.003$). In the Y-maze there was no effect of genotype, however in the location discrimination task HET mice were less able to discriminate between adjacent stimulus locations ($P<0.05$). In the electrophysiology study, HET mice were slower to acquire the T-maze task ($P=0.045$) and showed reduced hippocampal-prefrontal coherence in the theta range ($P=0.001$).

Discussion: These studies demonstrated a behavioral phenotype of 22q11 HET mice in PPI – an assay relevant to positive symptoms and in progressive ratio which is relevant to negative symptoms of schizophrenia. While the 22q11 HET mice did not show a phenotype in the Y-maze, in the other spatial memory tasks (T-maze and location discrimination reversal) which involved multiple sessions of training, HET mice showed some cognitive deficits. Furthermore, the deficit in coherence suggests impaired hippocampal-prefrontal network connectivity. This mouse model captures the key domains impacted in schizophrenia and could be useful for identifying novel treatments for schizophrenia.

Poster #S16**COMPARISON OF PHENCYCLIDINE-INDUCED DEFICITS IN MORRIS WATER MAZE TASK AND ITS REVERSAL BY SERTINDOLE BETWEEN WISTAR AND LISTER HOODED RATS**Jouni Ihlainen, Katja Savolainen, Jarkko Hiltunen, Markus M. Forsberg
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Background: The Morris water maze task is the most commonly used maze-based test to measure visuo-spatial components of learning and memory in rodents. Treatment with a NMDA-receptor antagonist, phencyclidine (PCP), has been shown to induce positive, negative and cognitive impairments relevant to schizophrenia in rats. Some second generation antipsychotics have been shown to partly reverse PCP-induced deficits in spatial navigation in Wistar rats. The most pronounced improvement was seen with sertindole but also risperidone and clozapine have restored water maze performance to some extent (Didriksen et al., 2007). However, pigmented (hooded) rats were used in the original version of the water maze task, probably due to their better vision. The aim of this study was to compare PCP-induced deficits in spatial navigation and reversal of deficits by sertindole in Wistar and Lister Hooded rats to assess whether the latter are more suitable in modeling of schizophrenia-like cognitive deficits and in testing of novel drug candidates.

Methods: A total of 248 male rats (Wistar: n=123 and Lister hooded n=125) were used. In the water maze test, the animal has to learn to locate a hidden escape platform in the pool. The rats were subjected to three swimming trials per day for four consecutive days. On day five, the probe trial was performed. PCP treatment was started 3 days before the first swimming trial. On test days, PCP was administered 30 min and sertindole 60 min before the test. The following parameters were measured in each trial: distance, latency, swim speed and platform finders. All compounds

were injected in a volume of 5 ml/kg (s.c). The treatment groups in water maze experiments were as follows: 1) PCP dose-response study: Wistar and Lister hooded rats, PCP 1.3–2.0 mg/kg; 2) Sertindole dose-response study: Wistar and Lister hooded rats, sertindole 0.6–1.6 mg/kg (PCP 2.0 mg/kg); 3) Main experiment: Wistar and Lister hooded rats, PCP 2.0 mg/kg and sertindole 1.6 mg/kg. The results are expressed as mean±SEM and analyzed by MANOVA followed by post-hoc Tukey test.

Results: PCP dose-response experiment revealed that already the lowest dose of PCP (1.3 mg/kg) caused significant deficits in spatial navigation in Lister hooded rats ($p<0.01$). In contrast, only highest PCP dose (2.0 mg/kg) impaired water maze performance in Wistar rats ($p<0.05$). Sertindole dose-response experiment revealed that sertindole 1.6 mg/kg was the most effective dose to reverse the PCP-induced deficit in spatial navigation in both strains. In the main experiment, sertindole 1.6 mg/kg did not reverse the PCP-induced (2.0 mg/kg) deficits in water maze performance in Wistar rats ($p>0.2$) but it significantly improved spatial navigation in Lister hooded rats ($p=0.001$).

Discussion: These findings indicate that PCP induces deficits in water maze performance at lower dose in Lister hooded rats than that in Wistar rats. Moreover, sertindole partly reverses PCP-induced spatial navigation deficits in Lister hooded rats but similar effects are not apparent in Wistar rats. In conclusion, Lister hooded rats seem to show better PCP-induced visuospatial learning and memory deficits than Wistar rats and thus are better in modeling the cognitive deficits relevant to schizophrenia.

Poster #S17

ARE DOPAMINE PARTIAL AGONIST ANTIPSYCHOTICS SIMILAR? PRECLINICAL COMPARISON OF ARIPIPRAZOLE, BIFEPRUNOX AND CARIPRAZINE

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Background: Aripiprazole, bifeprunox, and cariprazine are partial agonists at dopamine (DA) D₂, D₃ and serotonin 1A (5-HT_{1A}) receptors;¹ each compound is currently in a different developmental stage. We present head-to-head preclinical in vitro and in vivo comparisons of these 3 compounds.

Methods: Receptor binding assays were performed in membrane preparations from CHO cells transfected with human receptors. Functional activities were measured in rat striatum and hippocampus ([³⁵S]GTPγS binding for D_{2/3} and 5-HT_{1A}), or in CHO cells transfected with human D₂ or D₃ receptors (cAMP formation). In vivo assays included measurement of dopamine (DA) and serotonin (5-HT) turnover from rat striatum, olfactory tubercles, and prefrontal cortex; several different behavioral assays were performed to evaluate antipsychotic-like and procognitive activity.

Results: All 3 compounds showed subnanomolar affinity for DA D₂ (K_i [nM]: bifeprunox, 0.1; aripiprazole, 0.19; cariprazine, 0.49) and D₃ receptors (K_i [nM]: bifeprunox, 0.070; cariprazine, 0.085, aripiprazole, 0.94) and nanomolar affinity for 5-HT_{1A} receptors (K_i [nM]: aripiprazole, 1.1; bifeprunox, 1.1; cariprazine, 2.6). Aripiprazole and cariprazine displayed subnanomolar affinity for 5-HT_{2B} receptors (K_i values are 0.25 nM and 0.58 nM, respectively), bifeprunox showed much lower affinity for this receptor (K_i: 19 nM). The 3 compounds showed different and assay-dependent levels of agonism at DA D₂, D₃, and 5-HT_{1A} receptors. Aripiprazole and cariprazine did not show G-protein activation (ie, [³⁵S]GTPγS binding) in membranes from rat striatum and CHO cells expressing DA D₂ or D₃ receptors; in contrast, bifeprunox was slightly stimulatory (40%). All 3 drugs potently and fully antagonized DA-induced stimulation of [³⁵S]GTPγS binding in these preparations. In CHO cells expressing D₂ and D₃ receptors, the 3 drugs showed full (D₂: 92–96%) or partial agonism (D₃: aripiprazole, 48%; cariprazine, 42%; bifeprunox, 84%) in cAMP signalling. In D₃ receptor expressing cells, all 3 drugs only partially (up to 50–80%) antagonized DA-stimulated cAMP formation. In vivo, aripiprazole and cariprazine enhanced while bifeprunox did not change dopamine turnover in rat brain. Aripiprazole and cariprazine were partial agonists while bifeprunox was a full agonist at 5-HT_{1A} receptors in rat hippocampal membrane; only aripiprazole and cariprazine reduced 5-HT turnover in rat cerebral cortex. Despite these subtle differences in their neurochemical actions, all 3 drugs displayed antipsychotic-like activity in various behavioural

assays (eg, apomorphine-induced climbing, amphetamine-, MK801- and PCP-induced hyperlocomotion, conditioned avoidance response) and low cataleptogenic effects. Bifeprunox and cariprazine, but not aripiprazole, attenuated scopolamine-induced learning deficits in rats.

Discussion: Aripiprazole is approved for the treatment of schizophrenia and bipolar mania. Cariprazine showed positive results in multiple clinical trials in schizophrenia and bipolar mania and is currently in late stage clinical development. In contrast, bifeprunox development was terminated because of its insufficient efficacy in clinical trials. In rodent behavioral models they all showed antipsychotic-like activity with similar efficacy; however, in some in vitro tests bifeprunox displayed more agonist-like properties than aripiprazole and cariprazine and it qualitatively and sharply differed from the latter two in the DA turnover assays. The observed activity of bifeprunox in these assays may explain its limited clinical efficacy in schizophrenia.

Reference:

[1] Newman-Tancredi A et al.: Curr. Opin. Invest. Drugs. 2007; 8:539–554.

Poster #S18

ADVANCED PATERNAL AGE AS A RISK FACTOR FOR SCHIZOPHRENIA: A TRANSLATIONAL STUDY IN HUMANS AND RATS

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Background: Advanced paternal age (APA) is a well-replicated risk factor for schizophrenia. Even though it is understood that its effect is mainly caused by de novo mutations, the pathophysiological mechanisms occurring in offspring are not well understood. To gain a deeper understanding of these effects, paternal age was experimentally manipulated in rats and also investigated in a human cohort.

Methods: A sample of 370 healthy subjects was investigated with 3-Tesla structural MRI, the SPQ-B as well as the NEO-FFI. Rats were either offspring of 2 or 12 month old fathers, maternal age was kept constant at 2 months. Rodent offspring completed a number of tasks, including tests of social play behavior after 24h of social isolation.

Results: While rodent offspring of older fathers did not display any anomalies in a variety of tests (including maternal care behavior, motor behavior, learning, sucrose preference etc.) they showed a significant pattern of reduced 50 kHz vocalizations during social play with other rats, that is, in an appetitive measure of pro-social behavior. In humans, paternal age was correlated with hippocampal and anterior operculum size in the right hemisphere as well as increased fiber-tract integrity of the fasciculus uncinatus. In addition, paternal age was correlated with schizotypal behavior and elevated levels of neuroticism.

Discussion: The results demonstrate an influence of APA on social behavior in rodents and in humans. In addition, hippocampus and anterior operculum size are correlated with APA. In this study we could show that APA has a distinct influence on social behavior in offspring, which –due to reduced social functioning– might render these subjects more prone to the development of psychosis.

Poster #S19

PERIPUBERTAL HIGH FAT DIET EXPOSURE LEADS TO A DOPAMINE-DEPENDENT DISRUPTION OF SENSORIMOTOR GATING IN ADULTHOOD

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Background: Overconsumption of energy-dense foods, particularly high fat diets (HFD), has long been recognized to induce neuronal adaptations and lead to impairments in various forms of learning and memory. Owing to its impact on cognitive functions, we hypothesized that the negative consequences of HFD exposure may be extendable to other basic brain

functions, including central information processing. Central information processing is known to be disturbed in patients with schizophrenia and related disorders. Moreover, schizophrenic patients often display metabolic disturbances even prior to the initiation of chronic antipsychotic medication and are frequently reported to consume saturated fat diets more excessively than healthy controls. Yet, the extent to which excessive HFD intake in this clinical population may actually contribute to the emergence of psychopathological symptoms such as impaired information processing remains elusive. To gain more insights into these issues, the present study aimed at determining whether HFD exposure disrupts information processing in the form of sensorimotor gating.

Methods: We fed C57BL6/N male mice a diet containing either 60% (HFD) or 10% (LFD) of its calories derived from fat for 8 weeks throughout adolescent development (postnatal days [P] 28 to 84), after which they were subjected to the prepulse inhibition (PPI) test of sensorimotor gating. We also collected the brains of HFD and LFD animals to determine whether PPI levels correlate with presynaptic dopaminergic markers such as tyrosine hydroxylase (TH). Furthermore, we investigated whether the dopamine receptor antagonist haloperidol (HAL) might be effective in mitigating the anticipated disrupting effects of HFD on PPI. Finally, we examined whether the impact of chronic HFD consumption on sensorimotor gating might be influenced by the precise timing of diet exposures by exposing mice to HFD specifically during the peripubertal (P28 to P56) or adult (P70 to P96) stages of maturation.

Results: First, we revealed that adult mice exposed to chronic HFD throughout adolescent development displayed significant deficits in PPI compared to LFD-fed mice. Identical chronic HFD treatment further led to presynaptic dopaminergic abnormalities in the form of increased TH density in the nucleus accumbens (NAc) core and shell subregions. Moreover, we found that TH density in the NAc shell negatively correlated with the mean PPI scores, suggesting a potential contribution of the NAc dopamine system to HFD-induced PPI deficits. This impression was further supported by showing that the HFD-induced attenuation of PPI can be mitigated by systemic HAL. Finally, HFD feeding was sufficient to disrupt PPI when its exposure was restricted to the peripubertal period, whilst the same manipulation failed to affect PPI when limited to adulthood.

Discussion: Our findings thus demonstrate for the first time that excessive consumption of HFD may lead to schizophrenia-relevant behavioral deficits in the form of impaired sensorimotor gating, and that such deficits may depend on HFD-induced abnormalities in the NAc dopaminergic system. The present data further indicates that the peripubertal period is particularly detrimental to the deleterious effects of nutritional adversities, thus adding further support to the hypothesis that early-life environmental challenges may be critical in (adversely) shaping long-term brain and behavioral functions.

Poster #S20 SPREADING DEPRESSION MIMICS THE BEHAVIORAL FEATURES OF SCHIZOPHRENIA

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Background: Spreading depression (SD) known as an evoked neuronal activity and changes in ionic, metabolic and hemodynamic characteristics of the brain. From a clinical perspective SD plays a pathophysiological role in several neurological disorders, e.g., migraine, cerebrovascular disease, epilepsy, transient global amnesia, stroke, subarachnoid hemorrhage, and spinal cord disease. Pronounced release of dopamine in mesolimbic pathway, remarkably in nucleus accumbens during SD and the noted role of increased dopamine in schizophrenia suggests that SD could be a predisposing factor for the occurrence of schizophrenia.

Methods: To test this hypothesis, male Wistar rats (60–80gr) randomly chosen in 3 groups. For induction of repetitive SD, 3 mol/L KCl was injected four times in rats during 4 weeks. After 4 weeks rats' anxiety were evaluated using elevated plus-maze. Furthermore, all three groups of rats spent comparable times in social contact in order to determine social interaction. In the present study, we also tested the possible effect of SD induction on prepulse inhibition (PPI).

Results: SD induced rats had decreased threshold of anxiety in compar-

ison with control group. The percentage of aggressive behavior was also increased in SD induced rats. Finally, the amount of prepulse inhibition was decreased significantly in SD group of animals.

Discussion: The results suggest that SD can mimic some behavioral features of schizophrenia and might be a useful animal model in the study of this disease.

Poster #S21 CHARACTERIZATION OF A MOUSE MODEL OF THE 1Q21.1 MICRODELETION SYNDROME

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Background: Recently, a handful of copy-number variants (CNV) have been found in several independent studies to strongly increase the risk of schizophrenia. These CNVs constitute the first recurrent genetic alterations with high odds-ratios for schizophrenia. The 1q21.1 microdeletion syndrome with hemizygous deletion of 8 genes on human chromosome 1q21.1 is associated with an about 10-fold increased risk of developing schizophrenia. Other alterations are also observed in some carriers including mild intellectual disability and ADHD. The 1q21.1 microdeletion usually involves hemizygous deletion of an 8 gene segment: PRKAB2, FMOS, CHD1L, BCL9, ACP6, GJA5, GJA8 and GPR89B.

Methods: We have generated a mouse model (Df(h1q21)/+) of the 1q21.1 microdeletion by hemizygous deletion of the orthologous region in mice. The model was characterized in a broad behavioral test battery with focus on schizophrenia-relevant parameters. Further behavioral and electrophysiological experiments were performed to explore the altered dopaminergic signaling in the mice.

Results: Df(h1q21)/+ mice exhibit selective alterations in dopaminergic signaling. No effects of genotype were seen on gross brain morphology or basic functions such as reflexes, thermal pain sensitivity and motor performance. Baseline exploratory behavior, motility, anxiety, and prepulse inhibition were also unaltered in hemizygous mice. However, Df(h1q21)/+ mice displayed increased hyperactivity in response to amphetamine challenge. Furthermore, hemizygous mice were more sensitive to the disruptive effects of amphetamine and PCP on prepulse inhibition. Selective probing of the direct pathway (using the DA D1 agonist SKF81297) revealed no differences in induced activity between Df(h1q21)/+ mice and wild types, suggesting a presynaptic dysfunction. Electrophysiological characterization of dopamine neuron firing in the ventral tegmental area revealed an altered basal firing pattern in Df(h1q21)/+ mice.

Discussion: Df(h1q21)/+ mice show putative presynaptic changes in the dopamine system and an increased sensitivity to both amphetamine and PCP, reminiscent to what has been described in patients with schizophrenia. Given its strong construct validity, the Df(h1q21)/+ model may be used to gain insight into schizophrenia-relevant alterations in dopaminergic transmission. Further electrophysiological characterization of the mesolimbic dopamine neurons is ongoing.

Poster #S22 THE ANTI-ANHEDONIC PROPERTIES OF LURASIDONE IN THE CHRONIC MILD STRESS MODEL ARE ASSOCIATED WITH SYNAPTIC AND NEUROPLASTIC CHANGES IN THE RAT PREFRONTAL CORTEX

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Background: It is well established that the depressive phenotype is associated with profound changes in different brain structures, which are characterized by impaired synaptic function and reduced neuronal plasticity. With this respect, it is important to establish to what extent long-term treatment with psychotropic drugs is able to normalize genes and proteins whose expression and function is altered in animal models that have predictive validity for psychiatric disorders. In the present study we have investigated the antidepressant and neuroplastic properties of the

antipsychotic drug lurasidone in the chronic mild stress (CMS) model of depression.

Methods: Male Wistar rats were exposed to CMS for 2 weeks and sucrose consumption was used to distinguish between susceptible and non-susceptible animals. Control and CMS-susceptible rats were then randomized to receive chronic vehicle or the novel antipsychotic drug lurasidone (3 mg/kg/day) for 5 more weeks, while continuing the stress procedure, in order to evaluate the antidepressant properties and molecular changes set in motion by chronic drug treatment.

Results: After 2 weeks of CMS, 60–70% of the animals develop anhedonia and this is associated with reduced expression of a pool of BDNF transcripts that may be targeted to the synaptic compartment, suggesting the contribution of the neurotrophin to the behavioral dysfunction produced by CMS. The down-regulation of BDNF expression persisted until the end of the stress procedure (7 weeks) in vehicle-treated rats, whereas chronic lurasidone treatment was able to revert stress-induced anhedonia and normalized BDNF mRNA levels in the prefrontal cortex of CMS rats. We also found that prolonged exposure to CMS (7 weeks) produces synaptic deficits within the prefrontal cortex, as shown by reduced expression of PSD-95, as well as glial pathology, with a significant reduction of GFAP mRNA levels. These alterations, which reproduce changes observed in depressed subjects, were normalized by chronic treatment with lurasidone.

Discussion: Our results demonstrate that lurasidone shows antidepressant properties in the CMS model and this may occur through the modulation synaptic and neuroplastic proteins as well as through the regulation of glial function. The adaptive changes set in motion by chronic treatment with lurasidone may ameliorate functional capacities, closely associated with neuronal plasticity, which are deteriorated in patients with major depression and stress-related disorders.

Poster #S23

UPREGULATION OF STRIATAL DOPAMINE D2 RECEPTORS RESULTS IN PERSISTENT ALTERATIONS IN PRE-SYNAPTIC DOPAMINE FUNCTION

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Background: To model the increase in striatal Dopamine D2 receptor (D2R) activity observed in patients with schizophrenia, we previously generated transgenic mice which selectively and reversibly overexpress D2Rs in the striatum (D2R-OE mice). D2R-OE mice display phenotypes similar to the cognitive deficits of schizophrenia including impaired performance in assays of working memory, behavioral flexibility, conditional associative learning, and timing. We previously reported that expression of the D2R transgene during development is sufficient for these cognitive deficits to persist in adulthood, and that these behavioural phenotypes are accompanied by changes in cortical dopamine function. D2R overexpression restricted to the striatum led to alterations in the prefrontal cortex (PFC) of dopamine tissue levels, rates of dopamine turnover, and activation of D1 receptors in the prefrontal cortex. In addition, we have identified changes in inhibitory transmission and dopamine sensitivity in the PFC of D2R-OE mice.

Methods: That increased D2Rs restricted to the striatum led to changes in dopamine function in the cortex suggests that some central component of the dopamine system is perturbed in D2R-OE mice. We hypothesized that these changes may occur at the level of presynaptic dopamine neuron activity. We have therefore performed single-unit extracellular recordings combined with juxtaglomerular labeling and post hoc immunohistochemical identification of midbrain dopamine neurons *in vivo* from anaesthetized D2R-OE mice and their control littermates. We also performed single cell molecular analysis on identified VTA dopamine neurons in D2R-OE and control mice.

Results: We found that increased D2R activity in the striatum selectively affected the electrophysiological properties of identified dopamine neurons in the ventral tegmental area (VTA), while the firing properties of dopamine neurons of the substantia nigra (SN) were similar to controls. Specifically,

VTA dopamine neurons *in vivo* showed a reduced mean rate of spontaneous firing, which is generally thought to regulate dopamine tone, and also a reduction in burst firing activity, which is likely to impact fast phasic dopamine release. When D2R activity was normalized by switching off the transgene, the mean firing rate was rescued but the reduction in burst activity persisted. Because burst activity of dopamine VTA neurons has been shown to depend on NMDA receptor function, we performed single-cell molecular analysis of VTA dopamine neurons and found alterations in the level of mRNA for multiple NMDA-R subunits.

Discussion: In summary, our results show that the observed abnormalities in burst firing, which may underlie some of the persistent cognitive deficits, result from developmental rather than concurrent expression of the D2R transgene. This suggests that early striatal changes may have a lasting impact on core functions of dopamine neurons that may contribute to the enduring cognitive symptoms suffered by patients with schizophrenia.

Poster #S24

ABNORMAL STRESS RESPONSIVITY IN A RODENT DEVELOPMENTAL DISRUPTION MODEL OF SCHIZOPHRENIA

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Background: Although numerous studies have implicated stress in the pathophysiology of schizophrenia, less is known about how the effects of stress interact with genetic, developmental and/or environmental determinants to promote disease progression. In particular, it has been proposed that in humans, stress exposure in adolescence could combine with a predisposition towards increased stress sensitivity, leading to prodromal symptoms and eventually psychosis. However, the neurobiological substrates for this interaction are not fully characterized. Previous work in our lab has demonstrated that rats born to dams administered with the DNA-methylating agent methylazoxymethanol acetate (MAM) at gestational day 17 exhibit as adults behavioral and anatomical abnormalities consistent with those observed in patients with schizophrenia. We hypothesized that juvenile and adolescent MAM-treated animals would demonstrate altered behavioral and physiological responses to both acute and repeated stressors as compared to their saline-treated counterparts (SAL).

Methods: Single cohorts of MAM and SAL rats were exposed to inescapable footshock stress throughout development at prepubertal, peripubertal and adult time points. In these animals, we recorded and quantified 22kHz ultrasonic vocalizations (USVs) emitted in response to acute footshock and analyzed total number of calls, call duration and call frequency, as well as freezing behavior. In a separate experiment, we exposed adolescent MAM animals to 10 days of inescapable footshock stress (PND 31–40). Body weight gain was measured throughout the stress protocol, and plasma corticosterone levels were measured following acute, as well as repeated footshock exposure.

Results: We found that juvenile (PND 22) MAM-treated rats emitted significantly more calls, spend more time vocalizing and emitted calls at a higher rate in response to acute footshock stress when compared with SAL animals. Juvenile MAM-treated animals also exhibited more freezing behavior than SAL animals following the period of active footshock. None of these differences were present in adult animals. In addition, adolescent MAM animals exposed to footshock stress for 10 consecutive days did not show any differences in weight gain as compared to their MAM-SHAM counterparts. Finally, adolescent MAM-treated animals displayed a blunted HPA axis corticosterone response to acute footshock that did not adapt after 10 days of stress exposure.

Discussion: These data demonstrate abnormal stress responsivity in the MAM model of schizophrenia and suggest that these animals are more sensitive to the effects of stress in youth. This finding is consistent with human epidemiological data showing that, in children at risk for schizophrenia, those that show the greatest response to stressors are most likely to develop schizophrenia. In addition, this is the first report describing HPA axis abnormalities in MAM animals, and paves the way for future studies exploring a role for these abnormalities in mediating the expression of

schizophrenia-like phenotypes observed in this model. Finally, these findings lend support to the idea that stress during puberty and adolescence is indeed a contributing factor to the transition to psychosis, and that controlling stress at this vulnerable period may circumvent these pathological changes and prevent the emergence of psychosis later in life.

Poster #S25

ABERRANT A-I RNA EDITING PROFILE IN THE BRAINS OF SCHIZOPHRENIA PATIENTS

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Background: RNA editing has been implicated in the pathophysiology of schizophrenia. A-to-I RNA editing is an enzymatic conversion of genetically encoded Adenosine to Inosine that is recognized as Guanosine by the cellular translational machinery. Such RNA editing events can "re-code" the pre-mRNA message and may lead to modifications of the biochemical properties of the expressed proteins. Studies have shown that proper RNA editing is essential for the development of the CNS and for sustaining neural functioning mediated by the fine tuning of proteins involved in brain neurotransmission. In the current study, we aimed to identify genes that are subjected to deregulation of brain RNA editing in schizophrenia patients compared to non-affected controls.

Methods: Cortical brain tissue (BA10) from post mortem of schizophrenia patients (n=12) and controls (n=12) was kindly provided by the Harvard Brain Tissue Bank. To evaluate RNA editing profile, we used a multi sample, focused targeted DNA enrichment experimental system that is coupled to next generation sequencing platform. Using the Fluidigm Access Array system for library construction allows combining the throughput benefits of microfluidics with flexibility of PCR. This platform enables the parallel amplification and sequencing of 71 RNA editing sites located in the coding sequence of 44 genes in a single experiment- facilitating high throughput profiling of RNA editing patterns.

Results: We observed a general decrease in the levels of A-to-I RNA editing in schizophrenia patients compared to the non-affected controls. RNA editing rates were found to be significantly lower in the schizophrenia samples in as many as 19 out of the 71 editing sites which were evaluated ($P<0.05$). Among these genes are neurotransmitter receptors including GABRA3 (gamma-aminobutyric acid receptor subunit alpha-3 precursor, 17% decrease in RNA editing in schizophrenia samples compared to control), GRIA4 (glutamate receptor 4 ionotropic, AMPA 4, 25.1% decrease in RNA editing in patients), GRIK1 (glutamate receptor ionotropic, kainate 1, 12.53% decrease in RNA editing in patients) and two editing sites of the HTR2C gene (5-hydroxytryptamine receptor 2C, 36.31% and 25.32% decrease in RNA editing in patients).

Discussion: To date, scarce reports described deregulated RNA editing in specific genes in brains of schizophrenia patients, mostly the 5HT2C serotonin receptor. Using a high throughput platform, we were able to show a general decrease in brain RNA editing levels in schizophrenia samples compared to controls, and identify novel genes that are subjected to deregulated RNA editing that may be relevant to the pathophysiology of schizophrenia. These results suggest that aberrant A-I RNA editing may play a role in the etiology of schizophrenia and that specific RNA editing pattern might serve as a biomarker for the disease.

Poster #S26

WHITE BLOOD CELL LEVELS ARE RELATED TO POOR SOCIAL FUNCTIONING AND REDUCED INSULA, AMYGDALA, AND NUCLEUS ACCUMBENS VOLUMES IN A SUBGROUP OF PEOPLE WITH SCHIZOPHRENIA

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Background: Schizophrenia is a disease with significant biological het-

erogeneity. Previous studies have detected elevations in neutrophils and cytokines in the blood of at least some individuals with schizophrenia, suggesting that immune activation may be a component of the disease. Identifying markers for subgroups of patients with immune activation may lead to more effective, individualized treatments.

Methods: Peripheral blood cell counts, symptom severity ratings and structural MRI data were obtained from 93 individuals with schizophrenia or schizoaffective disorder and 23 healthy controls not significantly different on measured demographic variables. Symptom severity scores were obtained on the patients using the Positive and Negative Syndrome Scale. Daily functioning, depression ratings and schizotypal personality ratings (in healthy controls) were obtained using the Depression, Anxiety and Stress Scale, Short Form Health Survey 36 items, version 2, the Schizophrenia Quality of Life Scale, and the Schizotypal Personality Questionnaire. 3T structural MRI scans, which were available for 55 individuals with schizophrenia, were processed using Freesurfer to yield voxel-based brain volumes for specific regions of interest (ROIs). Subgrouping of data was done using SPSS to perform a recursive two-step cluster analysis. ROIs were chosen a priori based on function and a whole cortex analysis was performed to assess changes in overall brain volume.

Results: There was no significant difference in red blood cell count; however, the percent ratios of 3 of the 5 white blood cell (WBC) types between schizophrenia and healthy control groups were significantly different (neutrophil increased: $F(1,115)=8.450$, $p<0.01$, lymphocyte decreased: $F(1,115)=6.782$, $p<0.01$, basophil decreased: $F(1,115)=6.636$, $p<0.05$). The clustering analysis based on the percentage distribution of WBCs from the entire cohort produced three groups, two defined by opposite neutrophil and lymphocyte ratios, as well as an equal ratio group. The proportion of people with schizophrenia to healthy controls (31/2) was significantly different in the high neutrophil/low lymphocyte group compared to the ratio in either the low neutrophil/high lymphocyte (25/11) or equal ratio group (37/11) ($\chi^2=6.624$, $p<0.05$). These groups were not significantly different with respect to any demographic measures or antipsychotic treatment. Absolute neutrophil measurements showed a significant relationship with social functioning ($B=-0.507$, $R=0.507$, $F(1,29)=9.697$) and anxiety ($B=0.411$, $R=0.411$, $F(1,29)=5.897$) scores only in the high neutrophil/low lymphocyte group where the higher the level of neutrophils, the worse the social functioning. After taking into account age and sex in the model we also obtained significant inverse relationships between absolute neutrophil levels and right insula ($B=-0.355$, $R=0.495$, $F(53,2)=8.598$, $p<0.001$), left amygdala ($B=-0.304$, $R=0.304$, $F(54,1)=5.488$, $p<0.05$), left nucleus accumbens ($B=-0.269$, $R=0.269$, $F(54,1)=4.200$, $p<0.05$) and overall cortical ($B=-0.261$, $R=0.543$, $F(52,3)=7.264$, $p<0.001$) volumes.

Discussion: This study is the first to link peripheral white blood cell differences with symptomatic severity and brain volume reductions in a subgroup of individuals with schizophrenia. Elevated levels of neutrophils in these patients may indicate a chronic inflammatory process at work. It paves the way for use of more effective treatments of individuals with schizophrenia who concurrently display abnormal immune profiles.

Poster #S27

THE INFLAMMATION PARADOX: A LONGITUDINAL STUDY MONITORING BIOMARKERS OF IMMUNE FUNCTION FROM BEFORE BIRTH TO AFTER DIAGNOSIS IN NON-AFFECTIVE PSYCHOSIS CASES AND MATCHED CONTROLS

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Background: Our previous report indicated that acute phase proteins (APP), which are markers of inflammation and innate immune function, tended to be lower amongst cases compared to matched controls when measured in dried neonatal bloodspots (NDBS). However, previous studies have indicated that increased levels of inflammatory cytokines such as TNF-alpha and IL-8 in maternal serum samples were associated with risk of non-affective psychoses, and many studies describe elevated levels of inflammatory markers in affected cases at or after the time of diagnosis compared to controls. The aim of this study was to longitudinally characterize acute phase proteins in maternal serum samples drawn early in

pregnancy, NDBS taken at the time of birth, and adult plasma samples taken at the time of enrollment.

Methods: The study population for this case-control study was selected from individuals born in northern Sweden between 1975 and 1985, identified with the use of Swedish register data. Non-affective psychoses were defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and International Classification of Disease (ICD-9 and -10). Maternal serum samples were available for 138 cases and 394 age- and sex-matched controls. NDBS were available for 100 cases and 196 controls who consented to their collection. 87 cases and 183 controls further consented to have a blood sample taken at the time of enrollment. The concentration of nine different APP were measured in each sample using a magnetic bead-based multiplex panel (Bio-Rad, Hercules, CA, USA): alpha-2 microglobulin (a2m), C-reactive protein (CRP), haptoglobin, serum amyloid P (SAP), procalcitonin (PCT), ferritin, tissue plasminogen activator (tPA), fibrinogen, and serum amyloid A (SAA).

Results: Median values for all APP except ferritin were lower in maternal serum from cases compared to controls. Similarly, median values for a2m, SAP, PCT, and tPA were lower in NDBS from cases compared to controls. However in adult plasma samples, median CRP, tPA, haptoglobin, PCT, and SAA levels were higher in cases compared to controls, while levels of a2m and SAP remained lower in cases compared to controls. Values of APP were not correlated between maternal serum and NDBS, nor were they correlated between NDBS and adult plasma samples.

Discussion: To our knowledge, this is the first longitudinal biomarker study in a population diagnosed with non-affective psychoses to include perinatal as well as adult samples. The pattern of lower APP in cases compared to controls in perinatal samples was reversed in samples taken from adults after the time of diagnosis. Findings of lower APP in cases compared to controls in both maternal serum samples as well as NDBS are in contrast to the "Maternal Immune Activation" hypothesis that posits that inflammation during gestation increases risk for schizophrenia and non-affective psychoses later in life. Our study was, however, generally consistent with previous studies in adults, showing that some, but not all, APP were higher in cases compared to controls. Future studies include investigation of cytokines in maternal serum samples, to compare with the APP signature in maternal serum as well as to compare directly to previous studies. Additionally, we plan studies of antibodies to infectious agents and dietary antigens in the longitudinal sample set, in order to study whether exposures during different periods of life are correlated with changes in APP patterns over the life course.

Poster #S28

IMMUNE RESPONSE TO STRESS IN POSTPARTUM PSYCHOSIS

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Background: Postpartum Psychosis (PP) is a severe psychiatric disorder associated with childbirth. The incidence has been estimated at 1 or 2 in 1000 deliveries (Munk-Olsen T, et al., 2006). PP is considered predictable: up to 50% of women with a history of bipolar or schizoaffective disorder or up to 70% of women with a previous history of PP will suffer PP after giving birth (Jones I, et al., 2001). The onset is usually acute, within the first two weeks after delivery (Myint-Germeyns I, et al., 2007). Although PP occurs in conjunction with the biological changes of childbirth, its neurobiological basis is still poorly understood. Stress and inflammation may play a role in the development of Postpartum Psychosis, but little research has been done in both areas. The aim of this study was to investigate the role of stress and inflammation, examining the women's personal perception of stress and biological markers.

Methods: Twenty-one healthy women, 16 women at risk of PP and 14 women with PP, matched for age, ethnicity and education were included in the study and recruited from the South London and Maudsley (SLAM) NHS Foundation Trust (London, UK). All of them completed the Perceived

Stress Scale (PSS: Cohen and Williamson, 1988), a self-report questionnaire measuring the perception of stress. Samples of blood were collected to measure the high sensitivity-C Reactive Protein (hs-CRP), a marker of inflammation. Data were analyzed using the Statistical Package for Social Sciences, Version 21.0 (SPSS). One-way ANOVA, followed by LSD post-hoc tests, was used to investigate differences in continuous variables between PP women, at risk of PP women and healthy controls. We correlated the PSS score with hs-CRP value using Pearson's correlation.

Results: Women with PP and at risk of PP had higher scores on the Perceived Stress Scale compared to controls (N=13, M=19.00, SD=6.22; N=16, M=16.00, SD=7.75; N=21, M=8.48, SD=7.32, for PP, at risk of PP and controls, respectively; F(2)=9.87, p<0.001). These results show that women who have PP or who are at risk of PP perceive that the demands placed upon them exceed their ability to cope; therefore they perceive themselves as being more stressed than healthy postpartum women. Employing the LSD post-hoc test, women with PP showed a hyperactivation of the immune response, with significantly higher hs-CRP level compared with healthy controls (p=0.039). There was no significant difference in hs-CRP level between women at risk of PP and controls and between women at risk of PP and women with PP. The scores of the Perceived Stress Scale were positively correlated with hs-CRP level ($r=0.297$, N=47, p=0.042).

Discussion: We found higher levels of perceived stress in women with PP and those at risk of PP compared to healthy women. Moreover, biological abnormalities were observed, especially a hyperactivation of the inflammatory system in women with PP but not in women at risk of PP. These results suggest that inflammation may play a role in the onset of PP. The increased perception of stress and its correlation with a higher immunological response in women with PP needs to be further explored in order to understand the link between them.

Poster #S29

CEREBROSPINAL FLUID BIOMARKERS FOR SCHIZOPHRENIA REVEALED BY A cICAT PROTEOMIC ANALYSES

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Background: Recent studies suggest that cerebrospinal fluid (CSF) is mainly produced from brain tissue, rather than choroid plexus. The molecules released from each brain cell can directly diffuse into CSF. There are already established protein biomarkers for brain disorders, such as tau, p-tau and beta-amyloid proteins for Alzheimer's disease (AD), which can diagnose AD with high (80–90%) sensitivity and specificity. A proteomic approach by mass spectrometry (MS) has been improved rapidly in terms of labeling method, device performance, peptide identification algorithms and bioinformatics. Thus, in the present study, we aimed to develop biomarkers that can be used for diagnose, stratify and surrogate clinical aspects of schizophrenia, using a MS proteomic approach on CSF samples.

Methods: We first analyzed the CSFs from two case-control cohorts each containing 10 patients with schizophrenia and 10 controls. High abundant proteins were depleted by antibody column, and the remaining proteins were labeled by cleavable isotope coded affinity tag (cICAT). The samples were then trypsin-digested to peptides, divided into 30 fractions by strong cation exchange column and each fraction was analyzed by nano-liquid chromatography tandem MS. The primary data was merged and analyzed by HiSpec software based on Mascot database. The quantitative values of 656 proteins were then analyzed in terms of correlation with symptoms measured by PANSS, and the difference between schizophrenia and control group. The consensus between two cohorts was selected as candidate protein. The candidates were then verified using ELISA and CSF sample cohort consisting 40 schizophrenia and 40 controls.

Results: From cICAT proteome analyses on two sets of schizophrenia-control cohorts, we have selected 14 candidates among 656 proteins. Six proteins were selected because there were significant difference ($p<0.05$, t-test) in the expression levels between schizophrenia and the control

group, in both cohorts. Other 8 proteins were selected because there were significant correlation ($|r|>0.5$, pearson's correlation) between the expression levels and the PANSS scores (total, positive, negative or general) in the schizophrenia group, confirmed in both cohorts. Among the 14 proteins, we evaluated 11 proteins using each ELISA kit and larger sample cohort. Three proteins survived the verification; the level of one protein was increased in schizophrenia group and the levels of other 2 proteins were significantly correlated with the negative PANSS score. There were several findings detected by ELISA analyses. The level of one protein was significantly decreased in schizophrenia, and the levels of two proteins tended to be altered in schizophrenia. Also we found that the levels of several proteins were significantly correlated with cognitive function measured by Brief Assessment of Cognition in Schizophrenia in a Japanese-language version (BACS-J).

Discussion: We discovered several novel biomarker proteins for schizophrenia by a proteomic analyses and traditional ELISA methods. Five proteins that the expression levels were altered in schizophrenia can be used as diagnostic and classification markers as well as drug-targets. Two proteins that the expression levels were correlated with PANSS negative score can be used as surrogate markers and drug targets for negative symptoms. Also, unexpectedly, we found several proteins, that the expression levels were strongly correlated with BACS-J score. The proteins can be used as surrogate markers and drug target for cognitive function, which supposed to be central and debilitating aspects of schizophrenia.

Poster #S30

REVERSE-TRANSLATING BIOLOGICAL MARKERS FOR DISC1-ASSOCIATED BEHAVIORAL DISORDERS TO HUMAN PATIENTS

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Background: Chronic mental illnesses like schizophrenia or the recurrent affective disorders are caused by a combination of environmental and genetic factors. To date, diagnosis of those conditions is based entirely on clinical interview since - in the absence of a defined neurobiology - no assisting biological diagnostics is available. We have previously identified insoluble, aggregated Disrupted-in-schizophrenia 1 (DISC1) protein in post mortem brain material of patients with chronic mental illness, and tentatively termed this subset of neuropatho-biochemically defined conditions "DISC1opathies" assuming similar DISC1-involving pathophysiology. Our goal is to find ante mortem biological diagnostic markers able to identify patients with DISC1opathies.

Methods: We generated a transgenic rat model overexpressing full length human DISC1 and high-affinity monoclonal antibodies to human DISC1 allowing sensitive detection of the DISC1 protein in a variety of tissues. The rat displayed subtle behavioral changes consistent with a disturbance in dopamine homeostasis and perinuclear DISC1 aggregation (tgDISC1 rat; these findings are subject of another presentation submitted to SIRS 2014). We took advantage of this rat model to identify biological diagnostic markers present in the tgDISC1 rat but not in the littermate control. We used candidate, transcriptomic and proteomic approaches to analyze cerebrospinal fluid (CSF), plasma and peripheral blood mononuclear cells (PBMC). In addition, the same animals were subjected to a small animal NMR scan. Ultimately, candidate biomarkers identified in the tgDISC1 rat will then be tested in a cohort of patients with chronic mental illness.

Results: We could clearly detect DISC1 expression in lymphocytes of tgDISC1 rats and humans suggesting that DISC1 expression levels are a potential mental-illness dependent marker. We could also see high concentrations of DISC1 protein in the cerebrospinal fluid (CSF) of tgDISC1 rat indicating that the DISC1 protein is cleared from the brain via CSF and an additional direct window to DISC1 pathophysiology of the brain. Systematic microarray studies of lymphocytes and proteomics from CSF will be reported, as well as our attempts to transfer our insights on specific biomarkers in the tgDISC1 rat to similar tissues of patient cohorts. Our data from brain imaging of the tgDISC1 rat vs. control with NMR will be presented.

Discussion: There is urgent need for reliable diagnostic biological markers. These markers may not comprise all cases of one clinically defined diagnosis but rather be specific for subsets of biologically defined mental

illness categories, like, for example, DISC1-related behavioral disorders, or DISC1opathies. Our attempt to model such a behavioral disorder was successful in the tgDISC1 rat and now allows us to define biological diagnostic markers in more detail. In the second step, this will allow reverse translation of biological diagnostic markers to human patients from biologically defining disease categories.

Poster #S31

NEUTROPHIN BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) IN PSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Brain-derived neurotrophic factor (BDNF) is associated with the pathogenesis of several neuropsychiatric diseases but there are few studies evolving Systematic Lupus Erythematosus (SLE). The aim of this study was to investigate whether the plasma BDNF levels were associated with disease activity in SLE patients with severe psychiatric (PSLE) such as psychosis and major depression.

Methods: We assessed twenty-five severe PSLE patients (psicosis=13; major depression=12). All patients were diagnosed with SLE according to the ACR diagnostic classification criteria and the neuropsychiatric (NP) manifestations were classified following the ACR 1999 consensus. The diagnosis of psychiatric manifestations was based on the Structured Clinical Interview for DSM-IV Clinical Version (SCID-CV28), which had been translated and validated for the Portuguese language. All diagnoses were performed by trained psychiatrist. The plasma BDNF levels were measured at two different time-points: during active disease and after achieving remission. Disease activity was assessed according to the SLEDAI score. The plasma BDNF was measured by ELISA.

Results: We observed an inverse correlation between the plasma BDNF levels and the SLEDAI ($r=-0.54$; $p<0.0001$). The plasma BDNF levels in the stage of remission were significantly higher compared to the stage of active disease ($4,151\pm 1,289$ pg/uL versus $2,862\pm 1,475$ pg/uL, respectively; $p=0.009$), indicating that occurred an increased in BDNF levels in parallel with the improvement of psychiatric symptoms. These time points were separated by an interval of 2.36 ± 3.52 years.

Discussion: The plasma BDNF levels varied in an inversely proportional manner to SLE activity. In addition, the BDNF levels increased with the control of SLE activity. This finding is quite interesting because BDNF is thought to be a neurotrophic factor that is crucial for neuronal repair. Therefore, the elevated levels observed may point to the participation of BDNF in tissue repair following pharmacological treatment. All these findings point to the potential use of BDNF as a biomarker of the SLE treatment response. However, studies with a larger number of patients and more strict control of medications liable to interfere with plasma BDNF levels are needed to confirm our findings.

Poster #S32

PERIPHERAL BDNF: A CANDIDATE BIOMARKER OF HEALTHY NEURAL ACTIVITY DURING LEARNING IS DISRUPTED IN SCHIZOPHRENIA

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Background: Brain-derived neurotrophic factor (BDNF) is an important regulator of synaptogenesis and synaptic plasticity underlying learning. However, a relationship between circulating BDNF levels and brain activity has not been reported. Reduced brain BDNF levels are found in schizophrenia and functional neuroimaging studies of probabilistic association learning have demonstrated reduced activity in a neural network that includes the

prefrontal and parietal cortex, and the caudate nucleus in schizophrenia. We predicted that brain activity would positively correlate with peripheral BDNF levels during probabilistic association learning in healthy adults and that this relationship would be altered in schizophrenia.

Methods: Twenty-five healthy adults and 17 people with schizophrenia or schizoaffective disorder performed a probabilistic association learning test during functional magnetic resonance imaging (fMRI). Plasma BDNF levels were measured by ELISA.

Results: We found a positive correlation between circulating plasma BDNF levels and brain activity in the right parietal cortex in healthy adults. There was no relationship between plasma BDNF levels and task-related activity in the prefrontal, parietal or caudate regions in schizophrenia. A direct comparison of these relationships between groups revealed a significant difference.

Discussion: This is the first study to show a relationship between peripheral BDNF levels and cortical activity during learning suggesting that plasma BDNF levels may reflect brain activity in healthy humans. The lack of relationship between plasma BDNF and task related brain activity in patients demonstrates that circulating blood BDNF is not related to frontal-parietal-striatal activity during learning in schizophrenia.

Poster #S33

REDUCED DEACTIVATION IN MEDIAL PREFRONTAL CORTEX DURING AN INNER SPEECH TASK IN SCHIZOPHRENIA PATIENTS WITH AUDITORY VERBAL HALLUCINATIONS

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Background: Patients with schizophrenia often experience auditory verbal hallucinations, a phenomenon that has been explained as inner speech misattributed to an external source. However, the exact neural correlates of AVH and the relationship to the neural processes of inner speech are still unclear. We investigated brain activation during a performance based inner speech task in hallucinating schizophrenia patients as compared to healthy controls and non-hallucinating schizophrenia patients. We expected an aberrant response in hallucinating patients in brain areas that are involved in speech receptive processes.

Methods: Hallucinating patients (N=29), non-hallucinating patients (N=16) and healthy controls (N=39) performed a metrical stress evaluation task during fMRI scanning. In the phonetic condition, bisyllabic words were visually presented and subjects had to indicate which syllable carried the metrical stress by imagining hearing the words. The contrast maps of the phonetic condition > baseline were added in a full-factorial design, and the main effect of task in the three groups was calculated. Post-hoc comparisons were used to determine significant pairwise contrasts. Differences in accuracy and reaction times between the three groups were evaluated with ANOVA and post-hoc tests.

Results: The main effect of group for the phonetic > baseline condition shows a large cluster in the rostral part of the left medial frontal gyrus (MFG) extending into the left and right rostral part of the anterior cingulate cortex (ACC) ($k=173$, $p_{\text{FWE}}=0.002$). The hallucinating patients did not deactivate this area, whereas the non-hallucinating patients and healthy controls demonstrated deactivation. Post-hoc tests between the three groups confirm this result, although the contrast between hallucinating and non-hallucinating patients did not survive FWE correction. The hallucinating patients showed slower reaction times than the healthy controls during metrical stress evaluation ($p=0.019$), but the three groups were equally accurate.

Discussion: The rostral part of the middle frontal gyrus and anterior cingulate gyrus are found to be part of the Default Mode Network (DMN), the most active network in the brain during periods of rest, without external stimulation (Buckner et al. 2008). This state is associated with introspective processes. Garrity et al. (2007) found that hallucinations correlated positively with DMN activation during rest periods, as it is thought that schizophrenia patients with AVH are more focused on internal processes. Possibly, the hallucinating patients in present study showed greater resting state activity during the resting blocks, and thus deactivate less than the

non-hallucinating patients and healthy controls when an external stimulus appeared.

Poster #S34

IMPOVERISHED HIGH-FREQUENCY OSCILLATORY ACTIVITY IN FRONTAL CORTEX IN INDIVIDUALS WITH SCHIZOPHRENIA DURING IMPLICIT SEQUENCE LEARNING

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Background: Schizophrenia-related impairments in implicit and explicit learning undermine goal setting and achievement and are critical factors in determining functional and occupational outcome. These learning impairments that are currently not targeted by psychopharmacological and psychosocial interventions are thought to be driven in part by aberrant oscillatory patterns in key regions. Individuals with schizophrenia have showed impaired performance on most explicit learning tasks. However, studies that have investigated implicit learning in schizophrenia with Serial Reaction Time Tasks (SRTT) have produced inconclusive results. Increasing evidence suggests that schizophrenia-related implicit learning deficits are associated with functional abnormalities of the frontal cortex. Here we use magnetoencephalographic imaging (MEG-I) to test the hypothesis that impoverished frontal oscillatory activity over could impede efficient implicit sequence learning in individuals with schizophrenia.

Methods: MEG-I data were collected using a 275-channel biomagnetometer (VSM MedTech) from 10 individuals with schizophrenia and 10 healthy subjects during a modified SRTT. In each block, a train of speech sounds (/e/, /i/, /o/, /u/) was presented in the auditory domain either randomly or in an eight-step movement sequence. For each trial, individuals were instructed to repeat into an optical microphone the speech sound. Individuals were presented with a random block followed by three sequence blocks containing the sequence to learn and ending with a post-training random block. Adaptive spatial filtering and Bayesian algorithms implemented in the Neurodynamic Utility Toolbox for MEG were used to estimate neural sources in the time-frequency domains. Neural oscillatory power changes were computed in four frequency bands (theta (3-7), alpha (8-12), beta (15-25), gamma (30-50), high-gamma (70-160Hz) using overlapping time windows (200 ms/150 ms/100 ms) with a sliding step size of 10ms.

Results: Change in reaction time between sequence and random trials was statistically significant in healthy subjects ($p=0.01$) but not in individuals with schizophrenia ($p=0.3$). In healthy subjects, changes in beta-activity during sequence learning progressed from left-hemisphere language regions prior to the response (-70ms) to motor, frontal and temporal regions bilaterally post response (70 ms, 210 ms). In schizophrenia, impoverished beta power was observed over frontal cortices from -70ms to 210 ms, bilaterally. During sequence learning, an increase in high-gamma power localized to bilateral frontal cortex was observed in healthy subjects around the response onset. Changes in gamma activity progressed from frontal and temporal regions (-70ms) to bilateral motor and temporal regions post-response (70 ms, 210 ms). In individuals with schizophrenia, regions of frontal cortices involved in speech reception and production showed reduced changes in high-gamma activity post response (70 ms, 210 ms).

Discussion: In this study, we found significant implicit sequence learning impairment among people with schizophrenia consistent with impoverished beta and high gamma frontal activity. Reduced high-frequency neural synchrony in these regions could represent a neuroimaging-based marker that predicts deficits in auditory learning as well as receptiveness to neuroplasticity-based interventions. Further studies are needed to investigate whether neuroplasticity-guided cognitive training interventions that target these key neurophysiological processes have the potential to restore frontal oscillatory activity and hence improve implicit learning and functional outcome in schizophrenia.

Poster #S35**AFFECTIVE THEORY OF MIND AND ITS RELATIONSHIP WITH IMPAIRED INSIGHT IN PATIENTS WITH SCHIZOPHRENIA: AN FMRI STUDY**

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Background: Impaired insight is a common feature in patients with schizophrenia where it affects about 50 to 80% of the patients. It has a negative impact on the outcome of the illness, underlying the importance of investigating the underlying factors. Patients with schizophrenia often show impaired ability to affective Theory of Mind (affective TOM; or: affective mentalizing). Affective TOM is the ability to understand mental and emotional states of others and to predict someone's behavior based on that belief state. Several studies show less brain activation in patients with schizophrenia during an affective TOM-task. In this study, we used an affective TOM task to examine the relationship between brain activity and impaired insight in patients with schizophrenia.

Methods: A total of 35 patients with schizophrenia and with varying levels of insight viewed social scenes in an fMRI-scanner. Each social scene consisted of a False Belief character or a True Belief character. Patients were asked to identify the emotion of the character (emotion recognition) or to predict what the character would feel if he/she had full knowledge about the situation (emotion inference). Insight was measured using the Schedule of Assessment of Insight - Expanded (clinical insight, SAI-E) and the Beck Cognitive Insight Scale (cognitive insight, BCIS).

Results: We found that stronger activation of regions involved in emotion inference of the affective TOM (right temporal pole, left precuneus and right insula) was associated with better cognitive, but not clinical insight.

Discussion: These findings suggest a relationship between impaired cognitive insight and activation in brain areas that are involved in predicting other people's emotion based on a belief state. Thus, perspective taking and the ability to evaluate other people's beliefs and emotions, and use that information to reflect upon oneself could be an important underlying factor in the understanding and treatment of impaired cognitive insight.

Poster #S36**SIMULTANEOUS EEG-FMRI STUDY OF CHRONIC SCHIZOPHRENIC PATIENTS WITH AUDITORY HALLUCINATIONS**

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Background: Functional neuroimaging techniques are powerful tools to explore and understand the pathophysiology of auditory hallucinations (AHs). Several electrophysiological and fMRI studies have attempted to identify the neuronal trigger mechanisms underlying AHs by looking into the activation course preceding the onset of these spontaneous episodes. Nevertheless, prior methods were able to map only selective aspects of brain function and are limited with regard to spatial and temporal resolution. Therefore, we aim to use for the first time simultaneous EEG-fMRI acquisitions in a AHs capture experiment, in order to combine the findings and assess the spatiotemporal coupling between frequency alterations in neuronal oscillations (EEG) and hemodynamic signal activations (fMRI) over the course of the hallucinations.

Methods: Six chronic patients indicated the presence of AHs by pressing

a button during the time-course of simultaneous EEG-fMRI acquisitions. As a control group, four patients whose AHs were successfully controlled with medication, performed an inner-speech and verbal memory task. All subjects were clinically assessed with PSYRATS and PANSS scales, and gave written informed consent. EEG signals were recorded using a MR-compatible system with 64 electrodes while fMRI data were collected in a 3 T scanner. For the EEG frequency analysis, power spectral density was calculated in time intervals prior and following AHs (or control task) onsets. Normalized spectral power was obtained from three frequency bands (theta, alpha and beta) across eight regions of interest. The fMRI analysis was computed using AHs (or control task) onsets, along with pre and post time shifts, in different event-related designs to obtain a set of activation maps of AHs-onset surroundings.

Results: EEG spectral profiles, as well as fMRI activation maps, showed consistent differences between the hallucinatory and control patients. The hallucinatory group revealed a predominant theta band power and a statistically significant increase of this band activity, in cortical language and auditory areas, after AHs-onset. Interestingly, these findings were associated to significant fMRI activated regions preceding the AHs onset. Furthermore, hemodynamic activity in controls during inner-speech task was located in frontal areas, apparently without significant related changes in EEG spectral activity.

Discussion: These findings suggest that multimodal simultaneous EEG-fMRI techniques may elucidate the remaining questions about neuronal mechanisms underlying the initiation of AH episodes. Our results have demonstrated that both modalities are correlated during the spontaneous onset AHs, with EEG power modifications in specific frequency bands linked to hemodynamic activations in language and auditory cortical areas. We believe that this will provide a promising framework for insightful characterization of AHs in schizophrenia.

Poster #S37**SELF-REFLECTION IN SCHIZOPHRENIA: A PRELIMINARY ACTIVATION-LIKELIHOOD ESTIMATION META-ANALYSIS**

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Background: Lack of insight is a prominent feature of schizophrenia. Recently more research has focused on the neurological underpinnings of insight and self-reflection using neuroimaging. However, current evidence has been inconsistent as to which brain regions are the most affected in impaired self-reflection. In this meta-analysis we aim to address the research question of whether there are any significant differences in brain activation patterns between schizophrenia patients and healthy controls when performing self-reflection tasks.

Methods: A systematic search of Pubmed and Medline was performed with the keywords: (1) "neuroimaging" "fMRI" "PET", (2) "insight" "self-reflection" and (3) "schizophrenia" "psychosis". Only neuroimaging studies reporting contrasts between schizophrenia patients and healthy controls (with the exception of one study which used psychosis-proneness) with self-reflection tasks at a whole-brain level were selected; this strategy resulted in 8 studies (7 fMRI and 1 SPECT studies). Studies reporting functional connectivity and results from small volume correction were excluded. Using Brainmap GingerALE 2.3 the activation likelihood maps of statistically significant peak were computed. We converted MNI space coordinates into Talairach using GingerALE's convert foci function. We used GingerALE's single studies function and analysed four data sets individually: self-reflection > other-reflection, schizophrenia patients > healthy controls (15 foci); self-reflection > other-reflection, healthy controls > schizophrenia patients (6 foci); self-reflection > baseline, schizophrenia patients > healthy controls (16 foci); and self-reflection > baseline, healthy controls > schizophrenia patients (11 foci) with the false discovery rate (FDR) method to correct for multiple comparisons at a significance threshold of $P < 0.05$ and a cluster threshold of 100.

Results: The ALE analysis for self > other, schizophrenia patients > healthy controls yielded one cluster: schizophrenia patients demonstrated significantly greater activation in the right medial frontal gyrus (Brodmann's Area 10) with a volume of 120mm³, weighed centre (Talairach coordinates) x=36.01, y=49.47, z=16.8, extrema value=0.0083 and maximum ALE value

x=36, y=50, z=16. On the other hand the ALE analysis for self > baseline, schizophrenia patients > healthy controls yielded two clusters (both BA9). Schizophrenia patients showed significantly greater activation in the bilateral superior frontal gyri (left= Cluster 1, right= Cluster 2). Cluster 1 had a volume of 488mm³, weighed centre (Talairach coordinates) x=-4.85, y=56.45, z=22.17, extrema value=0.0144 and maximum ALE value x=-4, y=56, z=22 whereas Cluster 2 had a volume of 464mm³, weighed centre (Talairach coordinates) x=6.8, y=48.64, z=29.68, extrema value=0.0112 and maximum ALE value x=-6, y=50, z=30. No cluster was reported for the other two datasets.

Discussion: Due to the small number of studies available, the number of experiments and foci included was sub-optimal. Nevertheless, significant differences in ALE maps were found in schizophrenia patients who activated more of the superior and medial frontal gyri. The medial frontal region of the brain is a part of the cortical midline structures (CMS) which have been frequently studied as key areas in self-referential processing. The lack of significant activation in other CMS areas such as the anterior cingulate is likely to be resulted from a lack of experiments included. The observation that schizophrenia patients activated more of these regions than healthy controls could be due to a compensatory mechanism indicating a requirement of more effort when performing self-reflection tasks.

Poster #S38

LANGUAGE-RELATED LATERALIZATION BEFORE AND AFTER ANTIPSYCHOTIC TREATMENT IN PRODROMAL OR FIRST-EPISTOLE PSYCHOSIS: AN FMRI STUDY

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Background: Language disorder is one of the core symptoms of schizophrenia. Previous neuroimaging studies have found abnormal lateralization while performing language-related task in patients with schizophrenia. However, little is known whether the aberrant language-related lateralization could be reversed after treatment with antipsychotics in drug-naïve ultra-high risk (UHR) or first-episode psychotic (FEP) patients. This study aimed to investigate changes of language-related lateralization, clinical symptoms, and language-related functions after antipsychotics treatment.

Methods: Eleven drug-naïve patients (6 FEP and 5 UHR patients) and eleven age, sex and handedness-matched healthy controls were recruited. The patients received low dose aripiprazole treatment (average dose of 6.5 mg/day) for 4 weeks and clinical ratings with the Positive and Negative Syndrome Scale (PANSS) before and after treatment. All 22 subjects underwent fMRI examinations using a semantic judgment task at baseline and 4–6 weeks later. The magnitudes of brain activations were defined by using SPM and compared within and between groups before and after treatment.

Results: In the patient group, there were significant improvement in the total PANSS ($p<0.01$), positive subscale ($p<0.05$), negative subscale ($p<0.05$), and general psychopathology subscale ($p<0.01$) scores after 4-week treatment. Compare with baseline, there were significantly decreased activations of right inferior frontal gyrus (IFG) and right middle/inferior temporal gyrus (MTG/ITG) after treatment. In contrast, there were no significant differences in the activation of these regions between baseline and follow-up in the control group. The lateralization index (LI = (left β – right β)/(left β + right β)) of the IFG and ITG was reversed after aripiprazole treatment due to less activation of right IFG and ITG. Moreover, the LI of the ITG after treatment was negatively correlated with baseline P3 (hallucinatory behavior) score.

Discussion: Abnormal language-related lateralization pattern was reversed and clinical symptoms were improved after aripiprazole treatment in the patient group. The findings suggest that the aberrant language-related lateralization can be reversed after low dose antipsychotic treatment, and that the change of lateralization is related to improved clinical symptoms in patients with very early phase of psychosis.

Poster #S39

ENDOGENOUS TESTOSTERONE LEVELS ARE ASSOCIATED WITH NEURAL ACTIVITY IN MEN WITH SCHIZOPHRENIA DURING A FACIAL EMOTION PROCESSING TASK

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Background: Growing evidence suggests that testosterone may play a role in the pathophysiology of schizophrenia, yet the underlying biological mechanism remains poorly understood. Furthermore, testosterone has been linked to cognitive performance and the negative symptoms of schizophrenia, although little is known in regards to its relationship with emotion processing. This study was designed to determine the extent to which serum testosterone levels are related to neural activity in affective processing circuitry in healthy men and in men with schizophrenia during processing of emotional faces.

Methods: The study sample consisted of 16 males with schizophrenia and 16 healthy male comparison subjects. Functional magnetic resonance imaging was used to measure blood-oxygen-level-dependent (BOLD) signal changes as the participants viewed facial stimuli depicting angry versus nonthreatening expressions and performed an explicit emotion identification task. Both whole brain and ROI analyses were performed to determine regions of differential activity in controls and patients during facial emotional processing.

Results: Whole brain analyses revealed that during the processing of angry faces relative to non-threat, the control group activated the expected areas including frontal, limbic, parietal, temporal and occipital regions (FDR $p<0.05$). Between group, whole brain comparisons showed that patients activated a significantly smaller network and failed to activate limbic areas. ROI analyses showed that healthy controls elicited significantly greater activation than the patient group in the left inferior frontal gyrus (maximum z: 3.23; voxels: 35; coordinates: -38, 24, 6). The ROI was used in a regression model to determine the extent to which serum testosterone levels were related to neural activity in the patients and controls. Correlation analyses between ROI activation and testosterone levels revealed a significant positive association for patients ($r=0.56$, $p=0.02$). No strong, significant correlations between testosterone and activity in the ROI were found in the healthy comparison group.

Discussion: This study provides the first evidence that men with schizophrenia who display higher levels of endogenous testosterone have increased brain activation in a region implicated in emotion processing. This relationship suggests that testosterone may modulate emotion processing deficits and impaired social functioning in male patients.

Poster #S40

APATHY RELATED RESTING STATE CONNECTIVITY IN PATIENTS WITH SCHIZOPHRENIA

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Background: Apathy is a common symptom in several neuropathological disorders, like schizophrenia. Levy and Dubois (2006) described it as a quantitative reduction of purposeful behavior. Apathy is suggested to be a strong predictor of functional outcome and is considered as a burden for both patients and caregivers. Previous studies suggest that a distinction can be made between a cognitive form and a social-emotional form of apathy. Both forms of apathy result in a reduction of purposeful behavior, but

may reflect disruptions in different neural mechanisms. Cognitive apathy may result from disruptions in a cognitive control network, consisting of dorsal frontal, striatal and parietal regions. A more ventral frontostriatal salience network may be disrupted in social emotional apathy. However, whether these hypothesized networks are indeed related to apathy has not yet been examined. In this study, independent component analysis is used to examine the relation between apathy and resting state connectivity to cognitive control and salience networks in patients with schizophrenia.

Methods: 84 patients with schizophrenia underwent resting state functional Magnetic Resonance imaging (fMRI) and a Positive And Negative Syndrome Scale (PANSS) interview. Independent Component Analysis (ICA) was used to extract several components from the resting state data. From these components, the cognitive control and salience networks were selected for further analysis. Functional connectivity to these networks was correlated to a proxy of apathy, derived from apathy-related items of the PANSS, based on Faerden et al. (2008). Significance was set to $P=0.001$ FWE, cluster corrected.

Results: Preliminary results showed that there were several frontoparietal cognitive control networks and networks related to salience. However, only one frontoparietal cognitive control network showed functional connectivity that was associated with the level of apathy. This network consisted of the inferior parietal lobule, inferior frontal gyrus, middle frontal gyrus, anterior cingulate cortex, parahippocampal gyrus, and supplementary motor area. Apathy scores were positively correlated to resting state connectivity between this network and the inferior and middle temporal gyrus, putamen, insula and precuneus.

Discussion: Preliminary results suggested that in patients with schizophrenia functional connectivity between a cognitive frontoparietal control network and the inferior and middle temporal gyrus, putamen, insula and precuneus is related to the level of apathy. These areas are considered a part of the default mode network (DMN), which is thought to be involved in self-referential processing during rest. Patients with higher levels of apathy may have more difficulty activating frontoparietal cognitive control networks due to an overactive DMN. This could result in a lack of initiative and thus in reduced purposeful behavior. However, further investigation is needed in order to verify and possibly expand these results.

Poster #S41

HERITABILITY OF BRAIN ACTIVITY DURING EXPLICIT EMOTION PROCESSING: A STUDY IN TWINS

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Background: Previous neuroimaging studies in healthy subjects have indicated that specific environmental factors (e.g. prior exposure to severe adverse life events or alcohol abuse) are associated with altered amygdala reactivity to emotional stimuli (Ganzel et al., 2013; Sripada et al., 2011). On the other hand, imaging genetic results have suggested that amygdala response to emotional stimuli may be in part predicted by genetic variations (Hariri et al., 2002; Canli et al., 2002; Bertolino et al., 2005; Blasi et al., 2009). In the present study in healthy twins, we have investigated the relative contribution of genes and environment to activity in this brain region during explicit emotion processing.

Methods: 23 adult healthy twin pairs (13 MZ and 10 DZ; 21 M; Age: 30.81 ± 0.39 ; Handedness: 0.62 ± 0.003 ; Hollingshead: 35.54 ± 0.18 ; IQ: 105 ± 0.02) were included in the study. 3 Tesla fMRI scans were performed on 21 pairs (13 MZ and 8 DZ) during explicit processing (approach/avoid evaluation) of emotional faces (angry, fearful, happy, neutral). Zygosity was inferred using a standardized questionnaire (two peas in a pod), ad-

ministered to parents or caregivers (Peeters et al., 1998). SPM8 (Statistical Parametric Mapping) was used for imaging analyses. Region of interests (ROIs) in the left and right amygdala were defined using the PickAtlas AAL software toolbox (Maldjian et al., 2003; Tzourion-Mazoyer et al., 2002), and BOLD-fMRI parameter estimates from these areas were then extracted using Marsbar Toolbox (<http://marsbar.sourceforge.net>). Heritability of amygdala activity was first investigated by comparing the intra-class correlation (ICC) of MZ and DZ. Then, genetic and environmental contributions were jointly estimated by fitting an ACE model allowing to estimate the additive genetic (A), common environmental (C) and unique environmental (E) influences.

Results: ICC analysis indicated a significant correlation of right amygdala activity during explicit emotion processing of angry faces in MZ pairs only ($ICC = 0.80$, $p = 0.005$). All other ICCs for both MZ and DZ pairs were not significant (all $p > 0.05$). Moreover, variance of left amygdala activity in response to explicit evaluation of angry faces was better explained by additive genetic effects, as suggested by fits of the ACE model ($A^2 = 0.59$, $C^2 = 0.37$, $E^2 = 0.03$).

Discussion: This study provides evidence supporting greater weight of genetic variation in modulating amygdala response during processing of angry facial expressions as compared with environmental factors. Given that emotional abnormalities and genetic risk are crucial aspects of schizophrenia, relevance of these findings for this brain disorder should be further investigated.

Poster #S42

COMPARISON OF LARGE-SCALE HUMAN BRAIN FUNCTIONAL AND ANATOMICAL NETWORKS IN SCHIZOPHRENIA

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Background: Schizophrenia is a disease with disruptions in thought, emotion, and behavior. The disconnectivity hypothesis proposes that schizophrenia is due to aberrant brain connectivity. Imaging studies have found connectivity differences (Volkow et al. 1988; Weinberger et al. 1992; Friston 1998) but few have been able to unify findings of gray and white matter into one model. Our study developed an extension of NBS (Zalesky, NeuroImage, 2010) called NBSm to compare functional and anatomical networks.

Methods: Data was collected from 29 chronic schizophrenics and 29 healthy controls including structural (T1), resting state functional (6min in length, TR 2s, TE 30ms), and diffusion weighted (30 non-collinear, bval 1000s/mm²) magnetic resonance imaging. Images were preprocessed with standard pipelines. Average timecourses were extracted for 90 ROIs, regressed with motion parameters, and wavelet decomposed. Level 2 wavelets were extracted for each ROI and functional connectivity matrices made by ROI correlation. White matter tractography files were generated and anatomical connectivity matrices were made containing the count of white matter streamlines connecting each ROI to ROI combination. Global strength and regional strength measures were calculated for each imaging modality independently. NBS were calculated for each modality and then the NBSm was used to find statistically significant overlap between the functional component and the anatomical component.

Results: In probands, functional and anatomical global strength were decreased (diff -0.1128 $p < 0.0001$; diff -0.4509 $p = 0.0341$). Regional strength of anatomical data had 1 significant region after correction by FDR (Frontal_Sup_Medial_L diff -2.22394 $p = 0.00025$) whereas the functional data had 86 significant regional differences. NBSm produced 3 significant network components, 1 functional, 1 anatomical, and 1 multimodal. The functional component consisted of 46 nodes with 113 links with a pval < 0.001 . The diffusion component consisted of 47 nodes with 50 links with a pval of 0.0020. The intermodal component consisted of 26 nodes with 47 links with a pval < 0.0001 .

Discussion: NBSm is a powerful technique for understanding network differences present in both anatomical and functional data. When the dysconnectivity hypothesis is considered, these results provide compelling evidence of significant overlapping anatomical and functional disruption in those with schizophrenia.

Poster #S43**BRAIN'S FUNCTIONAL ALTERATIONS IN HIGH PERFORMANCE SCHIZOPHRENIC PATIENTS**

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Background: Alterations of both functional activations and functional connectivity in regions of Task Positive Network (TPN) and Default Mode Network (DMN) were reported in studies on cognition of schizophrenic patients. It has been supposed that an impairment of DMN suppression might cause an alteration of task-relevant signal processing, contributing to cognitive deficit of schizophrenic patients. Furthermore, both dorsal attention system and sensorimotor cortex show a hyperactivation in patients without cognitive impairment. Authors speculate that conserved cognitive functions in schizophrenic patients correlate with a compensatory increased activation in these regions. These results suggest an alteration of multiple functional sub-networks in schizophrenic patients during execution of different cognitive tasks. In this study, we want to detect if a better performance in schizophrenic patients is due to: 1) altered connectivity between DMN and TPN, 2) increased activations in compensatory regions, 3) a mixture between these two mechanisms.

Methods: The sample consisted of 9 schizophrenic patients with high task performance (HTP) on Variable Attentional Control (VAC) task, 6 patients with low task performance (LTP) on VAC test and 13 healthy volunteers (HC). fMRI acquisition was performed with a 3 Tesla Siemens scanner in two conditions: event-related modality (efMRI) and resting state. During efMRI all participants performed the VAC task. VAC is designed to measure the attentional control increasing conflict detection and allocation of attentional resources within the same stimuli. A repeated measure ANOVA was carried out for behavioral data using SPSS 20. A repeated measure ANOVA was employed for efMRI images using SPM8. Seed-to-voxel analysis, performed with fMRI functional connectivity toolbox, was utilized for resting state images using as seed regions the cluster of the previous analysis and two ROIs for ventral and dorsal DMN.

Results: Mixed Designs ANOVA for behavioral data demonstrated a significant effect of cognitive load in both reaction time and rate of correct responses [$F(2,48)=17.304$ $p<0.01$; $F(2,48)=54.151$ $p<0.01$], a significant group effect [$F(2,48)=25.878$ $p<0.01$] in the performance and an interaction between the factors [$F(4,48)=9.021$ $p<0.01$]. Post-hoc analysis, confirming the previous subdivision of patients, showed that LTP has lower mean rate of correct responses than both HTP and HC ($p<0.01$ Bonferroni). The efMRI analysis showed only a significant principal effect of group in left Postcentral Gyrus BA40 [$F(2,72)=16.960$ $p<0.05$ FWE-corrected, $k=45$, coordinates: -56 -24 18]. In particular, there was a greater activation of this region in HTP respect to LTP [$T(1,72)=7.24$ $p<0.05$ FWE-corrected, $k=80$]. The resting state analysis showed a hyperconnectivity of HTP compared to HC in left somatosensorial cortex BA2/3 and left supramarginal gyrus BA40 [$T(1,19)=3.58$ $p<0.01$ FDR-corrected, coordinates: 48 -24 44] from seed in postcentral gyrus BA40, while there was an increase of connectivity from dorsal DMN to right dorsal frontal cortex BA8, dorsolateral prefrontal cortex BA9 [$T(1,12)=3.93$ $p<0.05$ FDR-corrected, coordinates: -36 38 42] in LTP respect to HTP.

Discussion: Our results support both hypotheses, in line with the idea of alterations in different functional sub-networks. We suppose that the dysconnectivity between TPN and DMN in resting state could be a general mark of cognitive impairment in schizophrenic patients, but the nature of a particular task could require different compensatory activations. Future research could clarify the relationship between alteration of DMN-TPN functional connectivity and the development of compensatory alternative strategies.

Poster #S44**THE INTERACTION BETWEEN VARIATION IN DRD2 AND HTR2A GENES PREDICTS PREFRONTAL FUNCTION DURING WORKING MEMORY**

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Background: Working Memory (WM) deficits and related prefrontal activity are key features of schizophrenia. In particular, "inefficient" prefrontal response is considered an endophenotype linked with genetic risk for this brain disorder. Dopamine D2 and Serotonin 5HT2A receptors share downstream signaling effectors and are involved in prefrontal activity during WM. Previous studies have indicated that the T allele of a Single Nucleotide Polymorphism (SNP) in DRD2 (rs1076560, G>T) is associated with reduced ratio of expression between the D2 short/long isoforms. Furthermore, the T allele of a SNP in HTR2A (rs6314, C>T) is associated with reduced 5HT2A expression. Moreover, association between those genetic variations and Schizophrenia related phenotypes has been described. In particular, the T alleles of both SNPs separately predict inefficient WM processing in terms of prefrontal activity and behavior. Here, we have investigated the potential interaction between rs1076560 and rs6314 on fMRI dorsolateral prefrontal activity and behavior during WM in healthy subjects.

Methods: 322 healthy individuals (169 females, age 27.9+7.7, WAIS IQ: 109.0+12.4; Edinburgh Inventory handedness: 0.8+0.4) performed the 2-back WM task during fMRI. Furthermore, 523 healthy subjects (261 females, age: 26.9+7.6, WAIS IQ: 107.7+12.2; Edinburgh Inventory handedness: 0.7+0.46) performed the same task outside the scanner. The semi-structured interview SCID was used in order to exclude DSM-IV Axis I disorders.

Results: ANOVA in SPM8 indicated a rs1076560 by rs6314 interaction in left BA46 ($p<0.05$, FWE corrected) such that subjects carrying the T allele for both SNPs have greater left BA46 response compared with all other genotype configurations. ANOVA on behavioral data outside the scanner indicated again a rs1076560 by rs6314 interaction ($F=10.8$; $p=0.001$) on accuracy (% correct response). In particular subjects carrying the T allele for both genotypes had lower accuracy while performing the 2-Back task compared with other genotypic groups.

Discussion: These results are consistent with previous literature suggesting association of prefrontal activity and behavior during WM with rs1076560 and rs6314. Furthermore, they suggest epistatic interaction between these SNPs in modulating imaging and behavioral correlates relevant to Schizophrenia, such that subjects with the T allele for both genotypes have less efficient WM processing, as elicited by greater need for prefrontal resources and less accuracy at the 2-back WM task. Further studies could investigate the neurobiological mechanisms underlying this interaction and the implications of these results for the pathophysiology of Schizophrenia and for response to treatment with antipsychotics.

Poster #S45**DEVELOPMENT OF NOVEL PET LIGANDS (PF-04831704 AND PF-06327104) FOR PDE10A**

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Background: A disruption of corticostriatal signaling is believed to underlie the psychotic symptoms of schizophrenia and also contribute to many of the cognitive deficits associated with this disorder. Phosphodiesterase (PDE)10A is a dual substrate PDE highly expressed in striatal medium spiny neurons. Biochemical and behavioral studies indicate that the inhibition

of PDE10A enhances striatal output by increasing activity in the cGMP and cAMP signaling pathways. PDE10A inhibitors reduce exploratory activity and antagonize the stimulant response to both amphetamine and N-methyl-d-aspartate antagonists. Consistent with the role of PDE10A in the regulation of striatal function, PDE10A inhibitors enhance the activity of D2 antagonists in behavioral models such as conditioned avoidance responding (CAR). In addition, by enhancing corticostriatal signaling, PDE10A inhibitors have the potential to improve some of the cognitive symptoms of schizophrenia. Noninvasive imaging of PDE10A using Positron Emission Tomography (PET) would allow the distribution of this enzyme to be studied *in vivo* in both animals and humans and would be useful for the clinical development of these inhibitors by improving confidence in the selection of clinical doses.

Methods: Here we describe our progress in the development of novel PDE10A PET ligands by including behavioral assays as well as *in vitro* ligand characterization and *in vivo* target occupancy studies in rodents using [³H]PF-04831704. We also include preliminary data evaluating [¹¹C]PF-04831704 in primates and [¹⁸F]PF-06327104 in primates as well as PDE10A WT and KO mice.

Results: In *in-vitro* binding assays, [³H]PF-04831704 showed a K_d of 96 pM (B_{max} = 3.7 pmol/mg) in rat striatum and a K_d of 66 pM (B_{max} = 4.9 mol/mg) in mouse striatum. In *in-vivo* target occupancy studies in rats, [³H]PF-04831704 showed high binding to striatum and low binding to cerebellum, consistent with the target distribution of PDE10 enzyme. It was also well behaved in IVTO studies with dose-responsive receptor occupancy for several of our PDE10 inhibitors. High specific binding to PDE10A has also been clearly demonstrated by [¹¹C]PF-04831704 in non-human primates by its high binding potential (BP) (26 in putamen and 21 in caudate) compared to cortical regions, and the subsequent blocking studies. While this ligand should be amenable to clinical target occupancy studies, we opted to pursue an [¹⁸F] tracer to offer more flexibility to accommodate potential slow binding kinetics of the ¹¹C tracer. Prompted by the promising data of [¹¹C]PF-04831704, we sought a close in analog with a structural moiety that would allow facile [¹⁸F] radiolabeling. The close-in fluoroethoxy analog [¹⁸F]PF-06327104 also fit PET ligand selection criteria with a BP value of 30 in putamen and 25 in caudate. Baseline PET scans in 2 cynomolgus primates and test-retest studies show excellent reproducibility. In NHP, displacement studies showed a good RO versus drug exposure relationship. High specific (striatum) and low non-specific binding (cerebellum) was also demonstrated in WT and PDE10 KO mice.

Discussion: We have created closely related, potent and selective ³H, ¹¹C and ¹⁸F ligands to be used for identification of target occupancies in the brain as it relates to plasma exposures. Our preclinical efficacy models with multiple compounds all point to ~20% target occupancy as the middle of our pharmacodynamic range in behavioral assays such as CAR.

Poster #S46

WHITE MATTER PERFUSION FRACTION IN SCHIZOPHRENIA AND DEFICITS IN PROCESSING SPEED

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Background: Schizophrenia is a severe mental illness characterized not only by psychotic symptoms, but also severe neuropsychological deficits. Among these cognitive deficits, reduced speed of neurocognitive processing is the most profound among all cognitive domains. Understanding the neurobiology of processing speed may be essential for developing effective treatment for the cognitive deficits in schizophrenia. Information processing requires intact white matter connectivity and the positive relationship between processing speed and white matter integrity as measured by fractional anisotropy (FA) using diffusion tensor imaging (DTI) supports this proposition. However, the cause and consequence of the neuroimaging-based white matter deficit in schizophrenia are unclear. We tested if reduced blood perfusion to the white matter may be related to the white matter integrity and processing speed abnormalities in schizophrenia. Reduced white matter perfusion and/or integrity should impair intra-cerebral communications and thus signal processing in the brain, and reduce processing speed.

communications and thus signal processing in the brain, and reduce processing speed.

Methods: We examined cerebral white matter perfusion using pseudo-continuous arterial spin labeling (pCASL) and compared with gray matter perfusion, and also used high-angular resolution diffusion tensor imaging to examine white matter FA, in 46/61 age and gender matched patients/controls. Processing speed was measured by the digit-symbol substitution test. We performed a group comparison between average gray and white matter CBF and the fraction of WM by GM perfusion. Finally, we modeled the degree of variance on the patient-control differences in processing speed explained by white matter and gray matter perfusion and white matter FA.

Results: Patients had significantly reduced FA values, white matter perfusion fractions, and significantly lower processing speed, compared with controls. The white matter perfusion was highly and positively correlated with processing speed in both ($r=0.37$ vs. 0.57, $p<0.01$ for controls and patients, respectively). In comparison, association between processing speed and FA values was similar for both groups ($r\sim 0.36$, $p<0.01$). Whole brain white matter perfusion and white matter FA together explained about half of the variance in processing speed (46%). Further analysis showed that FA values were the best predictors in processing speed in controls, but not in patients, where white matter perfusion was a dominant contributor to processing speed performance in schizophrenia patients, and explained 34% of the variance. White matter perfusion in the associative white matter regions, including corpus callosum and corona radiata, served as the best predictors of processing speed variance.

Discussion: We discovered that a proportionally low perfusion in the white matter is evident in schizophrenia patients, which plays a significant role in their processing speed deficits. Whether the disproportionately low white matter perfusion in schizophrenia is primary or secondary deserves careful examination, although these findings are novel and offer a biological insight into the nature of cognitive deficits in this disorder.

Poster #S47

BRAIN ACTIVATION DURING SELF-REFLECTION IN SCHIZOPHRENIA COMPARED TO BIPOLAR DISORDER

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Background: Problems in self-related processing and social cognition have been shown in schizophrenia and bipolar disorder patients. Self-reflection is a psychological process important for self-related processing and social cognition. In addition, psychotic symptoms are very common in bipolar disorder. To our knowledge, it has not yet been investigated whether schizophrenia patients and patients with bipolar disorder show comparable or different brain activation during self-reflection.

Methods: During functional magnetic resonance imaging (fMRI), 17 patients with bipolar disorder with a history of psychosis, 17 schizophrenia patients and 21 healthy controls (HC) performed a self-reflection task. The task consisted of sentences belonging to three conditions: self-reflection, other-reflection and semantic baseline.

Results: Patients with bipolar disorder showed less activation in the posterior cingulate cortex (PCC) extending to the precuneus during other-reflection compared to HC. In schizophrenia patients, the level of activation in this area was intermediate between bipolar disorder and HC, however the difference between schizophrenia and bipolar disorder was not significant. There were also no other significant differences between bipolar disorder and schizophrenia during other-reflection, nor were there any group differences in brain activation during self-reflection.

Discussion: The role of the PCC and precuneus during self- and other-reflection has been suggested to be related to autographical memory processing. Less activation in these areas during other-reflection in patients with bipolar disorder may reflect impaired integration of past and current other-related information, which might be related to problems in social functioning, often reported in patients with bipolar disorder. In addition, our results show that the difference between bipolar disorder and healthy people is larger than the difference between schizophrenia patients and

healthy people, suggesting that presence of mood disorder influences brain activation during self- and other-reflection processing.

Poster #S48

THE REPRODUCIBILITY OF 1H-MRS GLUTAMATE CONCENTRATION ESTIMATES AT 3 TESLA, IMPLICATIONS FOR GLUTAMATE IMAGING IN SCHIZOPHRENIA

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Background: Glutamate levels may be abnormal in schizophrenia, but it is unclear whether glutamate levels change over time with symptom severity or antipsychotic treatment. Proton magnetic resonance spectroscopy (1H-MRS) can be used to estimate the concentration of brain glutamate (Glu), alone or in combination with its metabolite glutamine (Gln) (together termed Glx). To support future longitudinal studies in patients, we determined the reliability of 1H-MRS glutamate and Glx concentration estimates in the anterior cingulate cortex (ACC) and left thalamus (THAL) at 3 Tesla over a long time period in healthy volunteers.

Methods: 1H-MRS spectra were acquired in the ACC (20×20×20mm) and THAL (right-left 15×20×20mm) of 32 healthy volunteers (17 female, mean age 25, sd 4.5) at two time-points with a mean of 17 months (sd=6.8, range 9–36 months) apart. Spectra were acquired using Point RESolved Spectroscopy (PRESS), echo time (TE) = 30msec; repetition time (TR) = 3000msec, with 96 averages on a 3 Tesla General Electric magnetic resonance scanner. Spectra were analysed with two versions of LCModel, 6.1-4F and 6.3-0I (Provencher 1993). Concentration estimates with %Cramer-Rao lower bounds (CRLB) above 20% as reported by LCModel were excluded from analysis. Segmented inversion recovery prepared spoiled gradient echo (IR-SPGR) scans were used to correct metabolite estimates for voxel cerebrospinal fluid (CSF) content using the formula: uncorrected metabolite × [vol + 1.55 × (1 – vol)]/vol. (vol = grey matter + white matter) Reproducibility of Glu and Glx estimates were calculated as the percentage coefficient of variation: (%CV) = 100*($\sqrt{\text{mean}((\text{test} - \text{retest})^2/2)}$)/($\text{mean}((\text{test} + \text{retest})/2)$))

Results: Paired t-tests showed no difference between ACC Glu ($p=0.738$) and Glx ($p=0.658$) levels over time, or between THAL Glu ($p=0.307$) and Glx ($p=0.127$) levels over time. CSF-corrected Glu and Glx estimates showed low %CV in both the ACC (mean Glu 15.8, Glx 16.6) and THAL (mean Glu 21.5, Glx 20.3). The %CVs were slightly lower for Cr-scaled values in both the ACC (mean Glu 13.7, Glx 16.4) and THAL (mean Glu 18.2, Glx 18.3) than CSF-corrected values. The newer version of LCModel (6.3-0I) generally returned lower CRLB, indicating better fit of spectra, and lower %CV than version 6.1-4F. Power analysis performed in PS software (Dupont, Plummer, 2009) on CSF-corrected values indicated that at power=0.8 and alpha=0.05, to detect a between-group difference of 15% in ACC Glu requires a sample size of 20/group, and for THAL Glu 30/group. To detect a within-subjects 15% change in ACC Glu requires a sample size of 12/group, and 16/group in the THAL.

Discussion: Changes in Glu and Glx estimates over longer time periods are likely to reflect both biological and equipment variation. Our analysis suggests that measurement error is reduced by use of the newer version of LCModel for analysis, and that creatine-scaled rather than CSF-corrected Glu and Glx values are slightly more reproducible. However, this method assumes that creatine levels do not differ between groups or over time. The sample sizes indicated by power analysis are achievable for cross-sectional and longitudinal studies in patients with schizophrenia.

Poster #S49

AN INITIAL REPORT ON METABOLIC DEFECTS IN RECENT ONSET SCHIZOPHRENIA WITH A 7 TESLA MRI SCANNER: LINK TO CHANGES IN BRAIN TEMPERATURE AND COGNITION

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Background: Imaging modalities have attempted to elucidate the structural, functional and neurochemical underpinnings of schizophrenia. In vivo measurement of absolute metabolite concentrations and clear separation of metabolite peaks have been challenging, due to low signal to noise ratio and poor spectral resolution.

Methods: Thus far, 6 subjects with recent onset DSM-IV schizophrenia and 6 healthy volunteers matched for age, sex, race, education status and cigarette smoking have been studied using 7 Tesla proton magnetic resonance spectroscopy. A combination of STEAM, MEGA-PRESS and semi-LASER sequences are utilized to identify peaks of interest in the anterior cingulate: GABA, GSH, Glu, Gln, NAA, NAAG, and measure absolute brain temperature. All participants completed a broad neuropsychological battery, assessing a wide variety of cognitive domains.

Results: Processing speed, visual memory and ideational fluency were found to be impaired in patients compared to controls. Gln, NAA+NAAG correlated positively with verbal memory. Gln correlated negatively with executive function. GABA was positively correlated with processing speed and visual memory in the schizophrenia group. Verbal memory was positively correlated to absolute brain temperature. There was a positive correlation between Gln, Glu, Ins, NAA+NAAG, GABA and absolute brain temperature. Brain temperature correlated significantly with SANS. Core body temperature differed significantly from brain temperature in the patients, but not in the control group.

Discussion: To our knowledge, this is the first study to measure metabolite concentrations, moreover absolute brain temperature, in the anterior cingulate of recent onset schizophrenia patients utilizing a 7 Tesla system. Furthermore, it is the first to link brain temperature to brain metabolites and cognitive function. The results link abnormal energy turnover, as highlighted by increased brain-body core temperature difference, to metabolite disturbances and cognitive impairment, implying underlying pathophysiological mechanisms and highlighting the importance of brain temperature as a potential biomarker for schizophrenia.

Poster #S50

EFFECTS OF GLUTAMATERGIC FUNCTION ON MEMBRANE LIPID TURNOVER AND ENERGY METABOLISM – A COMBINED 1H- AND 31P-MR SPECTROSCOPIC IMAGING STUDY IN HEALTHY INDIVIDUALS

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Background: Altered brain morphology in different psychiatric conditions is often argued as being due to neurodegeneration, i.e. neurotoxic damage associated with deregulated glutamatergic excitation and altered cell membrane turnover. This study combined 1H- and 31P-MR brain spectroscopy to assess the relationships between the excitatory neurotransmitter glutamate, the focal balance of membrane phospholipid precursors (phosphomonoesters, PME) and breakdown products (phosphodiesters, PDE) and the related energy turnover (phosphocreatine, PCr).

Methods: We applied 3 T chemical shift imaging (3D 31P-MRS, 2D 1H-MRS) and hippocampal single-voxel 1H-MRS in 58 healthy and gender matched volunteers. Correlation analysis was used to assess focal associations between Glu or Gln and phospholipid metabolites (PME, PDE) or high energy phosphates (PCr, ATP).

Results: 1) In all examined brain regions, significant positive correlations were observed between glutamate and PDE (Spearman correlation, $\rho > 0.25$, $p \leq 0.05$). Similarly, positive correlations were observed between glutamate and PME without reaching statistical significance. 2) Furthermore, the higher PME and PDE levels, the lower the PCr intensities ($\rho < -0.3$, $p \leq 0.05$).

Discussion: Our first result is suggestive for a glutamate related shift to increased membrane turnover that could be the correlate of increased ac-

tivity dependent neuronal/synaptic plasticity. Our second finding is likely to indicate increased energy demand and elevated activation of fast glycolysis to compensate for increased energy demand in case of activated membrane turnover.

Poster #S51

SUICIDALITY AND CORTICAL STRUCTURE IN SCHIZOPHRENIA - EFFECTS ON CORTICAL THICKNESS AND FOLDING

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Background: Schizophrenia is characterized by a dramatically increased mortality leading to an earlier age of death of about ten years compared with the general population. Suicidality is the major determinant of this highly increased mortality. Thus, exploring the neuronal foundations of suicidality is essential for a better understanding, recognizing and prevention of suicidal behaviour in schizophrenia. Recent studies focused on grey matter volume differences between suicide-attempters and non-attempters in schizophrenia. However, an analysis of the cortex structure in terms of cortical thickness and folding in order to further elucidate the neuroanatomical correlates of suicidality in schizophrenia has yet not been performed. Thus, in the present study we sought to identify relevant brain regions with differences in cortical thickness and folding between patients with suicide-attempts, patients without any suicidal thoughts (neither active nor passive) and healthy controls with a fine grained surface-based MRI method.

Methods: A group of 37 patients with schizophrenia according to DSM-IV, therefrom 14 suicide-attempters and 23 non-suicidal, and 50 age- and gender-matched healthy controls were included. Suicidality was documented through clinical interview and chart review. All participants underwent high-resolution T1-weighted MRI scans (1.5-T). Whole brain node-by-node cortical thickness and folding were estimated (FreeSurfer Software) and compared between the three groups.

Results: Significant ($p < 0.05$, corrected) cortical thinning in patients with suicide attempts compared with non-suicidal patients in the right superior and middle temporal, temporopolar and insular cortex was found. Additionally, patients with suicide attempts showed reduced cortical thickness in the right dorsolateral prefrontal cortex ($p < 0.001$, uncorrected). No significant differences were found for cortical folding.

Discussion: Our findings provide new evidence for potential neuroanatomical underpinnings of suicidality in schizophrenia. The affected regions of cortical thinning in suicide attempters are strongly involved in cortical networks relevant for the regulation of impulsivity, emotions and planning of behaviour. Thus, anatomical alterations in these regions are highly suggestive to be of impact for suicidal behaviour in schizophrenia. Further studies in larger samples are needed to consolidate these initial findings.

Poster #S52

DOES SEASON OF BIRTH INFLUENCE CORTICAL THICKNESS CORRELATES OF PSYCHOTIC EXPERIENCES? A GENETICALLY INFORMATIVE MRI STUDY

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Background: Risk for several neuropsychiatric diseases is influenced by

season of birth (Davies, Welham, Chant, Torrey, & McGrath, 2003; Disanto et al., 2012). Besides, it has been suggested that season of birth modifies brain morphology (Pantazatos, 2013). As cortical thickness alterations have been reported across some levels of the psychosis-spectrum (Goldman et al., 2009), this study was aimed at i) evaluating the scarcely explored relationship between cortical thickness and severity of subclinical psychotic experiences (PEs) in healthy subjects, and ii) estimating the potential impact of season of birth in the previous thickness-PEs relationship. Since both PEs and brain cortical features are heritable (Latash et al., 2009; Panizzon et al., 2009), the current work used monozygotic twins to separately evaluate familial and unique environmental factors.

Methods: High-resolution structural MRI scans of 48 twins were analyzed to estimate cortical thickness using FreeSurfer. They were then examined in relation to PEs, accounting for the effects of birth season; putative differential relationships between PEs and cortical thickness depending on season of birth were also tested.

Results: Increases in the familial component (genes plus shared environment) of negative PEs was associated with cortical thickening in specific regions of both hemispheres. Furthermore, relationships between cortical thickness and the familial component of both negative and depressive PEs were different depending on season of birth: in some brain regions, individuals born during winter/spring showed cortical thickening associated with higher scores in either depressive or negative PEs, while the thickness-PEs association was in the opposite direction in subjects born during the rest of the year.

Discussion: The present results support previous findings indicative of cortical thickening in healthy individuals with high psychometrically assessed psychosis scores (Kuhn et al., 2012), probably in line with theories of compensatory aspects of brain features in non-clinical populations. Additionally, they suggest distinct patterns of cortical thickness-PEs relationships depending on birth seasonality. Familial factors underlying the presence of PEs may drive all these effects.

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Poster #S53

MEDIAL FRONTAL GYRUS ALTERATIONS IN SCHIZOPHRENIA: RELATIONSHIP WITH DURATION OF ILLNESS AND EXECUTIVE DYSFUNCTION

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Background: Gray matter alterations are thought to underlie schizophrenia clinical expression, especially cognitive dysfunction. One of the most widely neuropsychological instruments used to assess executive functioning is the Wisconsin Card Sorting Test (WCST). Performance in the WCST is particularly impaired in schizophrenic patients (SCZ) and it is associated with reduced gray matter volume in prefrontal areas. Among other variables influencing progressive brain changes in schizophrenia, duration of illness (Dol) is well known to play a significant role. Our aim was to test the impact of executive functioning and illness duration on prefrontal regions in SCZ.

Methods: 33 SCZ, 18 with DoI shorter than 10 years (SCZ<10y), 15 longer than 10 years (SCZ>10y), and 24 healthy controls (HC) were enrolled. T1 structural images were collected using 3T MRI scanner. Participants performed a WCST at the time of the scanning. The number of completed categories (CAT), perseverative responses (PR) and of perseverative errors (PE) were considered performance measures. An ANCOVA was run entering as a nuisance covariate the age of subject to analyse the difference in the WCST performance between the three groups. The effect size was computed using the Cohen's d. Group-related differences in gray matter volume (GMV) were examined using VBM, as implemented in SPM8. An ANOVA was performed in SPM8, entering gender, age and years of education as nuisance covariates, to compare in a whole brain analysis the three groups. The eigenvariates (radius=8 mm) were extracted for each cluster of interest and correlated (Pearson's r) with WCST performance.

Results: There were no significant differences in gender, level of education, number of admissions and antipsychotic dose at the time of the scanning. The SCZ>10y group was significantly older than the other two groups ($p<0.001$). There were significant between-group differences in the three WCST performance measures. Post hoc analyses showed significant difference in CAT between the HC and the SCZ>10y ($p=0.02$, Cohen's d=1.21). HC and SCZ≤10y groups performed better on PR scores than SCZ>10y (respectively $p=0.001$, Cohen's d=1.56, and $p=0.013$, Cohen's d=0.98). HC performed better on PE as compared to SCZ>10y ($p=0.047$, Cohen's d=1.01); there were no PE differences between SCZ>10y and SCZ≤10y. At whole brain level, there was a significant difference in the left medial frontal gyrus (LMFG) GMV (19 voxels, peak in $x=-9$, $y=30$, $z=36$) across the three groups ($t=5.48$ $p=0.009$ FWE corrected). Post hoc analyses identified a linear trend in this region, with greater GMV reduction in patients with a longer DoI compared to patients with a shorter DoI. There were not significant group by WCST performance interactions surviving multiple comparisons correction.

Discussion: The present study supports the hypothesis that medial frontal gyrus alterations in schizophrenia are sensitive to DoI but not associated to executive functioning. Patients with shorter DoI appeared to be less cognitively impaired, with no significant differences relative to HC and with a better performance on PR compared to patients with longer DoI. This is partially in line with previous findings. We found GMV reduction in the LMFG in SCZ. There was a linear trend across the three groups, with the shorter DoI patients in an intermediate position between the longer DoI patients (greater GMV reduction) and controls. Literature data showed that medial prefrontal cortex is affected by the illness but there are still not convergence on the relationship with illness duration or with the illness onset. We did not find any significant between-group DoI by executive functioning interaction in the medial prefrontal gyrus but more longitudinal studies are required to clarify this issue.

Poster #S54

BRAIN STRUCTURAL ABNORMALITIES IN POSTPARTUM PSYCHOSIS: AN MRI STUDY

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Background: Postpartum Psychosis (PP) is the most severe psychiatric disorder associated with childbirth with an incidence of about one per 1000 deliveries (1). This clinical entity takes the form of mania, severe depression symptoms, or acute polymorphic (cycloid) psychosis. Recent family and longitudinal studies linked the Postpartum Psychosis to the manic depressive psychosis (2). The aims of our study are: 1) to examine whether alterations in brain regions involved in psychoses in the affective spectrum such as the amygdala and the anterior cingulate cortex (3) are

also present in Postpartum Psychosis; 2) to explore whether there is an association between stressful life events, symptomatology and specific brain areas mentioned above in postpartum psychosis group.

Methods: This is a cross-sectional study of 21 healthy postpartum women and 24 women at risk of postpartum psychosis. Within this group, 12 developed postpartum psychosis ((PE) n=8, Bipolar Disorder n=4) and 12 did not develop postpartum psychosis ((NPE) Bipolar Disorder n= 10, Schizoaffective Disorder n=1, First-degree family history of PP n=1). After delivery all participants underwent an MRI scan and assessment of symptoms using Positive and Negative Syndrome Scale (PANSS), Young Mania Rating Scale (YMRS) and Beck Depression Inventory (BDI) as well as Intrusive Life Events scale (ILE). We examined Gray Matter Volume using Voxel Based Morphometry (VBM) and Freesurfer methods of image analysis.

Results: The subgroup that developed postpartum psychosis (PE) showed a reduction in the Anterior Cingulate Cortex (ACC) volume compared to those who did not develop PP (NPE), whereas we found at trend level, a reduction in right precuneus cortex in the at risk group ((PE+NPE) n=24) when comparing with postpartum control group (n=21). In this study the reduction in ACC volumes in PE compared to the NPE are not associated to symptomatology or life events.

Discussion: These preliminary findings suggest that women with postpartum psychotic disorders show specific volumetric abnormalities in areas relevant to the pathophysiology of affective psychosis.

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Poster #S55

PREFRONTAL CORTEX VOLUME IN PATIENTS WITH SCHIZOPHRENIA IS CORRELATED WITH VERBAL MEMORY PERFORMANCE

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Background: Several studies have shown brain volume changes in schizophrenia (SZ). Volume reduction of areas such as prefrontal cortex is particularly of interest regarding cognitive performance. Verbal memory (VM) is one of the most impaired cognitive domains in SZ and is linked to daily life functioning. Prefrontal cortex is one of the target areas in VM performance. The aims of this pilot study were: (1) to compare total and prefrontal cortex volumes in individuals at recent onset (RO) and chronic patients (CP) with SZ; (2) to correlate the volumes with Hopkins Verbal Learning Test-Revised (HVLT-R) total immediate free recall scores.

Methods: The double case-control design included 21 RO patients (within first 5 years of SZ diagnosis), 19 CP (minimum of 20 years after the diagnosis of SZ) and their respective matched controls for age, gender and level of education (19 and 18 subjects). Images were acquired at Philips Achieva 1.5T MRI scanner at the Hospital de Clínicas de Porto Alegre, Brazil. Images were processed using the automated pipeline of FreeSurfer v5.1. Intracranial volume and years of disease (only in the patients group) were regressed out from prefrontal and total cortex volumes.

Results: Either total ($p<0.0001$, $F=21.695$, RO controls = RO patients = CP controls > CP) or prefrontal ($p<0.0001$, $F=18.775$, RO controls = RO patients = CP controls > CP) cortices were different between groups. In patients, HVLT-R total immediate free recall scores were positively correlated with total cortex ($r=0.434$; $p=0.008$); a correlation trend with prefrontal cortex ($r=0.322$; $p=0.055$) was found. In controls, there were no significant correlations ($p=0.490$ for total and $p=0.697$ for prefrontal cortex volumes).

Discussion: Although preliminary and on a secondary prevention level perspective, these findings give us insights on therapeutic strategies to reduce the cortex atrophy and cognitive impairment at the first five years after diagnosis of SZ.

Poster #S56**THALAMIC VOLUME ABNORMALITIES ASSOCIATED WITH NEGATIVE SYMPTOMS PREDATING THE ONSET OF PSYCHOSIS**

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Background: Brain volume alterations as vulnerability markers of psychosis and schizophrenia have been widely investigated. The thalamus acts by its diverse cortical connections as a key node for cognitive processes. Aberrant cortico-cerebellar-thalamic-cortical circuit connectivity has been implicated as basis for cognitive deficits and clinical symptoms of schizophrenia [Andreasen et al., Arch Gen Psychiatry 1990]. Several meta-analyses investigating first episode of psychosis (FEP) as well as in schizophrenia (SZ) patients compared to healthy controls (HC) showed significantly reduced thalamic volumes [Adriano et al., Schizophr Res 2010]. Thalamic volumetric differences significantly correlated with the negative psychotic symptoms in antipsychotic-naïve schizophrenia patients [Danivas et al., Indian J Psychol Med 2013]. This preliminary study wanted to investigate thalamic volumetric abnormalities in individuals with an at-risk mental state (ARMS) and replicate previous results in FEP patients.

Methods: The 53 FEP, 46 ARMS and 24 HC individuals included in FePsy [4] Clinic were assessed using the Brief Psychiatric Rating Scale, the Scale for the Assessment of Negative Symptoms and the Global Assessment of Functioning. We acquired 3D T1 MPRAGE sequence on a 3-T Magnetom Verio, Siemens scanner with 1 mm³ voxel size, inversion time of 1000 ms, repetition time of 2 s, and echo time of 3.4 ms. Structural images were segmented using automated subcortical segmentation FMRIB's Integrated Registration and Segmentation Tool (FSL-FIRST). Thus, we assessed the L, R and bilateral thalamic volumes normalized to intracranial volume. Statistical analyses of demographic, clinical and volumetric group comparisons were performed using the R software version 2.15.2 One-way ANOVAs and chi-square tests were used to examine clinical and demographic differences between groups. Post-hoc analyses are Bonferroni-corrected.

Results: We found no significant differences in gender, handedness and verbal IQ. The FEP and ARMS group had more positive ($p<0.001$), negative ($p<0.001$) symptoms and worse global functioning ($p<0.001$) compared with HC. Significant group differences of left, right and bilateral thalamus volumes were observed after controlling for confounding effects of age. Compared to HC, ARMS and FEP individuals showed reduced thalamic brain volumes (Normalized mean bilateral thalamic volumes (standard deviation): HC: 0.0056 (0.0003); ARMS: 0.0054 (0.0003); FEP: 0.0054 (0.0003)). Furthermore, the volumetric differences correlated negatively with the negative symptoms in ARMS and in FEP ($p=0.01$).

Discussion: This study demonstrates reduced volumes of the thalamus in both ARMS and FEP compared to HC. We replicated previously reported correlation between thalamic volumes and negative symptoms in FEP patients and further showed that such a relation is also evident in the ARMS individuals. Therefore, thalamic alterations might account for negative symptoms of schizophrenia [Andreasen et al., Arch Gen Psychiatry 1990]. These alterations might already be present in the at-risk mental state of psychosis.

Poster #S57**EMOTION RECOGNITION AND THEORY OF MIND ARE RELATED TO GRAY MATTER VOLUME OF THE PREFRONTAL CORTEX IN SCHIZOPHRENIA**

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Background: Functional imaging studies in healthy individuals and schizophrenia patients, have revealed that social cognitive processing depends critically on the amygdala and the prefrontal cortex (PFC). However, the relationship between social cognition and structural brain abnormalities in these regions is less well examined.

Methods: Measures of (social) cognition, including facial emotion recogni-

tion and theory of mind (ToM) were assessed in patients with schizophrenia (N=166) and healthy control subjects (N=134). Of all participants MRI brain scans were acquired. Automated parcellation of the brain to determine gray matter volume of the amygdala and the superior, middle, inferior and orbital PFC, was performed.

Results: Between-group analyses showed poorer recognition of angry faces and ToM performance in schizophrenia patients as compared to healthy controls. Between-group analyses of gray matter volume showed that schizophrenia patients had decreased amygdala and PFC gray matter volume as compared to controls. Moreover, in schizophrenia patients, recognition of angry faces was associated with inferior PFC gray matter volume, particularly the pars triangulare ($p=0.006$), such that poor performance was related to reduced pars triangulare gray matter volume. In addition, ToM was related to PFC gray matter volume, particularly middle PFC ($p=0.001$), such that poor ToM skills in schizophrenia patients were associated with reduced middle PFC gray matter volume.

Discussion: The results demonstrate that in schizophrenia reduced PFC gray matter volume, but not amygdala gray matter volume, is associated with social cognitive deficits.

Poster #S58**SERUM LEVELS OF INNATE IMMUNE RESPONSE MARKERS CCL22, CXCL1 AND APOLIPROTEIN A1 ALTERED IN FIRST-EPIISODE PSYCHOSIS ASSOCIATE WITH WHITE MATTER VOLUME AND INTEGRITY**

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Background: Association of inflammatory markers and psychosis is repeatedly found, while no reports about possible association with brain imaging exist.

Methods: Thirty-seven first-episode psychosis (FEP) patients (with a median of 27 days of antipsychotic medication), and 19 matched controls were recruited from the capital area of Finland. Serum levels of 38 chemokines and cytokines and cardiovascular risk markers were measured. The association of psychosis-related markers with gray matter (GM) and white matter (WM) volume, based on T1-weighted MR images, and WM integrity, as measured with DTI, was analysed within patients, both with a whole-head and regions of interest (ROI) approaches. WM integrity was measured with fractional anisotropy (FA), mean diffusivity (MD) and radial diffusivity (RD). T1 images were analysed with voxel-based morphometry and DTI images with tract-based spatial statistics (TBSS). ROIs were based on a recent meta-analysis on diffusion tensor imaging findings on chronic schizophrenia patients.

Results: FEP patients as compared to healthy controls had higher CCL22 and lower TGFa, CXCL1, CCL7, IFNo2, ApoA-I and HDL-C. The findings remained significant after adjusting for age, sex and BMI. CCL22 was correlated with white matter volume and diffusion measures in the frontal lobe: a negative correlation was detected between CCL22 levels and WM volume and FA bilaterally, and a positive correlation between CCL22 and MD and RD measures in the WM tracts of the left hemisphere. CXCL1 correlated negatively with RD measures in multiple tracts, including the corpus callosum, cingulum, and frontal WM tracts, among others. Decreased serum level of ApoA-I was associated with smaller volume of the medial temporal WM. No association was found between the psychosis-related markers and GM volume.

Discussion: This is the first report to demonstrate an association between systemic innate immunity related inflammatory markers and WM integrity in FEP patients. Interestingly, CCL22 has been previously implicated in diseases associated with white matter pathology. These results give further support for the possible role of inflammation in the etiology of psychoses and link some inflammatory alterations to such white matter changes that are often observed in first-episode psychosis and chronic schizophrenia. The longitudinal course and predictive value of our findings need further investigation.

Poster #S59**DECREASED GREY MATTER VOLUME AS THE EXPRESSION OF DIFFERENTIAL SENSITIVITY TO ENVIRONMENTAL RISK EXPOSURE IN PSYCHOTIC DISORDER**

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Background: Cannabis use, childhood trauma and urban upbringing are important risk factors for psychotic disorder. Differential sensitivity to these environmental exposures may be expressed as structural brain alterations. The aim of this study was to examine whether cannabis use, childhood trauma and urban upbringing are associated with alterations in gray matter volume (GMV) and whether this is dependent on different genetic risk levels for psychotic disorder.

Methods: T1-weighted MRI scans were acquired from 89 patients with a psychotic disorder, 98 healthy siblings of patients with psychotic disorder and 87 controls. Freesurfer software was used to measure GMV. Cannabis use was assessed with the Composite International Diagnostic Interview and a urine test. Childhood trauma was measured with the Childhood Trauma Questionnaire Short Form. The developmental urbanicity exposure comprised 5 levels, reflecting the average population density between birth and the 15th birthday. Multilevel random regression analyses were used to examine the association between group and environment (as well as their interaction) on the one hand and GMV as the dependent variable on the other. The three-way interaction group x environment x sex was also investigated.

Results: There were significant main effects of group ($B=-10.44$, $p=0.04$) and cannabis ($B=-8.18$, $p<0.05$) on GMV, which was not the case for childhood trauma and urbanicity. Both the two-way interaction between group and cannabis ($\chi^2=5.31$, $p=0.07$) and between group and childhood trauma ($\chi^2=10.32$, $p=0.01$) in the model of GMV were significant. Stratified analyses showed that cannabis use and childhood trauma were associated with lower GMV in the patient group (cannabis use: $B=-14.89$, $p=0.03$; childhood trauma: B linear trend = -8.58 , $p=0.04$). Although three way interactions (group x cannabis or childhood trauma x sex) were inconclusive, environmental effects on GMV were found in male patients (cannabis: $B=-24.86$, $p<0.01$; childhood trauma: B linear trend = -12.16 , $p=0.02$) and not in female patients. The two-way interaction between group and developmental urbanicity was not significant ($\chi^2=1.79$, $p=0.41$).

Discussion: The findings suggest that exposure to cannabis and childhood trauma, but not urban upbringing, may impact global GMV in individuals at the highest genetic risk level for psychotic disorder. Thus, patients may be more sensitive to cannabis and childhood trauma, expressed as a reduction in GMV, than individuals at higher than average (siblings) or average (controls) genetic risk. This increased cerebral sensitivity to cannabis and trauma may be confined to male patients.

Poster #S60**WHITE MATTER ALTERATIONS AND STRUCTURAL CONNECTIVITY IN FIRST-EPIISODE ANTI-PSYCHOTIC-NAIVE SCHIZOPHRENIA PATIENTS**

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Background: While a great deal of progress has been made in delineating gray matter abnormalities in schizophrenia using magnetic resonance imaging (MRI), far less progress has been made in evaluating white matter (WM) abnormalities, or in evaluating WM fiber tracts in connecting brain regions. However, structural connectivity of the whole brain and specifically the reward circuit have not been evaluated in first-episode antipsychotic naïve schizophrenia patients.

Methods: MR Image acquisition: 38 first-episode anti-psychotic naïve patients with schizophrenia and 38 controls matched based on age, sex, and parental socioeconomic status were scanned on a Philips 3T Achieva MR scanner using a diffusion protocol with one reference image ($b=0$) and 30 diffusion weighted images with b value of 1000 s/mm^2 . Image processing & Statistical analyses: We used FSL software (<http://fsl.fmrib.ox.ac.uk/fsl/fdt/index.html>) to post-process and analyze the data. The diffusion data were corrected for head movement and eddy current distortion. Subsequently, brain parameter maps were calculated describing the degree of asymmetric water diffusion (fractional anisotropy, FA) as a measure of microstructural integrity. We used 2 methods to study WM differences: • Method 1: Tract Based Spatial Statistics (TBSS), which uses Fractional Anisotropy (FA) maps to find significant WM differences between controls and patients. • Method 2: Whole brain probabilistic tractography was performed to describe the structural connectivity between brain regions (method PROBTRACKX). The reward circuit was tracked in two segments (a. VTA to nucleus accumbens & b. nucleus accumbens to forebrain). These probabilistic streamline fiber connectivity maps were analysed for significant differences in WM connectivity between controls and patients. Permutation methods (also known as randomisation methods) were used to deal with the statistical problem of multiple comparisons in brain images.

Results: Group comparison using FA maps (TBSS) showed significant anisotropic differences (lower anisotropy in patients) in four regions: Cingulum, Corticospinal tract, Anterior thalamic radiation, and Inferior longitudinal fasciculus. Group comparisons using probabilistic WM fiber maps (PROBTRACKX) not only showed the regions identified using FA maps, but also several other regions such as forceps major, fronto-occipital fasciculus, thalamus, putamen, pallidum, VTA. All regions showed lower WM fiber integrity in patients. Group comparisons using probabilistic WM fiber maps (PROBTRACKX) did not show any significant differences within the reward circuit.

Discussion: First-episode anti-psychotic naïve schizophrenia patients showed WM alterations using both FA maps and whole brain tractography maps. Interestingly, the whole brain tractography maps also provide a measure of connectivity between distant brain regions. Hence, tractography may provide better understanding of how specific brain regions are connected and how changes in connectivity may be relevant to our understanding of the functional abnormalities, both cognitive, and clinical, observed in schizophrenia. Most importantly, this study shows the presence of widespread structural changes in schizophrenia, even early in the course of the disease, prior to effects of overt chronicity or drug-effects. Alterations within the reward circuit were not seen in the whole brain analyses. We specifically analysed the reward circuit to increase the sensitivity towards structural connectivity but we did not find any significant group differences. This might suggest that the reward dysfunction, in first-episode anti-psychotic naïve schizophrenia patients, is attributed to functional but not structural connectivity.

Poster #S61**HETEROGENEITY OF BRAIN STRUCTURAL CHANGES ACROSS SUBGROUPS OF SCHIZOPHRENIA: CORTICAL THICKNESS AND CORTICAL COMPLEXITY ANALYSES**

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Background: Despite numerous studies reporting brain structural changes in schizophrenia, there has been a paucity of data relating to potential subgroups or subtypes of the disease. It has therefore been difficult to reconcile variability in the brain structural endophenotype of schizophrenia and the delineation of biologically plausible subtypes. Direct correlations of single symptoms with brain structure, although replicable in cases like auditory hallucinations, suffer from various methodological limitations, such as intercorrelation of symptoms that tend to cluster into patterns. Genetic factors, on the other hand, have not successfully provided adequate stratification of patient samples with regards to brain structural abnormalities.

Methods: We analysed high-resolution 1.5 T MRI scans (T1-weighted, 1mm voxel dimensions) of 87 patients with DSM-IV schizophrenia (Sz) and 108 healthy controls (HC), who all provided written informed consent to a study protocol approved by the local ethics committee. Subjects were part of a larger initial study cohort or 99 patients (all on stable medication and with stable psychopathology) for which factor analysis (with Promax rotation) of SANS and SAPS scores had provided separation in three subgroups with predominantly negative, disorganized, and paranoid symptoms (groups and subgroups did not differ from controls in age and gender distribution). We extracted the cortical surface using Freesurfer software, and then analysed

cortical thickness, as well as applying a spherical harmonics-based approach to calculate fractal dimension (FD), as described previously (Yotter et al., NeuroImage 2011). Statistical analyses for both parameters were calculated on the global (hemisphere), regional (ROI derived from Desikan atlas), and vertex-wise level, where we focused as a main analysis on the ROIs to identify the regional patterns of deviations from the healthy controls groups.

Results: For cortical thickness, we found highly significant thinning on the hemisphere level for the Sz group, as well as each of the three subgroups. ROI analyses showed cortical thinning for the negative subgroup in almost all frontal, temporal, and parietal cortical areas. The paranoid subgroup (s3) also showed significant reductions across several prefrontal and temporal areas, sparing on the temporo-polar and fronto-polar regions, as well as cuneus bilaterally, while effects in inferior temporal and superior parietal areas varied across hemispheres. The disorganized subgroup showed the least effects on cortical thickness, but still revealed several significant reductions, including superior and middle prefrontal, as well as temporal cortices. For FD, negative subgroup showed most prominent reductions in left anterior cingulate, superior frontal, frontopolar, as well as right superior frontal and superior parietal cortices; the disorganized subgroup showed reductions in bilateral ventrolateral/orbitofrontal cortices, and several increases in the left hemisphere, including inferior parietal, middle temporal, and mid-cingulate areas; the paranoid subgroup showed only few changes, including decreases in the right superior parietal and left fusiform region, and increase in the left posterior cingulate cortex.

Discussion: Our findings provide an account on the variability and heterogeneity of the regional distribution of cortical thickness and cortical complexity (FD) measures within a large subgroup of schizophrenia. Such patterns might provide signatures for different subtypes with heterogeneous pathways towards the expression of the disease phenotype. Within the limitation of this symptom or phenotype-driven approach, they strongly suggest to consider the heterogeneity within brain structural parameters not only as noise within data, but rather a reflection of potentially diverging biological underpinnings of the schizophrenias.

Poster #S62

SCHIZOTYPAL TRAITS AND PSYCHOSIS PRONENESS DIFFERENTIALLY AFFECT BRAIN STRUCTURE IN HEALTHY PERSONS

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Background: Previous studies have suggested schizotypal features to provide a phenotypic marker across a schizophrenia-related continuum. In this study, we used the schizotypal personality questionnaire, German Version (SPQ-G), and the community assessment of psychic experiences (CAPE) questionnaires as psychometric tools to assess the hypothesis that variation in these measures of schizotypy (and psychosis proneness, resp.) would affect brain structure in healthy non-clinical subjects.

Methods: We obtained high-resolution 3T MRI scans (1mm voxel dimension) from 59 healthy control subjects without a history of psychiatric disorders or first-degree relatives with psychotic disorders. All subjects provided written informed consent to a study protocol approved by the local ethics committee. Data were analysed using voxel-based morphometry (VBM) to analyse correlations (positive and negative) for the positive and negative symptom dimensions of the SPQ-G and CAPE, resp. ($p < 0.001$, uncorr), correcting for age and gender effects in the general linear model framework of SPM.

Results: For the positive dimension scores, we found significant positive correlations between left anterior cingulate cortex (ACC) and the SPQ-G positive schizotypy factor, and a left lateral prefrontal cortical (PFC) cluster for the CAPE positive dimension score. For the negative dimension scores, we found significant positive correlations for the SPQ-G negative schizotypy factor and clusters in the right precuneus, right superior PFC, and left parietal cortex, as well as positive correlations between the CAPE negative dimension score and right SMA/medial PFC, left precuneus, and left parietal cortex. The positive correlation between negative schizotypy and the right precuneus also survived correction for multiple comparisons ($p < 0.05$, FDR).

Discussion: Our findings suggest a link between positive schizotypy and the positive symptom dimension of a psychosis proneness scale and prefrontal

brain structure, as well as negative schizotypy and symptom dimensions with precuneus and parietal brain structures. They hence provide further evidence for a biological schizophrenia spectrum, whereby even minor traits distributed across non-clinical samples might be associated with brain structures relevant for the pathophysiology of schizophrenia. Given that most of the associations are positive correlations, our findings can be considered either as a) a reflection of a linear correlation within a larger non-linear (for example, inverted U-shape curve) relation between phenotypes and brain structure, or b) protective factors in healthy subjects, which hence might correlate positively. Despite some divergence in the precise localisation of significant clusters, the two scales converge to some degree in the association in prefrontal and precuneus areas.

Poster #S63

REDUCED HIPPOCAMPAL VOLUME IN MALE BUT NOT FEMALE PATIENTS WITH FIRST EPISODE PSYCHOSIS: RELATIONSHIP TO CORTISOL LEVELS AND SYMPTOMS

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Background: Reduced hippocampal volume (HV) is a common finding in psychosis, with some indication that male patients are particularly affected. We recently reported a blunted cortisol awakening response (CAR) specifically in male patients with a first episode of psychosis (FEP). Goal of the present study was to investigate sex specific associations between these two markers of hypothalamus-pituitary adrenal (HPA) axis functioning and their relationship with symptoms in FEP patients.

Methods: Fifty-eight patients with a FEP (39 men, 19 women; mean age 24 ± 4.01) and 27 healthy community controls (15 men, 12 women; mean age 22.56 ± 3.61) underwent high-resolution ($1 \times 1 \times 1$ mm) magnetic resonance imaging on a 1.5T scanner. Hippocampal volume was determined using an appearance model-based automatic segmentation method with patch based local refinement. Saliva samples for cortisol assessment were collected at 0, 30 and 60 minutes after awakening. Psychotic symptoms were assessed with the Scale for Assessment of Positive Symptoms (SAPS), the Scale for Assessment of Negative Symptoms (SANS) and the Global Assessment of Functioning (GAF) scale.

Results: Male patients had significantly smaller left and right HV compared to male controls. The CAR was significantly lower in male patients compared to male controls. No such group differences were observed in women. Only in male patients, smaller left HV was significantly associated with a blunted CAR, and smaller HV bilaterally was related to more positive psychotic symptoms and lower levels of functioning.

Discussion: Our findings demonstrate reduced hippocampal volume and a relationship of this marker to HPA axis dysregulation and poor outcome particularly in male patients with FEP. We propose that hippocampal integrity is necessary for an adequate cortisol response and that deficits in both biological markers are related to increased vulnerability to stress contributing to the less favorable clinical picture in male patients.

Poster #S64

NEUROANATOMICAL PREDICTORS OF FUNCTIONAL OUTCOME IN THE AT-RISK MENTAL STATE

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Background: Poor psychosocial functioning has been shown to predate the onset of psychotic illness and is associated with poorer prognosis. While the majority of individuals at ultra-high risk (UHR) for psychosis do not progress to develop full-blown psychosis, many show poor functional outcome regardless of transition status. The current study adopted a voxel-based morphometry approach to predict functional outcome in a sample at UHR for psychosis.

Methods: 109 UHR individuals (54M;55F, mean age 19.5 years; SD=3.6) were recruited from the Personal Assessment and Crisis Evaluation (PACE) Clinic in Melbourne. They underwent magnetic resonance imaging at baseline and functional outcome (Social and Occupational Functioning Assessment Scale (SOFAS; Goldman et al., 1992) was assessed between 2.4 and 12.9 (median = 9.8) years later. Grey matter volume was examined controlling for gender, age at baseline, length of the follow-up period and field strength of the scanner (1.5T or 3T).

Results: Increased gray matter volume at baseline in a large medial pre-frontal cluster extending bilaterally into BA 9 and 10 and the cingulate gyrus, as well as clusters in the precuneus (bilateral), right paracentral lobule and left cerebellum, was associated with better functional outcome. Poorer functional outcome did not reveal significant areas of grey matter volume increase that survived correction for multiple comparisons. In addition, no significant relationship was observed between white matter volume and functional outcome.

Discussion: The observed brain pattern highlights areas of grey matter that in the at-risk mental state may be predictive of functional outcome years later. This may inform targeted treatment in the early stages of illness.

Poster #S65

CLASSIFICATION OF TWINS DISCORDANT FOR SCHIZOPHRENIA AND HEALTHY TWINS BASED ON THEIR STRUCTURAL MRI SCANS

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Background: In a recent study we built a structural-MRI-based schizophrenia classification model and tested its predictive capacity in an independent test sample (Nieuwenhuis et al, 2012). Here we apply such a model on a twin data set, including twins discordant for schizophrenia and healthy twin pairs to investigate whether the brain patterns used by the model to discriminate between patients and healthy subjects are based on illness effects or genetic vulnerability effects.

Methods: Structural magnetic resonance whole brain images of 24 discordant twin pairs and 27 healthy control pairs (Hulshoff Pol et al, 2006) were preprocessed to obtain so-called gray matter densities (used in voxel based morphometry (VBM)). A linear Support Vector Machine (SVM) (Vapnik, 1999) was trained on an independent data set to separate 215 schizophrenia patients (SZ) from 192 healthy subjects (HC). Effects of age, sex and handedness were regressed out in both sets. The model was applied to the twin data to classify each of the subjects as SZ or HC.

Results: Patients from the twin data set were correctly classified with an accuracy of 87%. Healthy co-twins of the patients were classified as SZ in 62% of the cases. Subjects from the healthy control twin pairs were classified as HC in 69% of the cases.

Discussion: We demonstrated the feasibility to use a classification model based on a large set of structural MRI scans from HC and SZ subjects to predict whether a twin subject is a schizophrenia patient or not. While most of the patients were classified correctly, the classification accuracy of healthy subjects was much lower, which was due to a relatively large percentage of co-twins of patients being classified as patient (62%). This suggests that the SZ/HC classification model is in part based on patterns of brain abnormalities shared by twins from discordant pairs. Whether these patterns are of genetic or familial origin remains to be investigated by taking into account the zygosity of the twins.

Poster #S66

THE POLYMORPHISM OF YWHAE, A GENE ENCODING 14-3-3EPSILON, AND ORBITOFRONTAL SULCOGYRAL PATTERN IN SCHIZOPHRENIA AND HEALTHY SUBJECTS

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Background: Altered sulcogyral pattern of the orbitofrontal cortex (OFC) has been implicated in schizophrenia as a possible marker of abnormal neurodevelopment, while its genetic mechanism remains unknown.

Methods: This magnetic resonance imaging study investigated the relationship between the polymorphism of YWHAE (rs28365859), a gene encoding a Disrupted-in-Schizophrenia 1 (DISC1)-interacting molecule associated with neuronal development (14-3-3epsilon), and the OFC subtypes of "H-shaped" sulcus [Type I, II, and III; defined by Chiavaras and Petrides (2000)] in a Japanese sample of 72 schizophrenia patients and 86 healthy controls.

Results: The patients with schizophrenia and healthy comparisons did not differ significantly in genotype distributions (chi-square = 1.62, p = 0.204) or allele frequencies (chi-square = 1.00, p = 0.317). The schizophrenia patients had a significantly increased Type III (chi-square = 8.24, p = 0.004) and decreased Type I (chi-square = 6.20, p = 0.013) expression on the right OFC compared to the controls. The subjects carrying the protective C allele had a decrease of Type III (chi-square = 8.01, p = 0.005) and increase of Type I (chi-square = 5.73, p = 0.017) compared to the G allele homozygotes, especially for the healthy subjects in the left hemisphere.

Discussion: The present study replicated an altered sulcogyral pattern of the OFC in schizophrenia and further suggested that genotype variation of YWHAE might be related to the development of cortical folding patterns in the orbitofrontal region. Although we did not observe a genotype effect of YWHAE on the OFC pattern specific to schizophrenia, our findings might support the possible role of the OFC sulcogyral pattern as an endophenotype for future genetic studies in schizophrenia.

Poster #S67

IN VIVO CHARACTERIZATION OF THE PDE10A PET TRACER [¹⁸F]MNI-659

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Background: Preclinical and early clinical evaluation of the PDE10A (phosphodiesterase 10A) occupancy and displacement by candidate drugs is an important part of in vivo characterization in the clinical development of potential new treatments for schizophrenia and other neuropsychiatric disorders. Such studies aid in prioritization among competing drug candidates and provide rational dosing strategies. The aim of this research is to validate the PDE10A tracer [¹⁸F]MNI-659 and to performed a Receptor occupancy study with a reference PDE10 molecule.

Methods: Positron emission tomography (PET) studies were carried out in baboon (*Papio anubis*). Ten PET studies (two baselines and high blockade studies using MP10, a selective PDE10 inhibitor) were conducted with [¹⁸F]MNI-659 (dose 181±6 MBq). MP10 doses of 1.8, 0.6, 0.2 and 0.07 mg/kg were administered i.v. over 30 min prior to tracer injection. Studies were modeled with a two-tissue compartment model (2TCM) to estimate the distribution volume. Binding potential BPnd was derived using the cerebellum as a reference region. BPnd was also estimated directly by non-invasive modeling with SRTM. Occupancy was estimated from BPnd at baseline and post blockade with MP10.

Results: [¹⁸F]MNI-659 displayed regional brain uptakes in accordance with expected PDE10A distribution: highest in putamen and globus pallidus and lowest in cerebellum, with a BPnd of up to ~8.0 in the putamen. [¹⁸F]MNI-659 PET imaging estimated a dose-dependent occupancy of PDE10A by MP10 similar to published results with [¹¹C]MP10 [1]. Occupancy estimates were very similar between 2TCM and SRTM, with an EC50 of 299 and 284 ng/mL, respectively, based on MP10 plasma levels at time of [¹⁸F]MNI-659 injection.

Discussion: Data suggest that [¹⁸F]MNI-659 may be quantified non-invasively and is a validated PET radiotracer for investigating PDE10A in Disease such as Huntington Disease and running occupancy studies against PDE10A inhibitors in non human primate as well as in man.

Poster #S68**GREY MATTER VOLUME ALTERATIONS IN PATIENTS WITH SCHIZOPHRENIA AND UNAFFECTED SIBLINGS SHOW REGION-SPECIFIC EFFECTS OF GENETIC RISK AND DISEASE-RELATED FACTORS**

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Background: Patients with schizophrenia (scz) display a pattern of grey matter abnormalities in the prefrontal cortex (PFC), the thalamus and the cerebellum, as shown by voxel-based morphometry studies. Furthermore, post-mortem studies indicate in patients neuronal loss in specific sub-regions of the thalamus such as the mediodorsal thalamic nucleus (MD). However, it is unclear to what extent these alterations in schizophrenia are associated with the genetic risk or with state-specific factors. The present study investigated the association between genetic risk for schizophrenia and grey matter volume abnormalities.

Methods: We recruited 65 patients diagnosed with scz (DSM-IV-TR), 45 non-affected siblings and 69 healthy controls. Groups were matched for socio-demographic variables, including age, education and gender. We collected 3D T1-weighted SPGR structural images using a 3 Tesla scanner (124 sagittal slices, thickness 1.3 mm; TR/TE = 25/3 ms; flip angle 6°; field of view 250 mm; matrix 256×256). Images were normalized using DARTEL, modulated to correct for warping effects and spatially smoothed. Effects were controlled for age, gender, and for total grey matter volume. Correction for multiple comparison was performed with non-stationary inference (cluster-level correction p-value <0.05). Given our findings and previous results on regional specificity of thalamic neuronal loss in schizophrenia, further analysis was performed in this brain area by defining 8 thalamic regions of interest (ROIs): anterior/midline nuclei; MD; intralaminar nuclei (ILN); ventrolateral nucleus (VL); ventral anterior nucleus; geniculate nuclei; pulvinar; posterior complex. Thus, grey matter volume estimates extracted from each thalamic ROI were used in a repeated measures ANCOVA with diagnosis (Patient, Sibling, Control) as categorical variable, side (left, right) and ROI (8 levels) as repeated measures factors. Furthermore, total thalamic grey matter was used as a covariate.

Results: We found significant effects of diagnosis bilaterally in the thalamus, the cerebellum, the PFC and the insula ($p<0.05$). Unaffected siblings differed significantly from controls in terms of grey matter volume in the cerebellum, in the insula, and in the orbitofrontal cortex (BA 11; $p<0.05$), and did not differ from patients. Further investigation of regional specific effects of diagnosis within the thalamus indicated main effects of ROI ($p=0.023$), of diagnosis ($p=0.003$) and a significant ROI × diagnosis interaction ($p<0.001$). Further analysis revealed that only the MD and the VL yielded significant differences between patients and controls ($p<0.05$). Moreover, there was a significant difference between siblings and patients.

Discussion: The present findings reveal region-specific association of grey matter abnormalities with genetic risk for schizophrenia. In particular, grey matter volume loss in the prefrontal cortex, the insula, and the cerebellum of scz are shared by their non-affected siblings. On the other hand, the thalamus presented a decrease in grey matter only in patients. Taken together, these findings suggest a primary association of genetic risk with reduced prefrontal and cerebellar grey matter volume, with a disease state-specific effect in the thalamic nuclei connected to these brain regions.

Poster #S69**STRUCTURAL BRAIN ABNORMALITIES, PSYCHOSOCIAL FUNCTIONING, AND GENETIC VULNERABILITY FOR SCHIZOPHRENIA**

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Background: Unaddressed deficits in psychosocial functioning present in

patients with schizophrenia may contribute to a significant barrier in achieving adequate social and work attainment for this population. Previous neuroimaging studies have identified structural brain abnormalities in both schizophrenia patients and their unaffected relatives compared with healthy individuals. It is unclear whether the degree to which these structural MRI vulnerability markers are associated with psychosocial outcomes. In this study, a family study design is used to explore underlying genetic risk by comparing patients with schizophrenia with their biological relatives and healthy controls. As healthy relatives share genes with their affected relatives, but not the disease process, abnormalities found in both affected and unaffected relatives are likely associated with the genes for schizophrenia.

Methods: Anatomical MRI scans were obtained from 27 healthy individuals, 28 individuals with schizophrenia, and 27 of their biological relatives, on a 3T scanner. Cortical thickness, surface area, and regional brain volumes were analyzed using Freesurfer. Whole-brain analyses were conducted using independent samples t-test, and significant findings are presented at a threshold of $p<0.001$. In addition, region-of-interest analyses were also conducted. We hypothesize that cortical thickness, surface area, and regional brain volumes will be reduced in affected and unaffected individuals compared to healthy controls. Furthermore, relatives of schizophrenia patients will be intermediate between patients and healthy individuals. Another hypothesis is that psychosocial functioning will be predicted by the indices of structural brain abnormality. Specifically, reduced cortical thickness, surface area and volume will predict worse psychosocial outcomes.

Results: No between group differences were found for age, gender, or intracranial volume. Preliminary data analyses suggested no differences between groups when whole-brain wide analyses were conducted; however, comparing 21 controls with 21 schizophrenia patients showed differences in a priori chosen frontal and temporal regions. Specifically, we found reduced cortical thickness in the bilateral inferior temporal gyrus, insular gyrus, fusiform gyrus, and superior frontal gyrus in the schizophrenia group.

Discussion: The next step will be to further analyze the surface area and volume data and test whether structural MRI indicators predict psychosocial outcomes in the patient group. In addition, data from the biological relatives group will be compared to both the healthy relatives and schizophrenia group to explore the effect of genetics on brain structure. Neurobiological markers found to be associated with poor psychosocial functioning in this study can be used to target new intervention strategies that focus on improving these outcomes for schizophrenia patients.

Poster #S70**IS GRAY MATTER VOLUME A STRUCTURAL ENDOPHENOTYPE FOR SCHIZOPHRENIA?**

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Background: Schizophrenia is a severe mental disorder with profound gray matter (GM) abnormalities (Fornito et al., 2009). Previous studies have suggested that part of these GM abnormalities might not solely be related to the illness state but instead serve as an endophenotype for schizophrenia (Moran et al., 2013; Turner et al., 2012). Several studies have examined gray matter differences between family members of patients with schizophrenia and healthy controls (for meta-analyses see Fusar-Poli et al, 2011; Palaniyappan et al., 2012). However, the results of these studies differ substantially. It has been proposed that differences in the age of included subjects might explain these discrepancies as included subjects are often past the critical ages for developing schizophrenia (Moran et al., 2013). Furthermore, differences in schizotypy and genetic loading might be accountable for the differences in results (Moran et al., 2013).

Methods: Eighty-nine siblings of patients with schizophrenia and 69 control subjects without a family history of psychotic disorders were included. Anatomical T1-scans were analyzed using unified voxel-based morphometry (VBM). The DARTEL approach was used for optimal registration of individual segments to a group mean template. A two-sample t-test was performed to examine GM differences between siblings and healthy controls. This analysis was repeated including only subjects below the age of

30 to examine whether this would generate different results. Furthermore, siblings and controls were split in a high schizotypy group and a low schizotypy group (by median split). The high schizotypy siblings and the high schizotypy controls were compared to low schizotypy controls with two-sample t-tests. Finally, GM of siblings with high genetic loading (≥ 2 family members with psychotic disorders) was compared to controls with low genetic loading (no psychiatric disorders in first- or second degree family members). The threshold for all analyses was set at $p < 0.05$ FWE corrected at the cluster level (initial voxel threshold of $p < 0.001$).

Results: The results revealed no significant differences in GM between siblings and controls. These results did not change by only including subjects below 30 years old (33 controls and 40 siblings). Comparing high schizotypy siblings with low schizotypy controls revealed larger GM volume in the left precuneus in the siblings. This result was also present in the high schizotypy control group. Comparing GM between high genetic loading siblings and low genetic loading controls (19 vs. 22) did not reveal any significant differences.

Discussion: The results revealed no significant differences in GM between siblings and controls. These results are consistent with previous large studies on GM differences between relatives and controls (Boos et al., 2012; Honea et al., 2008; Job et al., 2003). Furthermore, the current results show that explanations which were previously proposed to explain the negative findings in studies examining GM abnormalities in relatives of patients with schizophrenia, such as age, schizotypy and genetic loading (Moran et al., 2013), might not explain the lack of observed differences. Therefore, the current results indicate that GM might not be a suitable endophenotype for schizophrenia and that GM differences might be more related to the illness state than to the genetic risk for developing schizophrenia.

Poster #S71

CHANGE IN INTELLIGENCE IS ASSOCIATED WITH PROGRESSIVE GRAY MATTER LOSS IN THE EARLY YEARS OF SCHIZOPHRENIA

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Background: There is robust evidence for progressive gray matter volume loss after illness onset in schizophrenia, which is suggested to be most pronounced in the early phase of the illness. In addition, schizophrenia is characterized IQ deficits. In contrast to the general consensus that cognitive decline over time exist prior to the onset of the first psychosis, it is less clear whether cognitive functioning continues to deteriorate after illness onset. Interestingly, similar to the suggestion that the most pronounced gray matter volume loss takes place in the early stages of the disease, it has been reported that a (further) decline in cognitive functioning may take place in the first years after illness onset, reaching a stable course afterwards. Here, we investigate the association between change in global brain volumes and change in IQ in a cohort of schizophrenia patients and healthy control subjects during a three-year interval. We hypothesise that an association is present between loss of gray matter volume and decline (or less pronounced increase) in IQ in the early phases of the disease.

Methods: Two MRI scans were available with an average (sd) interval of 3.3 (0.4) years for 83 patients and 106 controls. Volumes of the intracranium, total brain (TB), cerebral gray matter (GM) and white matter (WM), lateral and third ventricles, and cerebellum were estimated. Four subtests (vocabulary, block design, information and digit symbol coding) of the Wechsler Adult Intelligence Scale-III (WAIS-III) were used to estimate total IQ scores. Illness duration at baseline was assessed using the CASH interview. Multiple linear regression analyses were used to test main and interaction effects.

Results: Baseline IQ was significantly lower in patients ($93.6 \pm SD 13.9$) than in controls (113.6 ± 15.4 ; $t = -9.17$, $p < 0.001$). Patients and controls showed a comparable mean increase in IQ scores during the interval (2.9 and 2.7 points, respectively; $t = 0.15$, $p = 0.88$). At baseline, total brain ($p < 0.001$) and white matter volume ($p < 0.001$) were significantly smaller and lateral ($p = 0.006$) and third ventricle volumes ($p = 0.04$) were significantly larger in patients as compared to controls. Patients showed significantly more pronounced gray matter loss during the interval ($p = 0.01$) as well as a larger increase in third ventricle volume ($p < 0.001$) as compared to controls. A trend was observed towards a more pronounced lateral ventricle increase

in patients ($p = 0.06$). A significant interaction effect was found between IQ change and illness duration on brain volume change in total brain ($p = 0.004$), GM ($p = 0.01$), and lateral ventricle ($p = 0.002$). A trend was observed for third ventricle volume change ($p = 0.09$). These findings indicate that the association between a smaller increase in IQ and more brain tissue loss was significantly more pronounced in those patients with a shorter duration of illness at baseline.

Discussion: This study is the first to report on the relationship between changes in brain volumes and change in IQ in schizophrenia patients and healthy subjects. We find that, despite a similar, subtle but significant, increase in IQ over time in patients and healthy individuals, gray matter volume loss over time is related to a relative decline (less increase) in IQ in those patients with shorter illness duration. These findings suggest that in the early phase of the illness, patients are particularly vulnerable to subtle cognitive decline in association with gray matter loss.

Poster #S72

ASSOCIATIONS BETWEEN CORTICAL THICKNESS AND TRAIT PHYSICAL AND SOCIAL ANHEDONIA IN NON-CLINICAL COLLEGE STUDENTS

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Background: Anhedonia is defined as reduced capacity to experience pleasure and it has been found not only in patients with psychosis, but also in non-clinical sample. Few studies have investigated the brain structural features associated with trait anhedonia, especially attributing to physical and social aspects.

Methods: We examined the relationship among cortical thickness, volumes of subcortical structures and the scores of physical and social anhedonia in a non-clinical sample ($N = 73$, 35 males) using the FreeSurfer.

Results: The results showed that inferior parietal cortex and the temporal pole were associated with both physical and social anhedonia. Interestingly, physical anhedonia was associated with the thickness of the orbitofrontal cortex and the lingual gyrus, the volumes of bilateral caudate; while social anhedonia was associated with the thickness of insula cortex and the superior temporal gyrus as well as the volume of amygdala.

Discussion: Taken together, these findings suggested there may be distinct correlation patterns of neural substrates in trait physical and social anhedonia even in non-clinical sample. These preliminary findings pave way for us to better understand the pathologies underlying the anhedonia phenotype in schizophrenia and other psychiatric disorders.

Poster #S73

TREATMENT AND OUTCOME OF YOUTH WITH EARLY-PHASE SCHIZOPHRENIA-SPECTRUM DISORDERS AND PSYCHOSIS NOS: 12-WEEK RESULTS FROM A NATURALISTIC COHORT STUDY

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Background: While scarce in the past, knowledge and research on early onset schizophrenia have increased in the last decades, and studies have supported the validity of the diagnosis and the use of antipsychotics in this age group. However, research on other psychotic disorders among children and adolescents is still scarce. Early onset schizophrenia is the most severe diagnosis among the psychotic disorders, but other psychotic disorders are more common and most pediatric patients are first diagnosed with Psychosis NOS. Little is known about the treatment response and outcomes for this group. The aim of this study was to help bridge this

gap by assessing differences in the outcomes of youth with schizophrenia-spectrum disorders (SCZ-S) and psychotic disorder NOS (PsyNOS) during early antipsychotic treatment.

Methods: Prospective, naturalistic, inception cohort study of youth <18 years old with SCZ-S (schizophrenia, schizoaffective disorder, schizophrenia-form disorder) or PsyNOS (PsyNOS, brief psychotic disorder) and <24 months of lifetime antipsychotic treatment receiving clinician's choice antipsychotic treatment. Baseline demographics, illness and treatment variables, and effectiveness outcomes were compared at 12-week last-observation-carried-forward endpoint across SCZ-S and PsyNOS patients, adjusting for significantly different baseline variables. Linear and ordered regression analyses were conducted on the outcome measures. CGI-I endpoint scores and CGAS scores categorized as good, moderate or poor outcome served as primary outcomes. All statistical analyses were carried out using Stata11.

Results: Altogether, 131 youth with SCZ-S (n=41) or PsyNOS (n=90), mean age of 15.4±2.9 years, mostly antipsychotic-naïve (77.1%), were initiated on risperidone (48.9%), olanzapine (16.8%), aripiprazole (16.0%), quetiapine (11.5%) or ziprasidone (6.9%). Compared to PsyNOS, SCZ-S youth were older (16.4±2.1 vs. 14.9±3.2, p=0.0090), more likely African-American (63.4% vs. 28.1%, p=0.0001), and less likely White (17.1% vs 42.7%, p=0.004). At baseline, SCZ-S patients were more severely ill than PsyNOS subjects: SCZ-S patients had significantly higher Clinical Global Impression-Severity (CGI-S) scores (6.0±0.8 vs. 5.5±0.8, p=0.0022), lower Children's Global Assessment of Functioning (CGAS) scores (29.7±9.2 vs 36.0±8.8, p=0.0002), were more likely inpatients (87.8% vs. 67.8%, p=0.015) and were more likely in the severely ill CGAS group (i.e., CGAS<40). More patients with SCZ-S had a second degree family member with SCZ-S disorders (33.3% vs. 13.2%, p=0.046). During 12 weeks of naturalistic treatment, SCZ-S responded less well to naturalistic antipsychotic treatment than PsyNOS: While SCZ-S and PsyNOS did not differ regarding all-cause discontinuation (51.2% vs. 43.7%, p=0.49), more SCZ-S patients discontinued treatment for inefficacy (22.5% vs. 7.0%, p=0.011). CGI-S and CGAS scores improved significantly in both diagnostic groups during the 12 weeks of treatment (p=0.0001). However, adjusting for baseline differences, PsyNOS patients experienced significantly better CGI-I improvement (p=0.033) and scored better in the categorical CGAS groups (p=0.030) than SCZ-S patients.

Discussion: Both youth with SCZ-S and PsyNOS experienced significant improvements during 12 weeks of clinician's choice antipsychotic treatment. However, treatment discontinuation was common within 12 weeks, with greater inefficacy-related discontinuation in the SCZ-S group, while CGI-I and CGAS score-based improvements were greater in the PsyNOS group, indicating the need for early acute and maintenance treatment in youth with non-affective psychotic disorders.

Poster #S74

INCREASED RISK OF SCHIZOPHRENIA SPECTRUM DISORDERS AFTER ALL CHILDHOOD PSYCHIATRIC DISORDERS - NATIONWIDE STUDY

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Background: Previous studies have shown associations between prior childhood psychiatric disorders and development of schizophrenia spectrum disorders, particularly after specific diagnoses of autism and attention-deficit/hyperactivity-disorder. However, large-scale prospective studies are lacking on the association between schizophrenia spectrum disorders and previous diagnoses of a broad range of childhood psychiatric disorders considered individually and in aggregate.

Methods: Danish nationwide registers were linked to establish a cohort consisting of all persons born during 1990-2000 conducting the largest study to date. Individuals with childhood psychiatric disorders were identified and the cohort was followed for a first-time psychiatric contact for schizophrenia spectrum disorder until December 31st 2012. Data were analyzed using survival analyses and adjusted for calendar year, age, and gender.

Results: The results presented are preliminary. In the entire cohort a total of 25,139 persons were diagnosed with a childhood psychiatric disorder

and 3,085 people had a first-time diagnosis with schizophrenia spectrum disorders. 1,420 was first diagnosed with a childhood psychiatric disorder and then secondly with a schizophrenia spectrum disorder corresponding to 5.6%. The risk of later being diagnosed with schizophrenia spectrum disorders was highly elevated and remained significantly elevated with an incidence rate ratio (IRR) of 5.57 (95% CI: 4.93-6.27) more than 5 years after the childhood psychiatric disorder had been diagnosed. The cumulative incidence of persons being diagnosed with schizophrenia spectrum disorders after the first diagnosis with a childhood psychiatric disorder was within the first year 2.56%, within the first to second year 0.60% and within the second to fifth year 1.22%. More than five years after the first diagnosis with a childhood psychiatric disorder was given the cumulative incidence was 1.38%.

Discussion: The risk of being diagnosed with a schizophrenia spectrum disorder was highly elevated after any childhood psychiatric disorder and remained significantly increased more than 5 years after the first diagnosis with a childhood psychiatric disorder.

Poster #S75

COPING, PSYCHOTIC SYMPTOMS AND FUNCTIONING IN ADOLESCENTS WITH MENTAL ILLNESS

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Background: Psychotic symptoms in the context of psychiatric disorders are associated with poor functional outcomes. Environmental stressors are important in the development of psychosis; however, distress may only be pathogenic when it exceeds an individual's ability to cope with it. Therefore, one interesting factor regarding poor functional outcomes in patients with psychotic symptoms may be poor coping.

Methods: In a clinical case-clinical control study of 106 newly-referred adolescent patients with non-psychotic psychiatric disorders, coping was investigated using the Adolescents Coping Scale. Severity of impairment in socio-occupational functioning was assessed with the Children's Global Assessment Scale.

Results: Patients (N=106) with non-psychotic psychiatric disorders and additional psychotic symptoms had poorer functioning and were more likely to use avoidance-oriented coping. No differences were found with respect to approach-oriented coping. When stratifying for poor/good coping, only those adolescent patients with psychotic symptoms who applied poor coping (i.e. less use of approach-oriented coping styles [OR 0.24, p<0.015] and more use of avoidance-oriented coping [OR 0.23, p<0.034]) had poorer functioning. However, these interactions were not significant, probably due to too small subgroups.

Discussion: Non-adaptive coping and poorer functioning were more often present in adolescents with non-psychotic psychiatric disorders and additional psychotic symptoms. Due to small subgroups, our analyses could not give definitive conclusions about the question whether coping moderated the association between psychotic symptoms and functioning. Improvement of coping skills may form an important target for intervention that may contribute to better clinical and functional outcomes in patients with psychotic symptoms.

Poster #S76

A RANDOMIZED TRIAL ADMINISTERING RALOXIFENE VS PLACEBO AS ADD-ON TO ANTIPSYCHOTICS IN POST-MENOPAUSAL FEMALE PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

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Background: Epidemiological evidence shows a potentially protective role for estrogen in women with schizophrenia. The onset of schizophrenia is later in women than in men, with generally a less severe course until after the menopause, when for many women, reductions in estrogen levels

appear to trigger an exacerbation or illness. ER α (Estrogen receptor alpha) expression is known to be reduced in schizophrenia (Wong, Woon et al. 2010). Raloxifene is a selective estrogen receptor modulator that acts as an estrogen antagonist in breast tissue and may have agonistic actions in the brain. Several studies (Kulkarni, Riedel et al. 2001; Chua, de Izquierdo et al. 2005; Kulkarni, Gurvich et al. 2010) indicate that treatment with estrogen and raloxifene improves symptoms in females with schizophrenia.

Methods: This was a multi-center trial performed in 32 sites in Romania and Moldova. Inclusion criteria were 34 (moderate) score on two of the following four PANSS items: delusions, hallucinatory behaviors, conceptual disorganization or suspiciousness/persecution, and/or a total PANSS negative symptoms score above 18. Throughout the trial all subjects received anti-psychotics. Subjects were randomized to raloxifene 120 mg/day (N=100) or placebo (N=100). Duration of the study was 16 weeks.

Results: Baseline means in PANSS total scores were 101.7 ± 18.5 for raloxifene and 101.2 ± 18.1 for placebo; the mean change between baseline and end of study were -16.2 ± 13.1 for raloxifene and -19.2 ± 15.1 for placebo. The difference between groups was non-significant ($t=-1.42$, $df=187$, $p=0.16$). Baseline means in the PANSS positive scale were 23.6 ± 4.3 for raloxifene and 23.4 ± 3.9 for placebo; mean changes were -5.16 ± 4.4 for raloxifene and -5.63 ± 4.9 for placebo. The difference between groups was non-significant ($t=-0.69$, $df=187$, $p=0.49$). Baseline means in the PANSS negative scale were 27.0 ± 5.9 for raloxifene and 26.5 ± 6.3 for placebo. The mean change in the PANSS negative scores were -3.7 ± 4.1 for raloxifene and -5.0 ± 4.8 for placebo. The difference between groups was non-significant ($t=-1.95$, $df=187$, $p=0.05$). Baseline means in the PANSS general psychopathology scale were 51.1 ± 11.4 for raloxifene and 51.2 ± 10.8 for placebo. The mean change in the PANSS psychopathology scores were -8.2 ± 8.4 for Raloxifene and -9.8 ± 9.2 for placebo. The difference between groups was non-significant ($t=-1.25$, $df=187$, $p=0.22$).

Discussion: The results show no statistically significant difference in any of the outcome measures between Raloxifene and placebo. The most reasonable explanation for that is that add-on Raloxifene administered at 120 mg/d is not an effective treatment for the symptoms of schizophrenia.

Poster #S77

RISK-BASED MONITORING FOR ABERRANT RATING PATTERNS AND PATIENT SELECTION ANOMALIES IN GLOBAL SCHIZOPHRENIA TRIALS

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Background: Risk-based outlier analysis of blinded data for aberrant rating patterns and patient selection anomalies can be paired with audio/video surveillance to cost effectively identify at-risk sites in global schizophrenia clinical trials.

Methods: Utilizing centralized, blinded data quality monitoring of 41,555 PANSS assessments in eleven international schizophrenia clinical trials, norms were created for a library of data patterns selected by sponsors as potentially at risk for measurement error or idiosyncratic patient selection. Based on these risk factors, a composite score or "dashboard" was created ranking each site based on quality measures. Sites of concern were subsequently subjected to more intensive, remote, centralized review of recorded patient interviews by external experts. The quality of recorded interviews and ratings was remotely assessed by independent reviewers for 2,943 PANSS assessments.

Results: Based on independent review of audio and/or video recorded PANSS assessments, interview quality was rated as excellent, adequate with some deficiencies or inadequate in 75.44% (n=2221), 23.2% (n=683) and 1.36% (n=40) of visits, respectively. Proper application of the PANSS instructions and anchor points was independently rated as excellent, adequate with some deficiencies, or inadequate in 75.98% (n=2221), 22.8% (n=671) and 1.22% (n=36) of visits, respectively. The following illustrate examples of adaptive monitoring. Sites 397 and 762 were evaluated on three risk factors specified by the sponsor: 1) large between visit changes in the total PANSS score; 2) erratic PANSS changes; and 3) 100% identical PANSS scores from visit to visit. If anomalies were determined by blinded data monitoring, additional scrutiny was employed by external review of recorded patient visits. Site 397 was an outlier on factors 1 and 2 (>3 SD above the mean) but refused to allow interviews to be recorded for external review to allow independent assessment of measurement error.

The site was closed. Site 762 was not an outlier on large score or erratic score changes but more than 15% of visits were 100% identical. Recordings of patient interviews were scrutinized. The proportion of discordant PANSS ratings (>2 difference between site and independent rater) exceeded 60%. The site was subjected to remedial training and close scrutiny for the remainder of its trial participation.

Discussion: Risk-based outlier analysis of blinded data for aberrant rating patterns and patient selection anomalies can be paired with audio/video surveillance to cost effectively identify at-risk sites in global schizophrenia clinical trials. Allowing sites to "opt out" of audio/video surveillance complicates interpretation of data anomalies. In addition, audio/visual surveillance has the potential to identify endpoint scoring irregularities that may not emerge in outlier analysis. Additional data is being collected. The analyses reported above are preliminary.

Poster #S78

THE NOVEL PHARMACOLOGY OF ITI-007 IS ENHANCED AND EXTENDED BY ITS METABOLIC BACK CONVERSION FROM IC200131

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Background: ITI-007 is currently being developed for the treatment of several neuropsychiatric disorders including acutely exacerbated schizophrenia. It is a potent serotonin-2A (5-HT2A) receptor antagonist, a dopaminergic protein phosphorylation modulator acting as a pre-synaptic partial agonist and a post-synaptic antagonist at D2 receptors, an inhibitor of serotonin reuptake and a glutamatergic protein phosphorylation modulator. Adding to this unique profile, ITI-007 is metabolized into two active metabolites, IC200131 and IC200161. IC200131, is a serotonin-2A (5-HT2A) receptor antagonist and inhibitor of serotonin reuptake with roughly equal potency at each of these two targets. IC200131 has a longer plasma half-life than ITI-007 or IC200161. In addition, IC200131 can be back converted into ITI-007. Thus, the pharmacology of ITI-007 is positively impacted by its metabolic conversion into IC200131.

Methods: The *in vitro* metabolism of ITI-007 and its metabolites were studied using subcellular fractions and isolated hepatocytes. In addition, the *in vivo* metabolism of ITI-007 was studied after oral administration to rats, dogs and humans. Plasma and brain levels of ITI-007 and metabolites were determined in rats; plasma levels were determined after dose solutions in dogs and after different dosing regimens in patients with stabilized schizophrenia. Further, orally administered IC200131 was evaluated for its ability to reduce head-twitch behavior induced by a 5-HT2A receptor agonist (quipazine) and to reduce amphetamine-induced hyperactivity in rats relative to ITI-007.

Results: In hepatocytes, ITI-007 is metabolized to IC200131 and to IC200161. Species differences are apparent in the rate of formation of these two metabolites of ITI-007. Interestingly, IC200131 can be back converted to ITI-007. *In vivo* studies revealed that after oral administration, ITI-007 and IC200131 are rapidly absorbed in rats and dogs. Both ITI-007 and IC200131 also can readily penetrate the brain of rodents with much higher brain than blood levels. In addition, oral administration of IC200131 results in measurable plasma levels of ITI-007. In rats, both ITI-007 and IC200131 reduced quipazine-induced head-twitches and inhibited amphetamine-induced locomotor activity. Exposure data for ITI-007 and IC200131 from a clinical trial of ITI-007 in patients with stable schizophrenia will be presented.

Discussion: IC200131, a predominant metabolite of ITI-007 in humans, penetrates the brain, has a long plasma half-life and exhibits behavioral activity consistent with 5-HT2A receptor antagonism and antipsychotic efficacy. Interestingly, IC200131 can be back-converted to ITI-007. Given its long half-life, IC200131 can act as a pool from which ITI-007 can be continuously extracted. This back-conversion extends the effective half-life and enhances the activity of ITI-007. Thus, the combined actions of IC200131 and ITI-007 present a novel pharmacologic profile that may have broad utility in treating neuropsychiatric and related disorders.

Poster #S79**EFFECTIVENESS OF INTEGRATED COGNITIVE REMEDIATION THERAPY FOR SCHIZOPHRENIA OUTPATIENTS: EARLY VERSUS LONG-TERM COURSE OF ILLNESS - RESULTS FROM AN INTERNATIONAL RCT**Daniel R. Müller¹, Valentin J. Benzing², Volker Roder²¹University Hospital of Psychiatry Bern; ²University Hospital Bern

Background: Nowadays there is extensive evidence available showing the efficacy of cognitive remediation therapies. Integrative approaches seem superior regarding the maintenance of proximal outcome at follow-up as well as generalization to other areas of functioning. To date, only limited evidence about the efficacy of CRT is available concerning elder schizophrenia patients. The Integrated Neurocognitive Therapy (INT) represents a new developed cognitive remediation approach. It is a manualized group therapy approach targeting all 11 NIMH-MATRICS dimensions within one therapy concept. In this study we compared the effects of INT on an early course group (duration of disease < 5 years) to a long-term group of schizophrenia outpatients (duration of disease > 15 years).

Methods: An international multicenter study carried out in Germany, Switzerland and Austria with a total of 90 outpatients diagnosed with Schizophrenia (DSM-IV-TR) were randomly assigned either to an INT-Therapy or to Treatment-As-Usual (TAU). 50 of the 90 Patients were an Early-Course (EC) group, suffering from schizophrenia for less than 5 years (Mean age=29 years, Mean duration of illness=3.3 years). The other 40 were a Long-term Course (LC) group, suffering from schizophrenia longer than 15 years (Mean age= 45 years, Mean duration of illness=22 years). Treatment comprised of 15 biweekly sessions. An extensive assessment battery was conducted before and after treatment and at follow up (1 year). Multivariate General Linear Models (GLM) (duration of illness x treatment x time) examined our hypothesis, if an EC group of schizophrenia outpatients differ in proximal and distal outcome from a LC group.

Results: Irrespective of the duration of illness, both groups (EC & LC) were able to benefit from the INT. INT was superior compared to TAU in most of the assessed domains. Dropout rate of EC group was much higher (21.4%) than LC group (8%) during therapy phase. However, interaction effects show that the LC group revealed significantly higher effects in the neurocognitive domains of speed of processing ($F>3.6$) and vigilance ($F>2.4$). In social cognition the EC group showed significantly higher effects in social schema ($F>2.5$) and social attribution (blame; $F>6.0$) compared to the LC group. Regarding more distal outcome, patients treated with INT obtained reduced general symptoms unaffected by the duration of illness during therapy phase and at follow-up ($F>4.3$).

Discussion: Results suggest that INT is a valid goal-oriented treatment to improve cognitive functions in schizophrenia outpatients. Irrespective of the duration of illness significant treatment effects were evident. Against common expectations, long-term, more chronic patients showed higher effects in basal cognitive functions compared to younger patients and patients without any active therapy (TAU). Consequently, more integrated therapy offers are also recommended for long-term course schizophrenia patients.

Poster #S80**UNDERSTANDING SOCIAL SITUATIONS (USS): DEVELOPMENT OF A NEW SOCIAL COGNITIVE INTERVENTION FOR INDIVIDUALS WITH PSYCHOSIS**David L. Roberts¹, Laura Diggins², Lori Parente³, Joanna Fiszdon²¹University of Texas Health Science Center; ²Yale University School of Medicine; ³VA Connecticut Healthcare System

Background: Social cognition – how an individual processes, interprets, and responds to social information – is increasingly recognized as a promising treatment target to improve social functioning in schizophrenia (SCZ). While existing social cognitive interventions have shown robust effects on emotion recognition, interventions specifically targeting attributional bias (AB) and Theory of Mind (ToM) have been few and have met with more limited success, suggesting that further treatment development, perhaps using another approach to learning, may be of benefit. Since SCZ is associated with significant cognitive impairments that are known to impact skill acquisition, our intervention was specifically designed to lessen cognitive load by relying on methods that have been successfully used in neurocogni-

tive rehabilitation with this population. These methods include massed drill and practice, graded increases in task difficulty, scaffolding and errorless learning. Here, we report on the development, and early pilot testing of this new intervention, called Understanding Social Situations (USS).

Methods: USS is an 8 to 10 session individually administered intervention targeting ToM and AB. Participant and trainer progress through four successive modules: (1) Separating Social Facts from Social Guesses, (2) Making Probability Judgments and Not Jumping to Conclusions, (3) Determining Others' Mental States, and (4) Inducing Positive Interpretative Bias in Ambiguous Situations. Content and methods of each module are based on previous laboratory or treatment research suggesting these methods' efficacy in improving ToM and AB. The training is administered via Powerpoint, and consists of photos, vignettes, videos, and audio-clips depicting different social situations. Development of the intervention consisted of: 1) initial treatment development informed by a series of uncontrolled cases, 2) treatment refinement and manualization, and 3) a small feasibility/preliminary efficacy trial. For the trial, comprehensive assessments, including measures of ToM and AB, were conducted pre- and post-intervention. Paired samples t-tests and within-group effect size analyses were conducted.

Results: Of the 19 individuals who consented for the initial development phase of the study, 9 were excluded from the trial because they did not meet threshold criteria for ToM/AB impairment. Eight participants began USS training, with two dropping out and six completing the intervention. Reasons given for drop-out were unrelated to the USS intervention. Feedback from completers was generally positive. Paired samples t-tests and conservative within-group effect sizes indicated statistically significant or trend level changes on a number of AB and ToM measures. All AB effects were in the expected direction (i.e. decreased tendency toward hostile attributions, d range: 0.56–1.41; p range: 0.040–0.101). For ToM, while there was improvement on the Reading the Mind in the Eyes Task ($d=0.55$; $p=0.056$), the two TASIT scales assessing inference of sarcasm and lying indicated worse performance following treatment ($d=-0.84$, -0.70 ; $p=0.054$, 0.063).

Discussion: Results provide direction for continued development of USS. The intervention appears to be feasible and well tolerated by patients. Preliminary data suggest that USS has the potential to improve AB and some ToM skills. USS does not specifically target the ToM ability to detect lying and sarcasm, and early results suggest that USS participants may not benefit in these domains. This potential limitation has been considered in ongoing development of the USS intervention.

Poster #S81**RANDOMIZED TRIAL OF CLOZAPINE VS. RISPERIDONE IN TREATMENT-NAÏVE FIRST-EPIISODE SCHIZOPHRENIA: PRELIMINARY RESULTS**Francisco Javier Sanz-Fuentenebro¹, Diana Taboada², Vicente Molina³¹Asoc. Prof. Complutense Univ. Madrid; ²Hospital 12 de Octubre; ³Hospital Clínico Univ. Valladolid. Spain

Background: Clozapine may be potentially valuable in first-episode patients with psychosis, as an initial treatment seeking to limit early on clinical and cognitive deterioration. Nevertheless, until recently its restricted use has limited the study of this possibility.

Methods: Our research group is developing a multicentric and open label study, on the differential efficacy between clozapine and risperidone in first-episode schizophrenia. Here we present clinical outcome results after one-year follow-up. For clinical assessment, we employed the Positive and Negative Syndrome Scale (PANSS), and the Udvalg for Kliniske Under-søgelser (UKU) Side Effects Rating Scale; applied at weeks 1, 2, 3, 4, 6, 8, 10 and 12, and months 6 and 12.

Results: Out of 33 patients included, 16 were randomized to clozapine and 17 to risperidone; 7 patients dropped the study by their will, and three other patients due to lack of response. Patients initially assigned to clozapine remained on this treatment for a longer period than patients assigned to risperidone (71,31 vs 45,88, t 1,838, $p=0,76$). By last observation carried forward (LOCF) analysis, patients on clozapine and risperidone displayed similar clinical improvements in Positive symptoms (58,92 vs 50,60; $t=1,02$, $p=0,31$), although larger improvement in Total (44,64 vs 28,93; $t=1,97$, $p=0,058$), and Negative (18,72 vs -19,12, t 2,13, $p=0,041$) symptoms scores were found in the clozapine group. At the 12-month point we observed a marginal improvement in negative symptom in patients on clozapine

(mean change -8.2, sd 10.3, $z=-1.66$, $p=0.09$), and marginal increase (mean change -0.4, sd 9.52, $z=0.27$, $p=0.78$) in this subscale in the risperidone group. We found an inverse, significant association between Subjective secondary effects, as measured with the UKU scale, and negative (Spearman's $\rho=-0.65$, $p=0.02$) symptoms improvement at 12 months.

Discussion: Our data, although preliminary, suggest that clozapine may have a slightly superior efficacy in the initial year of treatment of first-episode treatment-naïve patients with schizophrenia. The worsening of negative symptoms in the risperidone group seems attributable to secondary effects of the drug. Taken together with the larger attrition in this group, a better tolerability is suggested for clozapine. The larger improvements in Total and Negative symptom scores with clozapine may point to a superior efficacy in the earlier stages of illness, to be confirmed upon inclusion of a larger number of cases and follow-up completion.

Poster #S82

FAILURES IN THE FACIAL EMOTION RECOGNITION IN PATIENTS WITH SCHIZOPHRENIA, SIBLINGS, AND CONTROL SUBJECTS

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Background: Facial recognition is the ability to recognize basic forms of emotional expression on the faces of other individuals (Hall, 2004; Russell, 1994). The basic affective expressions are: happiness, sadness, fear, disgust, surprise, anger, and neutral face. These emotions are universal and accepted by all cultures (Ekman, 1994). Poor facial recognition is more frequent when recognizing negative emotions, included schizophrenic patients (Gard, 2011).

Methods: Our objective was to determinate which emotions were confused and for which were mistaken. It was an observational trial with three groups: 34 schizophrenic patients, 34 siblings and 34 control subjects. We used SCID-I and SCL-90 scale for siblings, and controls. PANSS, CDSS, and CGI in schizophrenic patients to determinate stability, and we used the pictures of facial affect developed by Ekman (1976).

Results: In all groups, the least recognized emotion was fear and the most recognized was surprise within the patient and the sibling groups. The control group acknowledged more the neutral emotion face. Happiness was recognized by patients in 84.9%, and was mistaken for the neutral face in 13%. The siblings recognized happiness in 89.8%, and change it for neutral face 8%. The control group recognized joy in 92.6%, and mistaken it for neutral face in 7.7% ($F=4.88$, 2gl, $p=0.009$). Sadness was recognized by patients in 62.3%, by siblings in 70.9%, and by controls in 77.16%. The patients had mistaken it for fear in 15.6%, for neutral face in 10.9%, and for anger in 6.1%. The siblings had mistaken it for fear in 14.1%, and for anger in 7.9%. The control group mistaken it for fear in 11.2%, and for anger in 4.5% ($F=6.50$, 2gl, $p=0.002$). Fear was the least recognized; by patients in 46.8%, siblings in 53.7% and control subjects in 69.6%. The patients group had mistaken it for surprise in 42.6% and anger in 6.9%. The siblings mistaken it for surprise in 41.3%, and control group also for surprise in 25.4% ($F=8.18$, 2gl, $p=0.001$). Anger was recognized by patients in 78.3%, siblings in 83.1%, and by controls in 91.1%. The patients had mistaken it for neutral face in 5.6%, fear in 5.2%, surprise in 5.04% and disgust in 4.9%. Siblings mistaken it for disgust in 4.7%, and control group for surprise in 2.6% ($F=6.70$, 2gl, $p=0.002$). Surprise was the most recognized by the patients group in 89.7%, the siblings in 92.2%, and control group in 97.4%. The confusion was lesser in the three groups ($F=3.42$, 2gl, $p=0.03$). Disgust was observed by patients group in 58.6%, siblings in 69.6%, and control group in 85.8%. It was mistaken for anger by patients in 25.6%, siblings in 23.3%, and control subjects in 11.5% ($F=12.17$, 2gl, $p<0.001$). Neutral face was recognized in 98.7% by control group, 89.9% by siblings group, and 85.5% by patients group. Only the patients group mistaken the neutral face for sadness in 4.6% ($F=4.35$, 2gl, $p=0.01$)

Discussion: The differences in the recognition of emotions on previous studies reported a poor recognition of fear and sadness. These findings have also been described in different ethnic groups and in different populations. In our study, we found that differences persisted, and the fear expression was mistaken for surprise in all groups. The patient group showed differences in relation to other groups, but the siblings group was closer to patients. The control group had a lesser degree of failure in recognition emotion. This supports the presence of basic cognitive failures in patients

and their siblings, which has been reported in literature before (Kohler, 2010).

Poster #S83

PALIPERIDONE ER TREATMENT AND THE IMPROVEMENT OF SOCIAL AND COGNITIVE FUNCTION IN PATIENTS WITH SCHIZOPHRENIA - A 24-WEEK, SINGLE ARM, OPEN-LABEL STUDY

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Background: A few studies have demonstrated that Paliperidone extended-release (ER) treatment could significantly improve positive and negative symptoms, interpersonal relationships in acute phase of schizophrenia with a benign safety profile. But its impact to the neurocognitive function as well as social function in patients with non-acute phase schizophrenia after long term treatment remains unclear.

Methods: This was a 24-week, single arm, open-label, multi-centered study conducted from Oct. 2010 to Dec. 2012. In order to evaluate the efficacy and safety of the drug, Paliperidone ER (flexible dose ranged from 3 to 12 mg, qd, po) was administered in patients with non-acute phase schizophrenia. The primary outcome indicators of the study were social function and neurocognitive function, assessed by the Personal and Social Performance scale (PSP), and Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative - Consensus Cognitive Battery (MCCB) respectively. Secondary outcome indicators included Positive and Negative Symptom Scale (PANSS), Clinical Global Impression-Severity (CGI-S); Safety and tolerability were assessed by Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS), Barnes Akathisia Scale (BARS) and Adverse events (AEs).

Results: Finally 90 patients were included in full analysis set (FAS), whereas 72 in per protocol set (PPS) and 93 in safety set (SS). The mean age of patients in FAS was 27.6±7.8 years and percentage of male subjects in the same group was 48.9%. PPS was analyzed, for the primary outcome. T, the PSP score was 54.3±14.3 at baseline, which was significantly increased to 73.4±12.6 at Week 24 ($p<0.001$, t test or sign rank test) with an increase of 19.1±16.1. The percentage of PSP score over 70 equal or more than 71 points was 65.3% of all subjects. PSP score change ≥10 points from baseline were found in 77.8% of all subjects. For the MCCB assessment, 6 of 9 individual subtests, 6 of 7 cognitive domains and the total cognitive score changed significantly ($p<0.05$, paired t test or sign rank test) from endpoint (week 24) to baseline, in both raw scores and T scores. The PANSS total scores and CGI-S scores decreased gradually and changed significantly ($p<0.001$, paired t test or sign rank test) since Week 4. SS was conducted the safety analysis, no significant change of vital signs, total scores of AIMS, SAS and BARS at endpoint (Week 24) comparing to those at baseline. The occurrence of AEs was 62.4% of patients, most of which were mild (44.1%) and moderate (32.3%) in severity. The most common AEs (incidence ≥5%) were extrapyramidal symptoms (34.4%), body weight gain (14.0%), amenorrhea (7.5%), anxiety (5.4%) and dysphoria (5.43%). 58.1% (54 patients with frequency of 121 times) of AEs were determined to be related to the study drug (Paliperidone). Two SAE cases (2.2%) were a cardiac arrest and an accidental pregnancy.

Discussion: In this study, treatment with Paliperidone ER 3 to 12 mg for 24 weeks in Chinese patients with schizophrenia, who were on non-acute phase, could significantly improve the social function and neurocognitive function as well as the positive and negative syndrome. The patients could well tolerate Paliperidone ER.

Poster #S84**THE EFFECT OF LIFESTYLE INTERVENTIONS ON PSYCHOSOCIAL FUNCTIONING AND WELL-BEING IN PATIENTS WITH SEVERE MENTAL ILLNESS**

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Background: Antipsychotic medication, genetic vulnerability and an unhealthy lifestyle increase the risk for severely ill (SMI) patients to develop cardio-metabolic syndrome. Also, an unhealthy lifestyle may lead to social dysfunction. Therefore, a lifestyle intervention may improve several aspects of mental well-being, besides physical fitness. Nonetheless, to date, studies investigating the psychosocial effects of lifestyle interventions in SMI patients are scarce, and lacking altogether for SMI residential patients. The aim of this study was to assess the psychosocial effects of a combined diet-and-exercise lifestyle intervention targeting the obesogenic environment of SMI residential patients.

Methods: This controlled multicenter, pragmatic study was conducted in several sheltered and long-stay facilities in the North of the Netherlands. Participants were patients who primarily suffer from psychotic disorders. Teams were matched based on level of intensity of care (long-term residential or long-term clinical care), caseload size, mean age of patients, mean duration of admission of patients, most frequently diagnosed disorder and location (urban or rural). Lifestyle interventions were set up to change the obesogenic environment into a healthier setting where patients are supported to make healthier choices (e.g. not only white bread but also whole wheat bread is available). During a three month intervention period, lifestyle coach students set up a combined diet-and-exercise intervention program in the experimental team, while the other team served as a control group. After three months, staff members took over the program activities, supported by a lifestyle coach. Psychosocial measures (quality of life, empowerment, psychosocial functioning and psychotic symptoms) were measured at baseline, after 3 and 12 months.

Results: Preliminary results show an increase of 0,9 cm in waist circumference (primary outcome) in the control group and a decrease of 0,3 cm in the intervention group. The intervention group shows small improvements on depression and psychosocial functioning and a decrease in quality of life compared to the control group.

Discussion: A combined lifestyle intervention may stabilize or even decrease the risk factors for cardio-metabolic syndrome (i.e. waist circumference) after a year. There seems to be no consistent association with psychosocial outcomes. As research has shown that improvement in long-term hospitalized patients is a slow process (Onken et al., 2002), further research should examine the long-term effect of a lifestyle intervention on psychosocial well-being.

Poster #S85**ABILITY TO SHIFT TO VOLUNTARY ATTENTION STRATEGIES AFFECTS PERFORMANCE ON A COVERT DETECTION TASK IN SCHIZOPHRENIA BUT NOT FOR COMPARISON PARTICIPANTS**

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Background: In psychology, focus on cognitive deficits in schizophrenia has suggested impaired cognition may underlie symptoms related to this disorder. In attention research it has been shown that individuals with a diagnosis of schizophrenia have difficulty inhibiting reflexive eye-movements in the anti-saccade paradigm. This has been shown to be consistent for covert attention (attention without eye movements) by Maruff, Danckert,

Pantelis and Currie (1998) who found that individuals in the schizophrenia group persisted with a reflexive attention strategy in a voluntary (anti-cue) version of the covert orienting of attention paradigm (COVAT). This was indicated by faster response times for the now less common valid cues (cue and target appearing in the same location). The aim of the current study was to examine attention strategies of individuals diagnosed with schizophrenia in a signal presence judgment version of the anti-cue COVAT. **Methods:** Thirteen individuals with a diagnosis of schizophrenia and 13 comparison subjects with equivalent age, gender and education profiles completed a detection version of the covert orienting of attention task (COVAT). Observers were required to respond as to whether they perceived a target (60ms presentation; present on 50% of trials) at one of two horizontal locations. In this version of the COVAT the traditional cue validity was reversed such that the target was preceded by a box cue (150ms presentation) that was predictive of target location on only 30% of trials (valid cue trials); the remaining 70% the target appeared in the opposite location to the cue (invalid cue trials). Cues also appeared on trials where no target was present. Participants completed selected WAIS-IV subsets, and the individuals with a diagnosis of schizophrenia also administered the Brief Psychiatric Rating Scale. Based on Signal Detection Theory analysis, the measures used were cue weighting (how well participants were able to use the cue information), response bias (λ), target sensitivity (d'), hit rate and reaction times.

Results: Participants in the schizophrenia group were found to be slower over all and showed reduced target sensitivity when compared to the control group. On average all participants were slower for the valid cued trials, over the invalid cued trials; however, only those in the schizophrenia group were showed a difference across hit rate for the two cue types, with better performance for the invalid cue trials. Within the Schizophrenia group the cue side weighting varied along with the scores on the BPRS, with higher scorers weighting right cues more and lower scorers rating left cues more.

Discussion: The individuals diagnosed with schizophrenia did manage to switch their attention strategy to a voluntary one, as they, and the control group, were faster for the invalid trials. In addition, for the schizophrenia group the cue type also affected their ability to detect the target. Therefore the voluntary strategy had a negative effect on their performance for the valid cues. There also was also an asymmetry effect that changed related to symptomatology, but not drug dose, suggesting that those with higher levels of symptoms showed an asymmetry related to a right-sided preference.

Poster #S86**METABOLIC SYNDROME IN YOUNG PATIENTS WITH SCHIZOPHRENIA IS ASSOCIATED WITH POOR COGNITIVE PERFORMANCE**

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Background: In schizophrenia about 40% of patients have an additional diagnosis of metabolic syndrome (MetS). A previous study found a relation between MetS and poor cognitive performance in chronic schizophrenia (Lindenmayer et al. 2012). In this present study the effect of MetS on cognition in a younger group of patients with schizophrenia was examined.

Methods: A subsample of schizophrenia patients (n=290; mean age/sd = 30/6.37 years old) of Caucasian origin from Genetic Risk and Outcome in Psychosis (GROUP) study were included in this study. For the GROUP study all patients were assessed extensively (see Korver et al. 2012). In addition physical examination and laboratory tests were performed to establish whether patients had a diagnosis of MetS according to the International Diabetes Federation criteria (Alberti et al. 2006). Neuropsychological performance was assessed using the Wechsler Adult Intelligence Scale-III Short form (IQ) (subtests Digit Symbol-Coding, Arithmetic, Block Design, Information) the Continuous Performance Test-HQ, the Word Learning Task and the Response Shifting Task. Patients were divided into two groups, those with MetS (MetS+) and those without MetS (MetS-). ANOVA's were used to examine differences between the two groups (MetS+/MetS-). Furthermore, linear regressions were performed to investigate the relation between waist circumference and neuropsychological performance.

Results: 124 (42%) patients with schizophrenia met the criteria for the MetS diagnosis. The two groups (MetS+ and MetS-) did not differ on

current/lifetime/amount of cigarettes, cannabis, alcohol and other drug use, duration and severity of illness, socioeconomic status, type and amount of antipsychotic medication. MetS+ had a significantly lower estimated IQ (sd) 94.9 (17.4) as compared to MetS- 100.1 (16.3) ($t=2.54$; $p=0.012$). Furthermore, MetS+ performed significantly worse on immediate ($t=3.12$; $p=0.002$) and delayed recall ($t=2.92$; $p=0.004$) as well as processing speed ($t=-2.80$; $p=0.006$) as compared to MetS. Linear regression analyses revealed that WAIS IQ scores ($\beta=-0.156$; $p=0.026$) and immediate memory ($\beta=-0.098$; $p=0.003$) were associated with waist circumference.

Discussion: At a mean age of 30 years old, patients with schizophrenia and an additional diagnosis of MetS had lower IQ and performed worse on immediate and delayed recall and processing speed as compared to schizophrenia patients without MetS. This suggests that, even in the early stages of the disease, metabolic abnormalities are related to poor cognition in schizophrenia. Future studies are needed to examine whether treatment of MetS will also have a beneficial effect on cognitive performance in schizophrenia.

Poster #S87

ATTENTIONAL BIAS FOR SELF-STIGMATIZING STIMULI IN PEOPLE WITH SCHIZOPHRENIA EXPERIENCING HABITUAL SELF-STIGMA: EVIDENCE FROM THE EMOTIONAL STROOP TASK

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Background: Schizophrenia research has indicated that self-stigma is associated with increased defensive coping strategies, specifically secrecy and withdrawal. People with schizophrenia who tend to avoid or suppress self-stigmatized experiences are prone to frequent and, over time, habitual (and thus, automatic) self-stigmatizing thinking. These individuals' unwillingness to nonjudgmentally accept self-stigmatizing thoughts and feelings may eventually result in a bias towards under-allocating attention to process the semantic content of self-stigmatizing stimuli (e.g. failure, stupid, incompetent) that could be interpreted as personally relevant but threatening. The present study aims to examine the nature of information-processing biases (i.e., automatic attentional biases) involved in the mental habit.

Methods: A community sample of 114 people with schizophrenia spectrum or psychotic disorder was recruited in Hong Kong. Habitual self-stigma was assessed with the Self-stigmatizing Thinking's Automaticity and Repetition (STAR) scale. Participants completed an Emotional Stroop Task designed with self-stigmatizing words as experimental stimuli, along with affectively neutral words as control stimuli. Attentional bias to (or away from) the meaning of self-stigmatizing stimuli was characterized by longer (or shorter) response latencies in naming the color of the self-stigmatizing words, compared to the affectively neutral words. As the Emotional Stroop task may tap into the cognitive ability of selective attention, this study also included the Cognitive Stroop Task to assess selective attention, so that the Emotional Stroop effects could be interpreted in light of other cognitive findings.

Results: Participants with a strong habit exhibited faster color-naming of the self-stigmatizing (compared to the non-affective) stimuli (latency difference = 10.23 ms), suggesting facilitation effect for (i.e., attentional bias to) the self-stigmatizing stimuli. Such facilitation effect was significantly correlated with habitual self-stigma ($r=-0.185$, $p=0.048$). The Cognitive Stroop effects were not correlated with habitual self-stigma ($r=-0.044$, $p=0.66$) and the Emotional Stroop effects ($r=0.019$, $p=0.853$).

Discussion: Our findings point to a specific relationship between habitual self-stigma and attentional bias away from self-stigmatizing stimuli. Such biased processing of self-stigmatizing information was not attributable to the selective attention competencies in participants, because the Cognitive Stroop effects were not correlated with the STAR scale. This study is the first to demonstrate a specific cognitive bias in processing negatively valenced stimuli in self-stigmatizing thinkers. Self-stigma interventions should target the information-processing biases (i.e., automatic attentional biases) involved in the mental habit.

Poster #S88

PROSPECTIVE MEMORY IMPAIRMENTS IN PATIENTS WITH FIRST-EPIISODE SCHIZOPHRENIA: A 1-YEAR FOLLOW-UP STUDY

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Background: Patients with schizophrenia have demonstrated a deficit in remembering for the future, i.e., prospective memory (PM). However, most of these studies were limited to chronic samples or cross-sectional study design. Very little is known about the change of PM from patients with first-episode psychosis across the stage of illness. The current study aimed to explore whether PM deficits persisted after a 12-month follow-up in an early psychosis intervention programme.

Methods: Ninety-four patients with first-episode psychosis and 81 healthy controls were administered a computerized PM task and a set of neurocognitive function tests. Twenty-nine of the patients were followed up at a 6-month and 12-month interval.

Results: MANOVA from baseline showed that there were significant group differences in time- and event-base PM and a group-by-PM type interaction between patients with psychosis and controls. Repeated measures of ANOVA showed that there was main effect of time-based PM and an interaction of time-by-PM type.

Discussion: The current findings suggested that PM impairments, in particular time-based PM, had been demonstrated in patients with first-episode psychosis. The deficit improved but remained severe as compared to controls at the end of the 12-month period.

Poster #S89

VALIDATION OF THE "BELIEFS ABOUT VOICES QUESTIONNAIRE – REVISED" (BAVQ-R) IN FRENCH SPEAKING SWITZERLAND

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Background: The "Voices" cognitive model posits that beliefs patients have of themselves are central. The BAVQ-R explores these beliefs. This study presents the psychometric characteristics of the French version of the BAVQ-R.

Methods: 76 patients (of which 36.8% are women) who hear voices completed the BAVQ-R as well as symptoms (BPRS 4.0), self-esteem (SERS-SF) and quality of life (WHOQOL-Short Form) measures. The BAVQ-R was also filled out six weeks later as well as after 7 sessions of "Voices Group".

Results: The internal consistency (Cronbach α) of the global score and of the 5 dimensions (Resistance, Omnipotence, Malevolence, Benevolence and Engagement) ranged between 0.64 and 0.83. The fidelity test-re test (ICC) varied between 0.64 (Resistance) and 0.84 (Benevolence). Regarding the fidelity of the construct, high correlations are observed between several different dimensions ($0.42 < r < 0.65$, $p < 0.001$). Omnipotence, Malevolence and Resistance correlate with depression ($r \geq 0.35$, $p \leq 0.002$) and negative self-esteem ($r \geq 0.32$, $p \leq 0.008$) as well as with a poor quality of life ($r \geq 0.26$, $p \leq 0.03$). No changes are observed after group therapy. The BAVQ-R is not associated with age or duration of illness. No gender effect is observed.

Discussion: The French version of the BAVQ-R has good psychometric properties. Nonetheless, it is not sensitive to change. This should be further investigated in the context of cognitive individual or group therapies delivered over longer periods and more focused on the beliefs about voices and depression.

Poster #S90**RELATIONSHIP OF KREMEN1 GENE VARIATION WITH SYMPTOMATOLOGY AND COGNITIVE FUNCTIONING IN SCHIZOPHRENIA**

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Background: Schizophrenia leads to functional and behavioral abnormalities, like cognitive impairments including poor social, language and motor skills. Schizophrenia is also known to be a neurodevelopmental disorder, including development of abnormal brain structures and abnormal neuronal organizations. Alterations in the Wnt signaling pathway are thought to play a critical role in regulating these neurodevelopmental changes. Hence, genetic associations of several Wnt pathway genes and schizophrenia have been found. A transmembrane protein KREMEN1 is also found to modulate Wnt signaling. This study is the first study to examine whether "rs713526" (G>A) variation on KREMEN1 gene can affect the symptomatologic and cognitive functioning in schizophrenia.

Methods: Our sample is comprised of 101 patients with schizophrenia. Genetic variation (rs713526) on KREMEN1 gene is genotyped through DNA sequence analysis. All patients were assessed with Positive and Negative Syndrome Scale (PANSS) and on a neurocognitive battery including attention, memory, executive functioning and language skills.

Results: As a result of genetic analysis, 25 patients were with variation of Heterozygous GA genotype, 76 patients were with no variation of Homozygous GG genotype and there were no patients observed with Homozygous AA genotype. An independent t-test was conducted to compare the patients' symptoms and cognitive test scores with and without variation on KREMEN1 gene. The patients with homozygous GG genotype had higher scores ($M=32.06$, $SE=1.37$) than the patients with heterozygous GA genotype ($M=26.33$, $SE=1.90$) on verbal fluency test ($p=0.02$). Also, the patients with homozygous GG genotype had higher scores ($M=18.65$, $SE=0.74$) than the patients with heterozygous GA genotype ($M=15.76$, $SE=1.21$) on category fluency test ($p=0.04$). A Mann-Whitney U test was used to compare the two populations. Results of the analysis indicated that the patients with heterozygous GA genotype had higher scores ($Mdn= 3.05$) than the patients with homozygous GC genotype ($Mdn=2.35$) on the G7 item (motor retardation) on PANSS ($U=554.00$, $z=-2.82$, $p<0.01$, $r=0.30$). Also analysis showed that the patients with homozygous GG genotype did less errors ($Mdn=0.00$) than the patients with heterozygous GA genotype ($Mdn=2.00$) on the interference task of the Stroop test ($U=607.50$, $z=2.39$, $p<0.05$, $r=0.30$).

Discussion: Results suggest that a variant (rs713526) on KREMEN1 gene in schizophrenia might modulate reduction of motor activity in symptomatology and in this respect this motor retardation might affect verbal fluency and interference effect in cognitive functioning. Although verbal fluency is seen as an indicator of executive functioning, effortful self-initiation is also appears to be a component of verbal fluency. Brain studies of fluency tasks showed that brain regions including initiation and activation (supplementary motor area) are also implicated in fluency performance. Additionally, errors on stroop interference task is thought to be related with indifference and slowing. Consequently, KREMEN1 gene variation seems to be a contributor of motor retardation and this motor retardation seems to lessen speech, diminish self-initiation and leads to indifference and slowing in schizophrenia. It might be more informative to replicate these results with a larger sample of schizophrenia patients.

Poster #S91**ECOLOGICALLY-VALID ASSESSMENT OF ATTENTION IN SCHIZOPHRENIA IN A VIRTUAL ENVIRONMENT**

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Background: Among the cognitive impairments that characterize schizophrenia, attentional deficits have been identified as a reliable and enduring feature of the illness. Such attentional deficits have been related to functional outcomes in schizophrenia, and identified as one important focus for neurobiological and treatment research. Assessments of attention to date, however, rely on abstract paradigms with limited direct relevance to everyday life. In recognition of this, we sought to evaluate a novel ecologically-valid strategy for evaluating attention deficits in schizophrenia. To this end, we used a virtual reality (VR) environment resembling a factory setting, whereby participants function as quality inspectors and identify defective or incorrect objects on conveyor belts. Within this environment, different task parameters enable the examination of selective attention (SA), divided attention (DA), and alternating attention (AA).

Methods: Stable outpatients with schizophrenia (SZ) and healthy controls (HC), between the ages of 18 and 55, were recruited. Participants underwent clinical assessments for positive and negative symptom severity using the Scales for the Assessment of Positive Symptoms and Negative Symptoms, motivational deficits with the Apathy Evaluation Scale, and depression with the Calgary Depression Scale for Schizophrenia. Cognitive function was assessed with the Brief Assessment of Cognition in Schizophrenia (BACS), and the Trail Making Test (TMT) A & B. Community functioning was evaluated using the Quality of Life Scale (QLS). Neurologic side effects from medications, and video game experience were also evaluated. Subsequently, participants were administered the VR conveyor belt tasks.

Results: We recruited a total of 68 participants (37 SZ and 31 HC) for this study. Examination of VR attention task performance revealed significant deficits in SZ participants in DA and AA tasks compared to HC participants ($z=-4.28$, $p<0.001$, and $z=-4.82$, $p<0.001$, respectively), although with no difference in the SA task. Moreover, DA and AA task performance was significantly correlated with global cognitive performance (BACS: $\rho = 0.583$, $p<0.001$; and $\rho = 0.635$, $p<0.001$, respectively), as well as with TMT performance (TMT A: $\rho = -0.521$, $p<0.001$, and $\rho = -0.482$, $p<0.001$, respectively; TMT B: $\rho = -0.486$, $p<0.001$, and $\rho = -0.523$, $p<0.001$, respectively). Further, DA and AA task performance was significantly correlated with community functioning (QLS: $\rho = 0.386$, $p=0.001$, and $\rho = 0.505$, $p<0.001$, respectively). Importantly, these relationships remained significant after controlling for motivational deficits and video game experience.

Discussion: In an effort to improve the ecological validity of tests of attention in schizophrenia, we utilized a novel strategy for evaluating attention in a series of VR conveyor belt tasks. We found performance in these VR tasks to be related to standard tests of cognitive ability and specifically attention. However, variance in performance was not entirely captured by standard paper-and-pencil measures, suggesting that the VR tasks measure attentional performance beyond what is capable in standard tests. Further, the relationship between VR task performance and community functioning offers some support for the predictive validity of this approach. Finally, individuals with schizophrenia exhibited specific impairments in divided and alternating attention compared to healthy controls. Overall, these findings offer support for the use of this novel assessment strategy for attentional deficits in schizophrenia, which may enable the neurobiological evaluation of attentional processes under conditions resembling daily life.

Poster #S92**LIMITED LITERACY AMONG PEOPLE WITH SERIOUS MENTAL ILLNESS IN THE US AND AUSTRALIA: A NATURAL EXPERIMENT?**

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Background: While there is a growing body of literature focused on literacy and a number of health outcomes, little work has been done to understand the ways in which people's literacy is related to their psychiatric symptoms and diagnoses, mental health service utilization, quality of life, and participation in the community. In the US, the few studies which have examined

literacy among people with serious mental illness (SMI) have demonstrated that people with SMI such as schizophrenia have literacy levels lower than that of the general population (Currier, Sitzman, & Trenton, 2001; Christensen & Grace, 1999; Lincoln, 2008). However, Galletly et al. (2012) recently reported that reading literacy rates among people with SMI using public mental health services in Australia are no different than those found in the general Australian population and that both are higher than levels of literacy in the U.S.

Methods: Building on a currently funded NIMH study exploring the meaning and impact of limited literacy in the lives of people with SMI (PI: Lincoln), a companion study will be conducted in Australia. One hundred, face-to-face, interviews will be conducted with people with SMI, assessing multiple types of literacy, cognitive functioning, stigma and discrimination associated with SMI and limited literacy, health services utilization, and attitudes and knowledge of recovery. Medical records of participants will also be reviewed. These methods replicate the methods of the ongoing parent study in the US using the same interview guide (with minor cultural adaptations) as well as similar interviewer training.

Results: By examining literacy in the lives of people with SMI, using identical methods, across populations, we will be able to determine whether the reported disparities in literacy levels are replicated or are a reflection of instrumentation differences.

Discussion: If no disparity in literacy is found between people with SMI and the general population in Australia and this disparity persists in the US sample, this provides a natural experiment to disentangle the mechanisms of association among multiple types of literacy and mental illness found in the US. These might include differences between the U.S. and Australian educational systems, health care systems, mental health care systems, societal levels of stigma, the integration of people with SMI in communities, and access to education and employment for people with SMI. Importantly though, if the disparity in literacy experienced by people with SMI in the U.S. is not found elsewhere, this suggests that limited literacy is not solely connected to the cognitive problems experienced by people with SMI due to associated symptoms, but is in fact shaped by social, cultural and structural factors, as are many other social consequences of mental illness.

Poster #S93

AMPA-RECEPTOR MODULATORS AS COGNITIVE ENHANCERS IN SCHIZOPHRENIA: WHY ARE THEY SO DIFFICULT TO DEVELOP?

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In Silico Biosciences

Background: Positive modulation of AMPA glutamate ion channels has shown promising effects in preclinical animal models of cognitive enhancement; however clinical trials in cognitive impairment in schizophrenia were not very successful. Conversely AMPA-R antagonists have been proposed for cognitive enhancement. We used a humanized quantitative systems pharmacology computer model for studying in detail the impact of AMPA-R modulators on the emergent property of a cortical network that is proportional to cognitive functioning.

Methods: The biophysically realistic cortical neuronal network consisted of 80 4-compartment pyramidal cells and 40 two-compartment GABA inhibitory cells with about 10000 synapses, was calibrated using primate electrophysiology data; the effect of GPCR systems such as dopamine, norepinephrine, serotonin and acetylcholine on ion channel conductances was derived from preclinical data and further calibrated using clinical data on working memory. Schizophrenia pathology was introduced as dopamine hypo-activity, NMDA and GABA dysfunction and increased noise; ketamine was implemented as a NR2C specific NMDA-R inhibitor that also increased cortical DA. The output was proportional to the strength of a memory trace and shown to be well correlated with a number of clinical cognitive readouts.

Results: We investigated three properties of AMPAR modulators: changing opening time, peak current and closing time and combinations thereof. In all cases the dose-response was non-monotonic and different between the effect on ketamine-induced deficit and in schizophrenia conditions. In all cases with ketamine-induced deficit, the AMPAkines showed an inverse U-shape dose-response with a small dose window of benefit. In most cases with schizophrenia pathology, the dose-response showed first a worsening of the outcome before plateauing at a level not different from placebo.

Only in the case where the increase in opening time was less than on the increase in closing time did AMPAkines show an improvement but only in a very limited dose-window. Interestingly, conversely, AMPA-antagonists improved cognitive outcome for the inverse combination where opening time was more affected than closing time but always in an inverse U-shape dose-response with a limited effective dose-window.

Discussion: This simulation illustrates the complex dose-relationship of AMPA-R modulators on emergent properties of a network that is proportional to a clinical readout of cognitive performance. This is most likely due to complex and non-linear timing relationships between AMPA-R and modulation of NMDA-channels and their effect on the excitation-inhibition balance, leading to complex non-monotonic dose-responses. There is only a limited window of cognitive benefit for specific combinations of changes on opening and closing time of the channel. The simulations also suggested that clinical trials with ketamine are not always predictive for the schizophrenia case. The results highlight the opportunity to use quantitative systems pharmacology modeling as a way to identify possible successful AMPA-R modulators, based on their electrophysiological properties.

Poster #S94

C-REACTIVE PROTEIN LEVELS ARE INVERSELY ASSOCIATED WITH NEUROCOGNITIVE PERFORMANCE IN ACUTELY ADMITTED PATIENTS WITH PSYCHOSIS

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Background: The etiology and pathophysiology of schizophrenia-related cognitive dysfunctions remain only fragmentarily known but new evidence implicates inflammatory processes. C-reactive protein (CRP) is a reliable marker of inflammation. In patients with chronic schizophrenia elevated serum levels of CRP has been found to be associated with severity of cognitive dysfunction but investigations in clinically representative samples including also antipsychotic drug naïve patients are scarce. The primary aim of the present study was to investigate the association between CRP levels and global neurocognitive performance in a clinically representative sample acutely admitted to hospital with psychosis. Secondary aims were to investigate whether any association was restricted to particular domains of neurocognitive dysfunction.

Methods: Patients (age ≥ 18 years) acutely admitted with psychosis to a single-site University Hospital were eligible for the study and were consecutively included. The hospital is responsible for all the acute admissions in the catchment area of 400000 inhabitants, thus supplying information from a diverse population representing everyday clinical practice. At admission a blood sample for CRP level estimation was collected and the patients underwent neurocognitive assessments by means of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

Results: A total of 124 patients, 68.0% males, were included with a mean age (SD) of 33.5 (12.4) years, and 31.9% had a diagnosis in the schizophrenia spectrum, whereas 25.9%, 18.1%, and 9.4% had diagnoses of delusional disorder, drug-induced psychosis, and affective psychosis, respectively. 47.5% were antipsychotic drug naïve, and a total of 20.2% and 12.1% had misuse or dependency of illicit drugs or alcohol in the 6 months prior to admittance, respectively. The total PANSS score was 73.4 (11.9). The mean CRP level at admission was 3.6 (5.2) mg/L, and the mean global neurocognitive function t-score was 37.8 (7.7). The Pearson correlation test revealed a statistically significant inverse relationship between global neurocognitive performance and CRP level ($r=-0.247$, $p=0.006$). In a linear regression model with global neurocognitive performance as the dependent variable and CRP, years of education and tobacco smoking status as independent variables, the association remained unaltered between neurocognitive performance and CRP ($B=-0.371$; $\text{Beta}=-0.257$; $p=0.004$). No interaction effects were found between CRP and smoking or years of education, respectively. In the secondary analyses there were statistically significant associations between CRP level and Delayed Memory ($B=-0.649$; $\text{Beta}=-0.283$; $p=0.002$) and Attention ($B=-0.437$; $\text{Beta}=-0.257$; $p=0.004$), whereas no association was found between CRP and Verbal/Language abilities, Visuospatial/Constructional abilities, or Immediate Memory, respectively.

Discussion: In this clinically relevant sample of patients in the acute phase of psychosis CRP levels were inversely associated with global neurocognitive performance, as well as memory and attention subdomains. The findings could thus be interpreted as further support for inflammation being involved in the neurocognitive dysfunctions related to psychosis per se and not restricted only to schizophrenia.

Poster #S95

ARE SPEECH ILLUSIONS IN A HEALTHY SAMPLE ASSOCIATED WITH PSYCHOMETRIC RISK FOR SCHIZOPHRENIA?

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Background: The tendency to extract meaning from ambiguous auditory stimuli is understood to be associated with risk for developing a schizophrenia-spectrum disorder. Hoffman et al. (2007, Brit. J. Psychiat., 191, 355) revealed that the length of speech illusions produced when listening to auditory "babble" predicted conversion to illness in prodromal patients. In the present study, a similar task was administered to determine whether this proclivity is associated with psychometrically defined schizotypy. A relationship between these variables would offer some support for the use of a babble task as a complementary measure for assessing psychometric risk for schizophrenia. A second aim was to investigate the relationship between the affective valence of speech illusions and schizotypy scores. It was predicted that, consistent with the themes of auditory hallucinations, the content of illusions produced by those with higher self-reported schizotypy would be more negative.

Methods: Undergraduate students ($n=146$; $M=20.44$ years, $SD=2.86$ years; 26.71% male) completed the Schizotypal Personality Questionnaire (SPQ; Raine, 1991, Schizophr. Bull., 17, 555) and a speech perception task based on Hoffman et al. (2007). In the speech perception task, participants listened to two-minute audio recordings of 12 overlapping voices and repeated aloud any words or phrases they identified. The dependent variable was the length of participants' longest speech illusions (LSI). Emotional content of responses was coded using the AFINN to determine affective valence of illusions (from -5 = strong negative valence to 5 = strong positive valence; Nielsen, 2011, arXiv:1103.2903). Prior to analysis, complete words and phrases reported by at least 5% of participants were removed. It was reasoned that these utterances did not represent speech illusions. LSI scores underwent an inverse transformation to correct for positive skew.

Results: LSI was significantly associated with the SPQ total score ($r=0.15$) and the cognitive perceptual ($r=0.18$) and disorganized factor scores ($r=0.15$) but not the interpersonal factor score ($r=0.06$). LSI was significantly associated with the self-reference ($r=0.16$), odd beliefs ($r=0.18$), and unusual experiences ($r=0.14$) subscales of the SPQ. Positive emotional content of utterances was not significantly associated with any SPQ subscale or factor score (range $r=-0.08$ to -0.01), whereas negative emotional content was associated with the cognitive-perceptual score ($r=-0.16$), odd beliefs ($r=-0.19$), unusual experiences ($r=-0.18$), and the disorganized factor score ($r=-0.16$).

Discussion: The length of speech illusion produced when listening to ambiguous auditory noise is positively associated with numerous features of psychometric risk for schizophrenia. This finding provides evidence that performance on the babble task may serve as an objective measure of schizophrenia or psychosis liability, complementing self-report. In addition, the findings suggest that individuals at greater risk of developing schizophrenia extract more negative meaning from auditory babble. This is consistent with reports that hallucinations commonly have a negative valence.

Poster #S96

SOCIAL COGNITION ANOMALIES IN AUTISM AND SCHIZOPHRENIA: A DIRECT COMPARISON USING THE FRENCH VERSION OF MOVIE FOR THE ASSESSMENT OF SOCIAL COGNITION (MASC)

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Background: Schizophrenia and autism are two neurodevelopmental disorders. Individuals with these disorders share some clinical features, especially in social cognition (Couture 2010, Sasson 2010) and could share some genetic background (Rapoport 2009, Crespi 2010). However, the social cognition deficits in schizophrenia and autism need to be better specified. Only a few studies have directly compared these individuals on evaluation of social cognition, and results are divergent (Bolte 2003, Couture 2010, Craig 2004). Theory of Mind (ToM) is defined by the ability to attribute mental states. Numerous tests were developed to assess different aspects of ToM, including naturalistic tasks. The Movie for the Assessment of Social Cognition (MASC) is a new video-based instrument designed for the evaluation of subtle mindreading difficulties. This test requires subjects to make inferences about video characters' mental states. The German version of the MASC was validated in subjects with high-functioning autism (HFA) (Dziobek 2006) and subjects with schizophrenia (Montag 2010). Here, we propose a direct comparison of individuals with HFA, individuals with schizophrenia and healthy controls using a French version of the MASC. Our hypothesis is that this task can discriminate the three groups.

Methods: Twenty subjects with schizophrenia (SCZ), fifteen subjects with HFA/Asperger Syndrome (HFA/AS) and nineteen healthy controls (HC) were included. Diagnosis was confirmed using the Diagnostic Interview for Genetic Studies (DIGS) and for HFA/AS subjects using the Autism Diagnostic Interview – Revised (ADI-R, Lord 1994). Intellectual efficiency was evaluated with WAIS-III, 9 subtests. The French version of the MASC developed in collaboration with Sainte-Justine Hospital team (Montreal) was administrated to all subjects.

Results: The three groups did not differ in age, gender and total Intellectual Quotient. In the MASC task, there was a difference in correct mental state inferences between HFA/AS (26.5 ± 7.1), SCZ (27.6 ± 5.6) and HC (32.8 ± 2.8). Furthermore, the difference was significant between HFA/AS and HC group ($p <0.01$), and between SCZ and HC ($p <0.01$). However, HFA/AS and SCZ were not significantly different, possibly due to the heterogeneity in the HFA/AS and SCZ groups ($SD = 7.1$ and 5.6). Moreover, the profile of error (reduced or exceed ToM, no ToM) and performance for the different mental states modalities (emotional or cognitive ToM) analysis shows no significant difference between HFA/AS and SCZ group.

Discussion: In this work, we introduced the French version of the MASC, a new task for assessment of subtle social cognition deficits. This tool proved to be sensitive in detecting mindreading difficulties in HFA and in schizophrenia group, versus healthy controls. The scores were similar to those previously reported in the original studies of Dziobek's team. Further analysis will explore whether the heterogeneity of results in patients could reflect clinical and evolutive subgroups. This study was part of the AUSZ program, supported by ERANET Neuron grant and Fondation de France.

Poster #S97

TIME PERCEPTION NETWORKS AND COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA: A META-ANALYSIS

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Background: Previous studies show that temporal perception and cognitive processes demanding cognitive control become interlinked when there is an increase in the level of cognitive effort demanded. The hypothesis of this study is that the brain networks that support temporal perception are dysfunctional in schizophrenia. This dysfunction underlies the failure on task involving working memory and executive functions. We performed a multimodal meta-analysis to identify common brain regions in the findings of an SDM meta-analysis of neuroimaging studies in healthy population and schizophrenia patients assessing the brain response to increasing levels

of cognitive difficulty (CD), and a meta-analysis on neuroimaging of time perception (TP).

Methods: A search at ISI Web of Science was carried out up to December 2013 using the keywords "PET" and "fMRI" cross-referenced with "working memory OR executive functions OR controlled processes" and then with "schizophrenia". Next, we performed a multimodal meta-analysis to combine the findings from the above-described SDM meta-analysis of studies comparing two levels of cognitive difficulty with the findings from another SDM meta-analysis time perception. Its search was based on the following keywords: PET, fMRI cross-referenced with time estimation, timing, OR time perception and then cross-referenced with "schizophrenia". Methodological exclusion criteria were a) studies from which peak coordinates or parametric maps could not be retrieved from the published article or after contacting the authors; b) studies limiting their analyses to specific regions of interest (ROI); and c) studies in which different thresholds were used in different regions of the brain.

Results: Our initial search returned several thousand neuroimaging papers in healthy population and schizophrenia. Subsequent application of inclusion criteria reduced the number of neuroimaging studies. The final sample of task difficulty studies comprised 56 studies in healthy population and 31 in schizophrenia. Whereas the sample of time perception studies comprised 35 in healthy population and only three in schizophrenia. The results of the multimodal meta-analysis in healthy population suggest a high degree of bilateral overlapping of cortical regions: specifically pre-frontal and cingulate areas (mainly Brodmann area (BA) 6, but also BA 8, 9, 10, 24, 32, 44, 45, 46, 47), as well as parietal (BA 5, 7, 19, 39, 40) and temporal regions (BA 41, 13, and the claustrum). Certain brain regions traditionally associated with time perception, most notably the insula (BA 13) and the left putamen, were found to be activated not only by time perception tasks but also by an increase in the difficulty of non-temporal executive functions. The meta-analysis of both task difficulty and temporal perception studies with schizophrenia subjects showed, relative to healthy subjects, significantly lower activation in all overlapping frontal, parietal and temporal and subcortical regions.

Discussion: The study in the healthy population supports the hypothesis that there exists a group of brain regions engaged both in time perception tasks and during tasks requiring cognitive effort. The implication is that temporal perception and cognitive processes demanding cognitive control become interlinked when there is an increase in the level of cognitive effort demanded. Meta-analysis of schizophrenia neuroimaging studies show a dysfunctional implication of brain regions engaged in time perception and cognitive effort. Thus, a dysfunctional time estimation network may be linked with other critically impaired functions in schizophrenia.

Poster #S98

AFFECTIVE PROSODY IN PSYCHOSIS: RECENT EVIDENCE AND FUTURE DIRECTIONS

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Background: Affective prosody (AP) is substantially impaired in schizophrenia, (1) yet little is known about AP in bipolar disorder. (2) Further, as there are no standardised measures of AP, examination of this ability is difficult. (3) It has also been proposed that AP deficits are the result of problems in basic auditory processing skills. The aims of this presentation are, in schizophrenia and bipolar disorder, to (1 & 2) examine AP performance on a newly released standardised assessment, and (3) highlight deficits in auditory processing that may contribute to AP performance.

Methods: Fifty-four patients with schizophrenia and 43 bipolar disorder patients were compared with 112 healthy controls on four AP subtests of the Comprehensive Affective Testing System (CATS). The four tasks examined affective prosody discrimination, naming affective prosody and two conflict tasks; the first asked participants to attend to prosody and ignore meaning whilst the second required them to attend to meaning and ignore prosody.

Results: Schizophrenia patients showed a 10% reduction in accuracy on two subtests (name emotional prosody and attend to prosody when meaning and tone were conflicting) compared to healthy controls. Bipolar patients showed a trend for performance intermediary to schizophrenia and healthy

controls. Severity of current auditory hallucination, across all patients, was related to task performance on three of the subtests.

Discussion: This data confirms that difficulties ascertaining the correct emotional tone of a spoken sentence contribute to the presentation of both schizophrenia and bipolar disorder. We have further confirmed some previous work that suggested a relationship between AP and hearing voices. These data suggest the importance of using standardised measures in the assessment of AP. Last, we will illustrate the importance of pitch, amplitude and duration perception to the understanding of AP.

Poster #S99

THE ASSOCIATION BETWEEN THOUGHT DISORDER AND MEMORY IMPAIRMENTS IN FIRST-EPIISODE PSYCHOSIS

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Background: Thought disorder is considered to be a hallmark feature of schizophrenia. Thought, language and communication deficits and cognitive impairments have been reported in relatives of schizophrenia patients as well. In respect to the areas of memory, executive functioning and attention, it has been shown that schizophrenia patients perform worse compared to healthy individuals. First-episode patients have been suggested to show impairments on executive and memory functions, including tasks on forming and initiating a strategy, inhibiting prepotent responses and verbal fluency. Dysfunctions in verbal learning and delayed non-verbal memory were within memory impairments seen in first-episode psychosis. The aim of the study was to evaluate whether thought disorder is related to memory impairments in first-episode psychosis.

Methods: Fifty-six patients experienced their first-episode of psychosis over the last 2 years and 32 controls were included into the study. All the participants were assessed with the Thought and Language Index (TLI) and underwent a battery of neuropsychological tests consisting of the Rey Auditory Verbal Learning Test, Digit Span Test/WAIS-R, Controlled Oral Word Association Test, Digit Symbol Substitution Test/WAIS-R, Wechsler Memory Scale/Visual Memory Subscale. Symptom severity of the patients were evaluated by using PANSS and SCID-I was administered to the controls to be able to screen out any psychiatric problems.

Results: There is no significant difference between patient and healthy control groups regarding age ($F=1,61$ $p=0,49$), education level ($F=0,68$ $p=0,21$) and gender ($\chi^2=0,21$ df.1 $p=0,65$). There were significant correlations between total TLI scores and Rey Auditory Verbal Learning Test scores (Trial1 $r=-0,292$, Trial5 $r=-0,300$, Trial1-5 $r=-0,382$, Recognition $r=-0,320$), Digit Span Forward ($r=-0,322$) and total ($r=-0,351$) scores, Controlled Oral Word Association Test number total word ($r=-0,316$) score, Wechsler Memory Scale/Visual Memory Subscale1 ($r=-0,288$) and Delayed1 ($r=-0,450$) scores in the patient group compared to the control group. Impoverishment of thought subscale score was associated with Rey Auditory Verbal Learning Test Trial5 ($r=-0,368$ $p=0,005$), Trial1-5 ($r=-0,386$ $p=0,003$), Digit Span Forward total score ($r=-0,418$ $p=0,001$), Wechsler Memory Scale/Visual Memory Subscale1 ($r=-0,383$ $p=0,004$) and Delayed1 ($r=-0,304$ $p=0,02$) score in our patient sample. Disorganization of thought subscale score was correlated with Rey Auditory Verbal Learning Test Recognition ($r=-0,288$ $p=0,03$) and Wechsler Memory Scale/Visual Memory Subscale Delayed1 ($r=-0,363$ $p=0,006$) scores.

Discussion: Memory impairments may be related to thought disorder in first episode psychosis, especially in a subgroup of patients. It may be relevant to follow up these patients with both memory impairment and thought disorder in order to understand whether this subgroup has different clinical manifestations and prognosis.

Poster #S100**NEUROCOGNITION, SOCIAL COGNITION AND THREE-YEAR FOLLOW-UP SOCIAL FUNCTIONING IN RECENT VERSUS NON-RECENT ONSET PSYCHOSIS**

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Background: The aim of this study was to examine the relationship between neurocognition, social cognition (affect recognition, theory of mind) and social functioning in a longitudinal design in both the early and chronic phase of psychotic disorder.

Methods: In a sample of 223 recent- and 490 non-recent onset patients with a non-affective psychotic disorder, the associations between neurocognition and social cognition at baseline on the one hand, and self-reported social functioning at three-year follow-up on the other, were analysed.

Results: In recent onset patients associations between cognitive variables and follow-up social functioning were non-significant. In contrast, in the non-recent onset group, neurocognition but not social cognition was associated with follow-up social functioning. In particular, information processing speed was associated with follow-up social functioning, which was mediated by symptoms.

Discussion: Although neurocognitive functioning is associated with social functioning in psychotic disorder, it may not be a robust predictor of later social functioning in early psychosis, whereas in non-recent onset psychosis, the association with social functioning is mediated by (negative) symptoms.

Poster #S101**SARCASM DETECTION, SYMPTOM SEVERITY AND FUNCTIONAL OUTCOME IN SCHIZOPHRENIA**

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Background: Impairments in social cognition are consistently found in schizophrenia and are associated with functional outcome. The Awareness of Social Inference Test (TASIT, Part II: Social Inference-Minimal & III: Social Inference-Enriched) assesses the ability to detect various types of counterfactual information (e.g. sarcasm) in social interactions. Patients with schizophrenia tend to have a worse overall TASIT performance compared to healthy controls and in particular show difficulties in comprehending sarcasm, paradoxical remarks and to some extent lies, while comprehension of sincere exchanges seems intact. In addition to overall TASIT performance, we investigated the predictive value of detecting specific types of remarks (sincere, sarcastic, paradoxical remarks) for determining functional outcome and symptom severity.

Methods: The present study included 25 patients who met the ICD-10 criteria for schizophrenia or schizoaffective disorder (20 males, Mean age = 38, SD = 8.41). Functional outcome and positive and negative symptoms were assessed using "Personal and Social Performance Scale" (PSP) and "Scale for the Assessment of Negative/Positive Symptoms" (SANS/SAPS), respectively. The patients were administered the Danish version of TASIT Part II A which includes 16 short video vignettes of conversational exchanges involving sincere (the speaker means what is said), sarcastic (the speaker means the opposite of what is said and intends for the other to know) and paradoxical remarks (the dialog is nonsensical unless it is assumed that one speaker is being sarcastic). We employed a model comparison approach: For each of the dependent variables investigated (PSP, SANS and SAPS), we constructed four linear models each with one of the following independent variables: ability to detect i) sincere remarks; ii) sarcastic remarks; iii) paradoxical remarks; and iv) overall TASIT performance. For each of the dependent variables investigated, the four models were compared according to the variance explained, measured as Adjusted R squared (AdjR²), and the likelihood of the model given the data, measured as Bayesian Information Criterion (BIC, the lower the value, the higher the likelihood). Finally, in order to assess whether the three subtests contained non-overlapping information, we ran a stepwise regression for each of the dependent variables.

Results: The ability to detect paradoxical remarks was significantly correlated with PSP (AdjR² = 0.224, P=0.01, BIC=213) and with SANS (AdjR² = 0.382, P=0.001, BIC=133). This was also true for the overall TASIT performance (PSP: AdjR² = 0.179, P=0.02, BIC=215; SANS: AdjR² = 0.253, P=0.006, BIC=137). The ability to detect sarcastic remarks was significantly correlated with SANS (AdjR² = 0.269, P=0.005, BIC=137) but failed to reach significance with PSP (AdjR² = 0.084, P=0.087, BIC=218). No relationship was found between detection of sincere remarks and PSP (AdjR² = -0.042, P=0.86, BIC=221) or SANS (AdjR² = 0.05, P=0.15, BIC=143). None of the TASIT scores correlated significantly with SAPS (Ps > 0.09). The ability to detect paradoxical remarks provides the best model for both PSP and SANS, with the highest variance explained and lowest Bayesian Information Criterion. The stepwise regressions support this picture, with paradoxical performance being the only selected variable in the models for PSP and SANS (no variable was selected for SAPS).

Discussion: The findings suggest that ability to detect paradoxical remarks is most closely related to negative symptom severity and functional outcome in schizophrenia and points to the usefulness of looking at performance on this subtest.

Poster #S102**INSIGHT INTO ILLNESS, COGNITIVE REASONING AND UNCOOPERATIVENESS IN CHRONIC SCHIZOPHRENIA**

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Background: Lack of insight into illness is a well-established phenomenon in schizophrenia. Poor insight has been associated with psychosocial dysfunction and increased re-hospitalization rates, as well as a barrier to accepting and staying in treatment. Reduced insight has been correlated with less rater-assessed functional performance, but better patient-reported well-being overall in previous studies. We hypothesized that insight might have an impact on uncooperativeness and self-report assessments of well-being by patients, both important domains of treatment compliance and outcomes. The objective of this study was to examine factors that might influence insight, uncooperativeness, and patient-reported quality-of-life outcomes using the large National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) dataset.

Methods: Insight was assessed by the Insight and Treatment Attitudes Questionnaire (ITAQ) and PANSS item G12 "lack of judgment and insight". Social and occupational functioning was assessed using the Heinrichs-Carpenter Quality of Life (HCQoL) scale, while self-report well-being overall was assessed with the Lehman QoL Interview (LQOLI) subjective scale. Uncooperativeness was assessed by PANSS item G8 ("Uncooperativeness"). We conducted a cross-sectional and longitudinal multivariate analysis to evaluate the potential mediating relationships.

Results: Consistent with previous reports, we found better insight into illness (higher ITAQ score) was associated with higher functioning (higher HCQoL total score, p<0.05), greater neurocognitive composite (p<0.05) and reasoning (p<0.05) performance, but there was an inverse correlation to lower patient-reported well-being overall (lower LQOLI, p<0.05) and a higher level of depressive symptoms (p<0.05) in patients with chronic schizophrenia. We also found the inverse relationship at baseline between insight and patient-reported LQOLI was explained, in part, by levels of depressive symptoms (p<0.001) and neurocognitive reasoning impairment (p<0.05). Overall cognitive performance was not significant in the model after adjusting for depression effect (p>0.05). Among subjects with mild or no depressive symptoms on all 9 items of the Calgary Depression Scale (N=839), better patient-reported well-being overall (LQOLI) was associated with poorer insight (p<0.05) and lower cognitive reasoning performance (p<0.05) after adjusting for age and symptom severity (CGI-S). Improved insight into illness over time was longitudinally associated with reductions in uncooperativeness symptoms (PANSS G8) (p<0.001).

Discussion: Our findings suggest that poorer insight and attitudes toward treatment has significant association with higher level of uncooperative-

ness, but lower level of neurocognitive reasoning, and less depression, which in turn impacts patient-reported assessment of well-being overall. Improvement in insight over time was longitudinally associated with reduction in uncooperativeness symptoms. These results support the importance of reducing impairments in insight and cognition both for functional performance and willingness to accept treatments.

Poster #S103

HIGH EDUCATIONAL PERFORMANCE IS A DISTINCT FEATURE OF BIPOLAR DISORDER COMPARED TO SCHIZOPHRENIA

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Background: Schizophrenia is associated with poor educational performance and lower intelligence. This is, although to a lesser degree, also found in first-degree relatives of schizophrenia patients. For bipolar disorder (BD) these relationships are much less clear. Although some studies suggest that intelligence is also lower in BD patients, the evidence is weak and often contradicting. Evidence for the presence of lower intelligence quotient (IQ) in relatives of BD patients is largely lacking. Interestingly, there is compelling evidence that there is superior educational performance in BD patients and their relatives. By studying educational performance and IQ in two large patient samples (bipolar disorder and schizophrenia spectrum disorder), their siblings and controls, we aim to illuminate the influence of the genetic vulnerability to bipolar disorder and schizophrenia on intelligence and educational performance.

Methods: This cross-sectional study included 540 euthymic bipolar I disorder (BD-I) patients, 138 parents and 110 siblings, 1026 schizophrenia spectrum disorder (SCZ) patients, 890 parents and 1011 siblings and 1221 controls derived from three Dutch studies (Bipolar Genetics, Dutch Genetic Risk and Outcome in Psychosis (GROUP) and CannabisQuest). IQ scores were estimated by a short version of the Wechsler Adult Intelligence Scale-III. Participants were also asked their highest completed level of education. We used a mixed linear model and linear regression analyses with IQ as outcome and group status as predictor. Educational achievements were analysed using logistic regression analyses with group status as indicator and several thresholds for educational performance as outcome.

Results: BD-I patients had significantly lower IQ scores (mean IQ=96.8, SD=14.1) compared to controls (mean IQ=108.1, SD=15.3) ($\beta=-9.34$, $p<0.01$), but a twofold increased probability to complete graduate school ($OR=1.95$, $p<0.01$). SCZ patients had the lowest IQ scores (mean IQ=95.3, SD=16.0) ($\beta=-15.12$, $p<0.01$ compared to controls; $\beta=3.30$, $p=0.01$ compared to BD-I patients) and completed significantly lower levels of education than BD-I patients and controls. First-degree relatives of BD-I and SCZ patients had comparable IQ scores, however, parents of BD-I patients had more often completed a higher level of education.

Discussion: In this large cross-sectional study in almost 5,000 participants drawn from the population, we show that lower intelligence is not limited to schizophrenia, but also occurs in euthymic BD-I patients. As BD-I patients have a twofold increased probability to complete graduate school compared to controls, our results pose a strong argument that high educational performance is associated with a genetic vulnerability to BD, whereas low educational performance is associated with a genetic vulnerability to schizophrenia.

Poster #S104

CHILDHOOD TRAUMA AND COGNITIVE IMPAIRMENTS IN PATIENTS WITH SCHIZOPHRENIA

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Background: Exposure to traumatic events during childhood is often associated with the development of psychiatric disorders, cognitive impairment, and poor functioning in adulthood. Schizophrenia is characterized by high

levels of childhood trauma as well as of cognitive deficits. The aim of this study was to identify the associations between early life trauma and cognitive functions in schizophrenia.

Methods: 37 patients with schizophrenia were included in the study as an 35 healthy controls who were matched on age, sex, years of education. Information about early life stress was obtained using the Childhood Trauma Questionnaire (CTQ). CTQ data was dichotomized into two groups (low or high trauma) based on the median split for each subscale and groups. Cognitive assessments were performed using the Digit Span Test, Continuous Performance Test, Rey Auditory & Visual Learning test, Complex Figure Test, Verbal Fluency Test, Wisconsin Card Sorting Test, and Finger Tapping Test.

Results: Emotional abuse was significantly associated with reduced scores on attention. Physical abuse was significantly associated with reduced scores on visual memory and cognitive flexibility. Emotional neglect, physical neglect, sexual abuse were not significantly associated with cognitive impairments across cognitive domains.

Discussion: Our results indicate that a history of childhood trauma was associated with worse cognitive performances in patients with schizophrenia.

Poster #S105

DISAPPEARANCE OF THE UNMASKING EFFECT OF TEMPORALLY PRE-PRESENTED LIPREADING CUES ON SPEECH RECOGNITION IN PEOPLE WITH CHRONIC SCHIZOPHRENIA

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Background: Schizophrenia patients showed deficits in audio-visual integration during speech perception tasks. Similar to healthy listeners, patients with schizophrenia can use either temporally pre-presented content cues or simultaneously presented lip-reading cues to improve speech recognition under masking conditions. This study investigated whether temporally pre-presented lip-reading cues also improve speech recognition under speech masking conditions in people with chronic schizophrenia.

Methods: 16 schizophrenia patients (mean age 41.06 ± 9.48) participated in this study. 8 of the patient participants had acoustic verbal hallucination (AVH) and 8 had no AVH. They all were clinically stable during the time of their participation and received antipsychotic medications with the average chlorpromazine equivalent of 625.2 mg/day. Healthy controls were screened with the SCID-DSM-IV as used for patient participants. None of the invited healthy volunteers had a history of Axis I psychiatric disorder as defined by the DSM-IV. Totally 16 demographics-matched healthy controls (mean age 37.63 ± 6.26) for the patient participants participated in the study. In a test trial, before the target sentence was co-presented with the two-talker-speech masker, one of the following visual cues was presented: the target-matched (true-priming), target-independent (false-priming), or speech-unrelated (no-priming) lip-reading video. Both target speech and masking speech were Chinese nonsense phrases which are syntactically correct but not semantically meaningful (For example, the English translation of a Chinese nonsense phrase is "order a sea"). Participants were instructed to listen to and repeat the target phrase.

Results: In healthy control participants, compared to the target-recognition performance under either the false-priming or no-priming condition, presenting the true-priming lip-reading video improved the performance at the low signal-to-masker ratio (SMR) of -8 dB. However, in participants with chronic schizophrenia, not only the speech-recognition performance was poorer than healthy controls at low SMRs, but also this unmasking effect did not appear. Moreover, the performance of patients with AVH was worse than that of patients without AVH, largely due to the lack of recognition responses.

Discussion: Speech recognition in chronic schizophrenics, particularly those with AVH, is more vulnerable to speech masking than that in healthy people. Healthy people, but not people with chronic schizophrenics, are able to use temporally pre-presented lip-reading cues to release target speech from speech masking. The complete loss of this unmasking effect in people with chronic schizophrenia indicates a combined effect of working-memory deficits and cross-modal-integration deficits. From the review of literatures of previous studies and the results of present study we infer that abnormal

activities of object-related attention cortical network, visual or face working memory related cortex network and audio-visual integration related brain areas may account for some of the complete loss of the unmasking effect of temporally pre-presented lip-reading cues in schizophrenia patients. In future studies, it will be examined whether the method established by this study for measuring the unmasking effect of pre-presented lip-reading cues is useful for improving the accuracy of diagnosing schizophrenia.

Poster #S106

IMPAIRED DEVELOPMENT OF BRAIN ACTIVATION UNDERLYING AFFECTIVE PROCESSING IN ADOLESCENTS AT FAMILIAL RISK FOR BIPOLAR DISORDER OR SCHIZOPHRENIA

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Background: Adolescence is a period of acting out and emotional instability. This may be due to an imbalance between the subcortical areas and the prefrontal cortex. Subcortical areas are thought to be more fully developed already early in adolescence, while cortical areas reach their mature state only at the very end of this period. Adolescence is also the time of onset of psychiatric disorders such as Schizophrenia (SZ) and Bipolar Disorder (BD). These disorders are characterized by impairments in networks involving subcortical and frontal brain regions. We hypothesize that these impairments are already present during adolescent development, prior to the overt manifestation of the disorder. Here, we investigate the development of limbic subcortical regions and the frontal cortex during emotion processing in offspring of SZ and BD patients compared to control subjects. These offspring have a ten-fold increased risk to develop a psychotic disorder themselves, and about 70% will develop non-specific psychopathology.

Methods: Fourteen offspring of schizophrenia patients (mean age 12.9, 11 females), twenty nine offspring of bipolar patients (mean age 14.1, 12 females) and 31 control offspring (mean age 13.7, 17 females) viewed and rated neutral, negative, and positive pictures (IAPS), while being scanned with functional MRI (2D-EPI, TR = 1.6s, TE = 23ms). All pictures were presented for 2 seconds, with another 2 second period for subjects to respond. Only those trials in which there was a match between the subjects' response and the IAPS rating were included. Activation during the presentation of negative pictures was contrasted against activity during the neutral pictures. Changes in activity levels with age were investigated using regression analyses in four a priori regions (amygdala, hippocampus, ventrolateral prefrontal cortex (vPFC), and the orbitofrontal cortex (OFC)). In addition, psychophysiological interaction (PPI) analyses were performed to reveal changes in functional coupling with age between the areas involved in the emotion network.

Results: There were no differences in task performance (reaction time, accuracy) between the groups. Compared to the control group, activation in the amygdala and hippocampus was decreased in the SZ offspring, but not in the BD offspring when processing emotional salient stimuli. In contrast, activation in the vPFC activity increased with age. Moreover, and in line with previous research (Vink et al., submitted), activation in these limbic subcortical regions decreased with age in the controls but not in the offspring groups. These changes in activation were paralleled by an increase in functional connectivity between the amygdala and vPFC in controls. No such increase was observed in the offspring groups.

Discussion: In sum, we found, using a simple emotion task, that SZ offspring already show impaired brain development during adolescence compared to controls. These findings of reduced limbic subcortical and frontal functioning are consistent with findings in adult patients (Aleman & Kahn, 2005). Remarkably, these deficits occur before the manifestation of the illness. Surprisingly, we did not observe differences between BD offspring and controls. These data provide evidence in support of the notion that psychiatric illnesses have their origin in early adolescence. We plan to follow these groups longitudinally to see if we can identify how the familial risk for SZ and BD impacts individual developmental trajectories.

Poster #S107

DIMENSIONS OF DELUSIONS AND SELF-SERVING BIAS ALONG THE CONTINUUM OF PSYCHOSIS

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Background: Research has shown that delusions occur in 10-20% of individuals in the community who do not have a psychiatric diagnosis. Studies assessing delusions multi-dimensionally suggested that delusional distress and preoccupation are more important than the severity of delusions in distinguishing clinical psychosis from non-clinical psychotic experiences. This study extended previous findings by including non-clinical individuals who met a cutoff for psychosis, as well as healthy controls. An exaggerated tendency to attribute positive events to the self and negative events to others has been shown to be a risk factor for delusions. However, it is not clear which aspect(s) of delusions are linked with self-serving bias, and how the bias compares between clinical patients and non-help-seeking individuals with psychosis. The present study aimed to investigate the relationship between self-serving bias and delusion dimensions along the continuum of psychosis. The key hypotheses were as follows: 1. Dimensions of delusions (conviction, distress and preoccupation) will be scored highest in the clinical group, followed by non-clinical individuals with psychosis, and then non-clinical individuals without psychosis. 2. There will be a stronger self-serving bias in patients than in the two non-clinical groups.

Methods: All participants completed the Internal, Personal and Situational Attributions Questionnaire (IPSAQ; Kinderman & Bentall, 1996) and Peters et al. Delusions Inventory (PDI; Peters et al., 1999, 2004), whereas Community Assessment of Psychic Experiences (CAPE; Stefanis et al., 2002) was completed by non-clinical participants only.

Results: Seventy patients with first-episode psychosis (hereafter "FEP") were included in this study. A total of 654 non-clinical participants were included, among whom 12 met the CAPE cutoff score for psychosis and were categorized as the "non-clinical psychotic" (NC-P) group, whereas 642 did not meet the cutoff score and were categorized as the "non-clinical non-psychotic" (NC-NP) group. Across the three delusion dimensions on PDI (conviction, distress and preoccupation), the FEP group had a higher score than the NC-P group, and the NC-P had a higher score than the NC-NP group. NC-P endorsed the greatest number of beliefs, followed by FEP, and then NC-NP. Self-serving bias was less common in the NC-NP than both the FEP and NC-P groups. Within the clinical group, self-serving bias was significantly associated with number of beliefs ($\beta=0.332$, $t=2.899$, $p<0.01$) and not with delusion dimensions. Within the non-clinical groups, self-serving bias was associated with number of beliefs ($\beta=0.104$, $t=2.473$, $p=0.014$) and distress ($\beta=0.182$, $t=4.315$, $p<0.001$).

Discussion: This study reported a graded difference in delusion dimensions among clinical patients, individuals with psychosis but without a need for care, and healthy individuals. Clinical patients reported fewer delusional beliefs than non-clinical individuals with diagnosable psychosis, but were more convinced, distressed and preoccupied with their delusional experiences. This confirms the importance of assessing delusions multidimensionally, rather than relying solely on delusion severity. Self-serving bias was prevalent in both the clinical and non-clinical psychotic groups. It was more strongly associated with number of delusional beliefs in the clinical group. This provides new evidence for a dose-response relationship between self-serving bias and delusions. Self-serving bias, therefore, is likely to bear clinical significance to the development of delusions shared by both clinical and non-clinical individuals.

Poster #S108

INSTRUMENTS EVALUATING EMOTIONAL BLUNTING IN SCHIZOPHRENIA PATIENTS WITH NEGATIVE SYMPTOMS: A SYSTEMATIC REVIEW

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Background: In recent years, negative symptoms have been receiving renewed attention. In comparison to positive symptoms, negative symptoms are more difficult to assess, do not respond well to antipsychotics and have a greater impact on patients' ability to function and live independently (Gold, 2013; Pogue-Geile & Harrow, 1985). In this systematic review we fo-

cus on the assessment of a particular negative symptom, namely emotional blunting (also referred to as blunted affect) (Sadock & Sadock, 2003). The assessment of emotional blunting is complex and requires an estimate of the degree of impairment of emotional expression (Gold, 2013). The assessment of emotional blunting is further complicated by the limited availability of unidimensional instruments specifically measuring this symptom. To the best of our knowledge, there is only one unidimensional instrument, known as the Rating Scale for Emotional blunting (RSEB), available that is designed to evaluate emotional blunting and this was developed in the 1970's by Abrams and Taylor (1978). From the time that the RSEB was developed several new multidimensional instruments have emerged. Most recently, the Brief Negative Symptom Scale (Strauss et al., 2012) and the Clinical Assessment Interview for Negative Symptoms (Kring et al., 2013) were validated. The aims of this paper are to:

- Provide an overview of the psychometric properties and other characteristics of the various instruments (unidimensional and multidimensional) used to assess emotional blunting in schizophrenia.
- Assess the quality of primary studies reporting on instruments that are designed to rate negative symptoms including emotional blunting.
- Recommend the appropriateness of the various instruments.

Methods: We used the following key words to search the PubMed and PsycArticles database: *schizophrenia and blunted affect or emotional blunting; schizophrenia and scale and blunted affect and reliability or validation; schizophrenia and scale and emotional blunting and reliability or validation; schizophrenia and rating scale and blunted affect and reliability or validation; schizophrenia and rating scale and emotional blunting and reliability or validation; schizophrenia and instrument and blunted affect and reliability or validation; schizophrenia and instrument and emotional blunting and reliability or validation; schizophrenia and interview and blunted affect and reliability or validation; schizophrenia and interview and emotional blunting and reliability or validation; schizophrenia and questionnaire and blunted affect and reliability or validation; schizophrenia and questionnaire and emotional blunting and reliability or validation*. We also used the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) (Whitting et al. 2011) tool to assess the quality of the primary studies reporting on the psychometric properties of the various instruments included in this review. The QUADAS-2 assist reviewers to evaluate aspects such as the bias and applicability.

Results: We identified 10 instruments of which 8 met our inclusion criteria.

Discussion: The strengths and limitations of each of the identified instruments, particularly in terms of their use in clinical and research settings, will be presented and discussed.

Poster #S109

THE BASEL INTERVIEW FOR PSYCHOSIS: STRUCTURE, RELIABILITY AND VALIDITY

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Background: Although several instruments have been developed to identify patients with an at-risk mental state (ARMS) for psychosis and first episode of psychosis (FEP), most of these instruments only ask for specific risk criteria and do not allow the assessment of a broad spectrum of risk factors and indicators for psychosis and the temporal development of psychiatric symptoms over the whole life span. To fill this gap, we developed the Basel Interview for Psychosis (BIP), which can be used to more thoroughly interview ARMS and FEP patients after having identified them with a screening instrument, such as the Basel Screening Instrument for Psychosis (BSIP) [1]. The aim of this study was to describe the development of the BIP and to evaluate its factorial structure, reliability and validity.

Methods: The BIP is a comprehensive semi-structured interview that was developed for the Basel Früherkennung von Psychosen (FePsy) study [2]. Its items were derived from the most important risk factors and indicators of psychosis described in literature and from several existing instruments assessing early symptoms of psychosis. It contains the following six sections: 1) Social and physical development and family, 2) Signs and Symptoms, 3) Vulnerability, 4) Help-seeking behavior, 5) Illness insight, 6) Evaluation

of the interview. To estimate the inter-rater reliabilities of the items of section 2 and 3, 20 interviews were conducted and rated by 7 well-trained clinicians. To explore the factorial structure of the BIP section 2.3 (Prodromes and Symptoms) and to construct new subscales, we conducted an exploratory factor analysis (EFA) on a sample of 94 ARMS and 66 FEP patients. The psychometric properties of the newly constructed subscales were studied by estimating their internal consistencies (Cronbach's α) and homogeneities (Revelle's β), as well as their convergent and discriminant validities.

Results: Inter-rater reliabilities were good to very good in 92% of the items (Gwet's AC1 0.61-1.00). An EFA on the items of section 2.3 indicated that a three factorial solution provided the best fit to the data. Based on the item-factor-loadings, three new subscales were constructed: "Attenuated Positive Psychotic Symptoms", "Depression, Anxiety and Cognitive Deficits" and "Social Withdrawal and Functional Decline". The new subscales demonstrated satisfactory to very good internal consistencies ($\alpha=0.78-0.92$) and homogeneities ($\beta=0.74-0.79$). Furthermore, correlations with the subscales of the Brief Psychiatric Rating Scale (BPRS) and Scale for the Assessment of Negative Symptoms (SANS) indicated good convergent and discriminant validities.

Discussion: This is the first study that investigated the psychometric properties of the BIP. Our results demonstrate that, overall, the items on signs and symptoms as well as vulnerability show very good inter-rater reliabilities when rated by trained clinicians. Furthermore, we have demonstrated that the items on early signs and symptoms can be grouped to three subscales with good to very good internal consistencies, homogeneities, and convergent and discriminant validities.

References:

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Poster #S110

REDEFINING SCHIZOPHRENIA SUBTYPES AND DIMENSIONS WITH STRUCTURAL BRAIN IMAGING: UNSUPERVISED AND MULTIVARIATE LEARNING ALGORITHMS APPLIED TO DIAGNOSTIC NOSOLOGY IN SCHIZOPHRENIA

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Background: The recent release of the DSM-5 eliminated the DSM-IV subtypes of schizophrenia due to their "limited diagnostic stability, poor validity", and lack of distinctive patterns of longitudinal course. Here we use unsupervised learning of symptom scores to define clinical subtypes with greater stability and validated with brain imaging.

Methods: T1-weighted images and DTI was acquired for 100 Singaporean Chinese patients with a DSM-IV diagnosis of schizophrenia and no comorbidities. They were screened and validated with the SCID, clinical data obtained and were scored on the PANSS for symptoms, GAF for function, SUMD for insight, WHOQOL-BREF for quality of life. Preprocessing was performed on SPM8 on Matlab 7.8.0 with DARTEL to generate volumes, modulated segmented images, jacobian determinant images and flow-fields. Kernels were generated from the dot-product of each image and cosine similarity matrices were calculated for hierarchical clustering and non-negative matrix factorisation. DTI processing and tractography was performed on FSL. K-means clustering was performed on cross-sectional PANSS scores using squared Euclidean distance on Matlab 7.8.0. Cluster stability was assessed by comparing centroid distances across 10 replications with different starting estimates and silhouette plots. Clusters were then compared across univariate measures and with voxel-based morphometry to identify cluster characteristics.

Results: In K-means clustering of PANSS scores, only 2- and 3-cluster solutions remained stable with mean silhouettes of 0.408 and 0.3873 respectively. The first cluster, PANSS2_1 (n=44), compared to the second

cluster, PANSS2_1 ($n=56$) had higher positive symptom ($p=2.5E-20$), higher negative symptoms ($p=0.0016$) and higher general symptoms ($p=3.11E-7$). Specifically, the first cluster had higher ratings on delusions ($p=9.2E-25$), hallucinatory behaviour ($p=9.4E-11$), suspiciousness/persecution ($p=7.0E-27$) and unusual thought content ($p=2.6E-24$). In addition, cluster 1 had impaired global functioning ($p=9.0E-14$, poorer insight ($p=0.0042$) and poorer QoL ($p=0.0022$). In the 3-cluster solution, cluster 2, PANSS3_2 ($N=47$) was almost identical to PANSS2_2, while cluster 3, PANSS3_3 ($N=14$) was a complete subset of PANSS2_1 ($N=44$). Comparing cluster 1, PANSS3_1 ($N=39$) and PANSS3_3, PANSS3_3 had larger CSF volume (594ml vs 508ml, $p=0.017$), worse symptoms-positive ($p=2.4E-5$), negative ($p=9.8E-13$), general ($p=2.7E-7$) and quality of life ($p=0.0069$) with similar levels of global functioning impairment. PANSS3_2 had decreased middle cingulate grey matter density compared to the other clusters. Clinical clusters are being replicated in a database of 1011 patients with early psychosis and 2 year follow-up, the 1-3 year follow-up of this cohort and a separate imaging cohort of over 100.

Discussion: We describe a 2-cluster model of schizophrenia from PANSS scores at onset differing in overall severity of symptoms, especially in persecution, delusions and unusual thought content. The severe symptom cluster is associated with impaired global functioning and further divides into a yet more severe symptom cluster with increased CSF volume and poorer quality of life and a cluster with relatively preserved CSF volume. In the early psychosis replication cohort, severe clusters are associated at 2 year follow-up with negative and general, but not positive symptoms with a trend towards functional impairment. The results suggest a method of using symptom scores at onset and structural brain imaging measures for prognostication in schizophrenia and indicate a clinically-defined subpopulation, for whom brain imaging markers may be useful for this purpose.

Poster #S111

CHARACTERIZING SCHIZOPHRENIA USING SEMANTIC JUDGMENTS AND BODY QUOTIENTS

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Background: The principal aim of this study is a step towards better understanding schizophrenia by examining the link between semantic judgment and body representation. We thus created an experimental device directly inspired by our explanatory model of body representation including kinesthesia, sensory-emotion and symbolic representations. Our model is constructed as an integrative solution of Damasio's (2012) and Vygotsky's (1989) models about links between mind and body representations. Our results show that it should be possible to distinguish schizophrenic from non-schizophrenic individuals considering the way they translate their representations using semantics judgments and body quotients.

Methods: Population: 100 schizophrenic patients and 100 control subjects (of equal age, sex and socio-cultural level); equipartition of sexes in each group. Tasks for each subject: 1. Describing closely a person on a picture 2. Making a semantic judgment of each picture 3. assessing their own body representation by a multiple choice quiz [three types of representations expressed in body quotients: Kinesthetic Quotient (KiQ), Sensory-emotion Quotient (SeQ) and Symbolic Quotient (SyQ)] Computerized device is shown on a touch screen. Two panels of pre-tested pictures are used: 18 pictures of "women" and 18 pictures of "men". As many men as women in each group will see both types of structured panels in three categories of images: 1 Bodily incongruities; 2 Emotions; 3 Actions. A semantic differentiation device with 18 semantics oppositions divided into three categories: shape, emotion and movement. Each semantic opposition shall be submitted separately under the image. Each subject thus performs 324 semantic judgments (18 by 18). Each reaction timing is recorded. Each semantic opposition includes 7 levels of intensity (corresponding to the levels proposed by Osgood (1962)). For example, for the opposition "strong/fragile", the 7 levels are divided as follows: [strong (+++), (++) or (+)]; [no opinion (0)] and [weak (+), (++) or (+++)]. By definition: (+++) = extreme judgment and (0) = judgment no opinion.

Results: - Significantly more "extreme" judgments by schizophrenics and more "no opinion" judgments by control subjects. - 1 discriminant function classifies properly 90.5% of the subjects into two groups: the schizophrenic one or the control one (λ Wilks of 0.333, canonical correlation: 0.817).

- 1 discriminant function classifies properly 94% of the women into two groups: the schizophrenic one or the control one (λ Wilks of 0.266, canonical correlation: 0.857). - These discriminant functions connects components concerning the types of semantic judgments, the latent periods of these judgments and the body quotients. - SyQ and KiQ significantly lower among schizophrenic patients and SeQ significantly higher. - There are strong correlations between certain aspects of body representation: a strong positive correlation between the SyQ and KiQ (Pearson coefficient: 0.366) and a significant positive correlation between SeQ and KiQ (Pearson coefficient: 0.305). - Significant gender differences: more extreme judgments by women with schizophrenia, but no gender difference among the control subjects: Qse higher only among men with schizophrenia; SyQ and KiQ lower only among women with schizophrenia.

Discussion: Discriminant function shows that body quotients and semantic judgments are necessary to distinguish schizophrenia from control. Our strong evidence is that schizophrenia is fundamentally different in men and women. We highlight the close link between each dimension of our model of body representation.

Poster #S112

CLINICAL STAGING IN PEOPLE DIAGNOSED WITH SCHIZOPHRENIA OR A RELATED DISORDER

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Background: To overcome some of the pitfalls in the current diagnostical system, McGorry and colleagues (2007) have introduced a "clinical staging" model. In the present study we made a first attempt to apply clinical staging to people already diagnosed with a psychotic disorder.

Methods: In a large ($n=1.119$) representative sample of people diagnosed with schizophrenia or a related disorder (GROUP), we made use of ratings on the PANSS, GAF and a "composite list" designed for the GROUP study to retrospectively determine clinical stage at baseline and three-year follow-up (i.e. "first episode psychosis", "incomplete remission", "recurrence/relapse", "multiple relapses", or "severe/persistent"). Comparisons between stages at baseline and three-year follow-up were conducted in terms of demographic characteristics, illness onset, social-, neuro-cognitive and premorbid functioning.

Results: The largest proportion of our sample was being assigned to the "incomplete remission" stage, but patients were represented in all stages. Apart from the clinical characteristics used to define our stages, the 869 patients that we were able to assign to a clinical stage at baseline differed across stages in terms of age, education, subjective quality of life, and premorbid functioning. However, these differences were largely accounted for by worse symptomatic, premorbid and social functioning in the earliest (first episode psychosis) and latest stage (severe/persisting) as compared to the stages in between. "Intermediate" stages were less clearly distinguishable in terms of demographic or clinical characteristics. Approximately half of the GROUP participants changed stages to either the worse (36.4%) or the better (21.4%). Stage at baseline was not significantly associated with number of relapses, functional or neurocognitive outcome at three year follow-up. Our findings did tentatively indicate that the chance of transition to a more chronic stage of the illness was significantly associated with higher baseline levels of hostility, and to a lesser extent to lower quality of life and higher depression scores.

Discussion: Our findings reflect the great variety in course of patients diagnosed with schizophrenia. The transition to more favourable stages in a small proportion of people who were initially assigned to the most chronic stage suggests that long-term poor functioning does not necessarily imply a persistent chronic illness course and that people can move back to more favourable stages. Our data also suggest that intermediate stages are hard to differentiate, and are not predictive for illness course. Partly in congruence with earlier work, depressive symptoms, hostility and lower quality of life may differentiate who will eventually progress to more chronic stages over time.

Poster #S113**A NOVEL KV3 POSITIVE MODULATOR AUGMENTS GAMMA FREQUENCY OSCILLATIONS IN THE MAMMALIAN NEOCORTEX IN VITRO**

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Background: Neocortical neuronal networks produce synchronized gamma frequency oscillations (30–80 Hz) that are critical for processing and integrating cognitive modalities. Experimental studies have demonstrated that, in the presence of an appropriate pharmacological drive, such neuronal network activity is orchestrated by inhibitory mechanisms, notably GABA_A receptor mediated events. Within this context, perisomatic targeting fast-spiking parvalbumin-containing (PV+) interneurons are capable of sustaining action potential output in the gamma frequency range. PV+ interneurons entrain the population of neocortical pyramidal neurons via gamma frequency GABA_A-mediated IPSPs. This synchronised synaptic activity manifests at a population level as a coherent gamma frequency oscillation recorded as a local field potential (LFP). Kv3-family potassium channels such as Kv3.1 are selectively expressed in PV+ interneurons in the neocortex. Kv3 channels allow fast-spiking PV+ interneurons to fire accurately at high frequencies to orchestrate the activity of neocortical networks. Such high rates of firing, with high temporal accuracy, are required for the generation of neocortical gamma rhythms. Previous studies in patients suffering from schizophrenia¹ and putative animal models² of the condition demonstrate an inability of neocortical networks to generate coherent gamma frequency oscillations. In addition, post-mortem studies using cortical tissue obtained from patients with schizophrenia report reductions in PV and in the expression of Kv3.1 channels in the remaining PV+ interneurons.

Methods: Given that pharmacological manipulation of PV+ interneurons is a tangible therapeutic target for schizophrenia, we have examined the effect of a novel class of agents that positively modulate Kv3 channels. Rodent brain slices containing primary auditory neocortex were prepared as previously detailed³. We also used slices of human inferior temporal neocortex obtained from elective neurosurgery. Using kainate (400 nM), persistent gamma frequency oscillations were recorded as LFPs using extracellular microelectrodes, we then applied Kv3 channels positive modulators (AUT1 and AUT6).

Results: Application of AUT1 and AUT6 significantly increased the peak power and area power of persistent gamma activity in the auditory cortex. The peak frequency of gamma frequency oscillations was not altered. Similar results were obtained using slices of human inferior temporal neocortex, persistent gamma frequency oscillation elicited by kainate, were also augmented with the addition of AUT1.

Discussion: Our results suggest that modulation of Kv3 channels by these novel compounds may have the potential to correct disruptions in neuronal synchronization in schizophrenic patients by augmenting gamma frequency oscillations.

References:

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Poster #S114**PLEIOTROPIC EFFECT OF DISRUPTED IN SCHIZOPHRENIA 1 GENE: ANALYSIS OF EVENT-RELATED POTENTIALS AND BRAIN STRUCTURE**

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Background: In a large Scottish family with a (1;11)(q42;q14.3) translocation, the carriers of this balanced translocation were significantly associated to reduction in the amplitude of the P300 event-related potential (ERP).

Methods: In healthy controls, we tested the association between two non-synonymous SNPs in DISC1 gene with P300 amplitude and the volumes of the brain structures that are the putative P300 generators. We have investigated the measurement of the visual P300 event-related potential (ERP) during a modified Stroop task. For this study, 32 healthy subjects (drug free) were recruited for the ERP arm and 100 subjects were recruited for

the structural MRI arm. The mean age in the ERP was 34.53±8.5. There were 18 males and 14 females. The analysis of the SNP rs 821616 (Cys704Ser) was performed using the ABI7000.

Results: For the neutral word condition, there was no difference between the subjects who were carrying the variant 704Ser and those who did not carry this variant [$F(1/26) = 1.732$, $p=0.200$]. In the structural MRI arm, we did not find association with the SNP rs821616.

Discussion: Although our results did not show an association between Cys704Ser in DISC1 and P300 amplitude, this pilot study suggests a new methodology to combine multiple samples with related endophenotypes to test the pleiotropic effect of specific functional variants.

Poster #S115**EFFECTS OF BLOCKING D2 RECEPTORS ON MISMATCH NEGATIVITY OF ANTIPSYCHOTIC NAÏVE, FIRST EPISODE SCHIZOPHRENIA PATIENTS**

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Background: Reduced mismatch negativity (MMN) and P3A amplitude have been suggested to be core deficits and perhaps even endophenotypic markers for schizophrenia. Involvement of the dopaminergic system in these deficits is suspected, as they are thought to underlie symptomatology in schizophrenia. Studies on medication effects on these deficits in initially antipsychotic-naïve, first-episode patients with schizophrenia are scarce. However, such studies would provide important information about the transmitter systems involved, since they would not only exclude treatment related changes in receptor systems but also changes related to disease progress. The aim of the present study was to investigate the involvement of dopamine, in particular the dopamine D2 receptor, on MMN and P3A in a group of initially antipsychotic-naïve, first-episode patients with schizophrenia.

Methods: Fifty-one antipsychotic-naïve, first-episode patients with schizophrenia and 49 age and gender matched healthy controls were tested in the Copenhagen psychophysiology test battery (CPTB, consisting of PPI, P50 suppression, MMN, selective attention and resting state paradigms) at baseline and after six weeks. During these 6 weeks the patients were treated with amisulpride (a rather specific D2/D3 antagonist) in flexible dosages based on their clinical needs, while the controls did not receive any treatment at all. Mismatch negativity was assessed from the midline electrodes Fz, FCz and Cz. The paradigm consisted of 1500 standard stimuli (50 ms, 1000 Hz) and 300 deviant stimuli consisting of equal numbers of duration deviants (100 ms, 1000 Hz), frequency deviants (50 ms, 1200 Hz) and duration/frequency deviants (100 ms, 1200 Hz). All stimuli were semi-randomly presented, i.e. no two deviant stimuli were presented in direct succession.

Results: Both at baseline and follow-up the patients showed significantly reduced P3A amplitude, yet normal levels of MMN, compared to the healthy controls. In fact, neither the patients nor the controls showed any significant difference between the baseline and follow-up values of these two phenomena this, in spite of the fact that both the patients' symptomatology (PANSS positive, general and total scores) as well as their daily functioning (GAF scores) improved in this 6 week period.

Discussion: This is the first study investigating the effects of a relatively selective D2/D3-antagonist (amisulpride) on MMN and P3A amplitude in a group of initially antipsychotic-naïve, first-episode patients with schizophrenia. The findings indicate that although amisulpride significantly reduced the patients' severity of psychotic symptoms, it did neither influence MMN nor P3A amplitude. Our results are not supportive for a dopaminergic D2/D3 involvement in MMN or P3A amplitude.

Poster #S116**INCREASING GLUTAMATE RELEASE IN A GENETIC MODEL OF COGNITIVE DEFICITS**

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Background: Deficits in glutamate transmission are a phenotype associ-

ated with multiple mouse models of schizophrenia susceptibility genes (Harrison, 2013). Dysbindin is part of the Biogenesis of lysosome-related organelle complexes 1 (BLOC-1 complex) and is encoded by dystrobrevin-binding-protein1 (DTNBP1). The BLOC-1 complex has been related to multiple cellular functions including synaptic vesicle biogenesis and dynamics. DTNBP1 lies within the chromosome 6p24-22 susceptibility locus, and multiple associations have been reported between variants of DTNBP1 and cognitive deficits in schizophrenia. Beyond association between sequence variants and the disorder, a large proportion of schizophrenia patients exhibit lower dysbindin protein in tissue from the prefrontal cortex and the hippocampus. Several reports show that loss of dysbindin elicits a decrease in glutamate release in the hippocampus and PFC, a very consistent finding across different animal models of schizophrenia. Impaired working memory is consistently observed in dys^{-/-} mice as well as decreases in number and duration of social contacts and decreases in novel object recognition. Moreover, spine formation is decreased and there is an increase in immature spines.

Methods: Using voltage clamp recordings in cortical slices of dys^{+/+}, ⁺⁻ and ^{-/-} mice, Western Blots, measures of [Ca²⁺]_i, measures of synaptic vesicles and behavior we explore the mechanisms underlying decreases in glutamate release in the PFC

Results: We have found that dysbindin deficient mice have smaller ready releasable pools of glutamate vesicles in the PFC, exhibit decreases in quantal size and probability of release, deficits in the rate of endo-and exocytosis, decreases in Ca²⁺ currents and decreases in N-type Ca²⁺ channels. Reduced levels of dysbindin in the PFC indicate that BLOC-1 sensitive cargos delivered to the nerve terminal are affected. Evidence indicates that of 3 proteins present in regulated secretory vesicles (VAMP7, P14Ilo and BDNF), only BDNF immunoreactivity is reduced in the absence of BLOC-1 (Faundez et al., 2013). Therefore, we hypothesize that loss of dysbindin = loss of BLOC-1 \diamond decrease in BDNF \diamond decrease in ERK activity. Evidence shows that voltage-dependent Ca²⁺ channels are tonically upregulated via Ras/ERK signaling. Thus, it follows that by upregulating BDNF levels in dysbindin deficient mice, we may be able to upregulate N-type Ca²⁺ channels and perhaps reestablish levels of glutamate in PFC and improve cognitive performance. Fingolimoid (FTY 720), a sphingolipid approved for treatment of Rett syndrome and multiple sclerosis crosses the blood brain barriers and increases endogenous BDNF. Dysbindin deficient mice treated systemically with FTY 720 (7 or 14 days 0.1 mg/kg daily), exhibit increases in endogenous BDNF, [Ca²⁺]_i, increases in Ca²⁺ currents and a strong improvement in social interaction and working memory.

Discussion: In conclusion, our preliminary results suggest that increasing [Ca²⁺]_i alleviate some of the cellular and cognitive deficits present in a genetic model of schizophrenia. It will be of benefit to examine the status of Ca²⁺ channels in other models of risk genes.

Poster #S117 THE EFFECT OF COGNITIVE TRAINING ON EVENT-RELATED POTENTIALS IN SCHIZOPHRENIA

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Background: Cognitive remediation has found entry into the adjunctive treatment of schizophrenia despite meta-analytic studies reporting only small-to-moderate effect sizes on cognition and functioning. Electrophysiological measures provide a tool to more specifically access effects of cognitive training on brain function in schizophrenia. Here we aimed to evaluate electrophysiological indicators of stimulus processing with regard to effects of an auditory (AUD) or visual training (VIS) compared to a waiting-list control group (TAU).

Methods: Forty-six patients with schizophrenia or schizoaffective disorder were randomized to the experimental groups. Training consisted of 10 1-hour sessions in two weeks with assessments before and after training and at 2 months follow up. The auditory training focused on basic perception including discriminations of tone frequencies, intensities and sequences.

Visual training comprised tasks on discriminations of patterns and scenes. ERPs were recorded from midline electrodes during an active odd-ball paradigm with frequent standard tones (1000 Hz, 80 ms, 80 dBA) and rare randomly interspersed targets (9.9%, 1300 Hz, 80 ms, 80 dBA, SOA 1000 ms) which had to be reacted to with a button press. Clinical evaluation of patients included SCID and PANSS ratings.

Results: Results revealed no pre-training group differences and no treatment related changes in behavioral data. PANSS data improved from pre to post assessment with no group specific effects. P200 latency showed a group x treatment x electrode effect. In the AUD and the VIS groups P200 latency decreased with training as compared to the TAU group and more so at posterior positions in the AUD and at frontal positions in the VIS group. This effect was reversed from post training to follow-up in the AUD group. No other effects involving the group factor were significant.

Discussion: While P200 latency has been previously related to aspects of stimulus classification speed, the effects of our training seem to be related more to the training itself but not to the type of modality it is focused on. Evaluation of cognitive training using electrophysiology may provide more sensitive marker to measure change in a limited intervention setting as compared to the evaluation of clinical and functional outcomes.

Poster #S118 THE EFFECT OF DIFFERENT DEFINITIONS OF SCHIZOPHRENIA

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Background: In previous Danish register-based studies concerning risk factors of schizophrenia, the first day of the first admission leading to a discharge diagnosis of schizophrenia has been used as definition of schizophrenia. Similar Swedish studies, however, tend to define schizophrenia as the first day of the second admission. The criterion of at least two admissions has been chosen to increase diagnostic precision. The aim of this study was to assess whether there was a significant difference in using first or second admission when estimating the effects of several known risk factors including parental age at birth of child, urbanicity at birth, gestational age, birth defects, parental loss, parental education, parental occupation, parental income, parental immigration status, and family history of mental illness.

Methods: All people born in Denmark between January 1st, 1955 and December 31st, 1997 with known mothers were identified (N=2,772,234). They were followed from their 15th birthday or January 1st, 1995, whichever came last, and until date of death, December 31st, 2012, or first or second admission, respectively, whichever came first. In this period 16,013 people received a first and 12,557 a second diagnosis of schizophrenia. Effects of known risk factors were estimated for each of the two outcomes using Cox proportional hazards models adjusted for sex and calendar time.

Results: We found no notable differences in the effects of risk factors for schizophrenia depending on whether schizophrenia was defined as the first or the second admission. Even family history of mental illness defined as no psychiatric diagnoses, any psychiatric diagnosis or schizophrenia in mothers, fathers and siblings showed no noteworthy differences. E.g. the hazard ratios for mentally ill mothers and schizophrenic mothers compared to mothers with no diagnoses were 2.45 (95% CI: 2.35-2.55) and 7.06 (95% CI: 6.36-7.85), respectively, when using first admission as outcome. In comparison, the corresponding hazard ratios were 2.50 (95% CI: 2.39-2.61) and 7.29 (95% CI: 6.49-8.19), respectively, when outcome was defined as the second admission.

Discussion: The criterion of at least two diagnoses of schizophrenia seems a simple and effective way to increase diagnostic precision. It increases the likelihood of patients actually having received the correct diagnosis. However, it also requires that people survive long enough to receive a second diagnosis. Considering the substantially increased mortality among schizophrenia patients, it seems plausible that some may die before they ever get the chance to receive a second diagnosis and valuable information

is therefore overlooked. In the future it would be interesting to examine the mortality in the two groups diagnosed with schizophrenia. We came to the conclusion that Danish and Swedish studies are comparable despite their different approaches of defining schizophrenia.

Poster #S119

THE PSYCHOSIS RECENT ONSET GRONINGEN SURVEY (PROGR-S): DEFINING DIMENSIONS AND IMPROVING OUTCOME IN EARLY PSYCHOSIS

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Background: Psychotic disorders are among the most complex medical conditions. Longitudinal cohort studies may give more insight in determinants of functional outcome after a psychotic episode. Here we describe the Psychosis Recent Onset in GRoningen Survey (PROGR-S) that contains data of over 700 early-onset psychotic patients, including symptoms, personality, cognition, life events and other determinants of outcome. Our goal is to give an overview of PROGR-S, as a point of reference for future publications that will investigate the effect of cognition, personality and psychosocial functioning on outcome.

Methods: PROGR-S contains an extensive, diagnostic battery including anamnesis, biography, socio-demographic characteristics, clinical status, drug use, neuropsychological assessment, personality questionnaires, and physical status tests. Extensive follow-up data is available on psychopathology, physical condition, medication use, and care consumption. Sample characteristics were determined and related to existing literature.

Results: PROGR-S included the majority of the expected referrals in the catchment area. The average age was 27 and two-third was male. The majority was diagnosed in the psychotic spectrum. A substantial amount of the patients had depressive symptoms and current cannabis or alcohol use. The level of community functioning was moderate, i.e. most patients had no relationship and were unemployed.

Discussion: The PROGR-S database contains a valuable cohort to study numerous aspects related to symptomatic and functional outcome of recent onset psychosis, which may play a role in the treatment of this complex and disabling disorder. The database contains interesting starting points for future research. Ultimately, we hope that this will contribute to health improvement of patients with psychotic disorders.

Poster #S120

HELP-SEEKING BEHAVIOUR AND AT-RISK CRITERIA OF PSYCHOSIS IN THE GENERAL POPULATION: PRELIMINARY RESULTS FROM A TELEPHONE SURVEY

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Background: An "Attenuated Psychosis Syndrome" was included in Section III (Conditions for further study) of DSM-5. Although help-seeking for attenuated psychotic symptoms is not part of the final set of criteria, it had been proposed as an obligate criterion before in an attempt to avoid the suspected diagnostic creep in clinical practice. Therefore, our aim was to examine (non-)help-seeking for mental problems including attenuated psychotic symptoms and other at-risk phenomena in the general population.

Methods: 1'229 persons of the general population were interviewed. Ultra-high risk criteria were assessed with the "Structured Interview for Psychosis-Risk Syndromes" (SIPS), basic symptom criteria with the "Schizophrenia Proneness Instrument, Adult version" (SPI-A), and help-seeking with a modified version of the WHO pathway-to-care questionnaire. Additionally, satisfaction with potential treatment outcome was assessed with the Brief Multidimensional Life Satisfaction Scale.

Results: 285 (21.9%) interviewees reported help-seeking for mental problems; 105 (8.1%) "help-seekers" also reported symptoms included in the

at-risk criteria for psychosis, irrespective of them fulfilling the respective time and frequency criteria (AtRisk). The group of AtRisk (29.5%) sought significantly more often help than persons not experiencing at-risk symptoms (NoRisk=19.1%; Cramer's V=0.112). Both groups mainly contacted a psychiatrist/psychologist or a general practitioner first. Main reasons for help-seeking in both groups were depressive mood (AtRisk=35.7%; NoRisk=38.5%), anxiousness (AtRisk=30.4%; NoRisk=20.9%) and family problems (AtRisk=30.4%; NoRisk=35.2%). Of the AtRisk, only two spontaneously named at-risk symptoms as a main reason for help-seeking; in both cases, these were cognitive basic symptom. Interestingly, AtRisk were less satisfied with treatment success than NoRisk, although their reasons to seek help, the type of first help contact and the reasons for delaying help-seeking did not differ.

Discussion: Persons experiencing mental problems often do not or only with considerable delay seek help. In terms of at-risk phenomena of psychosis, comorbidity with depression and anxiety are frequent and a main reason for help-seeking. The fact that persons experiencing current at-risk symptoms for psychosis do not differ in help-seeking behaviour but are less satisfied with treatment outcome might indicate that more awareness of professionals towards these symptoms is needed.

Poster #S121

MENTAL HEALTH LITERACY: IS PSYCHOSIS AS WELL RECOGNIZED AS DEPRESSION?

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Background: Earlier reports on mental health literacy reported that the knowledge about depression was much better than that about psychoses, yet increasing between 1990 and 2001. Mental health literacy, however, is assumed to influence help-seeking and, thus might be crucial in the early detection of psychosis. Therefore, we investigated the current knowledge about psychosis in comparison to that about depression in a general population sample of the Canton Bern that is within the age range of highest risk for developing a first episode psychosis.

Methods: 1'184 German-speaking participants of a telephone survey (age 16 to 40) were asked to answer a questionnaire on mental health literacy and attitudes whose two versions vary in their diagnostically unlabeled case vignette (schizophrenia or depression). 1'061 (89.6%) agreed to participate, 645 (60.8%) questionnaires were returned: 331 with a schizophrenia, 314 with a depression case vignette.

Results: The type of the vignette had a near moderate effect on the correct recognition of the disorder in an open question (Cramer's V= 0.269) with depression being recognized by 77.6%, psychosis by just 48% ($\chi^2 (1)= 58.142$, $p < 0.000$). A higher effect of the vignette was observed for the main causal attribution to be chosen from 18 categories ($\chi^2 (5)= 89.527$, $p < 0.000$; Cramer's V= 0.406): For depression, 51.2% gave any psychosocial, just 10.5% any biological factor; for schizophrenia, 36% any biological and just 17.5% any psychosocial factor; and intra-individual causes were each named as main cause by 20.6%. When correct recognition of the vignette was taken into account, the difference between the perceived impact of biological and psychosocial factors became even more pronounced. Persons recognizing the correct disorder ($\chi^2 (2)= 91.927$, $p < 0.000$; Cramer's V= 0.484) opted even more often for a biological cause for the schizophrenia and a psychosocial cause for the depression vignette than those using incorrect labels ($\chi^2 (2)= 25.074$, $p < 0.011$; Cramer's V= 0.317).

Discussion: Within the last 20 years, a continuous increase in the correct recognition of depression and psychosis can be observed with psychosis still being more frequently under-recognized. Furthermore, the trend towards adopting causal explanations approved of by psychiatrists continued. Yet, it remains to be studied if this has a positive effect on the desire for social distance and help-seeking.

Poster #S122**ASSOCIATION BETWEEN EPILEPSY AND PSYCHOTIC DISORDERS IN THE NORTHERN FINLAND 1966 BIRTH COHORT STUDY**

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Background: Individuals with epilepsy have commonly comorbid psychiatric disorders. There are a few studies which have focused on non-organic psychotic disorders (Bredkjaer et al. Br J Psychiatry 1998, Wotton et al. Epilepsia 2012). Our aim was to investigate how epilepsy and non-organic psychotic disorders associate in a large population based birth cohort.

Methods: The study sample comprised 10,925 individuals from the prospective Northern Finland 1966 Birth Cohort. The sample have been followed until age of 45 years. Cox regression analysis (Hazard Ratios, HR) were used to study risk of psychotic disorders with epilepsy status. Gender, mental retardation and family history of psychosis were used as covariates. Epilepsy diagnoses were based on various nationwide registers and questionnaires. Information on psychoses was based on nationwide registers, including both inpatients and outpatients.

Results: A total of 334 (3.0%) cohort members suffered from non-organic psychotic disorders and 331 (3.0%) of epilepsy by the age of 45 years. The cohort members with epilepsy had 1.7-fold risk for psychosis when compared to those without epilepsy (adjusted HR 1.7; 95% Confidence Interval 1.1-2.7). The risk was especially high for non-schizophrenic psychoses (adjusted HR 3.1; 1.7-5.8), whereas epilepsy did not associate with schizophrenia spectrum diagnoses (adjusted HR 1.1; 0.6-2.1). Especially individuals with localization-related epilepsies developed commonly (9 of 74, 12.2%) psychotic disorders.

Discussion: In our research we found that epilepsy increases risk for subsequent non-schizophrenic psychoses even when adjusted with other factors. The potential mechanisms will be discussed.

Poster #S123**SEX DIFFERENCES IN PREVALENCE AND COMORBID SUBSTANCE USE DISORDERS AMONG PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER: A FIVE-YEAR POPULATION-BASED STUDY**

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Background: Several lines of evidence indicate overlapping etiological and pathophysiological mechanisms for schizophrenia and bipolar disorder. Studies of sex differences in prevalence and comorbidity may shed light on similarities and differences between the two disorders. We aimed to investigate sex differences in the five-year prevalence of schizophrenia and bipolar disorder, and differences in the prevalence and type of comorbid substance use disorders (SUD) between men and women with schizophrenia or bipolar disorder.

Methods: The Norwegian Patient Register (NPR) contains administrative and diagnostic information on all patients who have been in contact with in- or outpatient specialist health care in Norway from 2008 and onwards. For the present study, diagnostic information about psychotic disorders and SUD (alcohol use disorders, AUD; non-alcohol drug use disorders, DUD) was retrieved for individuals born in the period 1950-1989 and registered with a psychotic disorder according to the ICD-10 diagnoses F20-F29, F30-F31, F32.3, or F33.3 in the NPR between 2008 and 2012 (N=38844). The sample was grouped into five-year cohorts. Prevalence in the five-year period (2008-2012) was estimated by dividing the number of patients with psychosis by the mean number of individuals in the population in the same time period. Male-to-female ratios of the five-year prevalence of schizophrenia and bipolar disorder, and male-to-female ratios of the

five-year prevalence of comorbid AUD and DUD across age and type of psychotic disorder were computed.

Results: A total of 10275 individuals (6583 men and 3692 women), constituting 0.39% of the population (0.49% of the men and 0.29% of the women), were diagnosed with schizophrenia and 19142 individuals (7901 men and 11241 women), constituting 0.73% of the population (0.59% of the men and 0.87% of the women), were diagnosed with bipolar disorder. Schizophrenia was diagnosed 1.7 times more often among men than women, while bipolar disorder was diagnosed 1.5 times more often among women than men. Sex differences were largest in younger age for both disorders. For patients with schizophrenia, the prevalence of AUD was about half the prevalence of DUD (9.6% and 19.8%, respectively), while for patients with bipolar disorder, AUD and DUD were equally prevalent (13.0% and 13.2%, respectively). The highest prevalence of AUD (24.1%) was found among 53-57 year old men with bipolar disorder, and the highest prevalence of DUD (40.6%) was found among 23-27 year old men with schizophrenia.

Discussion: Schizophrenia and bipolar disorder differed with respect to gender distribution. Schizophrenia was more prevalent in men, especially in younger age, while bipolar disorder was more prevalent in women. Drug abuse (non-alcohol) was more common than alcohol abuse among patients with schizophrenia, while for patients with bipolar disorder alcohol and non-alcohol drug abuse occurred on equal level. These age- and sex differences in five-year prevalence between schizophrenia and bipolar disorder, and differences in the pattern of SUD comorbidity between schizophrenia and bipolar disorder, may reflect specific and distinguishing etiological and pathophysiological mechanisms for the two disorders. The exceptionally high prevalence of SUD among young patients with schizophrenia and bipolar disorder should encourage preventive efforts to reduce illicit drug use in the population.

Poster #S124**DELAY IN ROUTINELY NEONATAL BLOOD SCREENING IS ASSOCIATED WITH INCREASED RISK OF SCHIZOPHRENIA**

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Background: The search for genetic and environmental risk factors for schizophrenia is rapidly going forward. The Danish Newborn Screening Biobank, based on heel blood spots stored, sampled few days after birth and stored on frozen filter paper, is a unique source of data that can be utilized for analyses of genetic and environmental exposures related to schizophrenia and other mental disorders. In previous analyses, we have found that early and late blood testing was associated with increased risk of schizophrenia. Therefore, we want to investigate whether the increased risk can be explained or partly explained by other risk factors for schizophrenia.

Methods: A case-control design was applied. A total of 846 cases with schizophrenia were selected from the Danish Psychiatric Case Register. One control was selected for each case, matched on sex and exact date of birth.

Results: Both early and late blood testing was associated with increased risk for schizophrenia. Blood testing at day 0 to 4 after birth was associated with an incidence rate ratio (IRR) of 1.46 (95% CI 1.15-1.87) for development of schizophrenia, blood testing at day 6 to 9 and at day 10 to 53 was with an IRR of 1.5 (95% CI 1.13-1.98) and 3.00 (95% CI 1.59-5.67) respectively. After adjusting the estimates for place of birth, both parents' psychiatric illness, maternal and paternal age at child birth, parents' country of origin and child admission at 0-30 days of age, the estimates were slightly different. Thus, blood testing at 0-4 day was associated with an IRR of 1.23 (95% CI 0.93-1.63), 6-9 days 1.42 (95% CI 1.04-1.94) and 10+ days 3.12 (95% CI 1.49 to 6.55).

Discussion: After adjusting risk estimates for well known risk factors, delay in sampling of blood for neonatal screening was associated with unexplained increased risk of schizophrenia. It is possible that the increased risk is associated with social variables which are not captured by parents' mental illness. Date of test will be included in future analyses of genetic and environmental risk factors.

Poster #S125**SOCIAL CLASS AND PSYCHOSIS**

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Background: An association between social class and psychiatric illness has long been recognised. In 1939 Faris and Dunham observed that there was a higher rate of schizophrenia in the lower social classes and in the more socially disadvantaged areas. This introduced the pertinent question, namely, was this observation a result of downward drift associated with schizophrenia, the "social drift" theory or was the disorder caused by the environment, the "social causation" theory. The aim of this study was to examine if the social class at birth is a risk factor for developing psychosis and schizophrenia. Secondly, we aimed to determine whether the social class at the time of presentation different from that at birth, i.e. whether social drift or upward mobility had occurred.

Methods: We included individuals with a first episode of psychosis (FEP) whose social class at birth was determined from birth records and classified according to the father's occupation at the time of birth. Social class at presentation was determined from the individual's occupation at the time of presentation. We employed a case-control study design and also compared the social class distribution at birth and at presentation of the cases to that of the general population.

Results: 430 individuals with a FEP were included in the study. The odds ratio for developing a FEP associated with social class (low vs high) was 0.68 (95% C.I. 0.54 to 0.87, $p<0.001$), indicating that individuals from a lower social class at birth have a reduced risk of psychosis. Individuals born between 1961 and 1980 who subsequently developed a psychotic disorder were more likely to be from a higher social class at birth compared to the general population (61% vs 37%, $\chi^2=60.85$, df=1, $p<0.001$). However this association was not seen for those born between 1981 to 1990. The above associations remained consistent in the sub-group of individuals with a diagnosis of a schizophrenia-spectrum disorder. At the time of presentation, individuals with a first episode of psychosis were more likely to be in the lower social classes compared to the general population (46% vs 24%, $\chi^2=91.30$, df=1, $p<0.001$). Upon comparison of an individual's social class at birth and at presentation, 43% experienced a social drift while 25% experienced an elevation in social class.

Discussion: A higher social class at birth is associated with an increased risk for developing a psychotic disorder however by the time of presentation with a first episode of psychosis, individuals are more likely to be represented in the lower social classes.

Poster #S126**MENTAL HEALTH LITERACY: DESIGN OF AND RESPONSE TO AN ADD-ON QUESTIONNAIRE STUDY TO A POPULATION SURVEY**

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Background: Earlier reports on mental health literacy reported a better knowledge about depression than psychoses. Mental health literacy and perceived stigma, however, is assumed to influence help-seeking and, thus might be crucial in the early detection of psychosis. Therefore, we compared current knowledge about and social rejection for psychosis and depression in a general population sample of the Canton Bern that is within the age range of highest risk for developing a first-episode of severe mental disorder.

Methods: As an add-on study to an ongoing epidemiological telephone survey about the prevalence of at-risk criteria of psychosis in the general population of the Canton Bern within the age range of 16 to 40 years the 1'233 participants of the telephone survey were asked to answer a questionnaire on mental health literacy and attitudes whose two versions vary in their diagnostically unlabeled case vignette (schizophrenia

or depression). Of 1'184 German-speaking participants in the telephone interview, 1'061 (89.6%) agreed to have the questionnaire send, 645 (60.8%) questionnaires were returned: 331 with a schizophrenia case vignette, 314 with a depression case vignette.

Results: Participants of the telephone interview who agreed in participating in the add-on survey did not substantially differ from those who refused in age, gender, education, marital status, nationality, help-seeking for own mental problems, or current axis-I disorder; there was a small bias towards participants having more frequently a 1st- or 2nd degree biological relative with mental problems. The two groups – persons returning a questionnaire with a schizophrenia case vignette (SZ vignette) and persons returning a questionnaire with a depression case vignette (MD vignette) – did not differ in clinical or sociodemographic characteristics.

Discussion: At the already good and still increasing response rate, the questionnaire survey has the potential to give good insight in the current mental health literacy, treatment recommendation and degree of social rejection of persons with mental disorders in the young adult general population of the Canton Bern and similar cultural regions, although results might be slightly positively biased for the more frequent familiarity with mental disorders of the responders.

Poster #S127**PREVALENCE OF AT-RISK CRITERIA OF PSYCHOSIS IN CHILDREN AND ADOLESCENTS, AND IN YOUNG ADULTS: RESULTS FROM TWO SWISS COMMUNITY SAMPLES**

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Background: Questionnaires cannot be considered a valid assessment of attenuated psychotic symptoms (APS) and tend to greatly overestimate their prevalence in the community. Thus, the prevalence and pathological value of APS in the general population, when assessed in the same way as in help-seeking persons, is still rather unclear. This lack of knowledge also exists for other risk criteria, especially basic symptom criteria. For APS and related risk criteria, data from Irish youth have suggested an age effect with declining rates of (attenuated) psychotic symptoms in early to mid-adolescence, and a predominance of perception related phenomena.

Methods: In two complimentary community studies, we studied the prevalence of ultra-high risk and basic symptom at-risk criteria and their included symptoms assessed with the Structured Interview for Psychosis-Risk Syndromes (SIPS) and the Schizophrenia Proneness Instrument, Adult version (SPI-A) and Child and Youth version (SPI-CY), respectively, in random Swiss general population samples of 8-17 years and 16-40 years. Children and adolescents were assessed in face-to-face interviews, young adults on the telephone by extensively trained clinical psychologists. Exclusion criteria were communication problems and life-time psychosis.

Results: At the time of writing, 1,229 interviews with young adults (18-40-years-of-age) and 55 interviews with children and adolescents (8-17-years-of age) were completed. While only 2.8% of the young adults acknowledged the presence of any one at-risk criterion (incl. frequency and onset requirements), 9.1% of the children and adolescents did so (1-dimensional Chi $\chi^2=3.34$, $p<0.10$). An even more pronounced, significant age-related difference was found in the prevalence of lifetime at-risk phenomena (1-dimensional Chi $\chi^2=5.83$, $p<0.025$): 25.2% of the young adults and 45.5% of the children and adolescents reported at least any one. Thereby, "perceptual abnormalities/hallucinations" of the SIPS, mainly on APS level, were the most frequent phenomenon in both samples.

Discussion: While at-risk phenomena occurred in a quarter of young adults of the general population and even in nearly half of the children and adolescents at least temporarily, only a minority reported sufficient recency, frequency or change in severity of these phenomena to meet present risk criteria according to SIPS and SPI-A – again with higher rates in children and adolescents. This highlights the importance of the recency, frequency or behavior-/conviction-related change-in-severity criteria included in the risk criteria, but also the need to further examine developmental peculiarities. These factors might play a crucial role in the differentiation between ill and non-ill persons and thus should be studied in more detail.

Poster #S128**RISK OF SCHIZOPHRENIA SPECTRUM AND AFFECTIVE DISORDERS ASSOCIATED WITH SMALL FOR GESTATIONAL AGE BIRTH AND HEIGHT IN ADULTHOOD**

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Background: Several studies have shown an association between pre-natal growth restriction or post-natal somatic growth and the risk of schizophrenia spectrum disorders. Whether such associations extend to affective disorders is unknown.

Methods: Records from the Danish Medical Birth Register, the Danish Psychiatric Register and the data from the Danish draft board were linked and samples were followed prospectively. We calculated hazard ratios (HRs) of small for gestational age (SGA, defined as the shortest 10% birth length percentile for a given gestational age) and adult height for schizophrenia spectrum disorders and affective disorders, adjusting for possible confounding variables.

Results: We identified 135,953 males with no previous schizophrenia spectrum disorders and 135,689 males without a past history of affective disorders at the time of the draft board examination. There were 489 new cases of schizophrenia spectrum disorders and 792 new cases of affective disorders during the study period. SGA was associated with higher risk of adult schizophrenia spectrum disorders (HR, 1.28; 95% CI, 1.02–1.62), but not with risk for adult affective disorders (HR, 1.03; 95%CI, 0.86–1.26). The association of SGA and the risk of adult schizophrenia spectrum disorders remained significant or nearly significant when familial psychiatric diagnoses (HR, 1.26; 95% CI, 1.00–1.59) or adult body mass index and parental education (HR, 1.19, 95% CI, 0.94–1.50) were considered. Short stature in adulthood (<178 cm) was associated with increased risks of both schizophrenia spectrum and affective disorders.

Discussion: Schizophrenia spectrum disorders and affective disorders may have both common and distinct causative pathways.

Poster #S129**EVIDENCE FOR A SHARED ETIOLOGICAL MECHANISM OF PSYCHOTIC SYMPTOMS AND OBSESSIVE-COMPULSIVE SYMPTOMS IN PATIENTS WITH PSYCHOTIC DISORDERS AND THEIR SIBLINGS**

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Background: The prevalence of obsessive-compulsive disorder in subjects with psychotic disorder is much higher than in the general population. The higher than chance co-occurrence has also been demonstrated at the level of subclinical expression of both phenotypes. Each of both extended phenotypes have been shown to cluster in families. However, little is known about the origins of their elevated co-occurrence.

Methods: In the present study, the evidence for a shared etiological mechanism was investigated in a sample of 3686 subjects, containing 3 groups with decreasing levels of familial psychosis liability: 987 patients, 973 of their unaffected siblings and 566 healthy controls. The association between the obsessive-compulsive and the psychosis phenotype was investigated in two ways. First, the association was assessed between (sub-clinical) obsessive-compulsive symptoms and psychosis liability. Second, in a cross-sib cross-trait analysis, it was examined whether (subclinical) obsessive-compulsive symptoms in the patient were associated with (subclinical) psychotic symptoms in the related unaffected sibling.

Results: Evidence was found for both associations. The first series of analyses demonstrated a dose-response association of the obsessive-compulsive phenotype with familial psychosis liability. Broadly defined OCS were significantly more prevalent in patients (22.7%, n=224) (OR=6.7, 95% CI: 4.3–10.6, p<0.000) and siblings (8.2%, n=80) (OR=1.8, 95% CI: 1.1–3.0, p<0.012) compared to controls (4.8%, n=27). Patients reported significantly more OCS

compared to siblings ($\chi^2(1)=70.4$, p<0.000). Clinical OCS were significantly more prevalent in patients (19.0%, n=188) (OR=18.4, 95% CI: 8.8–38.7, p<0.000) and siblings (4.3%, n=42) (OR=2.9, 95% CI: 1.4–6.2, p<0.006) compared to controls (1.6%, n=9). Patients reported significantly more clinical OCS compared to siblings ($\chi^2(1)=80.6$, p<0.00005). The associations remained significant after adjusting for confounders. In the next step, analyses were restricted to siblings and controls. It was examined whether the association between OCS and two-level status (siblings versus controls) remained significant when adjusted for positive and negative subclinical psychotic symptoms as assessed with the SIS-R. The association between OCS and two-level psychosis liability status remained significant (broadly defined OCS: OR=1.7, 95% CI: 1.0–2.6, p<0.032; clinical OCS: OR=2.7, 95% CI: 1.3–5.9, p<0.01). Additional adjustment for confounders did not substantially alter the results. The second series of analyses examined cross-sib cross-trait associations. Broadly defined OCS in the patients were at trend level associated with the subclinical positive psychotic symptoms in their unaffected siblings, assessed with the SIS-R (OR= 0.5, 95% CI: -0.02–0.95, p<0.06). When adjusted for gender, IQ, level of education and marital status in sibs and patients, the specificity of the association reached conventional alpha indicating significance (OR=0.5, 95% CI: -0.04–0.95, p<0.07). Clinical OCS in patients Showed directionaly similar associations without reaching significance.

Discussion: These findings are compatible with a partially shared etiological pathway underlying the obsessive-compulsive and psychosis extended phenotypes. This is the first study that used a cross-sib cross-trait design in patients and unaffected siblings, thus circumventing confounding by disease-related factors present in clinical samples.

Poster #S130**PREMATURE DEATH IS HIGHER IN PERSONS WITH PSYCHOTIC DISORDERS BUT NOT WITH PSYCHOTIC EXPERIENCES: A POPULATION-BASED LONGITUDINAL STUDY**

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Background: Psychotic disorders are associated with higher rates of mortality than those observed in the general population. Mortality in patients with schizophrenia is 2 to 4 times higher and life expectancy is 20% shorter. Previous studies have suggested that the mechanisms explaining the association between psychosis and death may include the cumulative effects of unhealthy lifestyle factors following disease onset, delay in diagnosis of medical comorbidities, lower quality of medical care, and treatment with antipsychotic medication. Psychotic experiences in the general population are far more prevalent than psychotic disorders and are associated with risk for later psychotic disorders, but mortality rates in persons with psychotic experiences have not been explored.

Methods: We utilized data from a two-stage epidemiological study of mental disorders among 4,914 young adults aged 25–34 in a population-based 10-year birth cohort (1949–1958) conducted in Israel in the 1980's. Twenty five years later, the epidemiological data (including assessment of psychotic experiences) was linked with the Israeli Psychiatric Hospitalization Case Registry and the National Death Registry. Cox Proportional Hazards regression was used to assess the association between psychotic disorders and experiences, and all-cause-mortality. The data were weighted to estimate rates in the original population from which the cohort sample was drawn.

Results: The prevalence of psychotic disorders in the current cohort was 1.5% (n=821) and the prevalence of psychotic experiences in the general population was 14.2% (n=83). One hundred and seventy four persons (3.6%) died during the follow-up period. Premature death (prior to the age of 57, the end of follow-up) was significantly more prevalent in persons with psychotic disorders (23.1%) but not psychotic experiences (3.4%) compared to the general population (3.3%) ($\chi^2=85.6$, p<0.001). Persons with psychotic disorders were 9 times more likely to die by the age of 57 than persons from the general population (95% CI: 3.32–23.30). Excess mortality in persons with psychotic disorders appears to be caused both by external causes of death and natural causes (namely, infectious and parasitic dis-

eases, circulatory system diseases, digestive system diseases and respiratory diseases).

Discussion: Persons with psychotic disorders, but not those with psychotic experiences, are at increased risk of premature death. Although persons with psychotic experiences share some demographic and clinical characteristics as those with psychotic disorders, premature death appears to be unique to patients with clinically diagnosed disorders.

Poster #S131

USE AND ABUSE: THE ROLE OF COMMUNITY TREATMENT ORDERS IN AN INTENSIVE OUTREACH TEAM

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Background: Use of Community Treatment Orders (CTOs) in Victoria, Australia have been increasing over time. Involuntary treatment has benefits to patients and the community, but also comes at a cost, including loss of autonomy and often diminished rapport with the treating clinical team. Victorian governments have undertaken a comprehensive review of the current Mental Health Act (MHA); the upcoming changes when implemented will directly and indirectly reduce the number of patients on CTOs through a variety of measures, including more stringent standards, monitoring, and resource limitations. In the lead-up to the implementation of the new MHA in 2014, our team undertook a concerted effort to reduce the number of patients on CTOs and to assess the effects this had in terms of relapse and readmission rates.

Methods: This audit was conducted at a Community Mental Health Clinic in an inner city suburb of Melbourne, Australia, and focused on the Mobile Support and Treatment Team (MSTT), an intensive outreach service. Clinicians on the team (1 psychiatrist, 1 registrar, 5 nurses, 2 occupational therapists, one enrolled nurse) were encouraged to proactively identify any patient who they thought currently or soon could be discharged off a CTO. These patients were then interviewed according to the MHA criteria to see if they still met the criteria. If not, they were made voluntary patients; those who still met the criteria were given psychoeducation with their doctor and case manager about measures needed to be put into place for them to become voluntary patients. Using the Victorian Statewide Database, a review of patients on a CTO any point during the study period of January 1, 2011 - November 1, 2013 was done. This was then correlated with admission data from the same period to assess for any change in admission rates for patients who were formerly on a CTO.

Results: The overall rate of patients on CTO in MSTT within the period peaked at 50% of our caseload at the start of the study period in Feb 2011; by the end of the study period only 24% were on CTOs. 73 patients were identified as being on a CTO at any point on the study period. Of those, 37 (50.7%) were actively discharged off their CTOs after review, and a further 5 (6.8%) were discharged off CTO but then required their CTOs to be reinstated. Of the patients discharged off CTO, 17 (45.9%) were subsequently admitted to hospital at any point during the audit period; 9 of those 17 (52.9%) patients accepted admission as a voluntary patient. Reasons for readmission were not always for relapse; other reasons included planned admissions for medication change (2 patients), medical investigations requiring admission (2 patients), and social/housing problems (3 patients).

Discussion: Many patients at the start of the audit period seemed to be on 'just in case CTOs', based largely on past rather than current risks. Usage of CTOs in our team decreased by 50% over the study period, with no commensurate increase in our overall admission rate. While nearly half the patients discharged off CTO required readmission during the period, there is no evidence that discharge off the CTO was causative and the high proportion of voluntary admissions suggests better engagement from our patient group. Interviewing the patients about their CTOs revealed themes of feeling disenfranchised due to the compulsory treatment. Many patients did not even know they were on a CTO, or did not understand the meaning of it or what their rights and obligations were, suggesting they did not meet the criteria. We also noted better awareness within MSTT about ethical issues around CTOs. Limitations are the limited sample size, in one unit, and it is unknown if patients admitted after being taken off CTO would have relapsed regardless of their MHA status.

Poster #S132

COPY NUMBER VARIANT ANALYSIS ON 401 CASES OF SCHIZOPHRENIA: A SEARCH FOR CAUSAL GENES FINDS DISRUPTION IN THE NEUROGENESIS REGULATOR JAGGED 2

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Background: While a large proportion of the risk of schizophrenia (SZ) is conveyed by common variants with a small effect size, rare variants with very large effect size can be highly informative despite the difficulties in finding statistical association. Large structural changes such as duplications or deletions, known as copy number variants (CNVs) are particularly penetrant and can be identified in large genetic studies designed for genome-wide SNP association. A number of these studies have been able to identify CNVs, and in some cases associate these with the risk of developing SZ. These genetic lesions, many of which occur spontaneously, may provide important insights into the genes disrupted more broadly in SZ. These variants assert their biological effects by altering gene dosage, methylation, chromatin structure and other mechanisms that disrupt the transcriptional equilibrium. Where these changes affect regulators of gene expression their impact can be more dramatic as their influence is amplified across the genome. Post-transcriptional regulators known as microRNA (miRNA), in particular, can alter the gene expression of many genes. Therefore changes in copy number within genomic segment containing these regulators may significantly alter gene pathways associated with the disease. In this study we investigated CNV in schizophrenia patients from the Australian Schizophrenia Research Bank (ASRB) using genome-wide SNP analysis and explore their effects on miRNA.

Methods: Genome-wide CNVs analysis was determined from Illumina Quad 610K-SNP array data generated for 672 samples (401 cases, 271 controls). After preprocessing in GenomeStudio, PennCNV was used to perform CNV calls. Association analysis was performed using PLINK with visualisation achieved with the Integrated Genomic Viewer and Circos. TaqMan multiplex CNV assays were used to validate SNP-array based CNV calls. Target genes for miRNA disrupted CNVs were predicted using TargetScan.

Results: Nine loci were overrepresented in cases ($p < 0.1$) including 4 cases with deletion of 11 exons encoding the transmembrane domain of the JAG2 gene. Interestingly, six cases were also observed to have CNVs at both the start of chr1 and chr14. We also observed five miRNA genes to be disrupted by these CNV-affected loci in cases with SZ. Nine CNV associated genes were also targets predicted for five disrupted miRNA genes, including MIR200A, MIR203, MIR429, MIR1236 and MIR4710. Six of these genes have neuron-associated functions. CNVs on 19q13.2 and 22q11.2 were validated via TaqMan multiplex CNV assay.

Discussion: This study has revealed some novel findings associated with SZ. JAG2, in particular, was found to be disrupted via deletion of the transmembrane domain, in multiple cases with the disorder. JAG2 is an important regulator of neurogenesis. We also observed tandem structural changes affecting the ends of both chr1 and chr14 in a surprisingly large number of cases. Five miRNA genes were also found to be affected in patient CNVs. Interestingly, nine target genes of these disrupted miRNA were also associated with CNVs in cases. Six of these, including JAG2 gene, have neural function suggesting that these molecules, particularly JAG2, could be potential candidate genes for SZ.

Poster #S133

ASSOCIATION OF A RISK ALLELE OF ANK3 WITH COGNITIVE PERFORMANCE AND CORTICAL THICKNESS IN PATIENTS WITH FIRST-EPIISODE PSYCHOSIS

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Background: The gene ANK3 is implicated in bipolar disorder and schizophrenia through findings from genome-wide association studies

(GWAS). This gene is involved in neural signaling and some risk variants have been associated with diminished cognitive performance. The present study investigated the influence of this gene on cognition and brain structure among individuals with first-episode psychosis (FEP). The brief illness duration of an FEP sample makes it well suited for studying the effects of genetic variation.

Methods: We genotyped 2 single nucleotide polymorphisms (SNPs; rs1938526 and rs10994336) in ANK3 in 173 patients with FEP. Multivariate analysis of variance compared risk allele carriers and noncarriers on 6 domains of cognition consistent with MATRICS consensus. A subsample of 82 patients was assessed using magnetic resonance imaging. We compared brain structure between carriers and noncarriers using cortical thickness analysis and voxel-based morphometry on white matter.

Results: rs1938526 and rs10994336 were in very high linkage disequilibrium ($d' = 0.95$), and analyses were therefore only carried out on the SNP (rs1938526) with the highest minor allele frequency (G). Allele G of rs1938526, was associated with lower cognitive performance across domains ($F_{6,164} = 2.38$, $p = 0.030$) and significantly lower scores on the domains of verbal memory ($p = 0.015$), working memory ($p = 0.006$) and attention ($p = 0.019$). Cortical thinning was observed in risk allele carriers at diverse sites across cortical lobes bilaterally at a threshold of $p < 0.01$, false discovery rate-corrected. Risk-allele carriers did not show any regions of reduced white matter volume.

Discussion: The ANK3 risk allele rs1938526 appears to be associated with general cognitive impairment and widespread cortical thinning in patients with FEP. These findings suggest that cognitive impairment and cortical thinning could be mechanisms through which ANK3 confers risk for psychotic illness, as observed in GWAS.

Poster #S134

IMPACT OF THE SCHIZOPHRENIA CANDIDATE GENE RGS4 ON PSYCHOSIS-PRONENESS

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Background: The dimensional view of schizophrenia suggests that schizotypal traits, which are present in the general population, are genetically related to schizophrenia. A number of studies have shown that schizotypy may reflect a spectrum of variation describing a predisposition to psychosis. Studies of endophenotypes, such as schizotypy and psychotic-like experiences, may thus facilitate the dissection of genetic components of schizophrenia.

Methods: The aim of the present study was to examine the candidate gene for schizophrenia RGS4 and its association with schizotypy (Wisconsin Schizotypy Scales) and psychotic-like experiences (Community Assessment of Psychic Experiences) in a sample of 547 healthy undergraduates from the Universitat Autònoma de Barcelona (UAB). Specifically, we analyzed 3 SNPs: rs951436, rs951439 and rs2661319.

Results: When we analyzed the association of the psychometric scores in relation to the RGS4 variability, we found significant association between the three polymorphisms analyzed and: i) the positive dimension of schizotypy (rs951436, $F=3.47$, $df=2$, $p=0.03$; rs951439, $F=3.74$, $df=2$, $p=0.02$) and ii) positive psychotic-like experiences (rs951436, $F=5.66$, $df=2$, $p=0.004$; rs2661319, $F=4.64$, $df=2$, $p=0.01$). The haplotypic analyses detected a risk haplotype for positive psychotic-like experiences.

Discussion: Our results extend the data reported in previous studies analysing these genes and psychosis proneness. According to our results, the implication of this gene in schizophrenia is still plausible. New analyses including psychometric variables not-autoevaluated, which are currently being collected in this sample, will be useful to confirm and discuss our results. Further genetic and molecular studies in new cohorts are needed to elucidate the role of these genes in psychosis and the validity of psychometric phenotypes.

Poster #S135

ANALYSIS OF NEURITIN1 GENE IN SCHIZOPHRENIA-SPECTRUM AND BIPOLAR DISORDERS: ITS INFLUENCE ON AGE AT ONSET AND COGNITIVE FUNCTIONING

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Background: Several studies have provided evidence for a substantial shared polygenic component between schizophrenia-spectrum disorders (SSD) and bipolar disorders (BPD) (Lee et al 2013). In the search for genetic factors related to these disorders, linkage data have shown the relationship between chromosome 6p25-p22 and both psychosis liability and intelligence (Straub et al 1995; Postuma et al 2005). This region includes the Neuritin-1 gene (NRN1), which is involved in neurodevelopment processes and synaptic plasticity. NRN1 expression is regulated by Brain-Derived Neurotrophic Factor (BDNF) (Karamoysyli et al 2008), which has been associated with age at onset of clinical symptoms and cognitive functioning in SSD (Numata et al 2006). We aimed to investigate the association of NRN1 with the risk for SSD and BPD and to explore its role in age at onset and cognitive functioning. We also tested the epistatic effects of NRN1 and BDNF on these phenotypes.

Methods: The sample consisted of 954 patients (49% schizophrenia, 27% bipolar disorder, 11% schizophreniform disorder, 8% schizoaffective disorder and 5% psychotic disorder NOS) and 715 healthy subjects. Age at onset was determined by means of the KSADS/CASH and/or the SOS inventory. The intelligence quotient (IQ) was estimated in 607 patients and 523 controls (WAIS-III/WISC-IV). Eleven SNPs in NRN1 and 1 in BDNF were genotyped using Taqman 5' exonuclease assays (NRN1: rs2208870, rs1233117, rs582186, rs645649, rs582262, rs3763180, rs10484320, rs4960155, rs9379002, rs9405890, rs1475157; BDNF: rs6265). The optimal set of NRN1 SNPs was selected by using SYSNPs. Hardy-Weinberg Equilibrium, Linkage Disequilibrium and Haplotypic Blocks were tested with HAPLOVIEW v4.1. The case-control genetic association analyses were conducted using UNPHASED v3.0.13. Plink 1.07 was used to test the association between NRN1 and: i) age at onset (adjusted by gender and diagnosis), ii) IQ (separately in SSD and BPD and adjusted by onset and months of evolution). Epistasis was analyzed using MB-MDR-3.0.3.

Results: The haplotype SNP4-SNPs (CC) was significantly associated to the risk for both SSD and BPD ($\chi^2 = 8.11$ $p = 0.0043$ OR (CI 95%) = 1.28 (1.08–1.51)). On the contrary, several 3 to 6-markers haplotypes including SNP6-SNP11 were related to a protective effect ($\chi^2 = 15.85$ $p = 6.864e-5$ OR (CI95%) = 0.08 (0.01–0.35)). The SNP2, SNP10 and the haplotype SNP9-11 (TCA) were related to age at onset ($b = -0.761$ $p = 0.032$, $b = 0.887$ $p = 0.020$, $b = 1.01$ $p = 0.021$, respectively). NRN1 was related with IQ scores only within SSD patients: the haplotype SNP6-SNP11 (GCTGCA) was associated with higher IQ scores ($b = 3.71$ $p = 0.035$). We finally found an epistatic effect between NRN1-SNP1 and BDNF on age at onset and IQ ($p = 0.001$ in both cases).

Discussion: Our findings suggest that NRN1 variability is a shared risk factor for both SSD and BPD and that it probably exerts its role by modifying the age at onset of these disorders. The association of NRN1 and IQ observed in SSD (and not in BPD nor in controls) may suggest a selective impact of NRN1 on intelligence in SSD. This result is in line with previous data showing the association of this gene with fluid intelligence deficits in schizophrenia (Chandler et al 2009). Finally, the epistasis between NRN1 and BDNF indicates the modulating effect of their interaction on age at onset and IQ scores. These results may contribute facilitating the heterogeneity of SSD and BPD.

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Poster #S136

RELATION OF RGS4 GENE WITH SCHIZOPHRENIA

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Background: RGS4 gene is one of schizophrenia candidate genes, which are figured to be related with schizophrenia after various association and linkage studies. The aim of this study is to genotype four of SNPs of RGS4 gene [SNP1 (rs10917670), SNP4 (rs951436), SNP7 (rs951439), SNP18 (rs2661319)] and to investigate the association of these determined genotypes with schizophrenia.

Methods: DNA samples, that had been extracted from two cc peripheral blood samples, were amplified via PCR by using specific primers. PCR products were shipped for sequence analysis. Outputs of the analysis were evaluated together with clinical symptoms.

Results: 100 patients and 52 control subjects were studied. As a result of χ^2 test for genotypes, p values are obtained as 0.12 for SNP1, 0.73 for SNP4, 0.10 for SNP7, and 0.14 for SNP18 ($p > 0.05$). P values for alleles were calculated as 0.057 for SNP1, 0.56 for SNP4, 0.06 for SNP7, and 0.066 for SNP18 ($p > 0.05$). In our study, it is indicated that there is no statistically significant association between four SNPs and schizophrenia.

Discussion: Although we can not be mentioned no significant difference in SNP allele and genotype distributions between patients and controls, p values of three SNPs (SNP1, SNP7, SNP18) was found very close to the specified range to achieve a significant result. If you increase the number of control and cases these data are likely to turn into a meaningful result. If done haplotype study with the data optained can be reached the definite conclusions.

Poster #S137

GENETIC VARIATIONS IN PREFRONTAL DOPAMINE: INFLUENCES ON SCHIZOTYPY AND COGNITION

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Background: Schizotypal traits are thought to lie on a continuum from a diagnosable mental illness (schizophrenia) to mental health. Unaffected biological relatives, sharing genetic risk, and individuals with high levels of schizotypy (e.g. unusual thoughts) are thought to lie in the middle of the spectrum. Cognitive deficits are a key feature of schizophrenia and also observed, to a lesser extent, in healthy individuals with schizotypal features. Dysregulation of dopaminergic neurotransmission is considered to play a central role in the pathophysiology of schizophrenia, as well as the cognitive deficits associated with this disorder. Dopamine D1 receptors are widespread throughout the cerebral cortex, particularly the prefrontal cortex (PFC - an area implicated in higher level cognitive abilities). Genetic polymorphisms in DRD1 are thought to affect the expression levels of the DRD1 and may influence the level of DRD1 stimulation in prefrontal regions, subsequently influencing cognition. The enzyme Catechol-O-Methyltransferase (COMT) also regulates dopamine activity in the PFC and the val(158)met polymorphism of the COMT gene predicts COMT activity. Here we explore the association of DRD1 and COMT polymorphisms in relation to schizotypy and cognitive performance in healthy adults.

Methods: 101 healthy volunteers (51% female) were assessed for schizotypy using the Oxford-Liverpool Inventory of Feelings (O-LIFE) and subscale scores were determined, which reflect the factors of schizophrenia (Unusual Experiences, Introvertive Anhedonia, Cognitive Disorganisation and Impulsive Nonconformity). Cognitive performance was assessed across working

memory (letter-number-span) and inhibition (STROOP). Participants were genotyped for the val(158)met polymorphism of the gene for COMT (rs4680 met/met, met/val, val/val) as well as rs 4532 on the DRD1 gene (CC, CT, TT).

Results: After corrections for multiple comparisons, ANOVAs revealed a significant main effect for DRD1 rs 4532 on Introvertive Anhedonia F(2,87)=4.612, p=0.012, $p_{\text{corr}}=0.096$.

Discussion: This research has shown that a polymorphism (rs4532) on the DRD1 gene shows an additive effect for increased scores on a schizotypy factor that resembles negative symptoms of schizophrenia. This finding extends previous research implicating the DRD1 SNP in treatment resistance and cognitive impairments in schizophrenia.

Poster #S138

SPATIO-TEMPORAL PROTEIN INTERACTION NETWORK DYNAMICS OF 16P11.2 GENES

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Background: Schizophrenia (SCZ) is a chronic devastating psychiatric disorder causing a major burden to the society. SCZ has a strong genetic component, and genomic Copy Number Variants (CNVs) are firmly implicated in SCZ. Recurrent CNV duplications of ~600 kb at chromosome 16p11.2 confer high susceptibility to SCZ. Moreover, both deletions and duplications of this CNV have been identified in patients with other psychiatric disorders such as autism, bipolar disorder and intellectual disability. Functional studies have shown that reciprocal deletion or duplication of 16p11.2 results in brain overgrowth or reduced brain volume in mice, respectively, and these results were further supported using zebra fish model. Recently, induced pluripotent stem cell technology is also starting to relate CNV deletions and duplications to cellular phenotypes in humans. Until now, most protein-protein interaction (PPI) network studies conducted on the CNV genes have been focused on static topological network properties. Yet, the dynamics of interactions of 16p11.2 genes throughout human brain development remains vastly unexplored.

Methods: To address this question, we integrated spatio-temporal brain transcriptome data from the BrainSpan database with 115 experimentally identified interactions of 33 proteins encoded by the 16p11.2 CNV genes. The expression profiles were divided into 20 combinations of anatomic brain regions and temporal brain developmental patterns. Four anatomic brain regions included prefrontal cortex (FC), temporal and parietal regions (TP), sensory-motor regions (SM), and subcortical regions (SC); and five stages of brain development included early fetal, mid-late fetal, infancy to childhood, adolescence and young adult. The expression Spearman correlation coefficient was calculated for all 16p11.2 interacting protein pairs.

Results: We observed that 16p11.2 PPIs distinctly clustered into three temporal general groups: fetal, childhood/adolescence, and young adult suggesting that different subnetworks may function during these three stages of brain development. When compared to co-expression patterns of background controls and randomly simulated genomic regions with the same number of genes and PPIs as 16p11.2, the prefrontal cortex, temporal and parietal brain regions in early fetal developmental stage were significantly depleted in co-expressed PPI pairs (cold-spots), whereas sensory-motor and parietal regions in adolescence stage were enriched in such pairs (hot-spots). Of note, the above patterns were not observed when the analysis was not restricted to physically interacting 16p11.2 pairs.

Discussion: Our study places 16p11.2 interactions into a spatio-temporal context and identifies dynamic subnetworks of interacting proteins at various stages of brain development and across different brain regions. Performing similar analysis using gene expression data from the brain regions of the patients carrying 16p11.2 duplications may help to identify protein interaction subnetworks that are relevant to schizophrenia.

Poster #S139**PLA2 GENE EXPRESSION IN FIRST EPISODE DRUG NAIVE PATIENTS**

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Background: Increased phospholipase A2 (PLA2) activity has been frequently reported in schizophrenia, whereas treatment with anti-psychotic drugs was found to reduce the enzyme activity to levels similar to those observed in control subjects. However the mechanisms underlying this reduction are not yet understood. The PLA2 family of enzymes is composed by three main groups: calcium-independent intra-cellular PLA2 (iPLA2), calcium-dependent secretory PLA2 (sPLA2) and calcium-dependent cytosolic PLA2 (cPLA2). To date, 27 genes and 2 pseudogenes have been identified as PLA2 subtypes at the NCBI Gene database. In the present study we evaluated in first episode, drug naïve schizophrenia patients and in healthy controls the mRNA expression of the iPLA2 and cPLA2 genes.

Methods: The sample comprised 9 first episode drug naïve patients with schizophrenia (DSM-IV, American Psychiatric Association) and 17 healthy controls. Peripheral blood was collected in Paxgene RNA tube and RNA was extracted with the recommended kit. Patients had their blood collected during first episode and after remission. RNA expression in peripheral blood was evaluated by qPCR. The reactions were carried out with Taqman gene expression assays in a Real Time PCR BIOER. Fluorescence data was used to calculate the quantification cycle (Cq). The Normalized Relative Quantification (NRQ) for each individual was obtained from the Cq to account for efficiency and loading discrepancies and the geometric averaging of multiple reference genes (TBP and GSTP1) was used to correct for inter reference variation. We used a non-parametric T test to access significant differences between first episode patients and healthy controls. Since only 4 patients had both samples collected so far, we opted to test for expression variations with a mixed effects models. All tests were performed with R statistical package version 3.0.2 with significance level of $p < 0.05$.

Results: The expressions of six genes for cPLA2 (PLA2G4A, PLA2G4C, PLA2G4B, PLA2G4D, PLA2G4E, PLA2G4F) and eleven genes for iPLA2 (PLA2G6, PLA2G7, PLA2G16, PNPLA1 to 8) were evaluated. Those genes with no amplification or with a Cq above 35 were excluded from further analysis. PLA2G4A, PLA2G4C, PLA2G6, PLA2G7, PLA2G16, PNPLA2, PNPLA4, PNPLA6 and PNPLA8 presented no significant difference between healthy controls and first episode patients. PNPLA1 was significantly higher in controls (1.145 ± 0.308) when compared to first episode patients (0.722 ± 0.280 ; $p=0.003$). The expression values of patients during first episode was not significantly different from those after remission. Not even for PNPLA1 (0.936 ± 0.300 ; $p=0.206$). PNPLA1 expression in patients after remission was also not significantly different from healthy controls ($p=0.270$). PLA2G4C and PNPLA8 gene expressions were significantly lower in remitted patients than in healthy controls.

Discussion: We observed here a difference in the expression of PNPLA1 in first episode patients compared with healthy controls. This difference disappeared with treatment. Also, treatment has significantly lowered the expression levels of PLA2G4C and PNPLA8 when compared to healthy controls. PNPLA1 and 8 are part of the iPLA2 subtype while PLA2G4C is a cPLA2. Our results suggest a complex role for gene expression in the modulation of PLA2 during antipsychotics treatment.

Poster #S140**THE INFLUENCE OF AHI1 VARIANTS ON THE DIAGNOSIS AND TREATMENT OUTCOME IN SCHIZOPHRENIA**

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Background: Genetic contribution for treatment outcome in schizophrenia

has been continuously suggested. Indeed, the effects of psychopharmacological treatments are mediated by biological processes, which are at least partially controlled by genetic factors. Genetic research in schizophrenia could therefore contribute to the prediction of treatment response and side effects in individual patients, thus leading to an optimization of treatment, and could help to better understand the mechanisms of the illness as well. The Abelson helper integration site-1 gene (AHI1), which is located on chromosome 6q23, encodes the protein Jouberin and is widely expressed in the brain. The mouse orthologue of Jouberin, AHI1, binds to huntingtin-associated protein 1 (Hap1) to form a stable protein complex in the brain that is important for maintaining the level of tyrosine kinase receptor B, which is critical for neuronal differentiation and brain development. In the present study, we focused on 4 single nucleotide polymorphisms (SNPs) within the AHI1 which could be potentially involved in the etiology of schizophrenia as well as in their treatment response.

Methods: Two hundred thirty-eight in-patients with schizophrenia and 170 psychiatrically healthy controls were genotyped for 4 AHI1 SNPs (rs11154801, rs7750586, rs9647635 and rs9321501). Baseline and clinical measures for schizophrenia patients were assessed through the Positive and Negative Symptoms Scale (PANSS). High-throughput genotyping using a pyrosequencer (Biotage AB, Sweden) was used for genotyping the four SNPs of AHI1. Haplovew 3.2 was used to generate a linkage disequilibrium (LD) map and to test for Hardy-Weinberg equilibrium. Allelic and genotypic frequencies in schizophrenia subjects were compared with those of controls using the χ^2 statistics. Repeated measures ANOVA were used to test possible influences of 4 SNPs on treatment response.

Results: All the considered SNPs were in HWE in the whole sample. Strong linkage disequilibrium was observed between all SNPs, particularly between rs7750586 and rs9647635, rs11154801 and rs9647635, rs11154801 and rs7750586. The rs11154801 C/C was significantly more represented in subjects with schizophrenia compared with controls. With regard to the allelic analysis, rs11154801 C was also significantly more presented in subjects with schizophrenia compared with controls. Further, a significant effect of this polymorphism on clinical improvement in schizophrenia patients was also detected.

Discussion: Our study provides a possible role of AHI1 gene variability in schizophrenia susceptibility and preliminarily suggests an association between AHI1 and clinical outcomes in schizophrenia patients. In particular, rs11154801 seems to be the most promising candidate polymorphism. However, further research is needed to confirm and extend our results including a higher number of SNPs covering larger portions of the gene and more homogeneous treatment of antipsychotics.

Poster #S141**ASSOCIATIONS BETWEEN POLYGENIC RISK SCORES FOR TYPE 2 DIABETES MELLITUS AND CO-MORBID DIABETES IN A SAMPLE OF SUBJECTS WITH SCHIZOPHRENIA, SCHIZOAFFECTIVE, OR BIPOLAR I DISORDERS**

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Background: Prevalence of co-morbid metabolic disorders, including Type 2 diabetes, is higher in schizophrenia and bipolar I disorders than in the general population. Multiple factors involving lifestyle, medical care, and antipsychotic medication may account for this finding. Increased genetic liability for diabetes mellitus in this population is another possibility, but this has not been consistently confirmed in the literature. In addition, diabetes has been correlated with changes in brain structure and function. This study compared polygenic risk scores for Type 2 diabetes, a measure of genetic risk, between psychiatrically healthy controls and probands with schizophrenia, schizoaffective disorder, or bipolar I disorders. It also eval-

uated whether these scores correlated with history of diabetes and total gray matter volumes in probands.

Methods: Subjects consisted of 354 individuals with schizophrenia, schizoaffective disorder, or psychotic bipolar I disorder, and 110 healthy controls enrolled in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study, on whom genomic, structural, and relevant clinical data were available. T1-weighted structural brain MRIs were collected on all subjects, and structural brain measurements were extracted using Freesurfer software. Subjects also provided self-reported medical histories, including history of diabetes mellitus. Genomic data was collected on subjects using the Illumina Human Omni1-Quad chip and BeadArray Platform. Genotypes were called and underwent quality control using a standardized protocol from Anderson et al (2010). Polygenic risk scores (PRS) for Type 2 diabetes were constructed using publicly available data from the DIAGRAM Consortium (Morris et al 2012; <http://diagram-consortium.org/>), selecting those SNPs with $p < 0.01$ for association with Type 2 diabetes (7,534 SNPs). The software program PLINK 1.07 was then used to calculate PRS for Type 2 Diabetes for each subject, using the following formula: the log of the odds ratio for each SNP was multiplied by the number of risk alleles carried by the individual (either 0, 1, or 2). The results for all SNPs were added and divided by the total number of SNPs to generate a PRS for each individual. PRS was then correlated with the self-reported history of diabetes mellitus in probands using a multivariate logistic regression model, with age, study site, and sex as co-variates. PRS was also compared between probands and healthy controls, using an ANCOVA with the same co-variates. Lastly, PRS was correlated with total gray matter volume in probands without diabetes mellitus, while co-varying for age, intracranial volume, site, and sex.

Results: Prevalence of self-reported diabetes mellitus was 2.7% among psychiatrically healthy controls and 10.2% among probands. PRS for Type 2 diabetes was associated with presence of diabetes mellitus among probands ($p < 0.05$). However, there was no significant difference in PRS between controls and probands ($p > 0.1$). PRS was inversely associated with total gray matter volume within non-diabetic probands ($p < 0.05$).

Discussion: PRS for Type 2 diabetes mellitus were associated with self-reported history of diabetes mellitus among probands, but PRS did not differ between probands and healthy controls, suggesting that overall genetic liability for Type 2 diabetes did not differ in the two groups. Limitations of this study were that medical histories were self-reported, and laboratory data was not available.

Poster #S142

GENETIC ASSOCIATION STUDIES OF SCHIZOPHRENIA RISK GENES WITH COGNITIVE AND NEUROIMAGING TRAITS IN THE GENUS CONSORTIUM COLLECTION

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Background: Recent GWAS have reliably identified genetic variants contributing to risk of schizophrenia (SCZ). However, their influence on brain function is unknown, hindering understanding of the neurobiological mechanisms underlying SCZ. The Genetics of Endophenotypes of Neurofunction to Understand Schizophrenia (GENUS) consortium aims to elucidate the disease role of SCZ risk genes by conducting genetic association analyses of brain abnormalities observed in SCZ. Data sharing across many samples will significantly amplify power to detect gene effects compared to individual samples. The main goals are to examine common genetic risk variants (independent and polygenic) identified by prior large-scale GWAS for association with cognitive and neuroanatomical measures, and to identify phenotypic profiles (i.e., trait clusters) associated with specific variants that may point to common neural mechanisms underlying the phenotypes.

Methods: Sample: Currently, 15 research groups worldwide have committed samples totaling ~10,000 SCZ cases, genetic high risk subjects, and controls with cognitive and/or neuroimaging (structural MRI, DTI) data. Phenotypes: Phenotypes for genetic analyses have been selected based on having high heritability and reliability, and consistent differences between SCZ and controls. Genotypes: Samples lacking genome-wide SNP data will be genotyped using the PsychChip array in early 2014. Genome-wide SNP data from all samples will be imputed using the 1000Genomes reference panel. Genetic homogeneity of the samples will be assessed via multi-

dimensional scaling. Known SNPs having prior GWAS evidence ($p < 5 \times 10^{-8}$) for association with SCZ risk, cognition, or neuroanatomical traits will be analyzed (currently ~130 SNPs). Using polygenic sets identified by prior GWAS, subsets of genes with shared features (e.g., biological function, regional and temporal brain expression) will be selected for analysis. Statistical analyses: Linear regression will test association between SNPs or polygene sets and the cognitive and neuroimaging phenotypes. Samples will be analyzed separately and results pooled by meta-analysis. Multivariate regression analysis across cognitive and neuroimaging domains will be used to identify phenotypic profiles associated with independent and polygenic risk variants.

Results: Protocols: Phenotype and genotype processing and quality assessment protocols are being developed to maximize comparability of neuroimaging and cognitive measures and genotype data across sites. A FreeSurfer-based pipeline has been developed for reprocessing scans and is currently being validated. Phenotypes: Literature review identified many cognitive and neuroanatomical traits having relatively high heritability ($h^2 > 0.6$). Cognitive tests/domains from the MATRICS battery that are present in the GENUS collection have been selected for genetic analyses (verbal and visual learning, attention/vigilance, processing speed, working memory, problem solving). Brain structures of primary interest include insula, superior temporal gyrus, medial temporal lobe, prefrontal cortex, and anterior cingulate (volume or cortical thickness).

Discussion: The GENUS consortium dataset is among the largest sample collections with neuropsychological and/or neuroimaging phenotypic data and genetic data (~10,000 SCZ, genetic high risk, and control subjects). Our planned association analyses of known SCZ risk variants and polygene sets with cognitive and neuroanatomical traits may contribute towards understanding the function of existing SCZ risk variants in specific neural processes that underlie SCZ pathophysiology.

Poster #S143

INTERACTIVE EFFECTS OF FKBP5 AND CHILDHOOD TRAUMA ON COGNITION IN SCHIZOPHRENIA

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Background: Childhood adversity is a significant risk factor for psychosis, and may influence genes regulating gluco-corticoid receptor activity, such as polymorphisms in the FK506 binding protein 5 (FKBP5) gene. Previous studies show that allele-specific methylation of the FKPB5 gene mediate functional interactions between specific polymorphisms and early life trauma, to increase the risk of stress-related psychiatric disorders. The aim of this research was to examine whether the effects of childhood adversity on executive function and symptoms in schizophrenia were moderated by two common FKBP5 polymorphisms (rs9470080 and rs1360780).

Methods: Participants were 617 clinical (SZ) cases with schizophrenia (n=526) or schizoaffective disorder (n=91) and 659 healthy controls. All participants completed the Childhood Adversity Questionnaire (CAQ), which was subject to an exploratory principal component analysis that identified 2 factors: (1) Emotional and Physical Abuse/Neglect and (2) Sexual abuse. Items contributing to Factor 1 were employed in focal analyses (owing to the small sample with high levels of sexual abuse and available genotyped data). Estimated premorbid IQ, and executive function were assessed with the Wechsler Test of Adult Reading (WTAR) and the Controlled Oral Word Association Test (COWAT), respectively; symptom levels were ascertained from items on the Diagnostic Interview for Psychosis. Hierarchical regressions were used to test the main effects of genotype and childhood adversity and their additive interactive effects on cognition and symptoms.

Results: For rs9470080 there were significant main effects of genotype and childhood adversity, and a significant interaction between FKPB5 and trauma on executive function in SZ cases, but not healthy controls. Post-hoc analyses identified lower cognitive performance in T-carriers of rs9470080, in the context of childhood adversity. There were no significant effects for FKPB5 rs1360780.

Discussion: The present findings of greater cognitive impairment in T-carriers of the FKPB5 rs9470080 polymorphism is consistent with previous studies, and suggests possible epigenetic modulation of the expression of the FKPB5 polymorphisms in association with early life adversity in SZ.

Poster #S144

NEURODEVELOPMENT GENES ARE DIFFERENTIALLY EXPRESSED IN BLOOD OF SUBJECTS AT ULTRA HIGH RISK (UHR) TO PSYCHOSIS COMPARED TO CONTROLS AND FIRST EPISODE OF PSYCHOSIS (FEP) PATIENTS

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Background: Schizophrenia (SCZ) is a complex and neurodevelopmental disease characterized by a dynamic interplay between multiple genes and environmental factors. The psychotic symptoms in SCZ usually manifest in the late adolescence and early adulthood causing an enormous burden of suffering and high morbidity. Thus, the investigation of subjects at Ultra High Risk (UHR) to develop psychosis and drug-naïve, first episode of psychosis patients (FEP) could be especially helpful to disentangle the biological underpinnings of disease development and onset. The aim of the present study was to analyze the expression in blood of 21 genes involved with neural functions in three groups: 1) control subjects (n=26); 2) UHR subjects (n=16); 3) antipsychotic-naïve FEP patients (n=27).

Methods: All subjects were under 27 years old. We used CAARMS criteria and SCID to identify subjects at UHR and FEP, respectively. After blood withdrawal, RNA was isolated and reverse-transcribed to cDNA. To verify gene expression we used Taqman Low Density Array technology, which assesses expression of 21 target genes plus two endogenous genes. We used deltaCT values to perform a multivariate General Linear Model (GLM) followed by Bonferroni post hoc test, and considered as significant p-values <0.05.

Results: We found three genes with differential expression in UHR group: UFD1L was upregulated in UHR compared to controls ($p=0.00002$) and FEP ($p=0.045$); DGCR2 ($p=0.0005$) and NDEL1 ($p=0.00001$) were down regulated in UHR compared to FEP. We were also able to observe moderate effect size for all three genes (GLM Eta Squared >0.2) and observed power >0.93 .

Discussion: UFD1L and DGCR2 genes are located on 22q11.2 region, previously associated to schizophrenia in several linkage studies. DGCR2 gene encodes a putative adhesion receptor protein, which is widely expressed with relatively high levels of expression in the developing nervous system. Some studies have already associated four polymorphisms within this gene with schizophrenia. Moreover, a study found that the expression of DGCR2 was elevated in the dorsolateral prefrontal cortex of schizophrenic patients relative to controls. The UFD1L gene encodes a protein that is involved in the degradation of ubiquitin fusion proteins. Ubiquitin-specific proteases are essential for regulating critical cellular pathways and overexpression or inhibition of these proteases results in programmed cell death. In addition, UFD1L polymorphisms were associated with schizophrenia in case-control and simplex families studies. Ndel1 oligopeptidase interacts with DISC1 (SCZ risk gene product) and mediates several functions related to neurite outgrowth and neuronal migration. Non-interaction of the DISC1/NDEL1 may determine disruption of key events (e.g., neurite outgrowth, neuronal migration) that are essential to the formation of normal brain structures. Recently, our group also verified that NDEL1 activity is reduced in SCZ patients compared to healthy controls. We were able to identify three genes with differential expression, correcting for multiple comparisons and with moderate effect size, in UHR subjects compared to controls and FEP patients. Since such genes were already involved in neurodevelopment and SCZ, we propose they may be involved in triggering of full psychosis. Further investigation on the role of these genes can help in the comprehension of risk to schizophrenia and conversion to first episode of psychosis.

Poster #S145

HEALTH-RELATED QUALITY OF LIFE OUTCOMES AMONG PATIENTS WITH SCHIZOPHRENIA: RESULTS FROM A LONG-TERM NATURALISTIC TRIAL OF PATIENTS SWITCHING TO LURASIDONE FROM OTHER ANTIPSYCHOTICS

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Background: Improvements in health-related quality of life (HRQoL) are associated with improved adherence to medications. In patients with schizophrenia, high adherence to antipsychotic medications may reduce relapse and rehospitalization rates. It is therefore important to ensure that HRQoL is maintained over a long period of time in patients with schizophrenia. Previous research showed that a 6-week core study of stable but symptomatic outpatients with schizophrenia who were switched from their current antipsychotic to lurasidone had significantly improved HRQoL following 6 weeks of therapy. Patients who completed this trial were enrolled in an open-label, flexible-dose, 24-week extension study. This analysis evaluated changes in HRQoL at 30-week for patients enrolled in the 6-week core study and continued on long-term treatment with lurasidone in the 24-week extension trial.

Methods: Stable but symptomatic outpatients with schizophrenia or schizoaffective disorder who completed the 6-week open-label switch study were initiated on the same dose of lurasidone in the 24-week extension study. Long-term changes in HRQoL were evaluated from baseline (BL) of the 6 week core study to extension study end point (Week 30; observed cases) using the Personal Evaluation of Transitions in Treatment (PETiT) scale. The PETiT is a validated 30-item instrument that measures self-reported overall HRQoL outcomes and two domain scores, psychosocial functioning (24 items) and adherence-related attitude (6 items), specifically among patients with schizophrenia. Four sub-domains measuring Activity (7 items), Cognitive (7 items), dysphoria (6 items) and social functioning (4 items) form the psychosocial domain. PETiT is assigned a rating of 2, 1, or 0, where 2 denotes positive change and 0 denotes negative change. Higher scores on the PETiT denote better HRQoL. Changes from baseline to 30-week study endpoint in PETiT total score (overall HRQoL) and domain scores (psychosocial functioning and adherence) were compared using ANCOVA with treatment as fixed effect, and baseline score and pooled site as covariates.

Results: Of the 198 patients who completed the 6-week core study, 148 entered the 24-week extension study and received the study medication. Of these, a total of 98 patients (65.8%) who completed the 24-week study and had available data on the PETiT were included in the current analysis. For all patients, the mean (SD) PETiT total BL score was 34.9 (9.3) and 39.1 (9.0) at the 30-week study endpoint, a statistically significant within-in group improvement of 5.1 (7.2) ($p<0.001$). Mean changes (SD) from baseline to 30-week study endpoint for the psychosocial functioning (3.8 [5.8]) domain was statistically significant, with significant improvements reported in activity (1.1 [2.6]), cognitive (1.3 [2.1]), dysphoria (1.2 [2.0]) subdomains. Mean changes (SD) from baseline to 30-week study endpoint for the adherence-related attitude (1.3 [2.5]) was also statistically significant ($p<0.001$).

Discussion: This post-hoc analysis indicates that patients switching from other antipsychotics to lurasidone show statistically significant improvements in overall HRQoL, psychosocial functioning, and adherence-related attitude at 30 weeks after the initial switch; with improvements in psychosocial functioning driven by improvements in activity, cognitive and dysphoria sub-domains. Switching stable but symptomatic patients with schizophrenia to lurasidone is therefore associated with a long-term improvement in HRQoL.

Poster #S146**ALEXITHYMIC AND EMOTION REGULATION STRATEGIES IN FIRST-DEGREE RELATIVES OF SCHIZOPHRENIA PATIENTS**

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Background: Schizophrenia has been associated with difficulties in emotion processing and regulation. Specifically, patients are less able to recognize and verbalize their feelings (alexithymia). It has been suggested, and some preliminary evidence presented, that such alexithymia, albeit less pronounced, may also be found in first-degree relatives of schizophrenia patients, suggesting that it may be part and parcel of a vulnerability for psychosis. We investigated this in a relatively large sample of relatives, which also allowed us to test a previous hypothesis that alexithymia would especially be present in male relatives.

Methods: We recruited 97 siblings (43 male, 54 female) of patients with schizophrenia (who also participated in the GROUP study of psychotic disorders) and 83 control subjects (40 male, 43 female) without a family history of psychotic disorders. Alexithymia was assessed with the Bermond-Vorst Alexithymia Scale (BVAQ); we also assessed previously defined emotion regulation strategies, suppression and reappraisal with the Emotion Regulation Questionnaire (ERQ).

Results: For the cognitive component of the BVAQ (which denotes difficulty identifying, analyzing and verbalizing feelings) there was a main effect of Group ($F=9.03$, $p=0.003$) and of Sex ($F=23.18$, $p<0.005$), with siblings and men scoring higher on alexithymia. There were no interaction effects. For Suppression subscale of the ERQ there was also a main effect of Group ($F=6.74$, $p=0.01$) and of Sex ($F=20.64$, $p<0.005$), with siblings and men using suppression to a stronger degree. There were no differences between groups for Reappraisal.

Discussion: Our results confirm that higher levels of alexithymia may be found in first-degree relatives of patients with schizophrenia as compared to control subjects and in men as compared to women. Accordingly, male siblings showed highest scores of all four groups. In addition to alexithymia, siblings and male subjects report a greater use of suppression as an emotion regulation strategy. Suppression has been shown to be nonoptimal for psychological and physical wellbeing. We suggest that the observed pattern of emotion regulation may contribute to risk for psychotic disorders, which is higher in siblings than in controls and higher in men than in women.

Poster #S147**EYE MOVEMENT ABNORMALITIES IN ADULTS WITH AN AT-RISK MENTAL STATE FOR PSYCHOSIS**

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Background: Abnormalities in eye movements are well known neurological findings in schizophrenia and also found in first-degree relatives [1]. We have previously found abnormalities of smooth pursuit eye movements (SPEM) in at-risk mental state (ARMS) for psychosis individuals [2]. In detail, the ARMS group had a significantly higher rate of correction saccades than healthy controls in a SPEM paradigm. The focus of our present study was to examine whether eye movement abnormalities differ between ARMS individuals who develop psychosis (ARMS-T) and ARMS who do not (ARMS-NT). We hypothesized that the ARMS-T have higher rates of correction saccades than the ARMS-NT group.

Methods: We investigated 18 ARMS-NT and 14 ARMS-T individuals as part of the Basel Früherkennung von Psychosen (FePsy; English: Early Detection of Psychosis) project [3,4] with Infrared oculography (IROG). Three different paradigms were used. During the saccade paradigm, subjects fixate a target and are instructed to make a saccade in the same direction of a stimulus. The anti-saccade paradigm requires subjects to fixate a target and make a saccade in the opposite direction of a stimulus. During the SPEM paradigm, patients have to visually follow slowly moving targets. Differences between the groups were examined using non-parametric Whitney-U tests.

Results: In contrast to our hypothesis, ARMS-T individuals did not show more correction saccades than ARMS-NT subjects during the SPEM paradigm (left gaze, $p=0.985$; right gaze, $p=0.745$). Neither did any significant group differences emerge during the saccade and anti-saccade paradigm.

Discussion: Although eye movement abnormalities have been observed in schizophrenia and in ARMS individuals, our results suggest that these do not appear to be of predictive value for the transition to psychosis. Accordingly, specific eye movement abnormalities such as SPEM appear to be associated with prodromal symptoms but not with the illness onset.

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Poster #S148**SOCIAL COGNITION, LANGUAGE, AND SOCIAL FUNCTIONING IN 7 YEAR OLD CHILDREN WITH FAMILIAL HIGH RISK FOR DEVELOPING SCHIZOPHRENIA SPECTRUM DISORDER OR BIPOLAR DISORDER. PART OF THE HIGH RISK AND RESILIENCE STUDY - VIA 7**

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Background: Schizophrenia and bipolar disorder are neurodevelopmental disorders with a multifactorial etiology. Both genetic and environmental factors are believed to contribute to the etiology of the two disorders, with substantial genetic influences. Social cognitive, language, and communicative impairments in familial high risk schizophrenia have been described in a few high risk studies, and with conflicting results. Some familial high risk studies and clinical high risk studies found that formal thought disorder predicted later onset psychosis. Familial high risk studies of offspring schizophrenia and bipolar disorder have found lowered social functioning compared to offspring of healthy parents. Whether social functioning deficits and possibly, social cognitive and language impairments could be risk markers for developing schizophrenia need further exploration. The main objective of this substudy is to characterize potential associations between children with familial high risk of developing schizophrenia or bipolar disorder and impairments in social functioning, social cognition (Theory of Mind, affect perception identification) and language (receptive and part of expressive). Hypothesis: 1) Children, with familial high risk for developing schizophrenia or bipolar disorder, will show social functioning deficits and social cognitive and language impairments compared to the control group. 2) The offspring of subjects with schizophrenia will have worse impairments in social cognition, language, and social functioning than the offspring of subjects with bipolar disorder. 3) Severity and chronicity of parental psychopathology, offspring's impulsivity, and the impairments of social cognition, language, and affects perception are significantly associated to current social functioning in SZ offspring. 4) Better social cognition is positively associated with better speed of information processing, verbal memory and verbal working memory in offspring of parents with schizophrenia and bipolar disorder and of healthy parents. Speed processing is a significant predictor of social cognitive functions, over and above the possible effects of verbal working memory and verbal memory.

Methods: We will establish a stratified cohort of 500 children, age 7, with one, two, or none parents with schizophrenia or bipolar disorder. The cohort will be drawn from the Danish Civil Registration System/Danish Psychiatric Central Register. Cohort 1: Children with two parents with schizophrenia (N=20) Cohort 2: Children with one parent with schizophrenia (N=180)

Cohort 3: Children with two parents with bipolar disorder (N=20) Cohort 4: Children with one parent with bipolar disorder (N=80) Cohort 5: Children with parents with no contact with the MHS ever (N=200) Cohort 1-4 will be matched to cohort 5 on age, gender, and urbanicity. Social cognitive functions will be assessed with Animated Triangles, Happés Strange Stories - Revised, and Emotion Recognition Task (CANTAB). Language will be assessed with Test for Reception of Grammar 2, and Children's Communication Checklist-II. Social functioning will be assessed with the Vineland Interview and the Social Responsiveness Scale.

Results: Data collection has started in December 2012 and is ongoing. By December 2013 we have included 149 families. Results will be available from 2015.

Poster #S149

DYSFUNCTIONAL EMOTION REGULATION AS A VULNERABILITY MARKER FOR PSYCHOSIS: THE TWINSSCAN CHINA STUDY

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Background: Individuals with psychosis have been found to engage in similar emotion regulation practices as those with mood and anxiety disorders. What remains unclear is whether these dysfunctional approaches arise as a reaction to the psychosis or are present before the onset of the disorder, thus potentially representing important vulnerability factors for psychosis. This pilot study aims to build on the existing literature through examining the relationship between psychosis proneness and two maladaptive forms of emotion regulation: rumination and emotion suppression. It is hypothesized that individuals with higher psychosis proneness scores will report ruminating more about a negative event as well as expressing less emotion in response to this event. To our knowledge, this is the first study to assess emotion regulation strategies using ESM (The Experienced Sampling method) in the normal Chinese population.

Methods: Pilot data were collected from 51 healthy Chinese adolescent participants (twin pairs = 22, individuals = 7) with no known history of mental disorder. Psychosis proneness was measured using the Community Assessment for Psychic Experiences: a 42-item questionnaire designed to measure the frequency and severity of psychotic-like experiences in the general population. Rumination and emotion suppression were measured using the Psymate, a pager-like device used for Experienced Sampling. Participants carried the Psymate for a mean of 5.8 days. Participants were asked daily to first think about the most negative event of the day. They were then asked to rate "I thought about it often" (rumination) and "I showed my emotions" (emotion suppression) on a 7-point likert scale.

Results: Multilevel regression analysis revealed rumination and emotion suppression to both significantly predict psychosis proneness (rumination: $b=0.11$, 95% CI = 0.020, 0.19, $p=0.017$; emotion suppression: $b=-0.12$, 95% CI = -0.21, -0.03, $p=0.009$). Supporting our hypothesis, individuals with higher psychosis proneness scores reported ruminating more after negative events and expressing less emotion than those participants with lower psychosis proneness scores.

Discussion: This pilot study provides insight into the relationship between psychosis proneness and dysfunctional emotion regulation strategies. Specifically, the findings show that rumination and emotion suppression may be present before the onset of the disorder, suggesting them as potential vulnerability markers for psychosis. These findings indicate that interventions aimed at changing emotion regulation strategies are likely to be beneficial for at risk individuals. Future research employing a longitudinal design would confirm these findings.

Poster #S150

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS DYSFUNCTION: AN EARLY MARKER OF PSYCHOSIS VULNERABILITY?

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Background: Abnormal hypothalamic-pituitary-adrenal (HPA) axis function, as indexed by elevated diurnal cortisol levels and a blunted cortisol awakening response (CAR), has been observed among patients with first-episode psychosis and also has been associated with neurocognitive deficits in this population. However, the extent to which HPA axis dysfunction precedes illness onset is currently unclear. Whilst elevated diurnal cortisol levels have been reported in samples of youth at ultra high-risk for psychosis, such elevations may relate to distress associated with emerging illness and might also be influenced by psychotropic medication. Furthermore, studies of high-risk individuals with a family history of illness have typically included adult relatives who have passed the peak age of illness onset. As yet, no study of high-risk youth has examined the CAR or the extent to which HPA axis dysfunction is associated with neurocognitive performance. The current study aimed to determine whether children at putatively elevated risk for schizophrenia who present psychotic-like experiences and other antecedents of schizophrenia (ASz) and high-risk children with a family history of illness (FHx) are characterised by abnormal HPA axis function relative to their typically-developing (TD) peers. A further aim was to examine associations between HPA axis function and performance on tasks of memory and executive function among ASz and FHx children.

Methods: Thirty-three ASz children, 20 FHx children, and 40 TD children were identified at age 9-12 years using a novel community-based screening procedure or as relatives of individuals with schizophrenia. All participants were antipsychotic-naïve and not currently seeking treatment for their symptoms. At age 11-14 years, participants provided salivary cortisol samples and completed measures assessing memory and executive function.

Results: FHx children, but not ASz children, were characterised by a blunted CAR relative to their TD peers ($d=0.73$, $p=0.01$); post-hoc tests indicated that the magnitude of differences between FHx children and TD children was twice as large among FHx children with a first-degree relative with schizophrenia ($d=-1.09$, $p=0.005$) compared to those with an affected second-degree relative ($d=-0.50$, $p=0.14$). Neither FHx nor ASz children were characterised by elevated diurnal cortisol. Among both FHx and ASz children, more abnormal HPA axis function (that is, higher diurnal cortisol levels and greater blunting of the CAR) was associated with poorer performance on tests of verbal memory and executive function.

Discussion: These findings support the notion that at least some HPA axis changes precede illness onset, rather than being a subsequent epiphomenon, and may participate in the development of neurocognitive abnormalities. We speculate that the blunted CAR may constitute an early (potentially genetically-mediated) marker of psychosis vulnerability, whilst elevated diurnal cortisol levels may not emerge until closer to disease onset. Interventions aimed at helping at-risk youth to cope more effectively with psychosocial stress might prevent the development of further HPA axis abnormalities.

Poster #S151

NEUROCOGNITIVE PROFILES IN 7-YEAR-OLD OFFSPRING OF PARENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER. PART OF THE HIGH RISK AND RESILIENCE STUDY - VIA 7

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Background: Schizophrenia and bipolar disorder are serious neurodevelopmental disorders with a multifactorial etiology of interacting genetic and environmental factors. Longitudinal high-risk studies and birth cohort

studies have reported, that offspring at genetic high risk for developing schizophrenia or bipolar disorder compared to children of parents without these disorders show delayed neuromotor development, language acquisition deficits, emotional problems, impaired social function, and cognitive deficits regarding general intelligence, processing speed, executive functions, memory, and attention. The aim of this sub study is to characterize the neurocognitive profiles of two groups of children at genetic high risk for developing schizophrenia spectrum psychosis or bipolar disorder. The neurocognitive domains are: Intelligence, memory, attention, processing speed, executive functions, and decision making. Hypotheses: 1) Children at genetic high risk for schizophrenia or bipolar disorder will display a broad array of cognitive deficits compared to children of parents without these disorders. 2) Children at genetic high risk for schizophrenia will show more severe neurocognitive impairments in general intelligence, processing speed, memory, attention, set shifting, planning and working memory compared to children at genetic high risk for bipolar disorder. 3) Children at genetic high risk for bipolar disorder will display more severe neurocognitive deficits in decision making (considered to be influenced by emotions) compared to children at genetic high risk for schizophrenia.

Methods: We will establish a stratified cohort of 500 children aged 7 with 0, 1 or 2 parents with schizophrenia spectrum psychosis or bipolar disorder and matched on age, gender, and urbanicity. A comprehensive neuropsychological test battery is used to characterize the following neurocognitive domains in all subgroups: Intelligence (Reynolds Intellectual Screening Test), verbal memory (Test of Memory and Learning, second edition), visual memory (Rey Complex Figure Test and Cambridge Neuropsychological Test Automated Battery (CANTAB)), attention (CANTAB and Theory of Visual Attention-based Whole Report), processing speed (Delis-Kaplan Executive Function System (D-KEFS) and Wechsler Intelligence Scale for Children, Fourth edition WISC-IV)), and executive functions including set shifting, planning, verbal fluency, and working memory (CANTAB, D-KEFS, and WISC-IV).

Results: Data collection has started December 2012 and is ongoing. 150 probands and their parents are included by December 2013. Results will be available in 2015.

Discussion: Results will be available in 2015.

Poster #S152

PSYCHOSIS RISK IN ADOLESCENCE: CLINICAL BASELINE DIFFERENCES BETWEEN PRODROMAL AND FAMILIAL HIGH RISK SAMPLES

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Background: Initial studies aimed at understanding psychosis risk focused on offspring of psychotic patients, reporting an estimated lifetime risk of psychosis of approximately 10-15%. Recent approaches have centered on Psychosis Risk Syndrome (PRS), defined by 1) attenuated positive symptoms; 2) brief, limited, intermittent psychotic symptoms or 3) genetic risk for psychosis combined with deterioration in functioning [Fusar-Poli P 2012], yielding 1-year transition rates ranging between 9-70% [Ziermans TB 2011]. To our knowledge no study to date has directly compared the two approaches. The transition to psychosis has been related with baseline and subsequent decline of Global Assessment of Functioning (GAF) scores [Velthorst E 2013], schizotypal traits, clinical symptoms and substance misuse. Although offspring studies have focused on children and adolescents, PRS studies have mostly been undertaken in adult samples. The aim of this study was to investigate baseline differences in clinical symptomatology, diagnosis and GAF between adolescents at familial risk of psychosis (GHR), adolescents with PRS and a gender and age matched community control group (CC).

Methods: GHR (N=22): Adolescent offspring of patients with a psychotic disorder were recruited through adult mental health services. PRS (N=23): Adolescents meeting prodromal criteria according to the Structured Inter-

view for Prodromal Syndromes (SIPS) were recruited through primary care and child and adolescent mental health services. CC (N=30) were recruited from the same geographic area through schools and adverts. Assessment of socio-demographic data and clinical diagnoses (DSM-IV; Kiddie-Schedule for Affective Disorders and Schizophrenia/K-SADS) was undertaken by experienced child and adolescent psychiatrists and psychologists. In addition, depressive (Hamilton Rating Scale of Depression/HRSD), manic (Young Scale of Mania/YSM), attenuated psychotic symptoms (SOPS), and GAF were also evaluated.

Results: A total of 75 subjects (50,7% female) aged 12-17 ($15,09 \pm 1,78$) were included. No differences were found in age or gender between groups. There were significant differences in rates of overall lifetime diagnoses: 95,2% for PRS, 59,1% for GHR and 20% for CC ($p=0,005$) and in externalizing disorders (55%, 18,2% and 0% respectively; $p=0,015$). Only PRS showed significantly higher rates of affective and anxiety disorders (>50%; $p=0,013$) relative to the other groups (both <20%). PRS subjects also had a significantly higher prevalence of substance use (47,80%; $p=0,035$) in comparison to the other groups (GHR:18,20%; CC:13,30%); mainly for alcohol (36,4%, 4,5% and 10%, respectively; $p=0,009$), but also for cannabis (non-significant trend). PRS had a significantly higher score in the HRSD ($13,54 \pm 7,12$; $F=57,921$; $p<0,001$), YSM ($4,32 \pm 3,6$; $F=17,48$; $p<0,001$) and SOPS ($38,3 \pm 10,70$; $F=154,96$; $p<0,001$) scales; but no statistical differences were found between the GHR and CC groups. PRS group had the worst global functioning (GAF: $47,9 \pm 11,69$; $F=105,411$; $p<0,001$) in comparison to both GHR ($80,94 \pm 10,4$) and CC ($82,20 \pm 6,95$).

Discussion: This study illustrates differences in severity of clinical symptoms, axis-I co-morbidity and substance use prevalence in two different adolescent psychosis risk groups relative to community controls. Longitudinal follow-up of this sample will allow to identify baseline characteristics predictive of transition to psychosis. Further studies in high risk adolescents are warranted in order to fully characterise psychosis risk status during this age period.

Poster #S153

CLINICAL AND FUNCTIONAL COURSE OF YOUTHS AT ULTRA-HIGH RISK FOR PSYCHOSIS: OUTCOMES OF NON-CONVERTERS IN JAPAN

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Background: While At-Risk Mental State (ARMS) was essentially conceptualized to predict future development of psychosis, previous ARMS research has been known to include a considerable proportion of non-converters. When delivering clinical services to ARMS individuals, however, there is a need to provide treatment suitable for non-converters as well as converters. However, reported rates of non-converters vary among studies, and their nature has not yet been sufficiently elucidated, especially in non-Western countries. In this study, we conducted an exploratory examination of the clinical course and features of non-converted ARMS in our specialized clinic in Japan.

Methods: Youths at ultra-high risk (UHR) for psychosis (N=106; mean age, 20 years; male, 40%) were recruited for this study; each was followed up with naturalistic treatment at a specialized clinic for early psychosis in Japan, and therapeutic sessions were continued according to individual needs. In the first three years after intake, participants who had not developed psychosis were regularly re-evaluated using the Comprehensive Assessment of ARMS (CAARMS) and Global Assessment of Functioning (GAF) to ascertain whether they met UHR criteria. In order to examine severity of functional impairment and subjective depression of non-converters, Social and Occupational Functioning (SOFAS) and Beck Depression Inventory (BDI) scores at Year 1 were compared among three groups: (1) those who were remitted from ARMS, (2) those who met ARMS criteria, and (3) those who converted to psychosis.

Results: Participants were followed up for 2.4 years on average. Out of 106 participants, 7 converted to full-blown psychosis at 6 months, 10 at 12, 13 at 24, and 14 at 36 months. Except for these, 73, 65, 39, and 27 participants, respectively, had continued to receive treatment and could be re-evaluated at each point, and 36 (49%), 19 (29%), 7 (18), and 3 (11%) met UHR criteria. SOFAS scores of the three groups at Year 1 were 62.5 ± 12.2 , 56.3 ± 12.9 , and 55.6 ± 13.3 , respectively, while BDI scores were 17.8 ± 11.8 , 23.3 ± 15.8 , and 19.5 ± 12.8 , respectively. An ANOVA revealed that neither SOFAS nor BDI scores significantly differed among the three groups.

Discussion: A simple comparison of the results with those obtained in previous studies is difficult because of the high cessation rate in this study; quite a few participants showed improvement from a state of high risk for psychosis. This may partly be because we tried to offer the best available interventions, including cognitive behavioral therapy and antipsychotic therapy. The results would encourage both ARMS youths and therapists in having an optimistic attitude toward prognoses. However, ARMS individuals were found to continue suffering from functional impairment and subjective distress, regardless of whether they had developed psychosis. Therefore, we need to keep in mind that some of these individuals may need on-going support, beyond treatment of their ARMS symptoms.

Poster #S154

EMOTIONAL DYSREGULATION, ATTRIBUTIONAL BIAS, NEUROCOGNITIVE IMPAIRMENT IN ULTRA-HIGH RISK FOR PSYCHOSIS AND SCHIZOPHRENIA: IT'S ASSOCIATION WITH PARANOIA

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Background: Paranoia is a complex phenomenon, affected by a number of factors. The emotional dysregulation, attributional bias, and neurocognitive deficits were reported to be associated with paranoia in schizophrenia. The aim of this study was to explore whether paranoia is associated with emotional dysregulation, attributional bias and neurocognitive impairment in both UHR for psychosis and schizophrenia patients.

Methods: 101 normal controls, 50 participants at UHR for psychosis, and 49 schizophrenia patients were recruited. All subjects were asked to complete self-reported paranoia scale and emotional dysregulation scales including Rosenberg's self-esteem, Spielberg's state-trait anxiety inventory and Beck depression inventory. The attributional style was assessed by Ambiguous Intentions Hostility Questionnaire (AIHQ). Participants were also requested to complete the comprehensive neurocognitive battery.

Results: Enhanced paranoia was found in both ultra-high risk for psychosis and schizophrenia groups. Multiple linear regression analysis showed that paranoia were found to be associated with emotional dysregulation (state anxiety, trait anxiety and depression), composite blaming bias in ambiguous situation, attention and working memory in whole participants [$F(14,185) = 22.8$, $p < 0.001$, adjusted $R^2=0.61$].

Discussion: The main findings suggest that paranoia is a complex affective and cognitive structure that may be associated with emotional dysregulation blaming attributional bias and attention and working memory impairment in clinical and non-clinical paranoia.

Poster #S155

PREDICTION OF PSYCHOPATHOLOGY AND FUNCTIONAL IMPAIRMENT BY POSITIVE AND NEGATIVE SCHIZOTYPY IN THE CHAPMANS' TEN-YEAR LONGITUDINAL STUDY

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Background: Schizotypy provides a unifying construct for understanding the development and expression of schizophrenic psychopathology. Schizotypy and schizophrenia share a common multidimensional structure that includes positive and negative symptom dimensions. The present study examined the predictive validity of psychometrically assessed positive and negative schizotypy in the Chapmans' ten-year longitudinal data set. Recent

cross-sectional studies have supported the validity of psychometric positive and negative schizotypy; however, the present study is the first to examine the predictive validity of these dimensions. The Chapmans' longitudinal data provided an ideal opportunity because of the large sample size, high reassessment rate, and extended interval between assessments.

Methods: A total of 534 psychometric high-risk and control participants were initially assessed, and 95% of this sample was re-interviewed ten years later.

Results: As hypothesized, positive and negative schizotypy uniquely predicted the development of schizophrenia-spectrum disorders, and positive schizotypy predicted the development of psychotic disorders. At the re-assessment, both positive and negative schizotypy predicted psychotic-like, schizotypal, and paranoid symptoms, as well as poorer adjustment. The positive dimension was associated with mood and substance use disorders, and mental health treatment. Negative schizotypy was associated with schizoid symptoms and social impairment at the follow-up.

Discussion: The results extend the growing validity findings for psychometrically assessed positive and negative schizotypy by demonstrating that they are associated with the development of differential patterns of symptoms and impairment. Schizotypy, and by extension schizophrenia, are multidimensional and clear operationalization and measurement of these dimensions are needed. Psychometric assessment provides a valuable and inexpensive method for identifying schizophrenia-spectrum psychopathology.

Poster #S156

SPEECH ILLUSION, PERCEIVED SOCIAL STANDING AND SELF-ESTEEM IN PSYCHOSIS PRONENESS: THE TWINSSCAN CHINA STUDY

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Background: Psychosis proneness refers to psychotic events experienced at sub-threshold level, and can be regarded as representing one part of the continuum that extends from normal daily experiences to clinical symptoms. Poor social cognition and low self-esteem are identified predictors of schizophrenia and possibly psychosis proneness. In light of this, the current study aimed to verify the predictive power of self-esteem, perceived social standing and speech illusion on psychosis proneness in a Chinese population and to verify the relationship between the three. It was hypothesized that self-esteem mediates the effect of perceived social standing on psychosis proneness.

Methods: 100 Chinese participants aged 15 to 21 were recruited in Beijing and Hong Kong (52 males, Mean age = 18.92, SD = 2.05). All participants were healthy without existing significant medical condition or mental illnesses and underwent a procedure that included three self-report questionnaires and a computerized task. More specifically, the Community Assessment of Psychic Experiences (CAPE) was administered to measure the frequency and distress of positive, negative and depressive symptoms (psychosis proneness). The Rosenberg Self-Esteem Scale (RSES) was used to measure individual's self-esteem. All 10 items were rated on a four-point scale in which a higher score reflected a higher global self-esteem. The Social Comparison Scale (SCS) measured relative social standing using a semantic differential methodology on 11 bipolar constructs. Finally, speech illusion was assessed by the White Noise Task (Galdos et al. (2011)). In this task sentences were embedded in white noise to compose three types of stimuli (i) noise, (ii) clearly audible sentence and (iii) barely audible sentences. Participants responded by indicating them as (1) positive, (2) negative, (3) neutral, (4) no speech, or (5) uncertain for each of the 75 recordings.

Results: Participants showed more negative and depressive psychotic symptoms than positive symptoms in general. Low self-esteem and low perceived social standing predicted higher psychosis proneness, more negative and depressive symptoms (self-esteem: all $p < 0.001$; perceived social standing: $p = 0.027$, 0.005, 0.001). Further, the effect of perceived social standing on psychosis proneness was completely mediated through self-esteem ($p < 0.001$). Nevertheless, no significant correlation was found between speech illusion with other variables.

Discussion: The results suggest that low self-esteem and perceived social standing are possible risk indicators of psychosis. The complete mediating

effect of self-esteem on the association between perceived social standing and psychosis proneness suggests that poor self-judgments based on internalized social information may intensify one's vulnerability in developing psychosis. Self-esteem and perceived social standing may add to the list of cognitive markers of psychosis identified so that at-risk individuals could be identified more effectively in the pre-morbid stage.

Poster #S157

THE COURSE OF NEUROCOGNITIVE FUNCTIONING IN HELPSEEKING INDIVIDUALS: COMPARISON OF RISK FOR PSYCHOSIS AND BIPOLAR DISORDER CRITERIA

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Background: Neurocognitive deficits are important aspects of the schizophrenic disorder because they have a strong impact on social and vocational outcomes. There is widespread agreement that such developmental deficits are evident in schizophrenia, and some research even suggests that the cognitive abilities progressively deteriorate before and after the illness onset. However, recent research controversially observes continuous or even improving performance in schizophrenic subjects or individuals at risk for psychosis. The objective of this longitudinal study was to examine the neurocognitive functioning of help seeking individuals meeting basic symptoms criteria (BS) or Ultra-High-Risk (UHR) criteria for schizophrenic psychosis or risk criteria for affective psychosis (at-risk bip). Progression of cognitive functioning in individuals who developed a psychosis was compared to that of at risk individuals who did not develop psychosis during the follow-up period.

Methods: Data were available from 85 study participants who completed neurocognitive and clinical assessments at baseline and, on average, 13.02 months later. During the follow-up period 11 of the participants converted to schizophrenic, and 4 to affective psychosis. Neurocognitive measures of a comprehensive test battery were grouped according to their load in factor analysis into five cognitive domains labeled as speed, attention, working memory, learning and memory, fluency and executive function.

Results: Across all cognitive domains neurocognitive functioning of BS, UHR and at-risk bip individuals improved significantly over time. However, those subjects who converted to manifest psychosis displayed a stable neurocognitive profile from baseline to follow-up. Compared to non-converters they demonstrated already at the time of the baseline examination a significantly lower level performance than the non-converters.

Discussion: In our data no evidence of progressive cognitive decline associated with psychotic vulnerability could be observed. In line with the neurodevelopmental model our findings suggest that cognitive deficits are present very early, already before or during the prodromal stage of the illness.

Poster #S158

CANNABIS USE AND NEUROPSYCHOLOGICAL FUNCTIONING IN ULTRA-HIGH RISK FOR DEVELOPING PSYCHOSIS IN CHILD AND ADOLESCENT PATIENTS AND HEALTHY CONTROLS

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Background: There is evidence in the literature of the association of cannabis use and psychosis as well as cannabis use and neurocognition. Numerous studies have investigated the cognitive effects of cannabis use in patients with psychosis but little is known about the impact of cannabis use in cognition of patients at risk for psychosis, or, what is the same, with Psychosis Risk Syndrome (PRS). Some studies have observed more neuropsychological dysfunction in cannabis-users patients at risk for psychosis (PRS+) than in non cannabis users patients at risk (PRS-). The aim of this study is to investigate the relationship between cannabis use, high-risk symptoms and cognitive performance.

Methods: A prospective longitudinal study with PRS help-seekers patients and healthy controls (HC) of child and adolescent population (age 10-17), recruited from the Child and Adolescent Psychiatry and Psychology departments of Hospital Clinic and Hospital Sant Joan de Déu (Barcelona, Spain). Inclusion criteria were: 1) Attenuated positive or negative symptoms in the previous 12 months; 2) Brief intermittent psychotic symptoms; 3) First or second degree relative with schizophrenia or schizotypal disorder plus impairment of functioning. Exclusion criteria: IQ<70 and a diagnosis of neurodevelopmental disorder. The Semistructured Interview for Prodromal Syndromes and Scale of Prodromal Symptoms (SIPS/SOPS) were administered to assess prodromal symptoms. Any time of CNN use was considered as lifetime CNN use. Neurocognitive battery was used to assess cognitive performance in general intelligence, learning and verbal memory, visual memory, speed processing, visuospatial abilities, working memory, attention and executive functions. The same assessment was performed in the HC sample. Data analysis was executed using SPSS 19.0 package.

Results: A total sample of 66 child and adolescent was included (46 PRS and 20 HC). Four groups were created: HC with cannabis use (HC+: n= 6, age 15,33 range 14-17, 16,7% male), HC non users (n=14, age 14,88 range 12-17, 21,4%male), PRS users (PRS+: n=10, age 16,3 range 16-17, 30%male) and PRS non users (PRS-: n=36, age 14,83 range 11-17, 41,7%male). Two groups of analysis were performed. Firstly, we analyze the difference in neuropsychological performance of the two sample groups (PRS and HC) depending on using or not CNN. No differences were found between HC+ and HC-. Likewise, no differences were founded between PRS+ and PRS-. Afterwards, we analyzed the difference between PRS+ and HC+. The PRS+ group show significant worse performance in specific domains of working memory (digit span: p= 0,032; letter-number span: p=0,018), verbal memory (Test of Memory and Learning, Immediate verbal memory: p=0,069; and late verbal memory: p= 0,036), and executive functioning (Wisconsin Sorting Test Card. Perseverations: p=0,017; preservative errors: p= 0,033) compared to HC+ group. The most important limitation of the study was the small size of the sample. We need to recruit more patients to report more data.

Discussion: Up to date, there are no differences in cognitive performance between children and adolescents at risk for psychosis depending on the cannabis use. On the other hand, children and adolescent at risk for psychosis using CNN show worse cognitive performance than HC using CNN in specific domains of verbal memory and learning, working memory and executive function.

Poster #S159

FUNCTIONAL IMPAIRMENT IN CHILDREN AND ADOLESCENTS WITH PSYCHOSIS RISK SYNDROME: SOCIAL AND ROLE FUNCTIONING COMPARED WITH CONTROLS AND RELATIONSHIPS TO PRODROMAL SYMPTOMS

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Background: Substantial functional impairment occurs early in the course

of psychosis and likely sets the stage for later social and occupational dysfunction (Malla&Payne, 2005; Cronblatt et al., 2012). Although adolescence is a critical developmental period in which social and role skills crystallize, few previous studies of prodromal phase or psychosis risk syndrome (PRS) include young adolescents. Objective: To study the functional characteristics of a sample of adolescents with PRS by: (1) comparing their social and role functioning with an age and gender matched healthy controls (HC) and (2) examining its clinical and cognitive correlates.

Methods: Sample included 37 PRS subjects (15.5 ± 1.6 years, 41% males) and 19 HC (15 ± 1.3 years, 21% males) from a prospective longitudinal study including help-seeking subjects who met PRS criteria (Child and Adolescent Psychiatry and Psychology departments of Hospital Clínic and Sant Joan de Déu, Barcelona, Spain). Inclusion criteria: age 10-17 years, meeting criteria for 1) attenuated positive or negative symptoms in the previous 12 months, 2) brief intermittent psychotic symptoms, 3) first or second degree relative with schizophrenia or schizotypal disorder plus impairment of functioning. Exclusion criteria: IQ < 70 and a diagnosis of neurodevelopmental disorder. For HC subjects, exclusion criteria were having 1st or 2nd degree familiar with a psychotic disorder; a diagnosis of neurodevelopmental disorder and/or IQ < 70. The Semistructured Interview for Prodromal Syndromes and Scale of Prodromal Symptoms (SIPS/SOPS) were administered. The Social and Role Functioning Scales (GF:S and GF:R) (Cornblatt et al., 2007) were also administered along with a clinical (K-SADS-PL) and a cognitive evaluation. The GF:S and GF:R are two measures of functioning specifically designed to address functioning in the prodromal phase of the illness. For both scales, scores range from 1 to 10, with 10 indicating superior functioning and 1 representing extreme dysfunction, with 7 as a cut-off point distinguishing subjects with poor to moderately poor functioning (scores between 1-6) and scores of 7-10 reflecting good functioning (Cornblatt et al., 2012).

Results: PRS and HC subjects did not significantly differ in age ($t=1.03$, $p=0.308$) and sex ($\chi^2=2.13$, $p=0.145$). PRS subjects showed lower social functioning scores than HC (6.19 ± 1.33 vs 8.79 ± 0.53 , $p < 0.001$) and worse role functioning (5.32 ± 1.11 vs 8.05 ± 0.71 , $p < 0.001$). A 37.8% of PRS subjects showed a poor to moderately poor social functioning (HC: 0%) and a 35.1% a poor to moderately poor role functioning (HC: 0%). Current social functioning of the PRS subjects were negatively correlated with the negative SOPS subscale scores ($r=-0.412$, $p=0.017$) and with the SOPS total score ($r=-0.412$, $p=0.017$), independently from IQ, global cognitive score and number of current K-SADS diagnostics (partial correlations GF:S with SOPS negative subscale: $rp=-0.458$, $p=0.032$; with SOPS total score: $rp=-0.435$, $p=0.043$). No significant correlates were found with role functioning.

Discussion: Adolescents meeting criteria for PRS showed social deficits and an impaired age-appropriate role functioning compared with controls. Poor social functioning but not role difficulties was related to negative and total prodromal symptoms, independently from other cognitive and clinical factors. These findings are consistent with the increasing emphasis on functional deficit decline as a critically important characteristic of prodromal phase of the illness (Cornblatt et al., 2012) and highlight the importance of early intervention in order to limit current and future functional disability.

Poster #S160

REVIEW OF FALSE NEGATIVES WITH THE COMPREHENSIVE ASSESSMENT OF AT RISK MENTAL STATE (CAARMS) SCREENING

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Background: The CAARMS has been used as a diagnostic tool in the Support for Wellness Achievement Programme (SWAP), which was initiated in March 2008 to treat individuals aged 16-30, with At Risk Mental State (ARMS) in Singapore. This descriptive study evaluates the number of individuals referred to SWAP, who were not correctly identified (false negatives) as having ARMS who subsequently developed a psychotic disorder. The sensitivity of CAARMS in predicting psychosis is 83%. Therefore, understanding the factors that lead to a false negative detection of ARMS will aid in improving this screening process and correctly identifying those at risk.

Methods: All individuals referred to SWAP were screened using the

CAARMS and functioning was assessed using the Social and Occupational Functioning Assessment Scale (SOFAS). Sociodemographic data was collected using a semi-structured questionnaire. False negatives on the CAARMS were identified and a review of the medical case notes was done to identify factors that contributed to a failure of identification of ARMS. Diagnosis upon conversion to psychosis was assessed using the Structured Clinical Interview for DSM IV (SCID).

Results: 510 clients were screened and 10 clients were found to be false negative subsequently, on converting to psychosis. Factors such as age, gender, education and assessing psychiatrist had not influenced the CAARMS negative status. The 10 clients were aged from 19 to 30 years (mean: 22.8). In 5 clients, the presence of comorbid disorders such as Asperger's Syndrome, alcohol dependence, computer addiction and borderline or mild intellectual disability appear to have clouded the presentation in addition to a lack of attenuated psychotic symptoms (APS). However, there was a poor baseline or decline in functioning although this was attributed to the comorbidity during the assessments. One of these clients with borderline intellectual disability had no decline in functioning or APS but had a history of Schizophrenia in his parents and this client was subsequently diagnosed with Schizophrenia. Two clients had APS and Brief Limited Intermittent Psychotic Symptoms (BLIPS) but were deemed to be negative on CAARMS as there was no functional decline. In 1 client, there was a lack of attenuated psychotic symptoms and the functional decline was attributed to major interpersonal family conflicts. In the remaining 2 clients, there was no APS, BLIPS or functional decline. Out of the 10 clients, 6 were subsequently diagnosed with Schizophrenia, 1 with Schizoaffective Disorder, 1 with Bipolar Disorder, mania with psychotic symptoms and 2 with Psychosis Not Otherwise Specified.

Discussion: The above findings indicate that comorbidity (5/10) often clouds the presentation of ARMS through its symptomatology and effect on functioning which may lead to a false negative finding on CAARMS. Although functional decline in the absence of clear attenuated symptoms (1/10) and BLIPS/APS in the absence of functional decline (2/10) do not fulfill criteria for CAARMS, we may need to monitor these clients closely particularly as the BLIPS subgroup is at highest risk of conversion. This reflects that intact functioning may mask underlying symptoms in the early phase of the prodrome. Therefore although the CAARMS is fairly effective in identifying ARMS, clients that do not meet the criteria may still need to be monitored closely.

Poster #S161

A JOINT LATENT CLASS MODELLING APPROACH FOR THE PREDICTION OF PSYCHOSIS BY BASIC SYMPTOM AND ULTRA-HIGH RISK CRITERIA

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Background: Basic symptom and ultra-high risk (UHR) criteria are commonly used for the prediction of psychosis. However, most studies have assessed these criteria at one specific moment in time. Thereby, they neglected that the dynamic pattern of at-risk criteria rather than their current level may be most predictive for the onset of a first psychotic episode. We, therefore, studied how the repeated marker and the risk of the event (i.e. onset of psychosis) are linked, in order to propose a dynamic prognostic tool for the prediction of first-episode psychosis.

Methods: In a naturalistic 24-month follow-up study, 146 patients at-risk for psychosis according to UHR and/or basic symptom criteria were repeatedly examined in an early detection of psychosis service (FETZ Cologne) for the conversion rate to first-episode psychosis (German version of the Structured Clinical Interview for DSM-IV; SCID-I), basic symptoms (Schizophrenia Proneness Instrument, Adult version; SPI-A), and UHR criteria (Structured Interview of Prodromal Syndromes; SIPS). Joint latent class analysis was applied 1) to define a model for the time-to-event, 2) to define a model for the marker trajectory, and 3) to link both models using a shared latent structure.

Results: Results: The joint latent class model with the best fit to the data included three latent classes (basic symptoms, attenuated psychotic symptoms, and a combination of basic symptoms and attenuated psychotic

symptoms). The three latent classes provided very good discrimination with an entropy measure being larger than 0.95. Class-specific trajectories and survival functions were associated with an increased risk for the conversion to psychosis from a mild to an intense degree. Results demonstrated that the combination of basic symptom and UHR criteria over time were more predictive of a later conversion to psychosis than the current level of basic symptoms and/or UHR criteria alone.

Discussion: Discussion: Our data suggest that the combined UHR and basic symptom trajectory should be repeatedly monitored in order to more reliably identify the prodromal state of psychosis and in order to more accurately predict transition to psychosis. This may also improve clinical decision making with regard to stage-dependent preventive interventions.

Poster #S162

DEFICITS IN FINE MOTOR SKILLS IN EMERGING PSYCHOSIS

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Background: Deficits in fine motor skills have been documented in psychosis patients as well as in individuals at increased clinical or familial risk for the disorder. Moreover, low performance on fine motor skill tests in children has been described as a risk factor for subsequent psychosis onset. However, it remains unknown whether deficits in fine motor skills are more severe in more advanced compared to earlier disease stages and whether fine motor skills may also serve as predictors of transition to psychosis in adults at clinical high risk. Hence, the main goal of this study was to compare the motor skills in healthy controls (HC), patients with an at-risk mental state (ARMS) and later transition to psychosis (ARMS-T), risk patients without later transition (ARMS-NT) and first episode psychosis (FEP) patients. Since changes in different domains such as loss of grey matter volume and impairment of cognitive function in these groups have been reported to be in the following order HC > ARMS-NT > ARMS-T > FEP, we hypothesized that a similar order would be observed with regard to fine motor functioning. Our secondary goal was to test whether fine motor functioning predicts later transition to psychosis in ARMS patients. **Methods:** As part of the prospective Basel Früherkennung von Psychosen (FePsy) study, psychomotor skills were assessed in 99 individuals with an ARMS for psychosis, 75 FEP patients, and 81 HC using the "Motorische Leistungsserie" (MLS), a computerized motor performance test battery. Of the 99 ARMS patients, 24 developed psychosis during the follow-up, whereas 45 did not develop psychosis and had a follow-up duration of at least 3 years. Fine motor functioning in the 4 groups (i.e., FEP, ARMS-T, ARMS-NT, and HC) were compared with analyses of covariances (ANCOVAs) using the 6 MLS factors (i.e., aiming, tremor, precision, dexterity, velocity of arm/hand and velocity of wrist/fingers) as dependent variables, group as between subject factor and age, sex, and medication as covariates. To examine whether deficits in fine motor skills can be used to predict transition to psychosis, a cox proportional hazard model was fitted which included the 6 distinct factors of the MLS as predictors.

Results: Preliminary analysis showed significant main effects of group in the factors tremor ($p=0.028$), precision ($p=0.008$), dexterity ($p=0.002$) and velocity of arm/hand ($p=0.006$). Post hoc tests indicated that HC performed better than ARMS-NT in terms of tremor ($p=0.016$), precision ($p=0.004$) and dexterity ($p=0.016$), better than ARMS-T in terms of dexterity ($p=0.006$) and velocity of arm/hand ($p=0.017$), and better than FEP in terms of velocity of arm/hand ($p=0.020$). A cox proportional hazard model revealed that none of the six fine motor functioning factors was predictive for transition to psychosis.

Discussion: Our results suggest that performance in fine motor functioning is not a predictor for transition to psychosis. This is a novel finding, as no study has yet tested the predictive value of fine motor functioning in ARMS patients. The finding that ARMS-NT, but not ARMS-T, performed worse than HC in 3 out of 6 MLS factors could be due to a larger sample size of ARMS-NT and thus increased power in the HC vs. ARMS-NT group comparisons. Another possible explanation is that ARMS-NT individuals develop other mental disorders than psychosis which are also associated with specific neurodevelopmental impairments.

Poster #S163

TITLE: WHAT HAPPENS IN THE BRAIN WHEN PSYCHOSIS PRONENESS SUBJECT UNDERGOES PSYCHIATRIC TREATMENT FOR 2 YEARS?

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Background: Until recently, focus of clinical interest has been concentrated on delineating so-called "psychosis proneness" group, otherwise referred as "clinical high risk of psychosis", for predicting their prognosis as converting to psychosis or non-converting to psychosis. However, as the percentage of psychosis proneness subjects who had converted to psychosis in 2 years of their clinical follow-up has been decreased to the point of less than 30 percentage, attention toward clinical trajectory of non-remitting psychosis proneness subjects has been elevated. We aimed to elucidate neuroscientific correlate of clinical trajectory of help-seeking neness subjects while they have been treated with conventional psychotropic medication adjusted for their psychiatric symptomatology for 2 years.

Methods: We recruited seventeen subjects fulfilling SIPS criteria for clinical high risk of psychosis at the Seoul Youth Clinic during 2010-2011. At baseline, clinical assessment, neuropsychological test battery and brain magnetic resonance imaging were conducted. After having been treated in Seoul Youth Clinic for their distressful psychiatric symptomatology for 2 years, follow-up evaluation which composed of clinical assessment including SIPS, neuropsychological test battery and brain magnetic resonance imaging was completed. To investigate their clinical trajectory in diverse dimension of clinical symptomatology and cognitive ability, we conducted Wilcoxon Signed rank test implemented in SPSS version 21. Morphological changes of their brain was analyzed in the domains of cortical thickness and white matter fiber track integrity, using the FREESURFER and TBSS software.

Results: After 2 years of conventional psychiatric treatment, most of the clinical symptomatology measured using SIPS, PANSS, SAPS, SANS and HAMD showed statistically significant improvement ($p<0.05$). In addition, several neurocognitive battery profiles including Rey-Osterreith Complex Figure Test subscores, Wisconsin Card Sorting Test and Trail-Making Test B became superior than those of their baseline performance. Their cortical thickness profile was changed in the brain areas of midcingulate, insula, posterior temporal cortices and some prefrontal area including dorsolateral prefrontal cortex.

Discussion: Psychosis proneness subjects, even without their conversion to psychosis, experience changes of their clinical symptomatology and demonstrate transition in their brain morphometry not only in their cortical thickness profile but also in their white matter tract integrity, along the conventional psychiatric treatment including psychotropic medication. Additional network analysis combining these clinical, neuropsychological and neuroscientific evidences could empower in predicting the clinical prognosis of the psychosis proneness subjects.

Poster #S164

DURATION OF UNTREATED PSYCHOSIS AND NEGATIVE SYMPTOMS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF INDIVIDUAL PATIENT DATA

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Background: Longer duration of untreated psychosis (DUP) is associated with poorer outcome in terms of positive symptoms, relapse rate, and time to remission. In contrast, the association with negative symptoms is less consistent. The study had three aims. First, to arrive at a more precise estimate of the correlation between DUP and negative symptoms than previous reviews, by substantially increasing the amount of available data. Second, to see whether the strength of this correlation attenuated

over longer follow-up intervals. Third, to determine whether there is a relationship between DUP and changes in negative symptoms.

Methods: Relevant databases were searched for studies published between December 1992 and March 2009 that reported data on DUP and negative symptoms. We obtained individual patient data where possible and calculated summary correlations between DUP and negative symptoms for each study at baseline, short and long-term follow-up. We used multilevel regression analysis to examine whether the effect of DUP on negative symptoms was the greatest in the early stages of illness.

Results: We included 28 non-overlapping studies from the 402 papers detected by the search strategy. After contacting the authors we obtained individual patient data from 16 of these studies involving 3339 participants. The mean DUP was 61.4 weeks (SD=132.7, median DUP=12.0). Shorter DUP was significantly associated with less severe negative symptoms at baseline and also at short (1–2 years) and longer term follow-up (5–8 years) ($r=0.117$, 0.180 and 0.202 respectively, $p<0.001$). The relationship between improvement in negative symptoms and DUP was found to be non-linear: people with a DUP shorter than 9 months showed substantially greater negative symptom reduction than those with a DUP of greater than 9 months.

Discussion: Shorter DUP is associated with less severe negative symptoms at short and long-term follow up, especially when the DUP is less than 9 months. Since there is no effective treatment for negative symptoms, reducing DUP to less than 9 months may be the best way to ameliorate them.

Poster #S165

APATHY BUT NOT DIMINISHED EXPRESSION IN SCHIZOPHRENIA IS ASSOCIATED WITH DISCOUNTING OF MONETARY REWARDS BY PHYSICAL EFFORT

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Background: Negative symptoms in schizophrenia have been grouped into the two factors of apathy and diminished expression, which might be caused by separable pathophysiological mechanisms. Recently, it has been proposed that apathy could be due to dysfunctional integration of costs and benefits during decision-making. The objective of the present study was to test whether the strength with which physical effort devalues ("discounts") monetary rewards specifically relates to apathy.

Methods: Thirty-one patients with schizophrenia and 20 healthy control participants performed a computerized binary choice effort discounting task in which they could choose to exert physical effort on a handgrip to obtain monetary rewards (see Hartmann et al., 2013, Behavioural Processes). This procedure yields an individual measure for the strength of effort discounting. Participants further provided self-report measures of reward valuation and perceived effort.

Results: The degree of effort discounting of monetary rewards was strongly correlated with apathy ($r(29)=-0.67$, $p<0.0001$, Bayes Factor = 624.81), but not with diminished expression ($r(29)=-0.14$, $p=0.45$, Bayes Factor = 0.18). Our data further suggest that this is not only due to decreased reward valuation but also to impaired cost-benefit computation. Importantly, the observed association between apathy and effort discounting was not driven by cognitive ability, antipsychotic medication or other clinical variables.

Discussion: This study provides the first evidence for a highly specific association of apathy with effort-based decision-making in patients with schizophrenia. Within a translational framework this human behavioral task could provide a bridge between apathy as a psychopathological phenomenon and established behavioral tasks to address similar phenomena in animals.

Poster #S166

IS QUALITY OF LIFE RELATED TO COGNITIVE PERFORMANCE OR NEGATIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA? RESULTS FROM A DOUBLE-BLIND, ACTIVE-CONTROLLED, LURASIDONE CONTINUATION STUDY

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Background: Everyday functioning and quality of life are markedly impaired in schizophrenia. These impairments are related to both negative symptoms and cognitive deficits. Treatment of these symptoms would seem to have the potential to improve these critical real-world outcomes. The objective of this post-hoc analysis was to examine the longitudinal relationships between quality of life and both negative symptoms and cognitive performance in patients with schizophrenia treated with lurasidone or quetiapine XR over a 6-month assessment period.

Methods: This double-blind, extension study included subjects with schizophrenia who had completed an initial randomized, double-blind, placebo-controlled, 6-week treatment trial. Subjects received continued treatment with flexible once-daily doses of lurasidone (40–160 mg; $n=151$, LUR-LUR) or quetiapine XR (200–800 mg; $n=85$, QXR-QXR) over a 12-month treatment period; results through the 6-month cognitive assessment period are presented here. Subjects initially treated with PBO were started on flexible once daily doses of lurasidone (40–160 mg; $N=56$) (PBO-LUR). Negative symptoms were assessed with the PANSS negative subscale. Cognitive performance and functional capacity were assessed by the CogState computerized cognitive. Quality of life was measured using the Quality of Well-Being (QWB-SA) scale.

Results: At the core phase baseline, the QWB-SA total score was similar for the LUR-LUR (0.57, SE 0.02) and QXR-QXR (0.57, SE 0.02) groups. Significant improvement in QWB-SA total score from core baseline at months 3 and 6 [0.20 (SE 0.01) and 0.22 (SE 0.01)], respectively, were found in the LUR-LUR group and the QXR-QXR group (0.20, SE 0.02 for both Months 3 and 6) ($p>0.05$, LUR-LUR vs. QXR-QXR). Improvement of the PANSS negative symptom subscale from baseline was significantly greater at the 6-month extension endpoint for LUR-LUR (-7.2, SE 0.31) vs. QXR-QXR (-5.97, SE 0.43) ($p=0.026$). Improvement in cognitive performance was also significantly better for LUR-LUR compared to QXR-QXR at both Months 3 ($d=0.32$, $p<0.05$) and 6 ($d=0.49$, $p<0.01$). Improved QWB-SA score was longitudinally associated with reductions in negative symptoms ($p<0.01$, in both the core and extension phases) and improvement in cognitive performance ($p<0.05$, in the extension phase only). Early reduction of negative symptoms and improvement of cognitive performance at Week 6 were significant predictors of quality of life outcome at Month-6 in the continuation study.

Discussion: In this active-controlled, double-blind extension study in patients with schizophrenia, improvement in quality of life was detected in a long term antipsychotic treatment, with improvements in cognition, and negative symptoms, being the significant predictors of improvement. These findings underscore the importance of improving cognitive impairments and negative symptoms in patients with schizophrenia.

Poster #S167

NEGATIVE SYMPTOMS: REVIEW FROM A LIFE COURSE APPROACH

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Background: Negative symptoms are regarded as a critical unmet therapeutic need for which the challenge of developing effective treatments is compounded by our limited understanding of their aetiology. The aim of this review was to consider negative symptoms from a life course approach in order to improve our understanding of their initial development and inform strategies for negative symptom prevention and treatment.

Methods: A review of previous literature for negative symptom studies was conducted and the relevance of negative symptoms at each phase of the life course was considered.

Results: Poorer premorbid adjustment has consistently been associated with greater negative symptoms. However there is evidence that negative symptoms may emerge in the premorbid phase of psychosis, and negative symptoms may frequently have onset in the putatively prodromal stage of psychosis. Furthermore long durations of both the psychosis prodrome and untreated psychosis have been associated with greater negative symptoms. There is also evidence that negative symptom deficits may progress over time and eventually dominate the presentation for some individuals.

Discussion: The initial onset of negative symptoms can occur at several phases of the life course and longitudinal consideration of the interplay between risk and protective factors may improve our understanding of these debilitating symptoms. Given the relatively poor efficacy reported in previous negative symptom treatment trials, consideration from a life course perspective may be an important step in the study of this often treatment refractory aspect of psychotic illness.

Poster #S168

SPANISH ADAPTATION AND VALIDATION OF THE BRIEF NEGATIVE SYNDROME SCALE

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Background: Negative symptoms are recognized as core features in schizophrenia related to poorer functioning and lower quality of life (Tas et al., 2013). The development of successful pharmacological strategies has been hampered, in part, due to the lack of appropriate assessment tools. In this regard, after the Consensus Development of Negative Symptoms (2005) organized by the National Institute of Mental Health (NIMH) the Brief Negative Syndrome Scale (BNSS) was developed (Kirkpatrick et al., 2010) focusing in five agreed negative domains: blunted affect, alogia, asociality, avolition and anhedonia. The BNSS is a 13-item brief scale that allows the study of these domains demonstrating strong inter-rater, test-retest and internal consistency properties. The aim of the present study is the adaptation into Spanish and the validation of the scale.

Methods: Initially, the Spanish adapted version (BNSS-Sp) was developed using the translation-retrotranslation method. We recruited twenty patients with DSM-IV diagnosis of schizophrenia from outpatient units at Parc de Salut Mar Barcelona, Hospital Clinic Barcelona and Universidad de Oviedo. Patients with IQ below 80, neurological disorders or substance dependence except tobacco and cannabis, were excluded. All subjects gave written informed consent. All subjects were interviewed and assessed with the BNSS-Sp, the PANSS (positive and negative symptom scale) and SANS (Scale for the Assessment of Negative Symptoms) by psychiatrists from their corresponding outpatient unit (DB, AM, CG, PG-P, LG). To assess test-retest reliability, ten of these patients were re-interviewed one week later. All these interviews were videotaped for later rating. Rating of all patients was carried out independently by seven psychiatrists (DB, AM, CG, PG-P, LG, EFE, GS) but test-retest reliability was performed by five psychiatrists (AM, CG, PG-P, LG, EFE). To determine interrater reliability, intraclass correlation coefficient (ICCs) was calculated for the BNSS-Sp total score and for each subscale. Internal consistency was calculated with Cronbach's alpha. To assess test-retest reliability Pearson's correlation for the total BNSS-Sp and subscales were calculated. Concurrent validity was assessed by correlating the total BNSS-Sp with PANSS negative subscale and SANS.

Results: Interrater reliability: The ICC was 0.966 for the total BNSS-Sp score; 0.956 for anhedonia; 0.861 for distress; 0.938 for asociality; 0.932 for avolition; 0.956 for blunted affect; and 0.956 for alogia. Internal consistency: Cronbach's alpha for the complete scale was 0.971. Test-retest reliability: Pearson's correlation were: total BNSS-Sp ($r=0.954$, $p<0.001$); anhedonia ($r=0.796$, $p=0.010$); distress ($r=0.619$, $p=0.056$); asociality ($r=0.774$, $p<0.009$); avolition ($r=0.919$, $p<0.001$); blunted affect ($r=0.974$, $p<0.001$); alogia ($r=0.987$, $p<0.001$). Concurrent validity: The BNSS-Sp total score was correlated with PANSS negative subscale ($r=0.741$, $p<0.001$) and SANS ($r=0.676$, $p<0.001$).

Discussion: This multicenter study demonstrates that the Spanish adapta-

tion of the BNSS (BNSS-Sp) has adequate psychometric properties in terms of reliability (very good interrater, test-retest and internal consistency properties) and validity (good concurrent validity).

Poster #S169

VERBAL MEMORY, BUT NOT WORKING MEMORY AS COGNITIVE MARKER OF NEGATIVE SYMPTOMS IN PATIENTS WITH FIRST EPISODE OF PSYCHOSIS

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Background: Negative symptoms are present approximately at the 24–27% of the first episode of psychosis (FEP). The presence of these symptoms has been associated with the presence of cognitive impairments in schizophrenia. Specifically, the anhedonia or the emotional withdrawal is one of the dimensions of the negative symptoms that describe the lack of interest in, involved with, and affective commitment to life's events. The aim of this study is to compare the verbal memory and the working memory in a sample of FEP subject with predominance of emotional withdrawal with FEP patients without emotional withdrawal. We hypothesized that the group with negative symptoms (specifically emotional withdrawal) will have greater verbal and working memory deficits compared with patients without this negative symptom.

Methods: The sample was formed by 57 subjects. They were selected from the population with FEP at the Hospital Clínic of Barcelona, from the national, multicenter, naturalistic, prospective and longitudinal PEPs project. This study was conducted in Spain from January 2009 to December 2011. The negative symptomatic assessment was made using the Positive and Negative Syndrome Scale (PANSS). Specifically, we focused on the item of Emotional withdrawal (N2) of Negative subscale of the PANSS, for its representation within the negative symptom. We realize two groups: with presence of emotional withdrawal (score 4–7) and with non-presence of emotional withdrawal (score 1–3). To assess the verbal memory we use the España-Complutense Verbal Learning Test-TAVEC for adults and children-TAVECi. The raw scores were converted into Z scores using norms adapted for age and educational level. For the working memory we use the Digit Span, subscale of the Wechsler Adult Intelligence Scale (WAIS-III). The raw scores were converted into T scores. All statistical analyses were carried out with the Statistical Package for the Social Sciences (SPSS) version 18.0 for Windows. The comparisons between the group with presence of emotional withdrawal and without emotional withdrawal were performed through a t-test.

Results: We found differences in verbal memory ($t=2.155$; $p=0.036$), but not in working memory ($t=-0.795$; $p=0.430$) between the two groups analyzed. The patients with emotional withdrawal have poorer performance in verbal memory but not in working memory compared to patients without emotional withdrawal. Further other variables will be interesting to analyze, like executive functions and attention.

Discussion: Our results suggest that negative symptoms in first-episode of psychosis, specifically the emotional withdrawal, contribute to verbal memory but not to working memory deficits. These findings could have implications for improving symptom-specific treatment. Moreover, these results suggest the possibility of considering these both symptomatic and cognitive variables as better predictors of the chronic course of the illness and prognosis than clinical variables.

Poster #S170**IDENTIFYING NEGATIVE SYMPTOMS IN SCHIZOPHRENIA AND ASSOCIATION WITH CLINICAL OUTCOMES USING NATURAL LANGUAGE PROCESSING**

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Background: Negative symptoms account for the greatest burden of illness amongst individuals with schizophrenia. They are an increasingly important target for therapy, particularly as their presence predicts poorer long term clinical outcomes. However, it has been difficult to develop practical methods for their assessment. In this study, we present a novel natural language processing application which identifies the presence of negative symptoms in electronic health records recorded during routine mental health care. This tool was used to assess the prevalence of negative symptoms, and their relationship with clinical outcomes, in a large sample of patients with schizophrenia.

Methods: Clinical data: Biomedical Research Council (BRC) Case Register, South London and Maudsley NHS Trust (SLAM), United Kingdom. Data extracted using the Clinical Record Interactive Search tool (CRIS). Participants: 7,678 patients with schizophrenia (1,612 inpatients) in 2011. The General Architecture for Text Engineering Machine Learning tool (Sheffield University) was used to develop an application (CRIS-NSS) to estimate the prevalence of negative symptoms recorded in electronic health records. Multivariable logistic and multiple linear regression analyses were performed to investigate the association of negative symptomatology with age, gender, marital status, employment status, social impairment, activities of daily living (ADL) impairment, presence of delusions/hallucinations, depression, risk of hospital admission and (amongst inpatients) risk of re-admission and length of stay in hospital.

Results: 4,269 patients (55.7%) had at least one negative symptom documented. Negative symptoms were particularly associated with patients who were aged 20-29 years, male and single. They were also associated with ADL impairment and delusions/hallucinations but not depression. Multivariable logistic regression and multiple linear regression analyses showed that the presence of two or more negative symptoms was associated with increased likelihood of hospital admission (odds ratio 1.24, 95% CI 1.10-1.39), re-admission (odds ratio 1.58, 95% CI 1.28-1.95) and length of stay (B coefficient 20.5, 95% CI 7.6-33.5). Poor eye contact, emotional withdrawal, poor rapport, mutism and apathy were particularly associated with re-admission risk and length of stay for inpatients.

Discussion: Using natural language processing, we were able to identify the presence of negative symptoms in electronic health records. The data suggest that negative symptoms are evident in most patients with schizophrenia and are associated with poorer clinical outcomes. These findings highlight the need for the development of new treatments that can alleviate negative symptoms and/or reduce associated disability. In addition, the increasing use of electronic health records highlights further opportunities to develop information extraction tools for ascertaining other symptom domains in schizophrenia as well as wider constructs of interest in other psychiatric disorders.

Poster #S171**DISSOCIATION OF ANTICIPATORY AND CONSUMMATORI PLEASURE IN SCHIZOPHRENIA**

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Background: Recent evidence has shown that patients with schizophrenia exhibit deficits in trait rather than state hedonic experience. Dissociation

between anticipatory and consummatory pleasure in schizophrenia might account for this emotional paradox. However, there is little empirical evidence to support such a speculation. In this study, we aimed to investigate anticipatory and consummatory pleasure experiences in patients with schizophrenia.

Methods: Forty-six patients with schizophrenia and 46 matched healthy controls were recruited in this study. A revised Monetary Incentive Delay task (MID) was administered to capture valence and arousal of anticipatory and consummatory pleasure. Participants were also required to predict their affective experience before completing the MID task. Repeated measure ANOVAs were separately performed for anticipatory and consummatory valence and arousal ratings with magnitude (none, small, large) as within-group variable and group (schizophrenia and controls) as between-group variable. Pearson correlation was calculated to examine the relationship between pleasure and negative symptoms.

Results: There were no significant differences in valence for group, group X magnitude interactions during reception of reward (Group: F(1,81) = 0.025, p=0.88; Interactions: F(2,80) = 0.38, p=0.68), and avoidance of punishments (Group: F(1,87) = 0.67, p=0.42; Interaction: F(2,86) = 2.04, p=0.14), reflecting that patients with schizophrenia showed comparable consummatory pleasurable experience as healthy controls. However, there were significant magnitude X group interactions indicating that compared with healthy controls, patients with schizophrenia reported less anticipatory pleasure especially when they were asked to predict the pleasantness in situations where they might have the chance to win (F(2,180) = 3.77, p=0.03) or receiving a reward (F(2,180) = 3.46, p=0.03). For arousal, patients with schizophrenia exhibited impairments in both anticipatory and consummatory pleasure relative to healthy controls, reflected by the significant group and magnitude X group interaction (almost all p's <0.05). Significant negative correlations were observed between negative symptoms and anticipatory and consummatory arousal ratings to large sum of money in patients with schizophrenia (r = from -0.40 to -0.29, p <0.05).

Discussion: Consistent with prior studies, patients with schizophrenia showed normal consummatory pleasurable experience, but impaired anticipatory pleasurable experience (especially when involving cognitive processing, like predicting), indicating a dissociation between anticipatory and consummatory pleasure in schizophrenia, which could partially explain the trait-state disjunction in patients. However, this dissociation was limited to the dimension of affective experience measured, such as valence, rather than arousal. In conclusion, trait-state hedonic disjunction in schizophrenia could be partially accounted for by the dissociation between anticipatory and consummatory pleasurable experiences in schizophrenia.

Poster #S172**ALTERATION OF THE EXPRESSION BALANCE OF HNRNP C1 AND C2 CHANGES THE EXPRESSION OF MYELINATION- AND SCHIZOPHRENIA-RELATED GENES IN THE HUMAN OLIGODENDROCYTIC CELL LINE**

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Background: The heterogeneous nuclear ribonucleoprotein C (hnRNP C) is involved in pre-mRNA splicing, stabilization of mRNA, and internal ribosome entry site-dependent translation of proteins. For the hnRNP C protein, two variants exist: hnRNP C1 and a slightly larger splicing variant (hnRNP C2) that contains a 13-aa insertion. Although, in many of previous studies, these two variants have been considered to be molecules with same cellular functions, functional differences between the two variants remain unknown. Recently, we have found that the expression level of both hnRNP C1 and C2 protein is significantly decreased in the post-mortem brains of patients with schizophrenia (Martins-de-Souza et al., 2009). However, it is unclear how hnRNP C1 and C2 variant are involved in the pathophysiology of schizophrenia. On the other hand, a large body of evidence suggests that the differential expression of myelination-related genes is associated to schizophrenia. In vitro studies shown that antipsychotic drugs change mRNA expression of splicing isoforms of the quaking (QKI), one of myelination- and schizophrenia-related genes (Jiang et al., 2009), suggesting that pre-mRNA splicing-related factors, such as hnRNP C, may regulate expressions of these genes. Additionally, myelin basic protein

(*MBP*), another myelination- and schizophrenia-related gene, is the best-characterized QKI mRNA ligand in mice (Larocque et al., 2002). Therefore, we tested this hypothesis using the human immature oligodendrocytic cell line, that levels of hnRNP C1 and C2 would influence the expression of these myelination-related genes. We also attempted to elucidate the functional differences between hnRNP C1 and C2.

Methods: We constructed expression vectors for the two hnRNP C variants (hnRNP C1 and C2), and investigated, using the quantitative real-time RT-PCR, whether the overexpression of these proteins would change the expression of myelination-related genes, such as the QKI isoforms (*QKI-5*, -6, -7, and -7b) and *MBP*, in the human immature oligodendrocytic cell line MO3.13 and during differentiation of this cell line by PMA treatment.

Results: Endogenous expressions of both *hnRNP C1* and *C2* were found decreased during MO3.13 differentiation. In the same condition, the levels of expression of *QKIs* (*QKI-5*, -6, -7, and -7b) were significantly elevated. The up-regulation of *QKIs* were not influenced by overexpression of either the hnRNP C or C2. *MBP* was increased during differentiation of MO3.13, consistent with previous reports (Buntinx et al., 2003; Boscia et al., 2012). The up-regulations were not influenced by overexpression of either the hnRNP C1 or C2. However, intriguingly, *MBP* was up-regulated under the overexpression of hnRNP C2, but not hnRNP C1, in PMA-untreated cells.

Discussion: We observed that the overexpression of *hnRNP C1* and *C2* do not affect the differential expression of *QKIs* and *MBP* during MO3.13 differentiation. But *MBP* seems to be regulated by hnRNP C2 in PMA-untreated cells. Similarly, we have reported previously that hnRNP C2 regulates *MBP* expression in a direct fashion, and that such regulation is not mediated by QKI in the human neuroblastoma cell line SK-N-SH (Iwata et al., 2011). Thus, we propose that the mechanism underlying the differential expression of hnRNP C1/2 in schizophrenia patients brains may involve changes of *MBP* expression. *MBP* has been found differentially expressed at gene and protein level (Martins-de-Souza et al. 2012; Matthews et al. 2012). Although no functional differences have been reported thus far for the two variants of hnRNP C protein, our findings indicate the existence of distinct functions between hnRNP C1 and C2. Further exploration of separate roles of hnRNP C1 and C2 associated to schizophrenia will lead to a better understanding the pathobiology of this disorder in a molecular level.

Poster #S173

METABOTROPIC GLUTAMATE RECEPTOR 5 DYSREGULATION IN SCHIZOPHRENIA

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Background: Evidence from genetic and animal studies suggests that metabotropic glutamate receptor 5 (mGluR5) is involved in the pathophysiology of schizophrenia. However, direct evidence of altered mGluR5 in the schizophrenia brain has been lacking. This is an important avenue to investigate as mGluR5 allosteric modulators are currently in development for the treatment of schizophrenia, especially the cognitive dysfunction. The aim of this study was to determine if mGluR5, or proteins that regulate mGluR5 are altered in the schizophrenia brain, specifically in the dorsolateral prefrontal cortex (DLPFC) and CA1 region of the hippocampus, which are brain regions associated with cognitive functions.

Methods: mGluR5 protein levels in the DLPFC (BA46) were examined in a large cohort of schizophrenia subjects and matched controls (n=37/group; obtained from the NSW Tissue Resource Centre, Australia). In addition we examined the protein expression of several fundamental regulators of mGluR5, including Norbin (neurochondrin), Tamalin (GRASP1), and Preso1 (FRMPD4). These regulatory proteins ensure proper trafficking, localisation, and phosphorylation of mGluR5. We examined these same proteins in the CA1 hippocampal subregion in a patient subset (n=20/group).

Results: In the DLPFC, mGluR5 total protein levels were significantly increased (+22%; p<0.001) in schizophrenia subjects compared to controls. This was accompanied by large reductions in mGluR5 regulatory proteins, Norbin (~37%, p<0.001), Tamalin (~30%, p=0.040) and Preso1 (~29%, p=0.001). There were significant negative associations between mGluR5 and Norbin ($r=-0.655$, p<0.001), Tamalin ($r=-0.520$, p=0.001) and Preso1 ($r=-0.428$, p=0.009) in control subjects, but not schizophrenia subjects. In the CA1 region, mGluR5 protein was significantly increased (+42%

p<0.001) in schizophrenia subjects, accompanied by increases in Norbin (+47%; p<0.001), Tamalin (+34%; p=0.009) and Preso1 (+83%; p<0.001). There were no associations between mGluR5 and the regulatory proteins in the CA1 of controls or schizophrenia subjects. None of the measured proteins were associated with average lifetime antipsychotic drug exposure (p>0.124).

Discussion: Our findings show that the mGluR5 system is disturbed in the schizophrenia brain. The changes in mGluR5 regulatory proteins (Norbin, Tamalin, and Preso1) provide the first evidence that there may be altered trafficking, cell surface expression or mGluR5 activation in schizophrenia. However, the differential changes between the DLPFC and CA1 suggest that the regulatory mechanism of mGluR5 may be brain-region dependent. As mGluR5 in these brain regions mediates cognitive functions, these alterations may contribute to underlying cognitive deficits in these patients. These findings have implications for the use of novel mGluR5-based therapeutics, which are highly dependent on cell-surface expression.

Poster #S174

STRESS, CORTISOL AND PITUITARY VOLUME DURING PSYCHOSIS

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Background: Several international studies have focused on the pituitary gland volume in groups at ultra high-risk (UHR) of developing psychosis and first episode schizophrenia (FES) patients. It has been hypothesized that the pituitary volume increases due to the production of corticotrophin releasing hormone, resulting in increased levels of cortisol. Studies have shown that the HPA axis might be affected prior to the patients transitioning to psychosis. The HPA-axis is one of the many biological systems involved in the development of psychosis and mediates the association between stress and onset of psychosis. The aim of this study is to investigate how pituitary volume and cortisol is affected during different stages of illness and how they volume correlates with other parameters of stress, since this kind of knowledge could improve our understanding of the biological mechanisms involved in psychosis.

Methods: We included 45 healthy controls, 41 UHR patients and 40 drug naïve FES patients. The UHR were assed and included according to the CAARMS (the Comprehensive Assessment of At-Risk Mental States) criteria and the diagnosis of the FEP patients was validated by the use of SCAN (Schedules for Clinical Assessment in Neuropsychiatry) interviews. The pituitary gland volume was measured (stereology) in MEASURE (software) and salivary cortisol was measured upon awakening and +15, 30, 60 minutes after awakening, at 12 am and 8 pm. The stress scales were perceived stress and recent life events.

Results: The UHR and FEP subjects experienced more perceived stress on perceived stress scale compared to healthy controls (healthy 10.0 (± 5.0), UHR 25.1 (± 6.5) and FEP 24.6 (± 5.3); p<0.001) and likewise on the recent life events scale. The UHR subjects had a higher cortisol morning reactivity (cortisol at +15 minutes minus awakening) compared to healthy controls (cortisol nmol/l: healthy 1.6 (± 2.9), UHR 4.4 (± 4.2) and FEP 2.6 (± 3.0); p=0.009). It was not present in the FEP subject and the UHR morning peak normalized after 30 minutes. Area under the curve cortisol levels showed no significant differences within the three groups. Recent life events were associated with a blunted cortisol morning response in the total population (Spearman's rho=-0.257, P=0.022). We found no difference in pituitary volume within the three groups (healthy 0.73 (± 0.13), UHR 0.75 (± 0.18) and FEP 0.78 (± 0.18)). Overall the females had larger volumes than the males, there was no significant association between pituitary volume and cortisol awakening response (Spearman's rho= 0.205, p=0.069) or cortisol during the day (Spearman's rho=0.120, p=0.667).

Discussion: It seems that the UHR patients are in an early stage of stress, and further changes in cortisol could be affected by number of recent life

events. It is possible that changes in cortisol and pituitary gland volume normalize after transition to psychosis since there was no difference between healthy controls and FES patients. The lack of difference in pituitary volume between the subgroups could reflect that many factors affect the pituitary volume, e.g. hormones and age. The findings of changes in stress response in UHR patients compared to healthy controls and an inverse correlation between cortisol morning response and recent life events support that further studies should investigate the stress levels in patients at UHR of developing psychosis.

Poster #S175

THE ERYTHROCYTE MEMBRANE LIPID ABNORMALITIES OBSERVED IN SCHIZOPHRENIA PATIENTS SUPPORT THE OXIDATIVE STRESS HYPOTHESIS IN SCHIZOPHRENIA

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Background: Markers of oxidative stress have been postulated as soon as in early brain development phases in patients with schizophrenia (SCZ) potentially leading to excitatory/inhibitory imbalance in particular for glutamate and GABA neurotransmission. Furthermore, a decrease in the total antioxidant status is also described in SCZ patients. In the present work dedicated to a thorough analysis of the composition and distribution of lipid in the erythrocyte membrane (EM) in SCZ patients, we examined to what extend some of the observed lipid abnormalities support the hypothesis of an increased oxidant status in SCZ patients.

Methods: The oxidative status of the EM lipids was examined in a population of chronic medicated patients with SCZ (n=75) and healthy control (HC, n=40). EM phospholipids (PL) as well as their constitutive fatty-acids (FA) were analysed using LC-MS/MS method. The distribution between the inner and outer membrane leaflet of lysophosphatidyl ethanolamine (LPE) was measured using trinitrobenzene sulfonic acid labelling. The antioxidant status was examined through the percentage of membrane plasmalogens (PLG), a group of PL with a vinyl ether bond in the sn-1 position, considered to be preventative biomolecules against oxidative stress. The oxidant status was assessed via the degree of unsaturation of phospholipids FA.

Results: The plasmalogen (alkenyl) percentage was calculated for the membrane LPE. A significant decreased percentage of PLG ($p=0.001$) was observed in the EM of SCZ patients (5.9 ± 1.1) vs HC (6.6 ± 1.3). PLG decrease was observed in 59% of the SCZ patients population versus only 27.5% for the HC population. The percentages of LPE fatty-acid species were calculated as well as their distribution on both sides of the membrane leaflet. A significant decrease of both n-3 and n-6 species percentage was found for the externally located LPE between patients and control ($n-3 p=0.038$; $n-6 p=0.036$).

Discussion: Among the several membrane PL abnormalities identified in the EM of patients with SCZ, we could identify 2 abnormalities compatible with the increased oxidative stress hypothesis in SCZ. This work could not determine whether these abnormalities are a cause or consequence of the general reduced antioxidant status in SCZ. Confounding factors such as antipsychotic drugs, duration of disease and age of onset were examined and could not account for the results.

Poster #S176

UNIQUELY TARGETED MOLECULAR THERAPEUTIC FOR SCHIZOPHRENIA: CHARACTERIZATION OF ITI-007 IN VITRO AND IN VIVO ANIMAL MODELS

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Background: ITI-007 is a unique therapeutic designed to target molecular systems capable of beneficially impacting the multiple symptom domains of schizophrenia, while not affecting systems known to cause undesirable

side effects such as cognitive dysfunction, cardiovascular abnormalities and metabolic consequences. Here we describe a combination of novel target mechanisms impacted by ITI-007 as defined by *in vitro* and *in vivo* characterization using animal models. The predicted spectrum of effects on positive, negative and cognitive symptoms is distinct from other therapeutic agents for schizophrenia. ITI-007 has been shown effective in human phase II clinical trials.

Methods: *In vitro* binding studies were performed using isolated membranes from cloned human receptor systems expressed in CHO or HEK cells. Affinity constants were expressed as Ki values after correction for radioligand Km affinity and represent 6-8 point curves. Animal models of conditioned avoidance response, catalepsy, quipazine-induced head twitch, *in vivo* microdialysis and dopamine turnover experiments were performed using standard methods (Snyder et al. 2014, in preparation).

Results: ITI-007 is a 0.54nM inhibitor of serotonin 5HT2A receptors, has a 32nM affinity against dopamine D2 receptors, is a 33nM inhibitor of serotonin transport systems (SERT), and displays a 52nM affinity versus dopamine D1 receptors. It has little or no activity versus systems that may contribute to weight gain and cognitive dysfunction, namely histamine H1 receptors and muscarinic cholinergic receptors. It has low affinity for serotonin 5HT2B, 5HT2c, and alpha adrenergic receptors and minimal activity versus a panel of off-target receptor/enzyme/channel systems. ITI-007 displays mesolimbic specificity resulting in the phosphorylation of the NMDA receptor NR2B subunit at Tyrosine-1472 in nucleus accumbens, but not in the striatum. This activity is known to enhance glutamate transmission resulting from agonist activity at dopamine D1 receptors. ITI-007 displays dopamine D2 activity *in vivo* that is consistent with pre-synaptic partial agonist and post-synaptic antagonist action. Pre-synaptic partial agonist activity leads to an absence of enhanced dopamine presynaptic synthesis and a resulting lack of extra-pyramidal side effects (EPS) liability. Using our platform technology, CNSProfileTM we determined that striatal tyrosine hydroxylase (the rate determining step in dopamine synthesis) Serine-40, essential for enzyme activity, was not phosphorylated in mice treated with ITI-007. In contrast, a panel of approved antipsychotic drugs, known to produce EPS, significantly increased Serine-40 phosphorylation. Dopamine metabolism and microdialysis experiments have confirmed the predictions of pre-synaptic D2 partial agonist activity. In the quipazine head-twitch model, ITI-007 was effective at an ED50 of 0.2 mg/kg and in the conditioned avoidance response model ITI-007 has an ED50 of 1.5 mg/kg. These results are consistent with the ~60-fold ratio of D2/5HT2A Ki affinity values, a ratio unlike any current antipsychotic agent. ITI-007 is bio-available after oral administration and rapidly enters the brain.

Discussion: The effects of ITI-007 in pre-clinical *in vitro* and *in vivo* models indicate that this agent is a unique therapeutic targeting receptors known to be beneficial for the multiple symptom domains of schizophrenia illness, namely negative symptoms, positive symptoms and associated depression. Furthermore, ITI-007 enhances glutamatergic transmission in brain areas involved in cognitive function. Due to a lack of interaction with undesirable receptor systems, side effects are predicted to be minimal.

Poster #S177

PROTEOMIC AND GENOMIC ANALYSES IMPLY THE POSTSYNAPTIC DENSITY IN SCHIZOPHRENIA

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Background: The PostSynaptic Density (PSD) is a highly organized structure, attached to the postsynaptic neuronal terminal, comprised of a complex network of cytoskeletal scaffolding and signalling proteins that facilitate the movement of receptor and signalling complexes. Candidate genes and signalling mechanisms, that converge on and act through it, include NMDA, AMPA and mGlu receptors. NMDA receptor hypo function contributes to the pathophysiology of schizophrenia and it has been proposed that the PSD may contribute to this by dysregulation of NMDA receptor recycling. We enriched for the PSD and conducted proteomic analysis of this fraction in order to test the hypothesis of altered clathrin-mediated endocytosis (CME) within the PSD in schizophrenia.

Methods: Sucrose density gradient centrifugation was employed to en-

rich for the PSD in the anterior cingulate cortex in schizophrenia and control tissue obtained from the Stanley Medical Research Institute. Liquid chromatography-mass spectrometry was used to quantify differential protein expression and to investigate the relevance of antipsychotic treatment for these findings. Validation methods were utilized to characterize differential protein expression of the PSD. In addition, we performed a gene-based test to test the association of PSD genes and related pathways with schizophrenia.

Results: Quantitative investigation of the PSD fraction revealed more than 700 protein identifications. Pathway analysis of the 143 significantly differentially expressed proteins revealed involvement in endocytosis, long-term potentiation, and calcium signalling. In line with our hypothesis, an altered expression of the core CME proteins Dynamin1 and AP2 was observed (both $p < 0.0005$); as well as differential expression of numerous NMDA interacting proteins such as CYFIP2, SYNPO, SHANK3, ESYT and MAPK3 (all $p < 0.0015$). Gene-based tests performed on the largest schizophrenia genome-wide association study to date, shows enrichment of PSD genes with schizophrenia ($p=0.034$), replicated in an independent sample ($p=0.0016$) and highlights HIST1H1E ($p=1.9 \times 10^{-5}$) and MAPK3 ($p=0.000186$) in particular.

Discussion: This is the first study to characterize the differential protein expression within the PSD in schizophrenia and our data implicates NMDA-interacting and endocytosis-related proteins. We also provide data implicating PSD associated genes in schizophrenia. Together the data provide robust complementary evidence implicating the PSD in schizophrenia.

Poster #S178

LEFT PARIETAL LOBE ARACHNOID CYST IN A PATIENT WITH PSYCHOSIS: CASE REPORT

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Background: Arachnoid cysts are rare benign space-occupying lesions of the brain containing cerebrospinal fluid (CSF). Though in most cases the diagnosis is accidental, arachnoid cysts may give rise to array of neurological and neurocognitive symptoms. Although arachnoid cysts are traditionally considered to be incidental lesions when found in people with psychiatric disorders with no neurological signs, some reports point towards a causal relationship.

Methods: Single case report describing a case of psychosis with left parietal lobe arachnoid cyst.

Results: A case of a 26 year old man with chronic psychosis is described. He was seeing a psychiatrist for the past 8 years after he started experiencing auditory hallucinations during his National Service with the army. He started becoming irritable, hyper-religious and started sleeping poorly after stopped taking his medications a few weeks prior to his admission. He became agitated and aggressive secondary to his abnormal religious beliefs on the day of admission. He was evaluated in a general hospital before he was transferred to our facility. Computed Tomography Scan (CT) of the brain showed a high left parietal lobe arachnoid cyst, with local mass effect onto the adjacent brain parenchyma. Blood investigations and detailed physical examination including a thorough neurological examination revealed no abnormality. He was restarted on aripiprazole and settled quickly in the ward. He was discharged with referral to a neurosurgeon for further management of the arachnoid cyst.

Discussion: It is difficult to conclude whether the lesion was related to the overall psychiatric picture of the patient. However due to the presence of mass effect in the brain parenchyma the possibility of the lesion contributing to the etiopathogeny of the psychotic symptoms can not be excluded. Given the growing number of cases being reported a more in-depth study of this type of cases is required.

Poster #S179

GENE EXPRESSION THROUGHOUT HUMAN POSTNATAL DEVELOPMENT IN SINGLE CELL POPULATIONS IN THE PREFRONTAL CORTEX

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Background: Schizophrenia (SZ) is a neurodevelopmental disorder that has

been associated with pre- and peri-natal insults such as maternal illness and poor nutrition during fetal development, as well as the season of birth and certain childhood infections. It is likely that hereditary factors also play a role. Together these genetic and environmental insults may explain, at least in part, cognitive deficits throughout childhood in things like attention, memory, and impulse control. For most individuals, however, the onset of the overt symptoms and deficits of schizophrenia do not occur until late adolescence or early adulthood, suggesting that additional events occurring during the peri-adolescent period contribute to the onset of illness. The prefrontal cortex (PFC), an area that has consistently shown severe disturbances in SZ, undergoes a very protracted course of maturation, not reaching full competence until the late teens—similar to the age of onset of the overt symptoms and deficits of schizophrenia. The functional maturation of the PFC during the peri-adolescent period is believed to be mediated by extensive remodeling of synaptic connectivities between pyramidal neurons. Dysregulation of the maturing cortical circuits would not only be problematic in itself, but it could also compound earlier deficits, thereby contributing to the onset of illness.

Methods: We profiled gene expression changes in pyramidal and parvalbumin (PV)-containing neurons in layer 3 of the PFC, both of which have been implicated in the pathophysiology of SZ, during normal human peri-adolescent development in order to understand genes and molecular pathways that underlie the maturation of these neurons. We examined a cohort of 18 normally developing individuals, with ages ranging from 1 to 24 years old. Three groups were formed for comparison: 6 Pre-pubescent, 6 pubescent, and 6 post-pubescent.

Results: While microarray data from PV neurons are still being gathered, we found that, in pyramidal neurons, TGF β signaling, EGFR signaling, folic acid network, cytoplasmic ribosomal proteins, mRNA processing, ubiquitin-mediated proteolysis and SNARE-mediated vesicular transport are among the pathways that are most significantly differentially regulated during peri-adolescent development. Of interest, TGF β signaling also appears to be dysregulated in layer 3 pyramidal neurons from the PFC in SZ

Discussion: By comparing normal developmental data with data obtained from SZ subjects, it may be possible to determine the molecular pathways that contribute to the onset of this devastating illness.

Poster #S180

DYNAMIC CAUSAL MODELLING OF ABNORMAL FRONTAL EVOKED GAMMA BAND ACTIVITY IN PATIENTS WITH SCHIZOPHRENIA

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Background: There is an increasing evidence that disorganized cerebral activity in schizophrenia during cognitive tasks involves abnormal balance of high-frequency activation and deactivation within the following systems: (i) the attention/response control mechanisms and (ii) the default mode network (DMN). Dynamic causal modelling (DCM) entails specification of a plausible model of event-related responses, elaborating conventional spatial forward models of EEG data in which the sources are coupled according to biological constraints. The inversion of a DCM provides information about the underlying cortical pathways and their causal architecture.

Methods: 25 patients with schizophrenia and 30 healthy controls underwent an EEG recording during an oddball paradigm. Frontal-parietal forward (F), backward (B) and forward-backward (FB) connectivity models were studied as possible mediators in the differences in the evoked gamma activity (35–45 Hz) to standard and target conditions. Two different pathway subsets were considered: P300 response models included the bi-hemispherical primary auditory and inferior parietal cortices, as well as the right dorsolateral prefrontal area; DMN models comprised the bi-hemispherical primary auditory cortex and precuneus, together with the right medial prefrontal region.

Results: Compared to healthy controls, patients with schizophrenia had

higher gamma band activity change between standard and target conditions in the left frontal area ($p < 0.001$). The standard to target activity change was positive in patients and negative in controls. For the proposed P300 response pathway, the F-model was a better fit than the other two in patients, while the B-model was better in healthy controls. Attending the DMN pathway, the FB-model was the best fit in patients while the F-model was the corresponding best option in healthy controls.

Discussion: Abnormal bi-directional (forward-backward) frontal connectivity in the DMN, mediating between task conditions, may underly the standard to target gamma band activity decrease found in the left frontal region in patients with schizophrenia. A lack of backward control (frontal to parietal) in the P300 response pathway may be also related to the high-frequency alteration in patients.

Poster #S181

GREATER LEFTWARD FRONTAL ALPHA ACTIVATION DURING CRITICISM IS ASSOCIATED WITH SCHIZOTYPAL TRAITS AND ANXIETY

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Background: Criticism from a caregiver predicts relapse, longer hospitalization and greater symptom severity in schizophrenia. Characterised by its tone and content, criticism may be seen as a standardised construct that elicits a specific neural response in those perceiving it. fMRI research indicates that listening to criticism activates the superior frontal gyrus in patients with schizophrenia and individuals with high schizotypy. Greater anxiety is associated with greater superior-to-middle frontal gyral connectivity during standardized criticism. The electrocortical response to insult is increased leftward frontal alpha (α) activation. The study aimed to determine the relation between leftward frontal α activation during standardised criticism and schizotypy, anxiety and criticism from a close relative.

Methods: Twenty-two healthy individuals (mean age=23 years; range 18-40 years; 15 women) underwent electroencephalography (EEG) while listening to a standard set of comments (criticism, positive and neutral comments) spoken in a male or female voice and imagining them to be spoken by a close relative. Ten of these participants (7 women; 3 men) were also assessed on schizotypy and anxiety. Their close relative (6 partners, 3 siblings, 1 parent) was assessed on Expressed Emotion (a standard measure of criticism) using the Camberwell Family Interview. The absolute spectral power during the comment and event-related synchronization/desynchronization (ERS/ERD) within 500ms epochs of the comment in the low (8-10Hz) and high (10-12 Hz) α frequency bands were extracted in the middle-lateral (F3, F4, FC3, FC4) and lateral frontal sites (F5, FC5, F6, FC6). Asymmetry was calculated by subtracting spectral power in the left from right hemisphere electrodes. Analysis of variance was performed followed by post hoc paired-sample t-tests. Planned Spearman correlations were performed between spectral power, schizotypy, anxiety and carer criticism.

Results: Three out of ten participants had a high EE relative. Participants, on average, had low positive schizotypy (mean number of unusual experiences=3.7, range 0-7). At the F3/F4, an emotion-by-hemisphere-gender interaction in low α -activation was explained by greater activation during female criticism than neutral comments. At F5/F6, a main effect of emotion in high α -activation revealed more activation during male criticism than neutral comments. At FC3/FC4, an emotion-by-hemisphere-by-gender interaction in low α ERS/ERD showed greater ERS during female criticism and positive comments than neutral comments at the 0-500ms epoch. Greater impulsive non-conformity and anxiety correlated with lower leftward low α -activation at F3/F4 sites during female criticism. More relative criticism correlated with greater leftward high α -activation at F5/F6 sites during male positive comments. Greater introvertive anhedonia correlated with lower leftward FC5/FC6 ERS/ERD asymmetry at 0-500ms during female positive comments.

Discussion: Greater frontal α -activation during criticism than neutral comments suggests greater cognitive appraisal of criticism, with low α -activation indicating greater general attention and high α -activation indicating greater semantic processing. The inverse association between

leftward frontal α -activation during criticism and schizotypy and anxiety suggests increasing withdrawal from and emotional reactivity to criticism. However, more criticism from predominantly low-EE relatives was associated with greater leftward frontal high α -activation during positive comments. This finding indicates greater 'approach motivation', i.e. both heightened attention to, and more evaluation of positive comments.

Poster #S182

THE EFFECT OF REBOXETINE AND HALOPERIDOL ON SENSORY GATING IN HEALTHY HUMANS AND RATS

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Background: Disruptions in filtering of sensory information have frequently been observed in patients with schizophrenia. Successful sensory gating is believed to prevent sensory overload of higher brain functions by filtering out irrelevant stimuli before they can reach the higher brain areas. Deficits in sensory gating may therefore result in an overload of irrelevant information reaching the higher brain areas, which in turn might contribute to the formation of psychotic symptoms. One well-established paradigm to assess sensory gating is P50 suppression in humans, or the very similar double click paradigm in rats. In this paradigm, patients with schizophrenia score significantly lower than healthy controls. In schizophrenia both a reduction in prefrontal dopaminergic activity and an increased noradrenergic activity have been suggested to be involved in the disease. In the current study we aimed to further investigate the involvement of these neurotransmitters by using the norepinephrine reuptake inhibitor (NRI) reboxetine and the dopamine antagonist haloperidol, respectively. Furthermore our aim was to investigate if any potential drug effect found in humans could be translated to rats.

Methods: The design of the human experiment was a double-blind, placebo-controlled, cross-over study. In the humans a dose of either reboxetine (8 mg), haloperidol (2 mg), their combination or placebo was administered to 21 healthy male subjects at four separate visits with a minimum of two weeks apart. The subjects were subsequently tested in The Copenhagen Psychophysiological Test Battery (CPTB) which, amongst others, measures P50 suppression using electroencephalography (EEG). Very similar to our human setting the animal experiment consisted of 22 rats (n=22) that received a dose of either, reboxetine (2 mg/kg), haloperidol (0.08 mg/kg), their combination or placebo with one week apart to allow washout of compounds. The rats were hereafter tested in an EEG setting.

Results: In humans we found a significant reduction in P50 suppression following separate administration of either reboxetine or haloperidol as well as following their combined administration compared to placebo. In the rats we found a similar significant reduction of sensory gating (N40) in the hippocampus (CA3-region), but not in cortical placed electrodes after the haloperidol and combination treatments and a trend in reducing sensory gating following the reboxetine treatment compared to placebo.

Discussion: The obtained results suggest that increased noradrenergic and decreased dopaminergic activities are involved in P50 suppression. However we did not observe a synergistic effect of the combination of the compounds, which may indicate either a ceiling effect or a drug/drug interaction. The animal studies confirmed the human data to some degree, suggesting a predictive validity of the P50 suppression to hippocampal sites but not cortical areas. Since sensory gating in schizophrenia patients is usually found to be reduced compared to controls our results may indicate similar underlying neurotransmitter activities.

Poster #S183

CHRONIC SOCIAL DEFEAT STRESS INDUCES INCREASED EXPRESSION OF D2-DIMMER IN THE PREFRONTAL CORTEX OF MICE

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Background: Chronic social defeat stress is a potent stressor that promotes the development of various psychiatric disorders such as depression, anxiety and schizophrenia. Dopaminergic dysfunctioning is a key mechanism

in pathogenesis of schizophrenia. Few studies with rodents have shown that social defeat leads to dopaminergic hyperactivity and to behavioral sensitization. The purposes of present study were to explore the effects of social defeat stress on the expression of D1DR, D2-dimmer, D2-long form, D2-short form, DAT and NCS-1 in mouse brain.

Methods: Male C57BL/6J mice were exposed to social defeat stress for 10 days. On 11th day social avoidance test were carried out to divide into two groups (susceptible and unsusceptible groups). D1DR, D2-dimmer, D2-long form, D2-short form, DAT and NCS-1 expression was measured in the mouse prefrontal cortex (PFC), striatum, amygdala and hippocampus using Western blotting technique and real time (RT)-PCR. The results were compared between susceptible and unsusceptible groups and control group.

Results: There was no significant difference in D1DR, DAT, and NCS-1 protein level between control, susceptible and unsusceptible groups. However, there were significant increased expression of D2 dimer in the prefrontal cortex (PFC), decreased expressions of D2-long form and D2-short form in hippocampus of susceptible group compared with control and unsusceptible group, and increased expression of D2-short form in the PFC of susceptible group compared to control group. For mRNA expression, there were no significant differences in D1DR and DAT mRNA level between control, susceptible and unsusceptible groups. However, there were significantly decreased D2-Long form mRNA levels in striatum, amygdala and hippocampus of susceptible group compared with control and unsusceptible group. Also, significantly decrease mRNA level of D2-short form was observed in the striatum of susceptible group compared to control group.

Discussion: Our finding, increased expression of D2 dimer in the PFC is in same line with a recent report that significantly enhanced expression of D2Rs dimers in post-mortem striatal tissue of schizophrenia patients was observed. This may suggest that social defeat stress causes a dopaminergic dysregulation and social defeat stress model could be used as an animal model for schizophrenia.

Poster #S184

META-ANALYSIS OF “LEARNING POTENTIAL” ON THE DYNAMIC WISCONSIN CARD SORTING TEST (D-WCST): DISTINCT COGNITIVE SUBGROUPS WITH DIVERGENT FUNCTIONAL OUTCOMES

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Background: Behavioral interventions have been shown to ameliorate some of the cognitive and functional deficits prevalent in schizophrenia. However, effect sizes of these interventions are typically modest and outcomes are highly heterogeneous. A better understanding of individual differences and their relationship to treatment response could facilitate better clinical decision making and improve treatment outcomes. The dynamic administration of the Wisconsin Card Sorting Test (D-WCST) is a test-train-retest method for identifying individual differences in “learning potential”. While there are several methodological variations, a categorical approach based on an index of reliable change is the most frequent (e.g., Wiedl, 1999). Individuals are categorized according to one of three groups based on performance. High Performers (HPs) score in the upper range on both tests; Learners (Ls) perform poorly at first but make significant gains after training; and Non-Retainers (NRs) perform poorly and do not improve after training. We conducted a systematic review and meta-analysis of the D-WCST learner groups to examine the relative frequency of each group, neurocognitive differences, and relationship between group membership and response to psychosocial intervention.

Methods: Studies were identified using PsychINFO, PubMed, and Google Scholar. We identified 11 studies reporting data on relative frequency (N=628), 6 studies on neurocognitive performance (N=442), and 3 studies on response to intervention (N=87). For relative frequency of each group we calculated mean relative frequencies with confidence intervals. For neurocognitive performance, effect sizes were calculated for the relative differences between the three groups using a fixed-effect model and corrections for small sample size. For response to intervention, categorical outcomes were first dichotomized as “improvement” vs. “no improvement”, and participants categorized as “Responders” vs. “Non-Responders”. We then ran Chi-squared tests and calculated odds ratios (OR).

Results: Across 9 different sites from 3 different counties, the mean relative

frequencies for each group were HPs: 45.7% [39.05%, 52.43%], Ls: 36.1% [31.87%, 40.33%], and NRs: 18.2% [13.63%, 22.77%]. Differences in the neurocognitive profiles were robust, and despite excluding data from D-WCST performance there was a complete separation of the three groups based on more than 20 neurocognitive data points, with HPs > Ls ($d=0.377^*$), HPs > NRs ($d=0.994^{***}$), and Ls > NRs ($d=0.623^{***}$). For response to psychosocial intervention, 70% of HPs were classified as “Responders” (23 of 33), and 53% of Ls (19 of 36), but only 6% of NRs (1 of 17). The effect of group on outcome was highly significant ($\chi^2=19.46$, $p<0.0001$). We then chose to examine the predictive value of NR status versus the other two groups (HPs and Ls). NR status was highly predictive of poor response to psychosocial intervention (OR=26.44, $p=0.002$).

Discussion: The three D-WCST groups showed a surprising degree of stability across multiple sites. The three groups also showed marked differences in neurocognition. Interestingly, while the Ls and NRs were indistinguishable on initial administration of the WCST, the overall neurocognitive performance of Ls was much closer to HPs. Moreover, Ls and HPs had similar outcomes, with >50% improving, while NRs were extremely unlikely to show improvement (6%). This may indicate a need for an alternate training approach for NRs such as errorless learning. While this finding is preliminary given the small number of studies, the strength of the effect (OR=26.44), suggests that the D-WCST may have strong predictive value for neurocognitive function and response to psychosocial intervention.

Poster #S185

ATTRIBUTION OF MENTAL STATES DURING CONVERSATION IN SCHIZOPHRENIA: PROFILE OF POOR MENTALISERS

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Background: A deficit in social cognition including theory of mind (ToM) is one of the most disabling clinical characteristics of schizophrenia. Very few studies have investigated these impairments in schizophrenia during natural communication situations (McCabe et al. 2004, Champagne-Lavau et al. 2009). Recent findings have shown that people with schizophrenia (SZ) may be more or less impaired in their ToM skills (Pickup and Frith, 2001; Champagne-Lavau et al., 2009; Brüne and Schaub, 2012). Indeed, 50% to 80% of SZ patients may show difficulties to attribute mental states (Brüne & Schaub, 2012). Using a classical ToM task (i.e. MSAT), Brüne & Schaub (2012) showed that, by comparison to SZ patients with fair ToM abilities, SZ patients with poor ToM abilities were characterized by social behavioral abnormalities, disorganization and excitement symptoms, with absence of executive dysfunction. However, observing a social interaction is not equivalent to participating in a social interaction in terms of the cognitive processes involved in the attribution of mental states to other. Thus, the aim of the present study was to examine characteristics of relatively impaired SZ patients (SZ-I) and relatively unimpaired SZ patients (SZ-U) on a ToM task assessing attribution of knowledge during a situation of conversation

Methods: Thirty individuals with a DSM-IV diagnosis of schizophrenia (SZ) were recruited. They were all native French speakers. Severity of symptoms was measured using the Positive and Negative Symptom Scale (PANSS; Kay et al., 1987). Patients were assessed on their ToM ability during a situation of conversation with the referential communication task (Champagne-Lavau et al., 2009). They were also submitted to a neuropsychological evaluation (flexibility, fluency, episodic and working memory, planning) and were assessed on their social functioning.

Results: A K-means cluster analysis was used to classify the SZ data into relatively unimpaired (SZ-U, N=15) versus relatively impaired (SZ-I, N=15) on the ToM task. A ToM index reflecting ToM performances of the SZ patients during the conversation was calculated and used for this K-means cluster analysis. A series of t-tests showed that the two SZ subgroups were comparable in age ($t(28) = 1.511$, $p>0.05$), education level ($t(28) = -0.564$, $p>0.05$), duration of illness ($t(28) = 1.895$, $p>0.05$), IQ (NART ($t(28) = 2.036$, $p>0.05$), flexibility measured by the WCST (WCST-categories: $t(28) = -0.696$, $p>0.05$, WCST-perseveration: $t(28) = 0.258$, $p>0.05$), mem-

ory (Digit span forward ($t(28) = 1.254$, $p > 0.05$), episodic memory (CVLT: $t(28) = -0.029$, $p > 0.05$), planning measured by the Zoo map test ($t(28) = 0.556$, $p > 0.05$) and fluency ($t(28) = -0.519$, $p > 0.05$). However, they significantly differed on symptoms (PANSS (positive): $t(28) = -3.216$, $p = 0.003$, PANSS (negative): $t(28) = -2.360$, $p = 0.025$, PANSS (general): $t(28) = -2.955$, $p = 0.006$), social functioning ($t(28) = 3.151$, $p = 0.004$) and working memory (Digit span backward ($t(28) = 2.082$, $p = 0.047$).

Discussion: Results of the present study confirm those of Brüne & Schaub (2012) showing that around 50% of the SZ patients present ToM impairments. SZ-U patients differed from SZ-I patients by the presence of more symptoms, poor social functioning and impaired working memory. It seems that whatever the ToM task used (the patients being involved or not in the social interaction) to assess the attribution of mental states to others, poor mentalisers exhibit the same profile.

Poster #S186

COGNITIVE PERFORMANCES OF JUVENILE OFFENDERS WITH SEVERE PSYCHIATRIC DISORDERS

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Background: Cognitive deficits in adolescent-onset schizophrenia are well-documented in literature. Major deficits in executive functioning, verbal episodic memory and sensory motor dexterity have been reported, as well as a reduced processing speed. As juvenile offenders also present inhibition deficits, our aim was to examine neuropsychological profiles among juvenile offenders with severe psychiatric disorders.

Methods: This study was conducted in Brussels, Belgium in a 14-bedded unit of the C.H.J. Titeca. The unit treats adolescents (aged 15 to 18) with early-onset schizophrenia and/or major affective disorders, who are involved in severe delinquency. As a part of a multidisciplinary approach, we systematically evaluated the cognitive functioning (assessment one month after admission) of all patients admitted since November 2010. The obtained scores were converted to standardized z scores based on published norms for the tests. We used one sample t-tests to compare standardized scores with norms.

Results: Compared to the norms, patients were significantly slower in D2 attention test and in Trail Making Test (all $p < 0.001$), but their quality was within normal range. During interference subtask of the Stroop test, speed and quality in patients were significantly lower than norms. Among them, performances on WISC-III Mazes were also significantly lower than norms ($p < 0.001$). Patients' scores on verbal working memory were significantly lower than norms on forward and backward Digit Span (all $p < 0.001$). Their performances on a verbal episodic memory task were not different from norms when evaluated with the California Verbal Learning Test, while they scored significantly lower than norms on the delayed recall ($p = 0.009$) and delayed recognition ($p = 0.002$) of the Stories CMS. Baddeley's Doors test revealed performances lower than norms (Part A $p = 0.048$; Part B $p = 0.001$). Mean performances among patients in tests evaluating visuo-spatial processing (Rey's Complex Figure, WISC-IV Picture Completion and WISC-IV Block Design, respectively, all $p < 0.001$) and processing speed (WISC-IV Coding, $p < 0.001$) were significantly lower compared to norms.

Discussion: Juvenile offenders with severe psychiatric disorders have a reduced processing speed. Poor performances in D2 attention test and in Trail Making Test may have been influenced by this reduced processing speed. Stroop test showed inhibition deficits which could partially explain low performances on WISC-III Mazes, as most errors illustrate patient's haste. Performances on memory tasks revealed impairments in verbal working memory and visual episodic memory, while verbal episodic memory seems partially preserved. Indeed, performances at California Verbal Learning Test suggest intact learning abilities. Nevertheless, difficulties to recall and recognize Stories (CMS) could be understood as an insufficient ability to structure information, or as a lack of comprehension. In this patient group, we observed presence of major cognitive impairments, and we emphasize the importance of integrating a cognitive approach into the multidisciplinary therapeutic process.

Poster #S187

AT-RISK STATES IN PSYCHOSIS: SCHIZOPHRENIA PRONENESS INSTRUMENT (SPI-A/SPI-CY) AND ITS NEUROPSYCHOLOGICAL CORRELATES

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Background: The at-risk state for developing psychosis is well established and there is a lot evidence for deficits in neuropsychological functioning already during the prepyschotic period. The purpose of this study was to compare the subjective perception of cognitive disturbances in individuals at risk for psychosis and objective variables according to neurocognitive measures.

Methods: Subjects were recruited from the ZInEP-Study, a prospective longitudinal multidimensional study of individuals at risk for psychosis, from the area of Zurich, Switzerland. For the current study, we targeted individuals meeting criteria for a risk-state for psychosis (either high-risk according to the Schizophrenia Proneness Instrument, SPI-A, adult version, SPI-CY, child and youth version, respectively, or ultra high-risk criteria according to the Structured Interview for Psychosis-Risk Syndromes, SIPS). We examined the relationship of the "cognitive-attentional impediments" (CAI) and "cognitive disturbances" (CD) items from the SPI-A/SPI-CY with performance on cognitive tests from the neuropsychological battery. The SPI-A/SPI-CY are suggested to indicate a subjective view of the individual concerning its symptoms.

Results: N=221 participants have fully completed the baseline examinations (incl. SPI-A/SPI-CY and neuropsychological battery). Using a latent class approach we empirically derived homogeneous subgroups that showed unique patterns of CAI and CD. Based on a three-class solution, a "low thought initiative level" (LTI) subgroup and a "low functioning in receptive speech" (LRS) subgroup was found. In subsequent regression models LTI was found linked to performance in verbal working memory and with perseveration-errors of the Wisconsin Card Test. The four-class solution derived another subgroup, "slowed down thinking" (SDT). SDT was associated with verbal fluency and associated with the Trail Making Test and the FAIR.

Discussion: Our findings suggest differential subjective perceptions of neuropsychological functioning that can be subdivided into impaired thought initiative and disturbances of receptive speech. Specific associations with neurocognitive variables support this view. This raises the question of whether there are distinctive impairment subtypes as indicated by specific psychopathological and functional outcomes.

Poster #S188

THE ROLE OF COGNITIVE RESERVE IN PREDICTING NEUROPSYCHOLOGICAL OUTCOME IN SCHIZOPHRENIA

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Background: The concept of cognitive reserve (CR) is applicable to any condition that impacts on brain function to aid understanding of prognosis (Stern, 2009). The relevance of applying the CR concept in schizophrenia and its clinical utility in predicting cognitive outcome is investigated. Cognitive impairment is one of the core features of schizophrenia. Barnett et al. (2006) posited that individuals with higher CR are hypothesized to have higher threshold to cognitive impairment than individuals with lower CR. This study builds on this proposition and takes a lifespan perspective

that uses a holistic conceptualization of CR comprising of CR "enhancers" (CR+) and CR "diminishers" (CR-) to investigate the relationship of CR with neuropsychological outcome in schizophrenia.

Methods: We recruited community dwelling, English-speaking Chinese participants with schizophrenia who were aged 21 to 55 years. Potential CR "enhancers" (CR+) included educational attainment, occupational complexity and social support. Potential CR "diminishers" (CR-) comprised of risks factors that compromise brain integrity and functioning such as presence of medical problems, history of substance use, and duration of psychiatric illness. Neuropsychological outcome was assessed by scores on tests of attention, working memory, speed of information processing, learning and memory, visuospatial skills, executive function and motor speed. Multivariate analysis of variance (MANOVA) was used to test the hypothesized effects of independent variables (i.e., CR+ and CR-) on dependent variables (made up of neuropsychological test scores). CR+ and CR- each contained multiple components that were considered simultaneously (i.e., CR+ included highest educational level, adjusted years of education, occupational complexity and living arrangement, and CR- included presence of medical problems, smoking status, duration of psychiatric illness and family history of mental illness). The effects of medications, and demographic variables such as age and gender on cognitive outcome were controlled for in the analyses.

Results: Data from 620 participants (332 males and 288 females) were analyzed in this study. The hypothesis that CR would have a significant impact on neuropsychological outcome such that higher levels of CR+ would be associated with better neuropsychological outcome in all cognitive domains examined was supported. MANOVA revealed that CR+ significantly predicted performance in all cognitive domains; $p < 0.0001$ for all CR+ effects. The hypothesis that higher levels of CR- would be associated with poorer neuropsychological outcome in all cognitive domains was partially supported because CR- did not significantly predict performance in visuospatial skills; CR- effects for executive function and motor speed were significant at $p < 0.0001$, $p = 0.002$ for speed of information processing, and $p < 0.05$ for attention, working memory, learning and memory. The covariate effects of age, gender and medications were significant although the pattern effects differed across CR+ and CR-.

Discussion: Our findings provided support for the role of CR in predicting cognitive outcome in schizophrenia. CR+ exerted neuroprotective effects on neuropsychological outcome in all cognitive domains. Importantly, besides investigating variables that enhance CR, this study also examined the effects of variables that may diminish CR. Findings showed that CR- posed vulnerability on all cognitive domains except visuospatial skills. This study provided a holistic perspective on the possible impact of CR on cognitive functioning, specifically that CR is multi-faceted. The relationship between CR and cognitive endophenotype may contribute to clinical outcome in schizophrenia.

Poster #S189

NEUROCOGNITIVE FUNCTIONING OF SUBJECTS WITH PUTATIVE PRE-PSYCHOTIC STATES AND EARLY PSYCHOSIS: BASELINE ASSESSMENT AND 1-YEAR FOLLOW-UP

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Background: A study on the psychopathological progress of the pre-psychotic state, SOPRES, was launched in Taiwan from 2006 to 2010. Four clinical groups, spanning from first episode psychosis (FEP), ultra-high risk group (UHR, with attenuated or brief intermittent psychotic symptoms), intermediate risk group (IRG, with some odd appearance, behavior, speeches, thoughts, or perceptual experiences), and marginal risk group (MRG, with some non-specific symptoms not fitting into common psychiatric diagnoses), together with a group of age- and gender- matched normal controls, were assessed with a set of neuropsychological battery at baseline and 1-year follow-up.

Methods: Participants' clinical risk groups were determined by a structured Thought and Perception Diagnostic Interview Schedule (TP-DIS). Among the UHR group, 15 converted into FEP during 1-year follow-up, was designated as UHR+, and the rest was UHR-. Continuous performance test (CPT), Wisconsin Card Sorting Test (WCST), Wechsler Adult Intelligence Scale-Third

Edition (WAIS-III), Trail Making Tests, Mandarin version of Verbal Fluency Test, Wechsler Memory Scale-Third Edition (WMS-III), logic memory tests and visual reproduction tests were conducted to measure intelligence, verbal and visual episodic memory, processing speed, executive function and attention. Z-scores for all variables were computed based on the mean and standard deviation of the control group after transforming to conform that higher scores indicate better performance. The differences in performance among groups were examined by ANOVA.

Results: Totally 324 participants, including 49 FEP, 53 UHR, 42 IRG, 43 MRG and 137 normal controls have completed assessments at baseline. Among them, 29 FEP, 15 UHR+, 22 UHR-, 23 IRG 29 MRG and 117 normal controls repeated assessments at 1-year follow-up. At baseline, all 4 clinical groups revealed significantly lower IQ compared to the normal controls. The FEP and IRG showed impaired executive function, processing speed, and immediate and delayed verbal memory, while the deficits in FEP were much greater than that in IRG. The UHR showed similar deficits except not in executive function. The MRG only showed mild sporadic neurocognitive deficits. The UHR+ showed significantly impaired executive function and attention which were not significant in their UHR- counterpart at baseline. At 1-year follow-up, the UHR- got improved in most domains, while the UHR+ revealed similar pattern to that of FEP. The FEP did not show much difference in deficit patterns from their baseline performance.

Discussion: The UHR+ group already demonstrated more deficits than UHR- at baseline and showed a pattern of neurocognitive deficits similar to that of FEP once transition into full-blown psychosis. The FEP demonstrates consistent neurocognitive deficits over time. This evidence supports that patient's cognitive deficits tend to persist once full-blown psychosis developed. UHR subjects with a lesser extent of deficits at baseline seem to be easier to divert from the trajectory of psychosis formation. Prediction of transition to psychosis might take into account this finding and intervention measures for UHR subjects can be designed based on these observations. The definition of our IRG is close to schizotypal disorder, and we found IRG showed similar neurocognitive deficits to that of FEP, while to a lesser extent and not got worsened during follow-up. This implies that traits of schizotypy might predispose them with certain neurocognitive deficits similar to that seen in schizophrenia.

Poster #S190

SCREENING FOR COGNITIVE IMPAIRMENT IN CHRONIC SCHIZOPHRENIA USING THE COGNIGRAM COGNITIVE ASSESSMENT SYSTEM

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Background: it is now accepted the impairment in cognitive function is an important part of the schizophrenia illness. While there has been substantial research conducted into determining the nature and magnitude of cognitive impairment in groups of patients with schizophrenia, there has been comparatively less effort aimed at defining and estimating the frequency of cognitive impairment in individual patients with schizophrenia. Recent studies have found a brief battery of computerized tests, the CogState Brief Battery, is highly sensitive to cognitive impairment in individual with neurologic disease. We therefore sought to determine the extent to which cognitive impairment could be identified in patients with chronic schizophrenia using this battery.

Methods: Cognitive function was measured in 345 patients with chronic schizophrenia using the MATRICS consensus battery and the CogState Brief battery. The data from the MATRICS battery were inspected by a team of clinical neuropsychologists with expertise in schizophrenia and each patient was classified as having or not having a cognitive impairment on the basis that they showed performance that was 1 SD below the means of healthy age matched controls on 3 or more of the seven outcome measures. The same group were assessed using four tasks (detection, identification, one back and one card learning) in the cogstate brief battery and impairment was classified when performance on two or more of these tests was 1SD below group mean. Rates of concordance were measured between the two methods of classification of cognitive impairment.

Results: using the MATRIC consensus battery and the expert panel of neuropsychologists, 157 of the 345 patients with schizophrenia were classified as having cognitive impairment. The tests most sensitive to this impairment where the measures of verbal list learning test ($n=162$ impaired), verbal

working memory test (n=102 cases) and attention. (n=121 cases). The time required for administration of the MATRICS battery was on average 67 minutes and the time required for analyses of scores and classification 45 minutes. Individuals with classified as having cognitive impairment had more greater severity of negative symptoms, and were slightly older than those without cognitive impairment. Using the Cognigram system, 162 cases of cognitive impairment were classified in the schizophrenia sample with an agreement in classification of 94%. Time for administration of the Cognigram system was 15 minutes and scoring was immediate.

Discussion: These data suggest that it is possible to use a small battery of cognitive tests to identify the presence of cognitive impairment in individual patients with schizophrenia. Use of the Cognigram system to identify cognitive impairment provided a high degree of agreement with conventional neuropsychological testing and analysis, yet was completed in much less time. Screening for cognitive impairment in schizophrenia may be important for identifying people who would benefit from treatment with putative cognitive enhancing drugs

Poster #S191

THE CHICKEN OR THE EGG? – AN INVESTIGATION OF COGNITIVE AND NON-COGNITIVE IMPAIRMENTS IN SCHIZOPHRENIA IN THE LIGHT OF GOAL-DIRECTED BEHAVIOURS' IMPLEMENTATION

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Background: For 20 years, deficits of goal-directed behaviours (GDB) have been considered a key feature in schizophrenia. GDB refer to behaviours generated following a given objective by building a plan and selecting actions. These actions should lead to the attended goal either immediately or within a longer period. These types of actions are involved in most of the complex or novel situations a subject may encounter, regardless of the cognitive, affective or social abilities this situation implies. Yet so far, few studies have attempted to investigate the clinical impact of these disorders. There is clearly a wide range of investigations in the field of the medical imagery; however, they do not capture the important relevance of these disorders in understanding cognitive and behavioural deficits in schizophrenia. Our study aims to address the question of GDB impairments from a clinical angle by investigating how constraints and instructions can impact the subject's performances in cognitive and visuomotor tasks.

Methods: 50 to 100 in- and outpatients are currently assessed with two programs: one using verbal fluency (semantic and letter fluencies), and the other using a visuomotor task (in which subjects have to hit targets on a touch screen). Those programs are built so as to vary the conditions for carrying out the task from the freer to the most constrained. To do so, in both of the tasks, the subjects have to complete a free condition task ("do however they want") and then they are given contextual cues that are either words (for the verbal fluency) or instructions (for the visuomotor task) which are supposed to structure their responses. Three conditions are then proposed: one free, one fully cued (structured) and one with less directive or indirect cues (semi-structured). Besides, anamnestic (age, sex, schooling), clinical (PANSS, BPRS, LARS, neuroleptic dose, additional treatment and duration of illness) and cognitive (mental flexibility, inhibition, attentional shifting, sustained attention and verbal IQ) features are considered.

Results: Preliminary data on 20 subjects (10 men and 10 women; age: 44±10.98; schooling: 10.8±1.79 school years completed) show that in verbal fluency, patients benefit from the structuring procedures in semantic fluency (number of words produced) as much as cueing is strong (structured fluency>classic fluency**; semi-structured fluency>classic fluency*); but also in letter fluency (structured fluency>classic fluency**) in which cues also help subjects in organizing their responses (clusters in structured letter fluency>clusters in classic letter fluency**). Results display the same pattern for the visuomotor task (number of hits) (structured condition>semi-structured condition>free condition**). Finally, among all the anamnestic, clinical and cognitive controlled features, only mental flexibility significantly correlates with the ability to benefit from cueing in the verbal, but also in the visuomotor task.

Discussion: Preliminary data show that patients could benefit from cueing in cognitive and visuomotor tasks in terms of efficiency but also in terms of responses organization, regardless of their anamnestic, cognitive or clinical

profile. This suggests that both cognitive and non-cognitive impairments found in a wide range of abilities in patients with schizophrenia could be underlined by the same deficit mechanism in the implementation of goal-directed behaviours; which could be offset by structuring procedures. Results of the entire sample (including subjects with schizophrenia and a control group) will be presented and the specific nature of the impaired mechanism (initiation versus planning) will be discussed. *p<0.05 **p<0.01

Poster #S192

EXAMINING THE IMPACT OF NEUROCOGNITIVE AND LANGUAGE IMPAIRMENTS ON FORMAL THOUGHT DISORDER IN SCHIZOPHRENIA

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Background: Formal thought disorder (FTD) in schizophrenia has been associated with both cognitive and language impairments. However, there is still considerable debate regarding the degree to which each contributes to FTD. There has also been evidence that neurocognition is related to language processing abilities (Bagger et al., 2003). In this study, we chose to focus on receptive language impairments in schizophrenia. In particular, we investigated receptive language impairments at both the single word and sentence levels. This study had two aims: (i) to examine which cognitive impairments are related to FTD and, (ii) to explore if FTD has any language-specific symptoms, independent of neurocognition.

Methods: 9 schizophrenia/schizoaffective patients with diagnosed FTD, 48 schizophrenia/schizoaffective disorder patients without diagnosed FTD and 48 healthy controls completed the MATRICS battery and D-KEFS Stroop task assessing general neurocognition and inhibition, as well as two language tasks assessing synonym identification (lexical semantics) and sentence meanings (syntax). Clinical symptoms were rated using the PANSS, and FTD was rated using the TLC (Andreasen, 1979) and PANSS P2.

Results: Cognitive assessment results revealed FTD patients performed worse than non-FTD patients on measures of semantic and executive processing ($p<0.05$), with both groups poorer than controls ($p<0.01$). This supports indications of concurrent semantic and executive dysfunction, and suggests that a combination of both may relate to manifest FTD. Language assessment results revealed impairments in FTD compared to non-FTD patients and controls in the recognition of homophones (but not antonyms) and sentence comprehension (syntax). This supports language processing impairments at both the single word and sentence levels in FTD. A significant relationship between positive FTD symptoms and syntactic problems ($p<0.001$) was found to hold even after controlling for neurocognitive deficits (semantic and executive). The relationship between FTD and homophone choice did not hold. This provides evidence that a language-specific impairment of syntactic ability is present in schizophrenia, and exacerbated in FTD.

Discussion: Overall, this study supports current cognitive and language theories of impairment in FTD, with evidence for concurrence of both. Syntactic impairments reflect a specific deficit in language processing; which contribute to FTD severity in combination with executive and semantic dysfunction.

Poster #S193

SOCIAL COGNITION TRAINING FOR PEOPLE WITH SCHIZOPHRENIA: A RANDOMISED STUDY

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Background: Social functioning deficits are common in people with schizophrenia and were shown to be important prognostic indicators. Social Cognition and Interaction Training (SCIT) is a manual-based treatment designed to improve social functioning in people with schizophrenia by enhancing social cognition. The aim of this study was to evaluate the feasibility, acceptability, and efficacy of SCIT in male inpatient forensic wards.

Methods: The study is a randomised single blind controlled, crossover design, with 21 participants randomised to SCIT and 15 to treatment as usual (TAU). SCIT treatment consisted of eight-week therapy sessions twice per week. Participants were assessed before and after the intervention period with measures of symptoms, affect recognition, theory of mind and attributional style. Feasibility was assessed through group attendance. Participant acceptability was evaluated through post-group satisfaction and social goals achievement.

Results: The group was well received by all participants and the majority reported their confidence had improved following the intervention. Almost two thirds of the SCIT participants agreed they had achieved their social goal as a result of the intervention. Participants in the SCIT group showed a significant improvement in affect recognition compared to TAU. However, the two groups did not differ in theory of mind and attributional style after therapy.

Discussion: It is feasible to deliver SCIT in forensic ward setting and the intervention improved affect recognition. Some adaptations may be needed in order to accommodate for the reduced social contact of forensic wards.

Poster #S194

ROLL-OUT AND IMPACTS OF DJ'S CHOICES WORKSHOPS

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Background: Since 2010, in Quebec province, several teams are familiar with the DJ's Choices program to promote treatment adherence in patients suffering from psychosis. In addition to a short introduction to the program, these teams have expressed a need for support and training to embrace an interdisciplinary approach combining psychosocial and medical perspectives. The goal of our communication is to describe our multicenter project that will assess the impact of DJ's Choices approach roll-out in different settings. This project therefore pursues the following objectives: 1) To ensure the roll-out of DJ's Choices workshops in their current format as resources for specialized and primary care teams. This means organizing and supporting the roll-out of such a program for teams caring for people with mental illness, including specialized and primary care teams from a representative selection of facilities within the Québec province; 2) To assess the impact of the distribution of this program on patients, care providers and the organization, using treatment adherence indicators in exposed individuals and satisfaction, skill enhancement and cross-sharing indicators in professionals involved in implementation.

Methods: The roll-out of DJ's Choices workshops will rely on INSPQ (Institut national de santé publique du Québec) theoretical model for knowledge transfer, including its eight stages (production/co-production of the support and training program content, program adaptation, distribution, reception, adoption, appropriation, use of knowledge and assessment of results). A first qualitative phase will be conducted through an initial telephone survey of key players (care providers already exposed to the program and individuals targeted to receive training) using a set questionnaire. Analysis of this data will provide a basis for creating a program targeting training and support for the DJ's Choices workshops roll-out. A roll-out kit will then be developed to support DJ's kit deployment in these identified settings.

Results: The impacts observed in care providers and individuals living with psychosis exposed to the program will be assessed before, during and after the program over a 3 years period. Nine sites will be included, some from university clinics, others, from community settings in the Quebec province. Several indicators of impact will be collected at three main levels: 1) In patients: Combined assessment measures for adherence (e.g., self-report adherence scales, prescription renewal at the pharmacy, overall clinical assessment according to care providers' impressions, medication counting where possible) will be collected before, during and after program roll-out. 2) In health care providers: basic knowledge concerning psychopharmacology and facilitation techniques inspired by the motivational approach and cognitive behavioral therapy will be assessed throughout the three stages of the project. 3) In organizations: We will carefully describe the different organizational environments in which the program will roll out and will identify the factors that promote or restrict program roll-out in the different settings.

Discussion: This project will include systematic assessment of the impacts of the DJ's Choices roll-out in a representative sample of different psychiatric care settings in Quebec. In the long term, it aims to improve the efficiency of the distribution of this innovative treatment adherence support to all settings in the province

Poster #S195

PREVENTION OF WEIGHT GAIN IN EARLY PSYCHOSIS: A RANDOMIZED CONTROLLED CLINICAL TRIAL OF 16-WEEK STEPPED BEHAVIORAL INTERVENTION

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Background: Patients with serious mental disorders are at higher risk of being overweight and obese which increases their vulnerability to cardiovascular morbidities and mortalities. Along with unhealthy dietary habits and higher physical inactivity in patients with psychosis, the use of novel antipsychotic drugs is highly associated with weight gain especially in early phase of treatment. The degree of weight gain varies by the type of antipsychotic medications being used, with clozapine and olanzapine are most likely to cause weight gain, followed closely by risperidone and quetiapine. The higher prevalence of obesity in patients receiving anti-psychotic treatment, directs our attention towards developing strategies to reduce weight gain in this high risk group. The aim of the study therefore, was to evaluate whether a "stepped behavioral intervention" is effective in preventing weight gain in early psychotic patients as compared to usual care.

Methods: This was a parallel group randomized control trial (RCT) in which sixty participants diagnosed with an early psychotic illness (schizophrenia, schizoaffective disorder, bipolar disorder, psychosis NOS, within 5 years of illness-onset) were recruited for a 16-week intervention program. After providing informed consent, the participants who met the enrollment criteria were randomly assigned to either get a stepped behavioral intervention (SBI) ($n \sim 30$) or treatment as usual (TAU) (routine care, $n \sim 30$). The prevention of weight gain (increase over baseline) in two groups, using chi-square test, was the primary outcome measure, with mean change in weight as a secondary outcome (t test).

Results: Sixty two percent of the participants were male, most were single and young with a mean age of 24.5 ± 5.8 years. Fifty five percent of the participants were of European ancestry followed by 22% of African ancestry. Only 4 of the participants were employed. Out of 60 participants, regardless of treatment assignment, 12 did not gain any weight. And of these 83% were in SBI group as compared to only 17% in the control group (P value = 0.034). The mean change in weight was 2.27 ± 4.7 in SBI group and 4.61 ± 4.6 in TAU group (P value = 0.08). Further, all participants gaining more than 20% over baseline weight were in the TAU group. Overall, the participants in the SBI were significantly less likely to gain weight and their mean weight gain was also lower (approaching significance) than for the TAU group.

Discussion: The findings of our study have important public health implications. Weight gain in early psychosis, partly associated with the use of antipsychotic medications make the psychotic individual vulnerable to obesity related complications which may lead to inferior quality of life and decrease life expectancy. The SBI, evaluated in this clinical trial, shows promise in preventing weight gain in these individuals with a serious mental disorder. Such interventions not only increase the awareness about the benefits of healthy life style but also motivate the patients to adopt them as part of their daily routine. Numerous studies of patients with chronic illness and established obesity have demonstrated that behavioral interventions can be effective in inducing weight loss. However, prevention of weight gain is likely to be even more effective in reducing the risk of both diabetes and cardiovascular diseases in this population, and to also more effectively reduce disability and premature mortality.

Poster #S196**COMMUNITY-BASED SKILLS TRAINING HELPS PSYCHOTIC CLIENTS OF VARYING AGES, EDUCATIONAL LEVEL, AND WORK EXPERIENCE MAKE FUNCTIONAL GAINS**Alice Medalia¹, William Jock², Alicia Ventresca³, Tiffany Herlands⁴¹Columbia University Department of Psychiatry; ²New School; ³Yeshiva University; ⁴Columbia University Medical Center

Background: A prior study showed Community-Based Skills Training to be a feasible adjunct to clinic-based training and particularly effective in improving functional outcomes for individuals identified as lower functioning at baseline. To these authors' knowledge there is no published study examining whether community-based skills training interventions are equally effective for younger adults and older adults or for individuals of varying levels of education and employment history. The aim of this study was to examine whether age, years of education, and years in the workforce are related to response to Community-Based Skills Training for people with psychosis.

Methods: This study used de-identified data collected as part of routine clinical outcomes assessment done at a private outpatient treatment program for people with severe and persistent mental illness (www.lieberclinic.com). 22 individuals (16 = male) were identified at intake as having extreme difficulty with community functioning and were offered the Community-Based Skills Training in addition to the clinic-based group program (cognitive remediation, CBT, DBT). Clients ranged in age from 19 to 57 (M = 29.41, SD = 9.52) had a diagnosis with psychotic features (17 = schizophrenia or schizoaffective disorder; 3 = affective psychosis; 2 = psychosis NOS). Four Masters-level clinicians were trained in Community-Based Skills Training. The coaches helped their clients practice identified deficient skills (e.g., social, travel, independent living) an average of 2 hrs./week. Coaching was done in the community, either one on one or in groups of up to 4 clients. We tracked the functional outcome of the sample at intake and 4 months later, using The Multnomah Community Ability Scale (MCAS). 3 individual care coordinators were trained to rate clients with the MCAS to good inter-rater reliability (0.87). Standardized residual gain scores were run from MCAS Time 1 to Time 2.

Results: As a group there was significant gain in MCAS scores over time ($t=-2.184$, $p=0.040$). Gain scores did not correlate significantly with age ($r=-0.040$, $p=0.859$), years in the workforce ($r=0.220$, $p=0.324$), or years of education ($r=0.129$, $p=0.566$).

Discussion: Prior research has shown that for the most impaired clients, practicing skills in the community may be an important adjunct to clinic based treatments. This study indicates that Community-Based Skills Training can help psychotic clients of varying ages, education and work experience progress toward better community functioning.

Poster #S197**ENHANCING COGNITIVE TRAINING THROUGH AEROBIC EXERCISE AFTER A FIRST SCHIZOPHRENIA EPISODE: THEORETICAL CONCEPTION AND PILOT STUDY**Keith H. Nuechterlein¹, Joseph Ventura², Denise Gretchen-Doorly¹, Sarah C. McEwen³, Sophia Vinogradov^{4,5}, Kenneth L. Subotnik¹¹UCLA; ²UCLA Department of Psychiatry & Biobehavioral Sciences; ³UCLA Department of Psychiatry; ⁴University of California, San Francisco; ⁵Associate Chief of Staff for Mental Health, SFVA Medical Center

Background: Structured cognitive training and aerobic exercise have separately shown promise for improving cognitive deficits in schizophrenia (SZ). Regular aerobic exercise releases brain-derived neurotrophic factor (BDNF) which promotes synaptic plasticity and neurogenesis. Thus, aerobic exercise provides a neurotrophic platform to enhance the impact of neuroplasticity-based cognitive training. The combination of aerobic exercise and cognitive training in SZ may yield more robust effects than cognitive training alone. Furthermore, providing this combined intervention in the initial period of illness may lead to greater impact and broader generalization to functional outcomes compared to periods in which chronic illness factors are well established.

Methods: In a pilot study, seven patients with a recent first episode of SZ were assigned to Cognitive Training & Exercise (CT&E) and nine to Cognitive

Training alone (CT) for a 3-month period. We used neuroplasticity-based programs from Posit Science (Brain HQ and SocialVille) in sequence for cognitive training. The auditory discrimination and verbal processing components of BrainHQ focus on basic neurocognitive functions designed to tune neural circuits related to perceptual processing and verbal learning and memory. The social cognitive training in SocialVille builds on this base using the same learning principles but with social and affective stimuli more relevant to everyday social interactions. Both treatment groups participated in these computerized cognitive training sessions at UCLA two days a week, two hours a day. To examine the hypothesized role of neurotrophin-releasing physical exercise in enhancing learning, the CT&E group also participated in an aerobic conditioning exercise program for 30 minutes at our clinic two days a week and at home two days a week.

Results: Attendance for the in-clinic CT&E sessions was excellent for both the cognitive training (100%) and the exercise groups (95%). Adherence with the CT&E at-home exercise component was similar (92%). For the MATRICS Consensus Cognitive Battery Overall Composite score, Group X Time (pre- vs. post-test) interaction results indicate that the CT&E patients improve notably more than the CT patients. The Cohen's f for this Group X Time interaction is 0.48, suggesting a large effect (Cohen defines f of 0.40 as large). In this initial feasibility study, the individual cognitive domains with largest differential gains for CT&E compared to CT alone are Social Cognition ($f=0.65$), Working Memory ($f=0.50$), Speed of Processing ($f=0.38$), and Attention/Vigilance ($f=0.33$). Group X Time interactions for functional outcome indicate that the CT&E group tended to improve more than the CT alone group in Independent Living ($f=0.88$), Family Network Relationships ($f=0.43$), and Working Productivity ($f=0.18$). Initial analyses in a sub-sample of patients suggest that changes in serum BDNF concentrations from baseline to follow-up are greater in the CT&E group (mean change 4220 pg/mL vs. 1544 pg/mL).

Discussion: Aerobic exercise produces neurotrophic factors that boost synaptic plasticity and learning potential, raising the possibility that it may increase the impact of neuroplasticity-based cognitive training. Our initial feasibility data indicate that it is possible to achieve excellent treatment adherence with a combined cognitive training and aerobic exercise program. Initial data also suggest that several effect sizes for differential gains in CT&E compared to CT may be large. These encouraging preliminary findings support the promise of combining cognitive training and aerobic exercise to improve the early course of SZ. A randomized controlled trial is now ongoing at UCLA.

Poster #S198**IS CORTICAL THICKNESS ASSOCIATED TO RESPONSIVENESS TO COGNITIVE REMEDIATION THERAPY IN SCHIZOPHRENIA?**Rafael Penadés^{1,2}, Rosa Catalán³, Núria Pujol⁴, Clemente García-Rizo⁵, Guillem Massana⁶, Carme Junqué⁴, Miquel Bernardo⁷¹Clinical Institute of Neurosciences, Hospital Clínic Barcelona, University of Barcelona, Barcelona, Spain; ²Departament of Psychiatry and Psychobiology, University of Barcelona, Hospital Clinic, Barcelona; ³Department of Psychiatry and Psychobiology, University of Barcelona; ⁴Department of Psychiatry and Psychobiology, University of Barcelona; ⁵Hospital Clínic de Barcelona;⁶Hospital Clínic, Barcelona; ⁷Hospital Clínic Barcelona; Fundació Clínic per a la Recerca Biomèdica; CIBERSAM; Universitat Barcelona, IDIBAPS

Background: Despite this evidence for the efficacy of CRT, comparatively little is known about potential predictors of a good treatment response (Kurtz, 2009, Wykes & Spaulding 2011). No study has previously tested neuroimaging data and only a few studies have examined patient characteristics like baseline cognitive functioning or symptoms as predictors of CRT outcome. We try to determine whether improvement in cognition following CRT in people with schizophrenia is positively associated with baseline CT measures or baseline symptoms level or baseline cognitive performance. We hypothesized that greater improvement in cognition following CRT would be associated with higher CT at baseline in the frontal lobes.

Methods: This is a retrospective study that uses data collected as part of a trial investigating a CRT programme in a partner study (Penadés et al., 2013). A controlled, randomized study (NCT 01318850) was carried out with three groups: patients receiving cognitive treatment, patients receiving a different psychological intervention as an active control, and a healthy control group (HC). All participants were assessed 2 to 3 days before

the first treatment session and also 2 to 3 days after the last treatment session through symptom scales, neuropsychological battery, and magnetic resonance imaging. HC were assessed at the recruitment and after a period of 4 months.

Results: After correction for multiple comparisons at the cluster level using Monte-Carlo simulation, associations between neurocognitive changes and cortical thickness were found to remain significant ($p < 0.05$). Contrary to our expectation, the brain areas associated with CRT responsiveness were not located mainly in the frontal lobes as we initially hypothesised but in the right temporal lobe. In the CRT group, greater verbal memory improvement was associated with greater CT in the right insula, superior and middle temporal gyrus, lateral orbitofrontal gyrus, and inferior frontal gyrus.

Discussion: To our knowledge, this is the first study to show a significant relationship between neuroimaging data and responsiveness to CRT. Our findings are consistent with the hypothesis that greater CT in specific brain areas could be associated with cognitive plasticity during CRT. Eventually if these results are confirmed in further studies, baseline measures of CT may assist clinicians in the prediction of responsiveness to CRT in patients with a diagnosis of schizophrenia.

Poster #S199

REFLEX: A METACOGNITIVE GROUP TREATMENT TO IMPROVE INSIGHT IN PSYCHOSIS

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Background: Many people with schizophrenia (50-80%) demonstrate impaired insight. A number of interventions aiming to improve insight have been proposed and evaluated, for example cognitive behavioral therapy and psycho-education. Results of these interventions leave room for improvement. Therefore, we proposed a new intervention to improve insight in people with schizophrenia: REFLEX. REFLEX focuses on insight in one's functioning in everyday life and changes in general functioning after psychosis by improving metacognitive acts necessary for insight (self-reflectiveness, idiosyncratic self-certainty) and reducing stigma-sensitivity. The primary objective was to improve insight. By increasing insight, we hoped to improve functional outcome.

Methods: 134 patients diagnosed with schizophrenia with poor insight were included in a multicenter randomized controlled trial. REFLEX was compared to an active control condition consisting of group wise simplified drill and practice cognitive remediation training (CRT).

Results: Clinical insight improved significantly in the REFLEX condition, but also in the control group. Self-reflectiveness, idiosyncratic self-certainty did not change during treatment. Improved clinical insight was associated with significantly less depression at follow-up.

Discussion: REFLEX leads to better insight, but interestingly this effect was not specific. Given that previous studies have shown that insight does not improve with treatment as usual, the insight increase in the control condition does not seem just an a-specific effect of time and attention in a treatment setting. Findings suggest that simplified CRT also has the potential to stimulate insight.

Poster #S200

A THREE MONTH FOLLOW UP STUDY EVALUATING CLINICAL CHANGE AND ATTITUDES TOWARDS INVOLUNTARY ADMISSION IN INDIVIDUALS DETAINED UNDER THE MENTAL HEALTH ACT 2001

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Background: We compared levels of insight, perceived coercion, attitudes

towards involuntary admission, beliefs regarding treatment and the fairness of involuntary admission (procedural justice) under the Mental Health Act (MHA) 2001, between baseline assessment (during an individuals' involuntary admission) and three months following revocation of their involuntary admission order.

Methods: All eligible participants (n=287) detained under the MHA 2001 in three approved centres (University hospital Galway, St Brigid's hospital, Ballinasloe, Roscommon County Hospital) over a 30 month period were invited to participate in the study. Demographic and clinical details were collected with the following psychometric instruments utilised: Brief Psychiatric Rating Scale (BPRS), Scale for Assessment of Insight in Psychosis (SAI-E), Client Assessment of Treatment (CAT), Global Assessment of Functioning (GAF), Hogan Drug Attitude Inventory (HDAI), MacArthur Admission Interview, Heinrichs' Quality of Life (QOL) and Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-1).

Results: One-hundred and ninety three participants engaged in baseline assessment with one-hundred and nine participants to date (57%) completing the follow-up assessment. The most common diagnoses were schizophrenia (n=39, 38%) and bipolar affective disorder (n=34, 30%). Significant beneficial changes were detected with the BPRS ($p < 0.001$), SAI-E ($p < 0.001$), GAF ($p < 0.001$), CAT ($p = 0.036$), HDAI ($p < 0.001$), procedural justice ($p = 0.002$), and attitudes to the process of admission ($p = 0.001$) at follow-up. No significant change in perceived coercion was detected at follow-up ($p = 0.118$). More positive views towards treatment were strongly associated with greater levels of insight ($r = 0.44$, $p < 0.001$), less symptomatology ($r = 0.383$, $p < 0.001$) higher procedural justice ($r = 0.321$, $p = 0.002$) and those with affective psychosis were found to have more positive attitudes to admission and treatment at follow up compared to those with non affective psychosis ($t = 2.06$, $p = 0.043$).

Discussion: Involuntary admission under MHA 2001 is persistently perceived as coercive by patients, however positive views towards the process and experience of involuntary admission develop with clinical recovery and are associated with improved insight.

Poster #S201

STABILITY OF RETROSPECTIVE SELF-REPORTS OF CHILDHOOD TRAUMA IN EARLY PSYCHOSIS

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Background: Over the last 10 years, it has become increasingly apparent from well-conducted research studies that childhood trauma (CT) is a risk factor for psychosis. Many studies rely on the use of retrospective self-reports to estimate the prevalence of CT. However, concerns have been raised that individuals experiencing psychosis may not be able to accurately report their experiences of CT, calling into question the validity of such research. Furthermore, people with psychotic disorders in psychiatric settings are less likely to be asked about abuse, partly because their responses are considered to be unreliable. While there is preliminary evidence that individuals experiencing psychosis report CT reasonably reliably across time, further research is required.

Methods: Retrospective reports of CT were collected using the Childhood Trauma Questionnaire from 25 young people experiencing first-episode psychosis (FEP) at two time points: within 2 weeks of first admission to acute first episode services and three months later. Psychopathology and other data was also collected. The Childhood Trauma Questionnaire was also given to 31 non-psychiatric controls at two time points, three months apart. All participants were aged 15-25 years.

Results: FEP participants reported higher CT than controls. Intraclass correlation coefficients suggested strong agreement between CT reports at baseline and follow-up for FEP participants (0.75) and almost perfect agreement (0.90) for controls. In the FEP group, there was no relationship between CT reports and positive symptom severity at baseline or follow-up, or in the change in these variables across the two time-points.

Discussion: Retrospective reports of childhood trauma are stable in those with acute early psychosis, although not as stable as in the general population. Positive psychotic symptoms are not a driver of retrospective

childhood trauma reports. This suggests that childhood trauma reports in those with acute psychosis should not be dismissed.

Poster #S202

CHARACTERIZATION OF A NUMBER OF ATYPICAL ANTIPSYCHOTICS IN VITRO

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Background: Background Atypical antipsychotics differ from the typical ones in that they are less prone to induce extrapyramidal symptoms (EPS) and that they have affinity for receptors other than the D2R, but the criteria for atypicality are not clearly defined. The antipsychotic agents have classically been characterized as D2R antagonists, based on their antagonist activity at the cyclic adenosine monophosphate (cAMP) signalling pathway. However, it has become increasingly clear that drugs may induce diverse functional responses through a single receptor depending on the measured endpoint. The aim of this study was to examine if atypical antipsychotics via the D2R are functionally selective, since functional selectivity at signalling pathways other than the cAMP signalling system could explain some of their atypical behaviour.

Methods: Antagonistic effects of the different compounds were assessed at two effector pathways and in binding and the obtained apparent affinity constants were compared. Compound-induced changes in intracellular cAMP was measured in CHO cells stably transfected with the Human dopamine D2 receptor using FlashPlates. The same cells were used to measure compound-mediated inhibition of dopamine-stimulated ERK1/2 phosphorylation (SureFire). Finally membranes bound to WGA-coated SPA beads were used to measure compound-mediated inhibition of 3H-raclopride binding.

Results: There was fairly good agreement of apparent affinities obtained in the binding assay, the cAMP assay and the pERK1/2 assay. The antagonists were in general weaker at the ERK1/2 pathway compared to binding and cAMP but the rank order was the same.

Discussion: It was not possible to identify compounds with functional selectivity based on the experiments performed in this study. Only antagonists were tested in this study; further studies using agonists and partial agonist are ongoing.

Poster #S203

INCREASED AUTONOMIC AROUSAL: IS IT A VULNERABILITY FACTOR AND SPECIFIC FOR PSYCHOSIS?

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Background: In vulnerability-stress models, alterations of the autonomic nervous system are proposed to contribute significantly to the development of psychosis. In psychotic disorders, increased autonomic arousal was found in affected and at-risk individuals and the findings indicate that this increase cannot solely be explained by medication. In the present study, we tested whether these characteristics can be associated with the extent of an individual's vulnerability for psychosis. Furthermore, the question of specificity was addressed by a comparison to depression, for which similar alterations have been reported. We expected vulnerability to be associated with more subjective stress, lower time-domain HRV, lower vagal activity, and higher sympathetic activity. We expected specificity to be evident in a difference between the psychosis and the depression group.

Methods: Twenty-three participants with psychosis (PSY; Mage = 40.2, SDage = 11.2), 21 first-degree relatives of individuals with psychosis (FDR; Mage = 39.1, SDage = 13.8), and 23 healthy participants with attenuated positive symptoms (APS; Mage = 34.0, SDage = 12.2) were compared to 24 participants with depression (DEP; Mage = 40.1, SDage = 10.4) and 24 healthy controls (HC; Mage = 33.8, SDage = 13.9). During a resting baseline, five minutes of skin conductance level were assessed and heart rate variability (HRV) was derived from photoplethysmography. As time-domain HRV, the standard deviation of normal-to-normal intervals (SDNN) and

the square root of the mean squared differences of successive normal-to-normal intervals (RMSSD), and as frequency-domain HRV, the absolute high frequency power (HFabs), percentage of high frequency power (HF%), and sympathovagal balance (LF/HF) were analyzed. Univariate and multivariate analyses of covariance were conducted with age and body mass index as significant covariates. Post-hoc t-tests were calculated with $\alpha=0.008$ (Bonferroni adjusted for the six comparisons within each hypothesis: PSY > FDR, APS, HC; PSY ≠ DEP; FDR, APS > HC).

Results: Significant between-group differences were found for subjective stress ($p=0.004$, $\eta^2 p=0.115$), time-domain HRV indices (SDNN: $p=0.027$, $\eta^2 p=0.096$; RMSSD: $p=0.012$, $\eta^2 p=0.111$), and vagal activity (HFabs, HF%: $p=0.017$, $\eta^2 p=0.082$), and a non-significant trend for sympathetic activity (LF/HF, skin conductance level; $p=0.069$). Subjective stress estimates were highest in PSY, with a significant difference to the estimation of APS ($p=0.001$). In psychophysiological data, low time-domain HRV was found in PSY when compared to HC (SDNN: $p=0.007$; RMSSD: $p=0.002$), to DEP (SDNN: $p=0.003$; RMSSD: $p=0.004$), and to APS (SDNN: $p=0.001$). Furthermore, PSY showed lower HFabs than HC ($p=0.002$) and than DEP ($p=0.005$).

Discussion: Despite being in a relaxation phase, participants with psychotic disorders perceived their stress levels as relatively high. In line with this subjective experience, time-domain HRV was decreased in these participants compared to healthy controls. Specificity for psychosis was indicated by a significant difference in the direct comparison to depression. Similarly, absolute vagal activity was found to be decreased in the participants with psychotic disorders compared to healthy and depressed participants. The hypothesized association of an alteration of arousal and vulnerability to psychosis was not confirmed in the present sample. However, the presented results are confined to the most robust findings in a thorough comparison of multiple groups.

Poster #S204

NON PSYCHOTIC PREGNANCY DENIAL: A CASE REPORT

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Background: Pregnancy denial is a woman's subjective unawareness of being pregnant. It could be associated with psychosis, social isolation, mental retardation, but it is often presented by women with no psychiatric disorder who are socially integrated.

Methods: A 25-year-old married woman was admitted after delivering her second daughter at home. She complained about never knowing that she was pregnant and about the lack of prenatal care she gave to her child (in contrast with the first pregnancy).

Results: Tests: SCID II, Beck Depression Interview, Beck Anxiety Interview, Edinburgh Postnatal Depression Scale, Beck Hopelessness Scale, and WHO-QoL were all below threshold. **Clinical:** No psychiatric signs or symptoms were elicited.

Discussion: Here we describe a woman without any sign of psychiatric illness or mental retardation, who gave birth to a child without realizing she was pregnant. She is extremely competent as a mother with both her daughters. Further psychiatric intervention was considered inappropriate.

Poster #S205

EXAMINING AND CONTRASTING THE SOCIAL STEREOTYPE OF SCHIZOPHRENIA AND DEPRESSION

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Background: Although the concept of a social stereotype is widely invoked in discussions of the stigma of schizophrenia, there has been little examination of the extent to which beliefs about schizophrenia or other mental illness really meet the criteria for being a stereotype. An essential aspect of

the concept of stereotype is that characteristics are differentially attributed to individuals on the basis of their membership in a social category as opposed to people in general. In the context of other putative stereotypes such as those associated with gender or race the diagnostic ratio has been used to assess the extent and significance of this differential attribution of characteristics, but this has never been applied to assess stereotypes associated with mental illness. In the current paper we use the diagnostic ratio to assess the presence of stereotypes concerning individuals diagnosed and treated for schizophrenia, depression or generic "mental illness".

Methods: Four hundred and eighty-six individuals completed a web-based survey in which they rated the probability of characteristics among individuals treated for either schizophrenia, depression, or mental illness in general, as well as the likelihood of the characteristics in the general population. The diagnostic ratio was used to identify stereotypic beliefs.

Results: There was evidence of stronger stereotypes for schizophrenia than for depression or generic mental illness. All three clinical labels were seen as associated with stereotypes presenting difficulties in interaction and psychological weakness. In addition, schizophrenia, but not the other labels, was associated with perceptions of danger and incompetence. Sex of the respondent and familiarity with the target condition had very limited effects on stereotypes.

Discussion: The research provides evidence of stronger socially shared stereotypes associated with schizophrenia than with depression or generic mental illness. It also suggests that schizophrenia is more likely to be seen as differentially related to danger and incompetence than are other descriptors of mental illness. Implications for programs to reduce the stigma of schizophrenia will be discussed.

Poster #S206

VITAMIN D DEFICIENCY IN DUTCH OUTPATIENTS WITH BIPOLAR DISORDER, SCHIZOAFFECTIVE DISORDER OR SCHIZOPHRENIA

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Background: Vitamin D has effects on bone mineralization, modulation of cell growth, neuromuscular and immune functions and reduction of inflammation. In addition vitamind D influences cognitive function and depression. Several studies have found subnormal vitamin D levels in adolescents with psychosis or mania and patients with chronic schizophrenia (Itzhaky 2012, Gracous et al. 2012, Sikoglu et al. 2013).

Methods: Outpatients between 18 and 65 years with bipolar disorder (group A) or schizophrenia/schizoaffective disorder (group B) in the Alkmaar region were asked for consent to an additional vitamin D-determination at their first regular laboratory control, often their annual laboratory screening.

Results: In total, 122 patients participated, 62 in group A (32% male) and 60 in group B (68% male). The mean age of group A was 48 (± 10.3) and of group B 44 (± 9.3). Normal vitamin D levels were found in 42% of bipolar and 45% of schizophrenia or schizoaffective patients. Insufficient levels (30–50nmol/L) were present in 29% resp. 30% of the populations, while 29% resp. 25% were vitamin D deficient (<30nmol/L).

Discussion: We found a high prevalence of insufficient vitamind D levels of 58% (95% CI 46 to 70%) in patients with bipolar disorder and of 55% (95% CI 42 to 67%) in patients with schizophrenia or schizoaffective disorder. This prevalence is six times higher compared to the general, native Dutch population (van der Meer 2011). According to the criteria of the Dutch Health Council, 29% resp. 25% of the groups are vitamin D deficient and therefore indicated for vitamin D suppletion in order to prevent osteoporosis. If confirmed, these results suggest inclusion of annual vitamin D screening in these two patient populations. An alternative could be standard supplementation of bipolar and psychosis patients with vitamin D 20 µgr/day as is already recommended for the general population of 70 years and older.

Poster #S207

ACCUMULATED ENVIRONMENTAL BUT NOT GENETIC GWAS-DERIVED RISK DETERMINES SCHIZOPHRENIA ONSET

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Background: With a worldwide lifetime prevalence of ~1%, an onset typically during early adulthood and still limited treatment options, schizophrenia is among the most devastating psychiatric illnesses. Substantial efforts have been made to identify genetic roots of schizophrenia, in view of heritability estimates of ~80%. However, it is becoming increasingly obvious that a biologically vastly heterogeneous, multigenic group of disorders is classified under the umbrella term 'schizophrenia' and that actual 'disease genes' do not exist. In fact, genes alone cannot explain the disease risk, as reflected by a concordance rate of just ~50% in monozygotic twins or the constantly low odds ratios (1.08–1.24) obtained from GWAS (genome-wide association studies), based on ever increasing numbers of individuals. Thus, intensified research into environmental risk factors is pivotal, also considering its inherent preventive potential. Perinatal brain insults, cannabis use, neurotrauma, psychotrauma, urbanicity, migration, paternal age and season of birth are among the most commonly replicated environmental hazards associated with increased schizophrenia risk. Apart from the disease risk per se, important, yet unexplored questions are whether environmental factors modulate age-at-onset or severity of schizophrenia, i.e. crucial determinants of individual fate and socioeconomic load.

Methods: Building on a large sample of comprehensively phenotyped male schizophrenic subjects (N=714), we analysed the predictive role of GWAS-derived genetic versus environmental risk factors.

Results: We show (i) a qualitatively and quantitatively differential impact of defined single environmental hazards on schizophrenia, (ii) a dramatic effect of accumulated environmental risk on age-at-onset (disease start up to 8 years earlier; $p=9.3 \times 10^{-11}$; OR ~10), and (iii) a complete lack of association of polygenic risk scores derived from GWAS of the Psychiatric GWAS Consortium (PGC) with any disease-relevant phenotypes.

Discussion: We also demonstrate that the relative significance of cannabis as avoidable environmental risk on age-at-onset is enormous ($p=3.8 \times 10^{-20}$). Cannabis consumption explains 10.2% of variance regarding age-at-onset compared to only 4.7% variance explained by all other environmental risks together. These finds strongly encourage more fundamental public education.

Poster #S208

BELIEFS ABOUT THE CONCEPT OF SCHIZOPHRENIA IN THE ARGENTINIAN POPULATION

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Background: Schizophrenia is conceptualized as a neurodevelopmental disorder, characterized by a fundamental alteration of thought. Its etiology is multifactorial, with genetic and epigenetic factors intervening in its genesis and development. This syndromic diagnosis lacking dissociation has a number of positive, negative and disorganization symptoms, associated with a variable degree of personal functioning. Cognitive, emotional and social alterations revealed by individuals with schizophrenia affect their family and community environments, determining interaction patterns. The information that these environments provide is central for the treatment of individuals, increasing or decreasing the chances of recovery. This demographic research examined the information that people have about schizophrenia.

Methods: The sample consisted of 980 people average educational level, which was self-administered a closed questionnaire of 20 questions about: schizophrenia diagnosis, etiology and symptomatology; and treatment, social and cognitive functioning of individuals.

Results: The data obtained suggest relatives have more information about the following: individuals with schizophrenia can work and have children; the disorder is not contagious; family psychoeducation is a key therapeutic resource; and hospitalization is not the only possible treatment alternative. Misinformation focused on the perception of individuals with schizophrenia as more violent than other people without the disorder. The highest level of ignorance was evident in the contributions of pharmacology to treatment and etiology polygenetic factors.

Discussion: The analyzed information highlights the importance of developing psychoeducational interventions on a social level to counteract the stigmatization produced by unknown by unknown or distorted information, as well as to strengthen the social reintegration of the individual and their adherence to treatment.

Poster #S209

EFFECTS OF OBJECT SIZE AND DISTANCE ON REACH-TO-GRASP MOVEMENT IN PATIENTS WITH SCHIZOPHRENIA AND HEALTHY CONTROLS

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Background: Patients with schizophrenia have movement problems, which diminish their potential work competency and life satisfaction. Movement problems are not solely induced by antipsychotics; schizophrenia itself induces movement abnormality. Therefore, it is necessary to analyze movement features in patients so that health care practitioners better understand the illness and plan the focus of treatment. The purpose of this study was to (1) compare reach-to-grasp movement between patients with mild schizophrenia (without extrapyramidal motor symptoms and with general cognitive abilities) and healthy controls, and (2) examine effects of object size and distance on movement kinematics in patients.

Methods: Twenty-nine patients and 15 age- and gender-matched healthy controls were required to use their dominant (right) hands to reach and grasp a cylindrical object with varying size (small: 3 cm in diameter, 1.4 cm high; large: 7 cm in diameter, 1.4 cm high) placed at a varying distance (near: 20 cm; far: 40 cm) as fast as possible. Movements were captured by an optical motion capture system (Qualisys AB, Gothenburg, Sweden). Kinematic variables were calculated to characterize reach-to-grasp movement, including movement time, percentage of movement time to peak velocity, peak velocity, and normalized total displacement to represent movement speed, control strategies, forcefulness, and straightness, respectively. Three-way ANOVA with one between factor (group) and two within factors (object size and distance) was conducted.

Results: No interaction effects were found. Patients with schizophrenia had longer movement time ($p=0.017$) and higher normalized total displacement ($p=0.007$) than healthy controls. Compared with the small object, the large object induced shorter movement time ($p=0.016$), higher percentage of movement time to peak velocity ($p=0.018$), and higher peak velocity ($p=0.010$). Compared with the far object, the near object induced shorter movement time ($p<0.001$), higher percentage of movement time to peak velocity ($p<0.001$), lower peak velocity ($p<0.001$), and higher normalized total displacement ($p<0.001$).

Discussion: Compared with healthy people, patients with mild schizophrenia had similar movement control strategy and forcefulness, but had a slower and less straight movement. Patients responded to changes in object size and distance in a similar pattern to that of healthy people. When larger or nearer objects were used, patients generated a faster and more pre-planned movement. A larger object also induced more forceful movement. A nearer object also induced a less forceful and less straight movement. The results point out the specific problems with reach-to-grasp movement in patients and suggest the consideration of changing object size and distance in movement rehabilitation. This research contributes to evidence-based treatment for patients with schizophrenia.

Poster #S210

MAORI PATIENTS WITH SCHIZOPHRENIA: HOW TO IMPROVE THEIR REHABILITATION AND RECOVERY

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Background: Over the past 30 years and especially over recent years, it has been increasingly evident the importance of cultural sensitive clinicians and cultural aware delivery of mental health services to Maori patients especially with a diagnosis of Schizophrenia. This poster reviews Maori patients perceptions and views towards Mental Health and suggests ways for improving engagement of Maori patients in Mental Health Services and enhanced rates of their rehabilitation and recovery.

Methods: MEDLINES and PsychINFO databases were searched for all English-language articles published between 1999 and 2013 containing the keywords 'Maori mental health' and 'Maori patients rehabilitation'. Analysis of mental health policies related to Maori patients were also reviewed. The most relevant articles were selected for review.

Results: The active engagement of Maori clients in mental health services offers far greater chances of successful outcomes. The identification of shared cultural goals, values, beliefs and behaviours it is of paramount importance in order to enable clients' rehabilitation and recovery. The importance of applying an integrated interpretation of mental illness, of understanding spiritual factors, Maori-focused group and family wellness models was highlighted.

Discussion: Over the past years there have been major changes on the delivery of Mental Health services to Maori patients in New Zealand (Aotearoa). Further work in this area is likely to benefit service development and Maori patients rehabilitation, especially around cultural sensitive training and policies developing.

Poster #S211

TREATMENT OUTCOMES, INSIGHT AND RECOVERY IN FIRST-EPIISODE SCHIZOPHRENIA

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Background: Lack of insight or awareness of illness is prevalent in schizophrenia and a barrier to effective treatment (Mohamed et al 2009). There are, however, controversies regarding the impact insight can have on clinical symptoms, neurocognitive impairment, functional outcome, and subjective quality-of-life (QOL). Previous studies have reported mixed or even contradictory results due to ambiguities in concepts, causality and interpretation (Lysaker et al 2007). The role of insight in predicting treatment outcomes is an important area of investigation. And the objective of this study was to investigate cross-sectional relationships between insight and cognitive performance, social functioning, and subjective quality of life rating in patients with first-episode schizophrenia who had attained symptom remission.

Methods: A total of 65 patients from two first-episode patient cohorts were investigated. Inclusion criteria included: 18-35 years of age, capable of providing informed consent, DSM-IV diagnosis of schizophrenia confirmed by the Mini International Neuropsychiatric Interview, and treatment for <1 year. Patients' clinical status was assessed using the PANSS (Cohort 1) or BPRS (Cohort 2). Insight was measured using the Schedule for Assessment of Insight (SAI), while cognitive functioning was evaluated using BACS (in Cohort 1 only). Functional performance was evaluated by SOFAS and the Social Functioning Scale (SFS). Subjective patient-reported outcomes were assessed using the Satisfaction with Life Scale (SWLS) and World Health Organization Quality of Life scale (WHOQOL-BREF, Cohort 1 only). Regression analysis was applied to investigate the relationships among these factors. No multiplicity adjustment was made in this exploratory analysis.

Results: All but 3 patients met criteria for symptom remission. Patients demonstrated good levels of insight (SAI total = 11.4, SD=2.6), and the mean BACS composite z-score was -2.05 (SD=1.27). The overall median SOFAS

score was 50 (IQR 45 to 60), indicating moderate to serious impairment in social and occupational functioning in a majority of patients. Patients also experienced marked functional impairment, being significantly lower on social engagement, interpersonal communication, recreation, pro-social, and employment SFS domains compared to normal controls ($p < 0.05$). There was a significant correlation between the overall SAI insight score and G12 of PANSS (lack of judgement and insight, $p < 0.05$). Higher level of insight was associated with increased cognitive performance ($p < 0.05$). Level of insight into illness was inversely related to both Interpersonal Communication (an objective SFS domain, $p < 0.05$) and lower Social Relationship (a subjective WHOQOL-BREF domain, $p < 0.05$).

Discussion: Our findings suggest that despite good insight, symptom remission and lack of depression, there is significant impairment in neurocognitive and social functioning in first-episode schizophrenia. Higher levels of insight were associated with better cognitive performance, but were inversely related to an objective measure of interpersonal communication (a domain of the Social Functioning Scale) and subjective measure of social relationships (a domain of the WHOQOL-BREF). Further research is needed to confirm these results using larger sample size and to investigate the role of other intervening variables such as medication adherence and longitudinal changes/outcomes.

Poster #S212

SEXUAL AND PHYSICAL TRAUMA AND THE SOCIAL AND VOCATIONAL FUNCTIONING IN FIRST-EPISEDE PSYCHOSIS PATIENTS

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Background: Evidence suggests a relationship between childhood trauma and impairments of social and vocational functioning in psychotic patients. **Methods:** 241 FEP patients aged 18-35 were enrolled. We examined the association between exposure to sexual and/or physical abuse (SPA) and patients' social functioning in the premorbid phase (with the premorbid adjustment scale (PAS), and over 36 months of treatment with the global assessment of functioning (GAF) and the social and occupational assessment Scale (SOFAS). SPA was classified as early SPA (childhood: from birth to 11 years old)) or late SPA (early adolescence: from 12-15 years old).

Results: 29.9% of patients had a history of SPA; they were more likely to be female and to present a substance abuse disorder. They had a lower pre-morbid social functioning than other FEP but this difference was significant only when trauma had occurred early. At 36 months, patients exposed to late SPA had a level of functioning that was similar to non exposed patients and better than patients exposed to early SPA.

Discussion: Early exposure to SPA is linked to decreased functional level compared to other FEP patients in the social and interpersonal domain before psychosis onset, which is maintained throughout the treatment phase. Exposure to trauma later in life is also linked with lower pre-morbid functioning compared to other FEP patients, but this difference disappears over the treatment period. These results suggest that impact of SPA on functional levels in FEP depends on time of exposure. The investigation of underlying biological mechanisms is warranted.

Poster #S213

PERFECTIONISM AND WORKING ALLIANCE IN A COGNITIVE-BEHAVIORAL INTERVENTION FOR WEIGHT LOSS IN PSYCHOTIC ILLNESS

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Background: Poor working alliance has been associated with worsened outcomes across several populations. Working alliance formation and maintenance seem to be impeded with those who are high in perfectionism, particularly perfectionistic self-presentation. Perfectionistic individuals seem to have problems disclosing their difficulties, which interferes with

therapists' ability to convey empathy and provide required assistance. Moreover, related shame in perfectionistic individuals interferes with help-seeking in general, limiting individuals' opportunity to benefit from social support and professional care. Poor working alliance formation and maintenance may be reasons that trait perfectionism and perfectionistic self-presentation have also been linked with worsened symptom severity and poor treatment outcome across several populations. Yet, working alliance, perfectionism, and perfectionistic self-presentation have not been formally evaluated in psychotic illness.

Methods: Fourteen persons (ages 38-66, 57.1% female) with a psychotic illness, who were participating in a larger study, completed a clinical interview, the Working Alliance Inventory Short-Form (WAI), and abbreviated versions of Hewitt & Flett's Multidimensional Perfectionism Scale and the Perfectionistic Self-Presentation Scale. Participants were randomized to receive treatment-as-usual or a cognitive-behavioral intervention for weight loss. Participation lasts 52 weeks and weight is the primary outcome measure.

Results: Data reported are preliminary, as this study is ongoing. The perfectionism subscales showed adequate reliability ($0.70 < \alpha < 0.84$), with the exception of non-disclosure of imperfections (DISC; $\alpha=0.11$) and non-display of imperfections (DISP; $\alpha=0.46$). Reliability for the WAI total score was acceptable across all timepoints ($0.66 < \alpha < 0.99$). SOP and SPP were significantly correlated with percentage weight loss at final timepoint measured (respectively, $r=0.56$, $p=0.046$; $r=0.68$, $p=0.015$). Relationships between PSP and DISC approached significance (respectively, $r=0.53$, $p=0.056$; $r=0.46$, $p=0.090$). Baseline bond was negatively correlated with final percentage weight loss ($r=-0.64$, $p=0.009$), and total baseline WAI approached significance ($r=-0.36$, $p=0.113$). Total WAI at time 1 for at least one therapist was negatively correlated with final percentage weight loss ($r=-0.60$, $p=0.033$), and task and bond ratings approached significance ($r=-0.36$, $p=0.141$; $r=-0.37$, $p=0.128$). Bond at final timepoint for at least one therapist was significantly correlated with final percentage weight loss ($r=0.58$, $p=0.023$).

Discussion: Those who were higher in self-oriented and socially prescribed perfectionism demonstrated greater weight loss at the final timepoint assessed. These preliminary data suggest that in this context, perfectionism may operate more like conscientiousness, whereby individuals' high standards for themselves and/or their perceptions that others expect perfection from them may promote weight loss behaviors. Similarly, individuals' desire to present themselves as perfect may promote weight loss behaviors. These findings are consistent with results from another study by Hassan and colleagues. Surprisingly and in contrast to other studies, it appears as though poorer working alliance is associated with more weight loss. One possibility is that social anxiety in individuals with psychotic illness may influence their willingness to provide negative feedback to therapists vis-à-vis responses to the WAI. Another possibility is that a sense of safety and acceptance with a therapist contributes to a sense of self-acceptance that then interferes with behavioral change. Clinical implications of these results will be discussed.

Poster #S214

REMISSION CRITERIA AND FUNCTIONAL OUTCOME IN SCHIZOPHRENIA PATIENTS, A LONGITUDINAL STUDY

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Background: The Remission in Schizophrenia Working Group (RSWG) has proposed remission criteria for schizophrenia, and these were shown to be valid in terms of functional and clinically relevant outcomes. However, research on the association between longitudinal stable remission status based on the RSWG remission criteria and longitudinal functional and clinical outcome are scarce. More knowledge on this matter is warranted, since it is increasingly recognised that both enduring symptomatic and functional remission should be considered as major treatment goals in schizophrenia patients. For the current study, we defined four aims. First (I), we want to validate the RSWG remission concept further by examining associations between symptomatic remission and clinical and functional

outcome variables at both baseline and follow-up measurement separately. Second (II), we aim to identify relevant baseline demographical, clinical and functional characteristics that distinguish patients who change in RSWG remission status over a three-year time period from patients who do not. Thirdly (III) we were interested in functional measures and clinical outcome at follow-up for each remission category. Finally (IV), we will investigate whether enduring remission is associated with improvement in functional outcome, as reflected in higher GAF scores, less unmet needs for care and higher life satisfaction at follow-up compared to other scenarios.

Methods: We divided a total of 705 patients into four change-in-remission categories, i.e., remission/remission, remission/no-remission, no-remission/remission, and no-remission/no-remission. RSWG remission status at baseline and follow-up was based on PANSS ratings. The relation between functioning and remission status was examined at each time point separately, as well as potential differences in baseline demographical, clinical and functional characteristics between change-in-remission categories. Multi-level linear modelling techniques were used to assess potential differences in functional and clinical outcome over time between remission categories.

Results: Both at baseline and follow-up patients with a remission status had higher GAF (psychopathology and impairment) scores, less unmet needs, and a higher appraisal of quality of life as compared with patients without a remission status (I). At baseline assessment, patients who lost their remission status could be characterized by more psychopathology, disabilities, unmet needs and worse quality of life compared with patients who continued to be in remission. Vice versa, patients who did not achieve remission distinguished themselves from patients who did achieve remission by a less favourable baseline profile in terms of illness severity, functioning, quality of life and needs for care (II). Remarkably in all four patient categories there was an increase in quality of life appraisal and needs for care at follow-up (III). Patients in the stable in-remission category were however characterised by significantly better functioning and clinical outcome at follow up compared to all other change-in-categories (IV).

Discussion: In a large sample of patients with a non-affective psychotic disorder, we showed further support for the functional and clinical validity of the RSWG remission criteria. Stable remission or reaching remission over time based on the RSWG criteria is associated with a favourable functional outcome and quality of life, providing further support that achieving longitudinal RSWG remission is proper treatment goal in patients with a schizophrenia spectrum disorder.

Poster #S215

EFFECTS OF CANNABIS USE ON CLINICAL AND PSYCHOSOCIAL OUTCOMES IN FIRST-EPIISODE PSYCHOSIS

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Background: Cannabis is currently the most frequently used illicit substance in the world as it appears to play a role in increasing their risk of poor prognosis. A study of psychotic patients with persistent cannabis use found that they were at risk of increased symptoms, hospital readmissions and absence of remission. Persistent cannabis use also led to a more continuous illness and made patients more likely to relapse and display increased violence and criminal behaviour. A systematic review also showed that persistent use by patients with psychosis was consistently associated with increased relapse and non-adherence to treatment. Variations in diagnostic criteria for psychosis, small sample sizes and lack of adequate adjustment for confounders are some of the methodological limitations in these studies. No research has examined the differences in prognosis after a first-episode of psychosis between lifetime and persistent cannabis users.

Methods: Four-hundred and thirty one patients with first-episode psychosis were recruited to the GAP study in London, UK; 308 were followed up over the course of 12 months. Chi-square tests were used to assess the association between lifetime (yes/no) and persistent cannabis use (yes/no and no/sporadic/regular) with (i) number of inpatient days (≤ 41 / > 41), (ii) GAF symptoms and disability (≤ 60 / > 60), (iii) relapse (yes/no) and (iv) employment (yes/no) at follow-up. A logistic regression approach was used to further assess the significant associations while adjusting for GAF disability at baseline (≤ 60 / > 60) and medication compliance (yes/no) throughout the follow-up.

Results: In the unadjusted analyses, lifetime cannabis use was not associated with any of the outcomes. Persistent cannabis use was associated with number of inpatient days and GAF disability at follow-up but not GAF symptoms, relapse or employment. In the 2-group (yes/no) adjusted analysis, persistent cannabis use was associated with increased odds of having more inpatient days (OR=3.6, 95% CI: 1.68, 7.75) and moderate/severe disability (OR=2.4, 95% CI: 1.07, 5.4), than non-use. In the 3-group (no/sporadic/regular) adjusted analysis, there was an association between cannabis use and number of admission days ($p=0.003$). Sporadic users had an increased odds of more inpatient days than non-users (OR=7.5, 95% CI: 2.31, 24.42) but no difference was observed between regular users and non-users after adjusting for confounders. There was no strong association between cannabis use and disability scores ($p=0.095$). Regular users showed a weak increase in odds of moderate/severe disability at follow-up than non-users (OR=3.3, 95% CI: 0.96, 11.58) but no difference was observed between sporadic users and non-users.

Discussion: These data partially support previous studies that have found cannabis use to be associated with poor prognostic outcome in psychosis. Cannabis users were almost 4 times more likely to spend over 41 days in hospital with sporadic users around 7 times more likely to do so than non-users, after adjusting for confounders. Although persistent users were twice as likely as non-users to score in the moderate/severe disability range of the GAF scale, no strong evidence of an association was observed with the 3 cannabis groups after adjusting for confounders. Consistent with previous research, adjusting for functioning at some earlier point might substantially reduce the size of the relationship between cannabis use and functioning at follow-up. The smaller group sizes in the 3-group categorisation may also have affected our power to detect any association between cannabis use and disability.

Poster #S216

VITAMIN D AS A PREDICTOR OF ILLNESS SEVERITY AT ONE YEAR IN FIRST EPISODE PSYCHOSIS

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Background: Vitamin D deficiency is seen in a high proportion of people with established psychotic disorders and there is emerging evidence that vitamin D deficiency is present in individuals at the onset of their psychotic illness. There is growing interest in the effects of vitamin D on both the prevention and course of psychotic illnesses. We hypothesised that vitamin D levels at baseline during the first episode of psychosis would negatively correlate with illness severity at 12 months.

Methods: The study population comprised 134 adults with a first episode of psychosis. All participants met the ICD-10 criteria for psychosis (codes F20-29 and F30-33). At baseline and 12 month follow up we recorded demographic data and measured serum Vitamin D levels (serum 25-hydroxyvitamin D (25 OHD)) using chemiluminescence immunoassay (DiaSorin, S.P.A. Saluggia (Vercelli), Italy). Vitamin D insufficiency was defined as 25 OHD levels between 10-20 mcg/L while levels below 10mcg/L were classed as vitamin D deficiency. A clinical assessment including PANSS scores was conducted at 12 month follow-up. Data analysis was performed using correlation coefficients and student-t tests for parametric data where appropriate. To control for the confounding factors of age, gender, ethnicity and season of vitamin D sampling we performed a multiple linear regression analysis and independently examined the association between baseline vitamin D levels and illness severity at 12 months as measured using PANSS scores. These variables were entered into a regression model as independent variables with the PANSS score as the dependent variable.

Results: Sixty two percent (n=85) of the study population (n=134) were male. The mean age of participants was 29.8 years (SD=9.7; Range 18-59). Forty-four percent were of Black African/Caribbean ethnicity and 44% of

White ethnicity. Forty-five percent ($n=60$) met criteria for Vitamin D deficiency, while a further 34% ($n=44$) were Vitamin D insufficient, leaving only 21% with levels in the sufficient range. Males had significantly lower serum Vitamin D levels at baseline (mean=11.8mcg/L (SD= 7.0) than female participants (mean vitamin D level=16.2mcg/L (SD=10.4) ($t=-2.953$, $df=132$, $p=0.04$). The mean PANSS score at 12 months was 50.7 (SD 15.5). There were significant negative correlation between baseline vitamin D levels at baseline and PANSS total scores at 12 months ($r=-0.235$, $p=0.043$). Vitamin D levels also showed a significant negative correlation with PANSS negative syndrome scale scores at 12 months ($r=-0.244$, $p=0.036$). The correlation between vitamin D levels at baseline didn't persist once potential confounding factors of age, gender, ethnicity and season of vitamin D blood sampling were controlled for. Using the enter method of multiple regression analysis, a significant model emerged ($F=2.448$, $df=5$, $p=0.042$). None of the independent variables contributed significantly to the regression model (adjusted $R^2=0.075$). Vitamin D levels at baseline were not a significant predictor of illness severity at 12 months as measured by PANSS scores ($B=-0.252$, $t=-1.124$, $df=1$, $p=0.265$). None of the other variables in the regression equation reached statistical significance in their prediction of PANSS scores. Fifty six (32 males) individuals had serum Vitamin D levels measured at both baseline and 12 months. Mean Vitamin D levels at baseline in this sub-group were 13.5 mcg/L (SD=8.7; range 4-55 mcg/L) and at 12 months were 12.8 mcg/L (SD=8.1; range=4-32.2). Thirty nine percent ($n=22$) of individuals showed a rise in Vitamin D levels and 57% ($n=32$) showed a reduction in vitamin D levels at 12 months, with two showing no change. Males ($n=32$) had significantly lower mean vitamin D levels of 10.7 mcg/L (SD=7.3) at 12 months, compared to females (mean vitamin D level of 15.5 mcg/L (SD=8.5)) ($t=-2.274$, $df=54$, $p=0.027$). Of those participants who had reduction in their mean vitamin D levels over the 12 month period, females ($n=13$) had a significantly greater reduction (mean decrease in vitamin D levels =13.2mcg/L (SD=10.4)) than male patients ($n=19$) (mean reduction in vitamin D levels 5.77 (SD=4.4) ($t=-2.699$, $df=30$, $p=0.011$). There was a significant negative correlation between the change in serum vitamin D levels between baseline and 12 months and the PANSS score at 12 months ($r=-0.311$, $p=0.02$).

Discussion: In this study we demonstrate a correlation between low serum vitamin D levels at first presentation and heightened illness severity at 12 months, both on total PANSS score and on the PANSS negative symptom score, but this effect disappeared when adjusted for age, sex ethnicity and season of sampling. The negative correlation noted between 12-month PANSS and change in Vitamin D may be mediated by reduced sun exposure. Further work is needed to explore whether intervention strategies using vitamin D supplementation may modify the course of the illness from illness onset.

Poster #S217

COMPARISON OF CHARACTERISTICS OF PSYCHOSIS PATIENTS WITH AND WITHOUT HOSPITALIZATION AT FIRST EPISODE

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Background: Hospitalization may cause psychological and social burden to patients and the society. One of the key aims of early intervention in psychosis is to reduce hospitalisation and promote recovery in the community. The current study compared the characteristics of psychosis patients with and without hospitalization at their first episode to explore the associated factors of hospitalization.

Methods: Patients, aged 26-55, with a diagnosis of schizophrenia spectrum disorders were recruited from the Jockey Club Early Psychosis Project in Hong Kong. The sociodemographic and clinical characteristics, including gender, age, educational level, age of onset, duration of untreated psychosis, symptoms and side effect, of patients with and without hospitalization at their first episode were compared.

Results: A total of 57.8% of patients with psychosis was hospitalized at their first episode. Baseline Hospitalization was associated with longer duration of untreated psychosis, higher dosage of antipsychotic treatment, more severe positive symptoms, less severe negative symptoms and more medication side effects.

Discussion: Inpatient treatment is common among patients with first episode psychosis in Hong Kong. Patients with hospitalization at their first episode of psychosis had different characteristics when compared to patients without hospitalization. Future study should explore the causal effect between these factors and hospitalization and its potential implication in early intervention services.

Poster #S218

META-ANALYSIS SHOWS THAT THE LEVEL OF CANNABIS USE DETERMINES THE RISK OF PSYCHOSIS

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Background: A dose-response relationship between cannabis use and psychosis related outcomes has been reported, the extent of this relationship remaining uncertain. We performed a systematic review investigating the association between the degree of cannabis consumption and psychosis-related outcomes and proceeded with a meta-analysis to quantify the magnitude of effect.

Methods: A search of Medline, Embase and PsycInfo database (to January 2013) was supplemented by manual searches of bibliographies and relevant reviews. Studies were originally considered if they provided data on cannabis consumption following a dose criterion used validated clinical measures, and reported psychosis-related outcomes. From 500 references, 17 studies were considered for the systematic review and 10 were inserted in the meta-analysis, enrolling a total of 66,816 individuals.

Results: We observed a consistent increase in the risk of psychosis related outcomes in all the included studies, corresponding to a 4-fold OR for the risk of schizophrenia and other psychosis-related outcomes among the most severe cannabis users compared to the non-users. Subgroup analyses by method or outcome measure gave remarkably similar results for each category. For a diagnosis of schizophrenia or psychotic disorder the OR reached the threshold of 5.

Discussion: Our meta-analysis confirms a positive association between the degree of cannabis use and the risk for psychosis, providing the most accurate estimate of the effect size of cannabis use as a risk factor for psychosis using all the available published data. In addition, it confirms a dose-response relationship between the level of use and the risk for psychosis.

Poster #S219

THE RELATIONSHIP BETWEEN NEUROCOGNITION AND REAL LIFE FUNCTIONING IN FIRST-EPIISODE SCHIZOPHRENIA: RESULTS FROM THE 2-YEAR FOLLOW-UP IN THE OSLO LONGITUDINAL RECOVERY STUDY

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Background: Substantial limitations of studies investigating the relationship between cognition and functional outcome have been identified. Among them are the lack of control of confounding variables, high attrition rate, and too few neurocognitive domains measured and completed at each assessment point. The Oslo longitudinal recovery study is one of very few long-term prospective studies of first-episode patients investigating the rate of recovery and the relationship between neurocognition and real life functioning in first-episode schizophrenia patients with multiple follow-up points during 10 years, using the MATRICS Consensus Cognitive Battery (MCCB). In studying the relationship between cognition and outcome, cognitive predictors should be weighed against other potential predictors of functional outcome, such as premorbid functioning, duration of untreated psychosis (DUP), sociodemographic variables, and baseline symptoms. It is also necessary for the MCCB to prove its usefulness in documenting longitudinal prospective relationships between cognition and functional outcome and to examine the contribution of specific cognitive domains.

Given their link to functional outcome, the domains executive functioning, verbal memory and attention seem particularly relevant for longitudinal studies. The study is ongoing, and here we present the results from the 2-year follow up assessment. We address the following research question: Is cognition significantly and independently predictive of social and role functioning after controlling for non-cognitive baseline factors?

Methods: 28 (17 men, 11 women, mean age 21.0, SD 2.6 years) individuals with first-episode schizophrenia and receiving a combination of medication and case management were assessed with the Positive and Negative Syndrome Scale (PANSS), the MCCB and a scale measuring social and role functioning at baseline and two years later.

Results: At 2-year follow-up 71.4% was in remission, out of which 60% had sustained their remission. Fourteen percent fulfilled criteria for full recovery, i.e. sustained improvement in both symptoms and social/vocational functioning for 2 years or longer. The attrition rate was 10.7%. No significant relationship was found between verbal memory and functional outcome. Attention/Vigilance ($\beta=0.55$, $p<0.05$) and executive function ($\beta=0.46$, $p<0.05$) at baseline were significant predictors of social function at follow up. Baseline positive symptoms ($\beta=0.46$, $p<0.01$), years of education ($\beta=0.61$, $p<0.01$), attention ($\beta=0.24$, $p<0.05$) and executive function ($\beta=0.41$, $p<0.01$) were all significantly related to role function at follow up. Assuming that these variables are intercorrelated, they were entered into new regression analyses with social and role function as dependent variables. Then only attention ($\beta=0.63$, $p<0.001$) and years of education ($\beta=0.47$, $p<0.01$) kept their significant contribution to social and role function, respectively. However, baseline attention and executive function explain nearly 47% of the variance in social function, and 48% of the variance in role function is explained by baseline positive symptoms, executive function, years of education and attention.

Discussion: The cognitive domain attention was predictive of both role and social functioning 2 years later. When controlling for other non-cognitive baseline factors, years of education was found to play a significant role in predicting social and role functioning, although the cognitive domain executive function alone explained nearly 50% of the variance in real life functioning. The results from the present study demonstrate the importance of a tailored design and good methods, showing that isolated univariate analyses of the relationship between cognition and outcome are inadequate.

Poster #S220

PREMORBID CANNABIS USE AND EARLIER AGE AT ONSET OF PSYCHOSIS: FINDINGS FROM TWO STUDIES IN THE U.S.

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Background: Schizophrenia is currently conceptualized as a disorder caused by both genetic predispositions and exposure to stressors or environmental factors, the latter being particularly influential when they occur during childhood and early adolescence. One such environmental factor is cannabis use, especially use occurring prior to the onset of clinically evident psychiatric symptoms, particularly in early adolescence. Cannabis is commonly used by adolescents and is the most frequently used illicit drug in the context of schizophrenia. Several studies have indicated that premorbid cannabis use may be associated with an earlier age at onset among those who develop a psychotic disorder. We conducted two consecutive studies to gather more definitive evidence of the association between premorbid, adolescent cannabis use and age at onset of psychosis.

Methods: In two consecutive National Institute of Mental Health (NIMH)-funded studies, we thoroughly characterized age at onset of psychosis in hospitalized first-episode psychosis patients (n=109 and n=252, respectively), as well as lifetime history of substance use. Analyses determined the association between premorbid cannabis use and age at onset of psychosis.

Results: In 109 first-episode patients in Atlanta, Georgia, analyses involving change in frequency of use prior to onset indicated that progression to daily cannabis and tobacco use was associated with increased risk of onset of psychotic symptoms. Similar or even stronger effects were observed when onset of illness/prodromal symptoms was the outcome. The effects of premorbid, adolescent cannabis use were confirmed and further characterized in the second, independent sample of 252 first-episode patients in Atlanta, Georgia and Washington, D.C.

Discussion: Several first-episode psychosis studies document that the initiation of substance use and abuse typically precedes the onset of psychosis. A number of epidemiological studies have suggested that cannabis use in adolescence is an independent risk factor for the later development of a psychotic disorder; as such, premorbid, adolescent cannabis use is thought to be a component cause of schizophrenia and other psychotic disorders. Convincing evidence now exists showing that premorbid, adolescent cannabis use also hastens the onset of psychosis among those developing a psychotic disorder. Age at onset is a crucial early-course feature as an earlier age at onset is associated with poorer clinical and functional outcomes, and the other known predictors of age at onset are not modifiable (e.g., family history of psychosis, gender). Based on the cumulative evidence, preventing or reducing cannabis use among adolescents, particularly those at elevated risk of developing psychosis, may delay the onset of psychotic disorders, or prevent it altogether.

Poster #S221

SUICIDALITY IN SCHIZOPHRENIA SPECTRUM DISORDERS: RELATION TO HALLUCINATIONS AND PERSECUTORY DELUSIONS

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Background: Hallucinations, most often auditory in nature, are highly prevalent in schizophrenia and related psychotic disorders. Hallucinations in this context can be dramatic and may have severe impact in affected individuals and are sometimes associated with suicide risk. Indeed suicidality is highly relevant in schizophrenia as up to 40% attempt suicide and 5% complete suicide. Depressed mood, hopelessness and previous suicide attempts are well established as risk factors for suicidal behavior in schizophrenia. The relationship between hallucinations and suicidality, on the other hand, is not extensively described and existing results are somewhat inconsistent, making the case for more research on hallucinations and associations with suicidal behavior. The identification of hallucinations or particular aspects of hallucinations being more closely associated with suicidality could have major clinical impact by contributing to a more focused suicidality screening procedure.

Methods: We present baseline findings from the Bergen psychosis project 1 (BP1), a prospective study including patients with psychosis across traditional diagnostic categories. A total of 124 patients with schizophrenia spectrum disorders were included in the statistical analysis. An ordinal regression analysis was conducted with item 8: Suicidality, in The Calgary Depression Scale for Schizophrenia (CDSS) as the dependent variable. Explanatory variables were Depression (CDSS), Hopelessness (CDSS), Lack of insight (the Positive And Negative Syndrome scale for Schizophrenia-PANSS), Suspiciousness/persecution (PANSS), Hallucinations (PANSS), Gender, Age, Anxiety (PANSS) and Drug use (Clinical Drug Use Scale-CDUS).

Results: The following variables were significantly associated with suicidality: PANSS item G6 Depression (0.646, $p<0.000$), PANSS P3 Hallucinations (0.300, $p<0.000$) and PANSS item G2 Anxiety (-0.128, $p<0.048$). The size of the association was largest for depression, followed by hallucinations. A structural model using Structural equation modelling (SEM) will also be presented. This SEM-model explores associations between variables in predetermined pattern in a clinically probable model. Even though Suspiciousness/persecution in the regression analysis did not directly predict Suicidality, it was significantly associated with Anxiety in the structural model. Anxiety in its own term predicted Depression which was strongly associated with Suicidality, indicating a more indirect path for the relationship between Paranoid delusions and Suicidality.

Discussion: In conclusion, Hallucinations were associated with suicidal thoughts, plans or attempts. There were indications from the SEM-analysis that Depression, Hopelessness and Anxiety could be seen as intermediate phenomena connecting Positive psychotic symptoms and Suicidality. Despite former heterogeneous results these results contribute to an increasing evidence base supporting thorough consideration of hallucinations as a vital part of the mental state examination and assessment of suicide risk. In future research we aim to analyse the prospective data of the presented study and in an on-going study to include data on qualitative aspects of auditory verbal hallucinations and their impact on suicidality in patients

suffering from schizophrenia including a more detailed history of suicidal attempts and non-suicidal self-harm.

Poster #S222

DISTURBED BODILY EXPERIENCES IN PATIENTS WITH FIRST-EPIISODE SCHIZOPHRENIA

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Background: Patients with schizophrenia often have disturbed bodily experiences that might hinder their engagement in physical activities. In the research project "Metabolic syndrome in patients with first-episode schizophrenia" the correlation between disturbed bodily experiences and physical activity is investigated.

Methods: The study was a clinical, prospective, observational study. All patients consecutively assigned to The OPUS project and inpatients in The Central Region, Denmark having an ICD-10 diagnosis of first -episode schizophrenia (18–45 years) was the population of interest (N=100). For all participants the disturbed bodily experiences, comprising morphological changes, bodily estrangement, cenesthetic disturbances, bodily disintegration, hypochondriasis, and motor disturbances, were assessed using items from "Examination of Anomalous Self Experience" and "The Body Awareness Scale". Each item is score 0-4 based on severity and intensity ("0" = absent and "4" = severe). Patients were asked if their bodily disturbances had equally, more or less physically active.

Results: In all, 101 patients with first-episode schizophrenia were included in the study. Disturbed bodily experiences were prevalent in 75% of the patients. There was a significant correlation between severity of disturbed bodily experiences and low levels of physical activity. Results from the specific analyses will be presented.

Discussion: Disturbed bodily experiences were common in patients with first-episode schizophrenia and negatively correlated to patient's physical activity-level. Although negative symptoms as well as sedative sideeffects might also contribute to this it would be beneficially to address disturbed bodily experiences specifically in health promoting programmes for schizophrenia.

Poster #S223

ASSOCIATION BETWEEN SUBTLE DYSKINESIA AND SCHIZOTYPY IN SUBJECTS WITH AUDITORY VERBAL HALLUCINATIONS AND HEALTHY CONTROLS

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Background: Spontaneous dyskinesia is associated with non-affective psychosis, however not much research has been done on its relation with subclinical psychotic experiences. The concept of psychosis as a continuous phenomenon suggests similar associations at the non-clinical end of the psychosis spectrum. We examined (subtle) spontaneous dyskinesia and schizotypy in subjects without a psychiatric diagnosis who experience auditory verbal hallucinations (AVH), patients with a non-affective psychotic disorder, and healthy controls. We hypothesized that 1. subjects with AVH may show more (subtle) spontaneous dyskinesia than healthy controls, and 2. (subtle) spontaneous dyskinesia may correlate positively with schizotypy in the combined group of subjects with AVH and healthy controls.

Methods: Subjects with AVH and healthy controls were recruited by means of a website with information about hearing voices (www.verkenuwgeest.nl). Patients with a non-affective psychotic disorder were recruited from the University Medical Centre Utrecht. To be included in the study, subjects with AVH and patients with a non-affective psychotic disorder had to hear voices at least once a month, and voices had to be distinct from thoughts and had to have a "hearing" quality. Dyskinesia was measured with a mechanical instrument that has been shown to be more sensitive and reliable than clinical rating scales. Participants had to exert a constant pressure of 3 Newton on a button, first with the index finger of their dominant hand and then with their non-dominant hand. Mean force variability (FV) in the 0-3 Hz range was taken as a proxy for dyskinetic

movements. Schizotypy was measured with the Schizotypal Personality Questionnaire (SPQ)

Results: Subjects with AVH (n=36), patients with a non-affective psychotic disorder (n=28) and healthy controls (n=32) did not differ with regard to age and gender. Testing the subjects with AVH against the healthy controls using a Mann Whitney test yielded FVs with an average rank of 38.1 and 30.5, respectively (U=704.0 and p=0.116). The difference between patients with a non-affective psychotic disorder and healthy controls was significant (ranks 40.3 and 21.9, respectively with U=723.0 and p=0.000). In the combined group of subjects with AVH and healthy controls, FV was positively correlated with total SPQ score (Spearman's r=0.31 p=0.005).

Discussion: The findings were that 1. the FV in subjects with AVH was non-significantly higher than in healthy controls. The inconclusive results may be due to the small sample size; 2. the FV in patients with a non-affective psychotic disorder was significantly higher than in healthy controls; and 3. the positive association between (subtle) dyskinesia and schizotypy in the combined group of subjects with AVH and healthy controls is in accordance with two previous studies. Our results provide a strong argument for the hypothesis that dyskinesia and schizotypy share neuropathology within a psychosis continuum.

Poster #S224

CORTISOL LEVELS IN EARLY PSYCHOSIS: SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Schizophrenia is a complex disorder with interaction between genetic vulnerability and environmental factors. Some of these latter, such as childhood adversity, urbanicity, daily hassles, minority group position, are known to dysregulate the hypothalamo-pituitary-adrenal axis (HPA) and lead to modifications of the cortisol level. The cortisol modulates many neurotransmission systems, including serotonergic, dopaminergic and glutamatergic systems and induces long-acting effects by modifying the epigenome. Some publications suggest that cortisol is increased in schizophrenic patients but this finding is not well-established at onset of the disease. We aimed to perform a meta-analysis of the differences seen in salivary basal cortisol level in early psychosis (ultra-high risk subjects (UHR) and first-episode psychosis (FEP)) compared to controls.

Methods: We performed a systematic bibliographic search using the keywords "cortisol", "glucocorticoid", "HPA" with "UHR", "CHR", "at-risk mental state", "first episode psychosis", "schizotypal", "prodromal schizophrenia" in Medline, Web of Knowledge (WOS), EBSCO. Then, we screened the bibliography to identify other studies not selected by our primary search. We included in the meta-analysis only the case-control studies with salivary dosage of morning cortisol. We excluded the non-original studies and we removed duplicates. We conduct a meta-analysis from these results using MIX and OpenMetaAnalysis softwares.

Results: We identified eleven original studies reporting on salivary basal cortisol measures in UHR and controls. Scores of heterogeneity between studies are highly significant. One study reports an inverse trend compared to all other studies. When excluding this study, we observed a significant elevation of the salivary basal cortisol rate in UHR subjects compared to controls. Four studies comparing cortisol level between FEP and controls were included in the meta-analysis. When excluding the same cohort, also discordant in FEP compared to all other studies, we found that basal cortisol rate is more elevated in FEP than in controls. No study was designed to directly compare salivary basal cortisol levels in UHR and FEP in the literature. Nevertheless the meta-analysis' Mean Difference in the FEP was more important than the Mean Difference in the UHR.

Discussion: The meta-analysis of previous studies indicates higher basal cortisol levels in UHR and in FEP compared to controls. It further suggests a more elevated basal cortisol in the FEP compared to UHR, which could reflects a worsening of cortisol dysregulation during conversion to psy-

chosis. However, no definitive conclusion can be drawn: in both UHR and FEP, one study reported discordant results, and confounding factors such as treatment, sex, age, contraception use, diet, circadian rhythm, tobacco or drug abuse, childhood trauma are not always controlled. Further studies are needed. If confirmed the progressive dysregulation of the HPA axis could be a major factor leading to psychotic conversion in UHR.

Poster #S225
PREDICTING PSYCHOSIS IN A GENERAL ADOLESCENT PSYCHIATRIC SAMPLE

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Background: Current psychosis risk criteria have often been studied on a pre-selected population at specialized clinics so the results cannot be generalized to all psychiatric patients. We investigated whether the Structured Interview for Prodromal Syndromes (SIPS) is a useful tool for psychosis risk screening among adolescents in general psychiatric care.

Methods: 169 adolescents aged 15-18 years with first admission to adolescent psychiatric services in Helsinki, Finland were interviewed with SIPS to ascertain Clinical High-Risk (CHR) state. The mental health of the participants was followed via the national hospital discharge register, patient files, and for a proportion of the participants, with a follow-up assessment. DSM-IV Axis I and SIPS diagnoses were made at baseline and 12 months using all available data. Register follow-up spanned 2.8-9.0 years, and hospital care for a primary psychotic disorder and any psychiatric disorder were used as outcomes.

Results: 59 (34.9%) adolescents in general psychiatric care met criteria for CHR at baseline. Four conversions of psychosis as defined by SIPS emerged during the 12 months of follow-up, three of whom belonged to the CHR group. 5.4% of the CHR and 1.0% of the non-CHR individuals converted to psychosis. The weighted sensitivity and specificity of the CHR status were 31.1% and 74.4%, respectively. The positive predictive value of the CHR status was weak (2.6%) but its negative predictive value was 98.0%. Using the DSM-IV definition of psychosis instead, there were five conversions, 5.9% of the CHR group and 2.1% of the non-CHR group. The sensitivity and specificity of the CHR status were 28.2% and 75.7%. The positive predictive value of the CHR status was 2.8% and negative predictive value 97.7%. In a regression model, CHR status did not predict hospital admissions for primary psychotic disorders. In a separate Cox analysis, using symptom factors derived from the SIPS, positive symptom intensity in the baseline SIPS predicted primary psychotic disorder ($OR=2.2$, $p=0.016$), while General and Negative symptom factors did not. Hospital admissions for any psychiatric disorder were predicted by CHR status ($OR=3.1$, $p=0.005$). Of the SIPS symptom factors, Positive symptoms ($OR=1.9$, $p=0.001$) and General symptoms ($OR=2.2$, $p=0.001$) predicted hospitalization for any psychiatric disorder.

Discussion: Psychosis incidence was low among an unselected sample of adolescent psychiatric patients. CHR status failed to predict SIPS or DSM-IV psychoses significantly at 12 months; 94.6% of 56 adolescent psychiatric patients in the CHR group were false positives for conversion at one-year follow-up. Psychosis risk was over five times higher in the CHR group than in the non-CHR group, however. Besides SIPS and DSM-IV psychoses as outcomes, a long register follow-up was used in the current study. Admissions for any mental disorder during the follow-up were predicted by CHR status and SIPS positive and general symptoms, and hospital admissions for psychotic disorder were predicted by SIPS positive symptoms. Our findings are consistent with recent critique suggesting that the high transition rate in many high-risk studies reflects sampling strategy more than the specific high-risk criteria. Also, the current results reflect the heterogeneity of psychotic-like symptoms. Given the current results, one can conclude that in a non-selected public health care sample, where the patients have sought help for other reasons than positive symptoms, the

significance of the CHR status is limited in predicting psychosis. However, the SIPS can bring other prognosis information to clinical work. Information on psychotic-like symptoms and other risk symptoms can be advantageous in ways that call for additional research.

Poster #S226

NEURAL NETWORKS INVOLVED IN SELF-REFERENTIAL PROCESSING AND PERSPECTIVE TAKING IN HEALTHY PEOPLE: IT'S ASSOCIATION WITH THEORY OF MIND ABILITY AND ANOMALOUS SELF EXPERIENCE

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Background: Theory of mind deficits and anomalous self experience were reported to be already emerged from prodromal phase of schizophrenia. These disturbances may be closely associated with dysfunctional neural networks that involved in neural networks of self-referential processing and perspective taking. The aim of this study was to explore the neural networks of each dimension of self, and its association with theory of mind ability and anomalous self-experience in healthy people.

Methods: Twenty-eight healthy participants were asked to judge the relevance of personality traits adjectives for self versus close relative, taking either a first person or a third person perspective. Functional magnetic resonance imaging was taken during these tasks. Theory of mind picture stories task and Examinations of anomalous self-experience (EASE) were also assessed. Whole brain and regions of interest (ROI) analysis were conducted using the SPM8.

Results: The main effect of judgment target (self versus other) revealed activation in anterior and midcingulate cortex (1695 voxels, uncorrected $p<0.005$) and ventromedial prefrontal cortex (1072 voxels, uncorrected $p<0.005$). The main effect of perspective taking (third person versus first person) in lingual gyrus (821 voxels, uncorrected $p<0.005$), and left inferior parietal lobule extending the superior temporal sulcus and superior temporal gyrus (318 voxels, uncorrected $p<0.005$). Interaction effect was found in right insula in trend level (57 voxels, uncorrected $p<0.005$). The extracted contrast estimates of ROI of left inferior parietal lobule extending superior temporal gyrus and sulcus were found to be correlated with anomalous self-experience during the both perspectives when judging oneself as a target. The estimates of ROI of right insula were inversely correlated with theory of mind ability when participants judged their relatives using first-person perspective.

Discussion: The main findings show that differential neural networks are recruited during self-referential processing and perspective taking. The implication of its association with theory of mind ability and anomalous self-experience will be discussed in the points of the self disorder (basic symptoms) and socio-cognition impairments in the prodromal phase of schizophrenia.

Poster #S227

REMEMBERING DAILY COGNITIVE FUNCTIONING IN SUBJECTS AT ULTRA-HIGH RISK FOR PSYCHOSIS: A CROSS-SECTIONAL STUDY ON EVERYDAY MANIFESTATIONS OF COGNITIVE DEFICITS IN AN ULTRA-HIGH RISK COHORT

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Background: The neurocognitive impairment in subjects at ultra-high risk (UHR) for psychosis is well-established, but there is a profound paucity

of ecologically valid data on daily cognitive functioning in this population. To our knowledge, only one pilot study has addressed this issue previously. Therefore, not much is known about how cognitive deficits manifest themselves in the daily lives of UHR subjects, i.e. how the neuropsychologically measured impairments impact on life outside of the laboratory. The relationship between everyday cognitive functioning and clinical symptomatology and the relationship between everyday cognitive functioning and real-life functioning are also not well understood. There is an urgent need to investigate this area since it may potentially be part of elucidating cognitive characteristics of UHR subjects. Furthermore, daily cognitive functioning may explain unique variance in both symptomatology and real-life functioning. Identifying cognitive deficits as manifested in everyday life may also be of importance in identifying cognitive treatment targets for UHR subjects and evaluating the efficacy of UHR treatment programs. Therefore, the purpose of this study is to assess daily cognitive functioning as expressed in UHR subjects' everyday environments, and to relate these findings to neurocognition, clinical symptomatology and real-life functioning.

Methods: We will assess a minimum of 50 UHR and 50 matched healthy control subjects cross-sectionally with a comprehensive cognitive assessment battery. Measures of daily cognitive functioning are the Schizophrenia Cognition Rating Scale (SCoRS), an interview-based assessment of cognitive deficits using both patient and informant information, and the Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A), a standardised patient and informant questionnaire assessing executive functioning in everyday environments. The neurocognitive test battery includes the Cambridge Neuropsychological Test Automated Battery (CANTAB), the Brief Assessment of Cognition in Schizophrenia (BACS) and the Wechsler Adult Intelligence Scale – 3rd Edition (WAIS III). We will also assess all subjects using multiple clinical and functional measures. Clinical measures include the Comprehensive Assessment of At-Risk Mental States (CAARMS), the Brief Psychiatric Rating Scale – Expanded Version (BPRS-E), the Scale for the Assessment of Negative Symptoms (SANS) and the Montgomery-Åsberg Depression Rating Scale (MADRS). Functional measures include the Social and Occupational Functioning Assessment Scale (SOFAS), and the Global Functioning: Social (GF: Social) and Global Functioning: Role (GF: Role).

Results: Data collection began in 2009 and will end in the beginning of 2014. We will present results on the relationship between daily cognitive functioning and neurocognitive functioning, clinical symptoms and real-life functioning in a UHR cohort consisting of a minimum of 50 UHR and 50 healthy control subjects.

Discussion: The results will show if measures of everyday cognitive functioning in UHR subjects are related to measures of neurocognition, clinical symptomatology and real-life functioning. This may point towards important cognitive treatment targets in UHR subjects.

Poster #S228

THE ASSOCIATION BETWEEN REPORTED CHILDHOOD TRAUMA, PERCEIVED PARENTING AND PSYCHOPATHOLOGICAL RISK

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Background: Extensive and solid evidence shows that early traumatic experiences like sexual, emotional abuse and neglectful parenting are associated to psychopathology in general and psychosis in particular. Current etiopathogenetic models of psychosis do not usually highlight the role of early interactions with primary care-givers as possible triggers for psychosis. There has been a recent, renewed interest in tracing the quality of such interactions, possibly in light of new methodologies that promise to objectively measure the impact of early emotional experiences during critical periods on the biology, personality and mental health.

Methods: A sample of 666 young persons, aged 14 to 29, were recruited from the community and administered the Comprehensive Assessment of At Risk Mental State (CAARMS), the Structured Clinical Interview for DSM IV Axis I disorders (SCID-I) and the Parental Bonding Instrument (PBI). Those participants who were deemed At Risk Mental State (UHR+) were also administered the Positive And Negative Syndrome Scale (PANSS), Beck's Anxiety Inventory (BAI), the Calgary Depression Scale for Schizophrenia

(CDSS) and the Childhood Trauma Questionnaire (CTQ). The sample was segregated in four groups: 157 participants at risk who never converted to psychosis within the 24-month followup period (UHR+NP), 401 participants not at risk and with no SCID diagnosis (UHR-/SCID-), 93 participants not at risk but with a SCID diagnosis other than psychosis (UHR-/SCID+) and 15 participants who converted within 24 months (UHR+/P). Chi-Square was computed to assess the distribution frequency of these four categories of participants across the four PBI quadrants. Analysis of Variance (ANOVA) was computed across the same four groups to assess mean differences by CAARMS composite score and PBI dimensions. Stepwise, backward multilinear regression analysis was computed to determine the association between PBI dimensions and CAARMS composite score, PANSS, CTQ, CDSS and BAI scores. Logistic regression was computed to determine to what extent PBI dimensions predict UHR/SCID group inclusion.

Results: We found that high levels of emotional abuse and parental control are associated with severity of acute psychopathological symptoms (PANSS, CDSS and BAI) in UHR+NP participants. We also found that reported sexual abuse is associated with higher CAARMS composite score in UHR+NP participants. High levels of maternal care are associated to a lower probability of having a SCID diagnosis and lower CAARMS composite score. Finally, the vast majority of participants who converted to psychosis (UHR+P) had reported "affectionless control" received parenting at baseline: reporting "affectionless control" received parenting was also associated to SCID diagnosis.

Discussion: The association between the affectionless control parental style – maternal in particular – and psychopathology is well established in the literature. Such association was more recently confirmed in samples of UHR+ participants. The results we collected show the importance of the early emotional environment in shaping up the risk for psychosis and psychopathology in general. Such information could possibly complement screening tools that are solely based on sub-clinical symptomatology. Also, more comprehensive and objective measures, like the Adult Attachment Interview and epigenetic and biological markers of stress response may help overcome the limitations of self-report measures.

Poster #S229

DOSING AND CLINICAL STRATEGIES OF PALIPERIDONE ER IN ACUTELY EXACERBATED SCHIZOPHRENIA: AN EXPERT CONSENSUS IN TAIWAN

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Background: Paliperidone ER is the first atypical antipsychotic approved by FDA to improve patients' personal and social performance, which can benefit patients from the acute phase. The optimal dosing for patients with acute exacerbation is important for initial clinical efficacy and the following maintenance treatment. However, the related clinical information is limited. Paliperidone ER has been launched in Taiwan for 6 years, the key opinion leaders of psychiatrists all around Taiwan were invited to establish the Taiwan consensus for dosing and clinical strategies of Paliperidone ER in acutely exacerbated schizophrenia.

Methods: The 7 Taiwan expert consensus meetings were held in 5 cities in 2013 with the participation of 61 psychiatrists. They provided the experts' opinions of clinical strategies including initial dosing, titration speed of Paliperidone ER according to patients' CGI-S score, switching strategies and the concomitant medications for aggression, insomnia, akathisia and extrapyramidal side effect (EPS).

Results: 1. Initial dose and titration speed: In general, the consensus for initial dose of Paliperidone ER is at least 9mg Paliperidone ER in acutely exacerbated schizophrenia patients. For patients who are moderately to markedly ill (ex. CGI-S=4 or 5), it is suggested to initiate from 9mg/day of Paliperidone ER and to titrate the dose within one week. For patients who are severely or extremely ill (ex. CGI-S≥6), physicians may consider to initiate from 9–12 mg/day of Paliperidone ER and accelerate the titration speed to 3 days. For patients with long duration of illness or high dose of previous antipsychotics, physician may consider to initiate from

dose of 12mg/day; however, for patients with first episode of psychosis or drug naïve, it is recommended to initiate with lower dose of 6mg/day. The maximum targeting dose of Paliperidone ER for acutely exacerbated schizophrenia may be up to 18mg/day. 2. Switching strategies: If the patients are non-compliant to previous antipsychotics, physicians may switch to Paliperidone ER with the recommended initial dose directly. For patients who are compliant with Multi-acting Receptor Targeted Antipsychotics (MARTA) antipsychotics previously, it is suggested to cross titrate from MARTA to Paliperidone ER to avoid withdrawal symptoms; especially for clozapine. 3. Concomitant medications: Concomitant oral benzodiazepines and short-acting injection (ex. Haloperidol injection and Lorazepam) are suggested for patients with agitation. Cognitive behavioral therapy, benzodiazepines and hypnotics are suggested for patients with insomnia. 4. Side effect management: The Paliperidone ER related EPS is not frequently noted; the preventative anticholinergic is considered only for patients sensitive to side effect. For patients noted with akathesia, propranolol or benzodiazepines are suggested. For patients with palpitation, propranolol is suggested.

Discussion: Paliperidone ER has been launched in Taiwan since 2008. From recent studies and accumulating clinical experience, higher dose of Paliperidone ER is noted with better efficacy. This Taiwan expert consensus suggested the initial dose of Paliperidone ER for acutely exacerbated schizophrenia patient is at least 9mg/day in general, and the maximum targeting dose may be up to 18mg/day to achieve better clinical efficacy, and the side effects are generally fairly tolerable and manageable.

Poster #S230

NATURAL MEDICINES IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW

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Background: Despite progress in treatment options in the last century, the results of pharmacological treatment of schizophrenia are frequently unsatisfactory. Therefore some patients use natural medicines, although it is unclear whether natural medicines are effective and safe. We assessed the evidence for natural medicines with and without antipsychotics in treating symptoms or reducing side effects of antipsychotics in schizophrenia.

Methods: A systematic review until April 2013. Only RCTs with a Jadad score of 3 or higher were included.

Results: 105 RCTs were identified. Evidence was found for glycine, sarcosine, NAC, some Chinese and ayurvedic herbs, ginkgo biloba, estradiol and vitamin B6 for improving symptoms of schizophrenia when added to antipsychotics (glycine not when added to clozapine). Inconclusive or no evidence was found for omega-3 fatty acids, D-serine, D-alanine, D-cycloserine, B vitamins, vitamin C, dehydroepiandrosteron (DHEA), pregnenolone (PREG), inositol, gamma-hydroxybutyrate (GHB) and des-tyr-gamma-endorphin when added to antipsychotics. Omega-3 fatty acids without antipsychotics might be beneficial in the prevention of schizophrenia. In one large study, ayurvedic herbs seemed effective without antipsychotics. Other agents without antipsychotics (vitamin B3, vitamin C, sarcosine, glycine, Protilerin) were not effective or had only been tested in single or small trials. Ginkgo and vitamin B6 seemed to be effective in reducing side effects of antipsychotics (tardive dyskinesia and akathisia). The evidence for reducing side effects of antipsychotics by omega-3 fatty acids, melatonin and DHEA appeared to be inconclusive. All natural agents produced only mild or no side effects.

Discussion: High-quality research on natural medicines for schizophrenia is scarce. However, there is emerging evidence for improved outcome for glycine, sarcosine, NAC, some Chinese and Ayurvedic herbs, ginkgo biloba, estradiol and vitamin B6, all with only mild or no side effects. Most study samples are small, the study periods are generally short, the studies only cover a modest part of the world's population and most results need replication.

Poster #S231

TREATMENT OF VIOLENT DISSOCIAL PERSONALITY DISORDER PATIENTS WITH CLOZAPINE REQUIRES LOWER DOSE AND THERAPEUTIC LEVELS THAN IN SCHIZOPHRENIA

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Background: Clozapine is effective in treatment-resistant schizophrenia and in reducing aggression and violence in these patients. Studies investigating clozapine treatment in schizophrenia and have recommended that to minimise relapse rates, the maintenance dose of clozapine should yield a plasma serum level of at least 350 ng/ml. There is emerging evidence to support its use of clozapine in personality disorders. A number of small studies have shown the benefit of clozapine in borderline personality disorder reporting its effectiveness in reducing self-harm, aggression and improving overall clinical severity. A further study reports effectiveness in borderline personality disorder using low-dose clozapine. We report a case-series of 6 patients with primary dissociative personality disorder (DPD), treated with clozapine to determine its efficacy and the dose required for therapeutic response in comparison to the existing literature in schizophrenia. The patients did not have co-morbid schizophrenia. All patients had significant history of violence, and were deemed to pose a level of risk that they were detained in a high secure hospital.

Methods: Clozapine plasma serum levels were measured after patients were established on an effective clozapine dose. To assess treatment efficacy, Clinical Global Impression (CGI) scores were formulated retrospectively on case note review and the treating psychiatrist reported improvement in specific symptom domains of cognitive-perceptual, impulsive-behaviour dyscontrol and affective dysregulation. Records were reviewed for violent incidents, aggression and positive factors of engagement with staff, occupational and psychological therapy. Metabolic parameters before and after clozapine were assessed, and side-effects noted.

Results: All 6 patients showed improvement in CGI on low-dose clozapine and benefit was demonstrated in all symptom domains. There was a significant reduction in violent incidents in five of the six patients. The remaining patient did not have incidents before or after clozapine treatment, but reported reduction in frequency and severity of violent thoughts. The risk of violence toward others was reduced for all patients after clozapine treatment and three of the six patients progressed to lower dependency wards. These positive results were achieved on lower doses than are traditionally used to treat schizophrenia. The mean dose of clozapine used was only 208 mg (Range 100–325mg) and the duration of clozapine was at least 12 weeks (Range 12–67 weeks, median 26 weeks). Five of six patients had clozapine serum plasma levels below 300 ng/ml, the remaining patient's level was 350 ng/ml.

Discussion: We found that clozapine treatment in our 6 patients with DPD led to a reduction in illness severity and reduction in levels of violence. This was achieved in 5 of the 6 patients with low-dose clozapine and lower recommended therapeutic plasma level than is traditionally used in reference to schizophrenia treatment. To our knowledge this is the first account of clozapine being effective in primary DPD. The reasons for the effectiveness of lower doses of clozapine in these patients can be because of differing pharmacodynamics and target-symptoms compared to that in schizophrenia, and require further investigation. This may be particularly relevant because a proportion of patients with DPD also have co-morbid schizophrenia spectrum disorders.

Poster #S232

EFFICACY OF SECOND- VERSUS FIRST-GENERATION ANTIPSYCHOTIC DRUGS FOR TREATMENT-RESISTANT SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: Treatment resistance to antipsychotic drugs is a critical issue in the management of schizophrenia. Despite adequate antipsychotic phar-

macotherapy, many schizophrenic patients do not achieve full remission of symptoms. At present, clozapine is classified to be gold standard in case of treatment-resistance but primarily because of its risk profile (especially in terms of agranulocytosis) most guidelines suggest the realization of at least two adequate trials with other different antipsychotic agents before administering clozapine. Currently, there is no clear evidence which compound should be preferably chosen as second one in case of non-response to an initial antipsychotic trial before considering clozapine. Second-generation antipsychotics (SGAs) could be beneficial in this regard but there are currently no actual meta-analytic data available to appraise their efficacy in therapy-refractory schizophrenia.

Methods: We conducted a meta-analysis of all blinded randomized controlled trials (RCTs) that compared SGAs with first-generation antipsychotics (FGAs) and SGAs head-to-head in treatment-resistant patients with schizophrenia and/or related disorders (schizoaffective, schizophreniform, or delusional disorder). The primary outcome was overall efficacy of the antipsychotic agents (assessed by mean changes in Positive and Negative Syndrome Scale [PANSS] and mean changes in Brief Psychiatric Rating Scale [BPRS]). Secondary outcomes were positive and negative symptoms of schizophrenia as well as drop-outs due to any reason. Continuous endpoints were analyzed by calculating standardized mean differences Hedges's g with 95% confidence intervals (CI) and dichotomous outcomes by applying risk ratios (RR) with 95% CI.

Results: We included 33 RCTs with 40 direct drug comparisons and 4499 participants. Clozapine was the most investigated drug ($N=19$, $n=1121$) followed by olanzapine ($N=14$, $n=792$), risperidone ($N=12$, $n=489$), and haloperidol ($N=11$, $n=755$). In terms of treating overall symptoms clozapine was more efficacious than chlorpromazine (Hedges's $g=-0.8$, 95% CI: -1.01 to -0.59) and haloperidol (Hedges's $g=-0.17$, 95% CI: -0.33 to -0.01) and olanzapine was superior to haloperidol (Hedges's $g=-0.28$, 95% CI: -0.43 to -0.12). For the management of positive symptoms we identified a statistically significant superiority of clozapine over chlorpromazine and haloperidol and of risperidone over haloperidol and quetiapine. Regarding negative symptoms clozapine was more efficacious than chlorpromazine and haloperidol, olanzapine than haloperidol and risperidone, and ziprasidone than chlorpromazine. There were no significant differences in drop-outs due to any reason.

Discussion: We could demonstrate that clozapine is more efficacious than other FGAs in treatment-resistant schizophrenia. This result was consistent for the outcomes overall efficacy as well as for positive and negative symptoms. Surprisingly, clozapine's superiority could not be verified in comparison to the SGAs. Consistent with the CATIE phase 2 results our meta-analytic findings suggest that patients who do not respond to an initial antipsychotic drug could probably benefit from a switch of medication to olanzapine (especially in case of predominant negative symptoms) or risperidone (especially in case of predominant positive symptoms) as second step within a treatment algorithm for treatment-resistant schizophrenia. According to the non-significant differences in terms of the drop-out rates in the included trials it can be assumed that the investigated antipsychotics are characterized by comparable acceptability.

Poster #S233

ALL-CAUSE DISCONTINUATION AND SAFETY OF ARIPIPRAZOLE ONCE-MONTHLY FOR THE TREATMENT OF SCHIZOPHRENIA: A POOLED ANALYSIS OF TWO DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIALS

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Background: Switching medications is a common feature of psychiatric practice. When a change in antipsychotic medication is considered, the potential benefits and risks of switching should be evaluated. Aripiprazole once-monthly, a long-acting injectable formulation of oral aripiprazole, is the first dopamine partial agonist available as a long-acting injectable formulation. The objective of this pooled analysis was to evaluate the initial (3 months) all-cause discontinuation and safety of aripiprazole once-monthly

400mg, an extended release injectable suspension of aripiprazole, stratified by previous treatment.

Methods: These two studies (NCT00705783 & NCT00706654) were double-blind, placebo- or active-controlled, assessing the efficacy and safety of aripiprazole once-monthly 400mg. Detailed study designs have been reported previously (1, 2). This analysis was conducted on the pooled population in the first 3 months after initiating aripiprazole once-monthly 400mg treatment in patients who received at least one dose of aripiprazole once-monthly 400mg. Outcome measures are reported for groups stratified by prior treatment.

Results: In total, 841 patients received at least one aripiprazole once-monthly 400 mg injection. During the first 3 months of treatment, discontinuation due to all-causes (not including those who discontinued due to the sponsor stopping the NCT00705783 study early after pre-specified efficacy parameters were met) were 13.2% (111/841) overall, 12.0% (23/191) for patients entering on oral aripiprazole, and 13.1% (76/581) for patients who converted from another antipsychotic, and 17.4% (12/69) for patients not on antipsychotic treatment prior to entering the trials. Discontinuations due to adverse events in the first 3 months were 2.5% (21/841) overall; 1.6% (3/191) for patients entering the study on oral aripiprazole, 2.4% (14/581) for converted patients, and 5.8% (4/69) for those who were not on antipsychotic treatment. In the first three months, insomnia was the most common adverse event: 8.4% (71/841) overall, and ranged from 3.1% (6/191) for the oral aripiprazole group to 11.6% (8/69) for patients not on antipsychotic treatment. The frequency of akathisia was 7.0% (59/841) overall, and ranged from 6.7% (39/581) for the converted group to 7.9% (15/191) for the patients entering on oral aripiprazole.

Discussion: Aripiprazole once-monthly 400mg appeared equally safe and effective (as measured by all cause discontinuation) in the first 3 months after initiation, regardless of treatment prior to entering trials.

Poster #S234

RESTING CEREBRAL BLOOD FLOW (rCBF) IN FIRST EPISODE PSYCHOSIS AND CHANGES INDUCED BY ANTIPSYCHOTIC MEDICATION

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Background: Response to antipsychotic treatment is highly variable, but most of all, unpredictable. There are currently no reliable neurobiological assessment methods to predict treatment efficacy. Furthermore, the effects of antipsychotic medication on brain physiology and the mechanisms of antipsychotic action remain poorly understood. Studies investigating resting cerebral blood flow (rCBF) in schizophrenia suggest that antipsychotics have regional effects on rCBF (Handley et al., 2012) consistent with the known location of receptors targeted by the drug but also indicative of downstream effects associated with the functional projections of those regions (Viviani, et al. 2013). Unfortunately, studies to date have been conducted in heterogeneous populations, using uncontrolled antipsychotic regimes and differing methodologies.

Methods: We have evaluated rCBF in minimally treated, first episode psychosis patients ($n=11$), using a pseudo-continuous arterial spin labelling (pCASL) (Dai et al., 2008) sequence whilst at rest with eyes open, before and after four weeks of treatment with the dopamine D2-receptor antagonist drug amisulpride. A group of matched healthy controls ($n=14$) was also scanned with the same sequence.

Results: Whole brain analysis revealed a significant decrease in global rCBF following antipsychotic treatment ($t = 2.43$, $p=0.036$). Further analyses were carried out with and without global rCBF values as a covariate. Without global covariate in patients following treatment, we identified four statistically significant ($p < 0.05$ cluster corrected for multiple comparison) clusters of decreased rCBF in superior temporal gyrus, medial frontal gyrus, lingual gyrus and inferior temporal gyrus. There were no regions of increased rCBF. Using global rCBF as a covariate, analysis showed that clusters of decreased rCBF remained in superior temporal gyrus and lingual gyrus, although in some cases the clusters were smaller. Additionally, several regions of increased rCBF became apparent in the midbrain, cerebellar regions, superior

frontal gyrus and regions of the temporal lobe including the precuneus. Regional analysis of extracted values from anatomically defined regions of interest suggested that there were significant decreases in rCBF in the insula bilaterally ($t=3.431$, $p=0.007$) and the occipital gyrus ($t=2.265$, $p=0.05$). **Discussion:** Our results suggest that short-term treatment with amisulpride leads to widespread decreases in rCBF, both globally and regionally. These changes overlap with regions identified elsewhere as showing structural and/or functional changes in the disease (Viviani et al. 2013). Due to the inextricable link between regional rCBF and neuronal activity (Atwell et al., 2012) these changes may reflect an interaction between the pathophysiology of the disorder and the therapeutic effect of the drug. Elucidating the effects of antipsychotics on measures of brain function, such as rCBF, could reveal neurobiological mechanisms underlying antipsychotic action and therapeutic response.

Poster #S235

LIFETIME USE OF ANTIPSYCHOTIC MEDICATION AND CHANGE OF VERBAL LEARNING AND MEMORY IN SCHIZOPHRENIA IN 9-YEARS FOLLOW-UP IN A GENERAL POPULATION SAMPLE

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Background: The longitudinal course of cognitive deficit in schizophrenia and its associations with antipsychotic medication remain unclear. The aim of this study was to analyze the association between cumulative lifetime antipsychotic dose and change of verbal learning and memory in schizophrenia during a 9-year follow-up.

Methods: Forty schizophrenia spectrum subjects and 73 non-psychotic controls from the Northern Finland Birth Cohort 1966 were assessed diagnostically and cognitively, including California Verbal Learning Test (CVLT), at the ages of 34 and 43 years. Data of the subjects' lifetime antipsychotic doses in chlorpromazine equivalents were collected from records and interviews. The association between dose-years of antipsychotics and both baseline performance and change of verbal learning and memory was analyzed by linear regression model, controlling for baseline performance, gender, age of illness onset and severity of illness.

Results: Higher dose-years of any and typical antipsychotics by the baseline study associated statistically significantly with poorer baseline performance in several dimensions of verbal learning and memory. Higher dose-years of antipsychotics by baseline associated statistically significantly with a larger decrease of short-delay free recall during the follow-up ($p=0.029$). Higher dose-years of antipsychotics during the 9-year follow-up associated statistically significantly with a larger decrease of immediate free recall of trials 1-5 during the same follow-up period ($p=0.040$).

Discussion: To our knowledge, this is a first report on an association between cumulative lifetime antipsychotic use and change in cognition in a long-term naturalistic follow-up. Based on this data, the use of high doses of antipsychotics may relate to a decrease of verbal learning and memory functions in schizophrenia after ten years of illness. The results do not support the view that antipsychotics prevent cognitive decline or promote cognitive recovery in schizophrenia.

Poster #S236

CORRELATION BETWEEN EXPECTED AND EFFECTIVE PLASMA CONCENTRATIONS OF ANTIPSYCHOTICS AND CHANGES IN PSYCHOPATHOLOGY IN PATIENTS WITH SCHIZOPHRENIA

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Background: Therapeutic drug monitoring (TDM) should be a valid tool to

optimize pharmacotherapy. It is based on the assumption that there is a correlation between plasma levels and the clinical efficacy of medication. This is the case for desirable effects as well as for undesirable toxicity. However, with respect to antipsychotics the current literature reports divergent results. Our study investigated whether the ratio of the expected and the effective plasma levels of new generation antipsychotics is related to psychopathology after initiating or changing the current antipsychotic treatment in patients with schizophrenic disorders.

Methods: Patients with a schizophrenic disorder according to ICD-10 who started a clinically indicated monotherapy with a new generation antipsychotic or changed to a monotherapy with a new generation antipsychotic because of ineffectiveness or intolerance of the existing antipsychotic therapy were followed prospectively in a naturalistic drug monitoring program after having provided written informed consent. Antipsychotics were chosen by the psychiatrist treating the patients, dosing followed clinical needs. Visits were made at baseline and after 2, 4, and 12 weeks of treatment. Prescribed substances were amisulpride, olanzapine, risperidone, ziprasidone, clozapine, quetiapine, aripiprazole, and sertindole. The effective plasma levels were determined through blood tests, the expected plasma levels were calculated using the program "AutoKinetic v34b" (Toennes), with consideration of body weight, distribution volume, bioavailability, the time at which the maximum concentration (c_{max}) is reached (t_{max}), and half-life ($t_{1/2}$). Psychopathology was evaluated by means of the Positive and Negative Syndrome Scale (PANSS).

Results: 127 patients were included into the study (81 men and 46 women). Their mean age was 35.6 ± 9.7 years. 22.0% of the patients were treated with amisulpride, 20.5% with olanzapine, 14.2% with risperidone, 14.2% with ziprasidone, 11.8% with clozapine, 11.8% with quetiapine, 3.9% with aripiprazole, and 1.6% with sertindole. A total number of 268 ratios of effective plasma levels/expected plasma levels were eligible for analysis. 50.4% of the ratios showed a value of 0.5-2 (approximately normal), 37.3% of 0-0.5 (rather too low), and 12.3% of >2 (rather too high). No significant variances in ratio were found throughout the study duration. However, all patients who remained in the study showed significant reductions in PANSS subscores (positive symptoms, negative symptoms, general symptoms) and in the PANSS total score compared to baseline throughout the study period. A correlation analysis between psychopathology (PANSS) and ratio did not show a significant interrelation at any time.

Discussion: In summary, our results indicate that the ratio of expected and effective plasma levels is not correlated with changes of psychopathology in patients with schizophrenic disorders. However, studies about the significance of therapeutic drug monitoring in this regard are inadequate, and the field clearly warrants further studies to find out the meaningful use of therapeutic drug monitoring and factors influencing psychopathological changes in patients with schizophrenia.

Poster #S237

SIMULATION OF DOPAMINE D2 RECEPTOR OCCUPANCY BY ARIPIPRAZOLE IN STEADY STATE: BASED ON PK-PD MODELING

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Background: Receptor occupancy study has been performed to evaluate pharmacokinetic profiles in antipsychotic drug development. In particular, dopamine D2 receptor occupancy is a meaningful biomarker in that it reflects the antipsychotic action at the target site in the brain and predicts both the clinical response to antipsychotic drugs and the emergence of drug side effects. The importance of measuring dopamine D2 receptor occupancy by a novel antipsychotic drug is further emphasized by studies showing wide discrepancy between the time courses of drug concentration in plasma and receptor occupancy in the brain. While these findings highlight the value of measuring receptor occupancy in dose-finding study, a challenge is the impossibility of obtaining as many receptor occupancy data as would be necessary to design clinical trials with various dosing strategies. This raises the necessity of in-silico simulation of dopamine receptor occupancy by antipsychotic drugs.

Methods: We previously reported a novel methodology using pharmacokinetic-pharmacodynamic (PK-PD) modeling for the concentration-occupancy

pancy relationship analysis and estimated parameters for the PK-PD model after single administration of aripiprazole (*J Cereb Blood Flow Metab.* 2011 Dec 21. doi: 10.1038/jcbfm.2011.180.) Based on the parameter estimates from the PK-PD model, we simulated dopamine D2 receptor occupancy by aripiprazole in steady state.

Results: In the case of once-a-day dosing schedule, the simulation shows that dopamine D2 receptors would be almost fully occupied in steady state even with 10mg of aripiprazole. In addition, the fluctuation index (=maximal level-tough level)/trough level) in steady state was lower than 5% in occupancy while higher than 100% in plasma concentration. These findings suggest that aripiprazole is likely to be given with higher dose and shorter interval than is required for the treatment of schizophrenia in terms of receptor occupancy.

Discussion: This study shows in-silico simulation based on the PK-PD modeling can be useful for exploring appropriate doses for antipsychotic drugs.

Poster #S238

PHARMACOLOGICAL MODULATION OF KV3 POTASSIUM CHANNELS ON PARVALBUMIN-POSITIVE FAST-SPIKING INTERNEURONS – A NOVEL APPROACH TO THE TREATMENT OF SCHIZOPHRENIA

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Background: Fast spiking (FS) parvalbumin (PV)-positive interneurons, which represent a major class of inhibitory interneuron in cortico-limbic brain circuits, have been hypothesized to be dysfunctional in psychiatric disorders such as schizophrenia [1]. Kv3-family voltage-gated potassium channels are specifically expressed by FS interneurons. Kv3 channels activate in response to transient depolarization of the plasma membrane to positive potentials during an action potential in order to initiate rapid repolarisation. Thus Kv3 channels allow FS interneurons to fire accurately at high frequency to orchestrate the activity of cortical networks. Consequently, pharmacological manipulation of FS interneuron firing through modulation of Kv3 channels may have potential in the treatment of schizophrenia. We now report that the imidazolidinedione derivative, AUT1, specifically increases currents mediated by recombinant Kv3.1 and Kv3.2 channels expressed in cell lines. In cortical slices, AUT1 rescues the FS phenotype of parvalbumin-positive interneurons when their activity is reduced by low concentrations of the non-selective potassium channel blocker, tetraethylammonium (TEA).

Methods: The effects of AUT1 on recombinant human Kv3.1b and Kv3.2 channels expressed in cell lines were studied with patch-clamp electrophysiology using Ionworks Quattro® and QPatch® platforms. The effects of AUT1 on native FS interneurons were studied using brain slices obtained from CB6-Tg (Gad1-EGFP)G42Zjh/J mice (Jackson Labs), which selectively express enhanced green fluorescent protein (EGFP) in the subclass of basket interneurons that express PV. Confirmation of the co-expression of Kv3 channels in PV-positive interneurons in these mice was carried out by immunohistochemistry using anti-Kv3.1b (Sigma P 9732) and anti-Kv3.2 (custom-made by CRB) antibodies.

Results: AUT1 increased current mediated by human recombinant Kv3.1b and Kv3.2 channels in a concentration and voltage-dependent manner (EC50 4.7 and 4.9 microM, respectively). In the CB6-Tg mice, immunofluorescence studies revealed that 75% of PV-expressing cells also contained Kv3.1b in layers II-III, and IV of the somatosensory cortex. In the deep layers (V-VI), 81% of cells expressing PV also expressed Kv3.1b. Similarly, in the deep layers, 75% of cells expressing PV also expressed Kv3.2; however, in layers II-IV, only 44% of PV-expressing cells also expressed Kv3.2. Whole-cell current clamp recording from fluorescent PV-positive cells in the deep layers of the somatosensory cortex of the CB6-Tg mice confirmed their fast-spiking phenotype. Maximum firing frequency and action potential half-width in response to depolarizing current pulses were both reduced by application of 0.5 mM TEA, consistent with partial inhibition of Kv3 channels. Application of AUT1 (1-10 µM) significantly reversed both the TEA-induced reduction in maximum firing frequency ($P<0.05$), and the TEA-induced increase in action potential half-width ($P<0.01$).

Discussion: These results show that pharmacological, selective manipulation of fast-firing PV-positive interneurons can be achieved with a novel

class of agent that modulates Kv3 channels. We suggest that these compounds may be useful in the treatment of disorders associated with reduced function of FS interneurons, such as schizophrenia.

Poster #S239

AZD8529, A POSITIVE ALLOSTERIC MODULATOR AT THE MGLUR2 RECEPTOR, DOES NOT IMPROVE SYMPTOMS IN SCHIZOPHRENIA: A PROOF OF PRINCIPLE STUDY

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Background: Aberrant cortical connectivity and hypofunction of NMDA receptor signaling may underlie some schizophrenia symptoms. Direct activation of mGluR2/3 receptors has been shown to reduce effects of NMDA antagonists in animal studies. In humans, this mechanism has been shown to reduce the working memory deficit induced by ketamine; one study showed an antipsychotic effect in acute schizophrenia, an effect not reproduced in subsequent studies. We have investigated the efficacy and tolerability of AZD8529, a selective positive allosteric modulator (PAM) at the mGluR2 receptor, in symptomatic patients with schizophrenia.

Methods: Following 7 days washout, patients were randomized to receive either AZD8529 40mg (n=61), risperidone 4mg (n=31), or placebo (n=60) for 28 days. Clinical efficacy was assessed using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression -Severity (CGI-S) and -Improvement (CGI-I) Scales as primary outcome measures. Change from baseline to endpoint was analyzed by MMRM methods.

Results: Baseline PANSS did not differ between groups (AZD8529: 92.9; placebo: 93.6; risperidone: 91.0). After 28 days of treatment there was no significant difference between the AZD8529 and placebo groups in the PANSS total score change from baseline ($\Delta=1.8$, $p=0.41$). Reductions in PANSS total score were significantly greater for risperidone as compared to placebo ($\Delta=-9.8$, $p<0.001$). Similarly, significant differences versus placebo were observed for risperidone but not AZD8529 for the PANSS subscale and CGI-S scores.

Discussion: This single dose study does not support a role for positive modulation of mGluR2 receptors as a mechanism for monotherapy to treat acute schizophrenia. It remains to be determined whether different treatment regimens or adjunct treatment would provide benefit.

Poster #S240

OXYTOCIN AND PSYCHOSIS: EXPLORATORY META ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: There is considerable evidence that affiliative and social cognitive processes are linked to oxytocin (OXT). There is evidence that oxytonergic systems are involved in psychosis and emerging evidence that synthetic OXT may represent a novel treatment paradigm. Evidence from animal studies indicates proof of concept of OXT as an antipsychotic treatment for schizophrenia. As treatment trials of OXT in human clinical samples increase, we conducted an exploratory meta-analysis to estimate an effect size for OXT treatment on psychotic symptoms. We hypothesized that OXT would be associated with lower levels of psychotic symptoms compared with placebo.

Methods: We conducted a systematic search of electronic databases from 1980 and November 2013 for randomized controlled trials (RCT's) of OXT in schizophrenia. Participants had a diagnosis of Schizophrenia or psychosis and the outcome variables explored the effects of OXT in relation to symptom outcomes or social cognition. Preclinical studies of OXT and schizophrenia, unpublished studies, dissertations, conference abstracts and book chapters were excluded. Effect sizes for OXT on symptoms were extracted and converted to Hedge's "g". Symptom scores were reported on the PANSS scale or converted to PANSS equivalence. Meta-analyses were conducted with both fixed and random effects meta-analyses, incorporating assessment of heterogeneity, publication bias and influence bias.

Results: After applying exclusion criteria there were 7 randomised controlled trials that met the inclusion criteria for this review. Three of these were studies of social cognition and did not report data for symptoms. We conducted an exploratory meta-analysis of data from the 4 studies reporting treatment data on a total sample size of n=115. For overall symptoms, using a random effects model, OXT was associated with a pre-post treatment effect size of $g=0.67$ (95% CI = 0.30 to 1.05; $z=3.50$; $p=0.0005$), equivalent to a medium to large effect size. Fixed effects meta-analysis produced a standardised effect size of $g=-0.44$ (95% CI = -0.83 to -0.05; $z=2.19$; $p=0.03$), indicating a medium effect for OXT in reducing total psychotic symptoms, compared to placebo. However heterogeneity was significant ($Q=129$, $p<0.0001$, $Tau^2=0.98$, $I^2=85.9\%$). Fitting of a random effects model to the same data was non-significant, indicating insufficient evidence to support the effectiveness of OXT. An Influence analysis indicated one study accounted for a significant component of the heterogeneity and the study effect. There was evidence of significant heterogeneity ($Q=96.4$, $p<0.001$; $I^2=96.5\%$).

Discussion: Although there is evidence for a positive effect of OXT on symptoms there are several obstacles in interpreting the current evidence base. The small number of published studies hinders assessment of follow-up length or OXT dosage. We note that 8 further studies are ongoing or just completed. Treatment effects appeared stronger for within-group pre-post treatment gain, compared with group comparison with placebo. Recent review evidence also suggests that positive OXT effects may be lowered in the presence of negative childhood experiences, suggesting potential environmental modulation of oxytonergic systems. Further research in the areas of treatment development and exploration of modulators of oxytonergic systems would be merited.

Poster #S241

THE POSITION OF BLONANSERIN AS A TREATMENT FOR SCHIZOPHRENIA: EVIDENCE FROM META-ANALYSIS OF RANDOMIZED, PLACEBO-CONTROLLED TRIALS

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Background: Because previous multiple-network meta-analysis did not include blonanserin, the position of blonanserin in the treatment of schizophrenia remains unclear.

Methods: The blonanserin study that was compared with previous meta-analysis was a double-blind, randomized, placebo-controlled study, and it included patients with acute schizophrenia. The primary outcomes were efficacy and all-cause discontinuation. In order to compare this study with previous meta-analysis, the standardized mean differences (SMD) and odds ratios (OR) were calculated.

Results: Blonanserin was more efficacious than placebo in efficacy (SMD = -0.56, $p=0.0002$) and all-cause discontinuation (OR=0.48, $p=0.02$). However, blonanserin caused more weight gain than placebo but the effect size was small (SMD=0.31, $p=0.03$). Blonanserin did not differ from placebo for extrapyramidal side effects ($p=0.52$), prolactin increase ($p=0.96$), or sedation ($p=0.66$). There were no patients who had QTc prolongation in the blonanserin group. When we added these results for blonanserin to compare with placebo in previous meta-analysis, blonanserin was fourth in the list of efficacious and tolerable antipsychotics.

Discussion: The evidence suggests that blonanserin has a beneficial effect on the psychopathology of schizophrenia similar to the other antipsychotics that are used in the world and that blonanserin is a safe and well-tolerated potential treatment for schizophrenia.

Poster #S242

THE SUBJECTIVE TREATMENT SATISFACTION OF SWITCHING ANTIPSYCHOTICS IN JAPANESE PATIENTS WITH SCHIZOPHRENIA; J-BETA (JAPAN-BROAD EFFECTIVENESS TRIAL OF ARIPIPRAZOLE)

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Background: This study examined the change in subjective evaluation and the predictive factors for improving subjective evaluation after switching

from a previous antipsychotic to aripiprazole in Japanese patients with schizophrenia.

Methods: This was a 12-week, prospective, open-label, multicenter study. Outpatients and inpatients with schizophrenia who were treated with a single antipsychotic, except for aripiprazole, and who were switched from a previous antipsychotic to aripiprazole due to factors including side effects, lack of efficacy, patient's wishes were enrolled. The dose of aripiprazole was flexible, 6mg/day to 30mg/day, and was based on the judgment of the investigator. Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents. The primary outcome measure was the preference of medicine (POM) questionnaire by patients and their caregivers [1]. Satisfaction with medication was assessed with the POM questionnaire at 12 weeks post-switching. The secondary outcome measure included the Clinical Global Impression-Impression (CGI-I) and the 10 item version-Drug Attitude Inventory (DAI-10) at endpoint.

Results: A total of 303 patients who were diagnosed with schizophrenia were recruited in this study, of whom 292 were eligible for enrollment. One hundred thirty eight patients (47%) were male and the mean age of all subjects was 44.6 ± 15.5 years old. Two hundred six patients (71%) completed the 12-week trial. The most common reasons for discontinuation were loss to follow-up ($n=15$) and lack of efficacy ($n=12$). The mean dosage of aripiprazole was 15.7 ± 1.5 mg/day. Prior antipsychotics included risperidone (38%) and olanzapine (23%). The main reasons for switching were daytime somnolence (34%), lack of efficacy (positive symptoms) (27%), weight gain (22%). At 12 weeks post-switching, 84.7% of patients and 83.0% of their caregivers rated aripiprazole as slightly better or much better than the prior antipsychotics in the POM (OC). Patients with much or very much improvement in the mean CGI-I scores comprised 49.6% at endpoint. Switching to aripiprazole significantly increased the mean DAI-10 scores at endpoint ($p<0.001$, Wilcoxon signed rank test). Predictive factor for improving both POM and CGI-I after switching to aripiprazole was weight gain as the reason of switching (OR=3.60; $p=0.010$, OR=2.31; $p=0.045$, respectively), using multivariate logistic analysis. And dull headache also was detected as predictive factor for improving POM (OR=8.71; $p=0.036$). After switching from risperidone to aripiprazole, predictive factor for improving both POM and CGI-I was dull headache (OR=5.02; $p=0.006$, OR=4.080; $p=0.0246$, respectively). Regarding olanzapine, predictive factor for improving both POM and CGI-I probably might be weight gain, since a prior antipsychotic was significantly relative to weight gain (chi square, $p=0.0016$) and olanzapine has the highest risk of weight gain among major prior agents [2].

Discussion: The proportion of POM rated as slightly better or much better was more than 80%. In Japanese people with schizophrenia, alleviating burden of side effect (i.e. weight gain and dull headache) after switching to aripiprazole, improves both subjective treatment satisfaction and objective CGI.

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Poster #S243

CLOZAPINE TREATMENT IN PEDIATRIC ONSET SCHIZOPHRENIA: LESSONS FROM THE NIMH EXPERIENCE

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Background: Childhood onset schizophrenia (COS) with onset of psychosis before age 13, is a chronic, severe, and treatment refractory form of schizophrenia where the treatment of last resort remains clozapine. Despite its proven superiority, due to its side effect profile, clozapine treatment in children remains challenging. We review our experience in managing the challenges in long term clozapine treatment in the largest to-date studied cohort of COS.

Methods: Through nationwide recruitment, to date, 136 children with COS have been enrolled in a prospective study where diagnosis was confirmed, in most cases, after an inpatient observation that included a complete medication washout. Clozapine was started after the diagnosis confirmation and dose was stabilized before the child was discharged, typically after 6-8 wks.

Results: The average age of onset of psychosis was 10.4 ± 1.8 . Average duration of inpatient stay prior to the first NIH admission was 5.3 ± 8.2 months, whereas post-NIH almost none required inpatient stay during up to 15+ yr follow up ($p < 0.05$). A high incidence of comorbid affective and anxiety disorders is seen with the NIMH COS sample. The most common comorbid diagnosis at admission was depression (54%) followed by obsessive compulsive disorder (21%), generalized anxiety disorder (15%), attention deficit hyperactivity disorder (15%), and separation anxiety disorder (5%). Once the children were stabilized on clozapine, the addition of selective serotonin reuptake inhibitor (SSRI) was found to provide additional benefits. 14 children were stabilized on clozapine with SSRIs with a beneficial response. In children where comorbid ADHD was a significant problem, once the clozapine dosage was stabilized, the addition of methylphenidate proved beneficial in five children, with significant improvement in ADHD symptoms. Of the children who were on clozapine at discharge and followed up 83% (50 out of 60) have remained on clozapine at 2 years, and 73% (22 out of 30) at 4 years follow up. At 2 years follow up, patients receiving clozapine showed evidence of sustained clinical improvement, but additional adverse events also emerged. Lipid abnormalities (1 out of 12 patients) and hypertension or tachycardia (7 out of 12 patients) were the main reason for discontinuing the medication. 11 patients showed neutropenia on clozapine which was successfully managed by adjuvant Lithium treatment in 10 out of 11 cases. Other serious side effects included significant weight gain (42; 20 males, 22 females), seizure activity (5 patients) and akathisia (14 patients). Additionally, drooling, incontinence, sedation, tachycardia with postural hypotension were common.

Discussion: Clozapine offers significant superiority over other antipsychotic medications in pediatric psychosis. This study discusses the overall profile of clozapine response in children with COS, treatment strategies for starting and maintaining clozapine, along with management of common side effects.

Poster #S244

CONSULTANT PSYCHIATRISTS' PERSPECTIVES REGARDING ANTIPSYCHOTIC DOSE CHOICE AND PLASMA CONCENTRATION THERAPEUTIC DRUG MONITORING

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Background: Little is known about how clinicians determine a patient's optimum antipsychotic dose and how they adjust dose in response to clinical symptomatology. This study aimed to examine current prescribing practices and clinicians' perspectives regarding therapeutic drug monitoring (TDM) using plasma concentrations, with exploration of predictive factors for future use of TDM.

Methods: A cross-sectional study for consultant psychiatrists using a quantitative postal questionnaire was conducted in North-West England. Questions on current prescribing practices and clinicians' perspectives of TDM were included. Agreement with each statement was scored using a six point Likert scale. Additional data was taken from a former similar study conducted in the London region.

Results: There were 76 responses from the North-West England group and 105 from the London group. For the total combined sample, optimum dose was mainly determined by clinicians' usual dosing regimen (84.5%) and half (50.8%) believed that there was no maximum to the number of times it is acceptable to switch antipsychotics for a patient. The majority (82.9%, 95% CI: 76.7–87.7%) of the total sample agreed that they would use TDM for antipsychotics if it were readily available. Principal axis factoring analysis conducted on 35 items regarding TDM identified five factors with good internal consistency: positive attitudes and expectations ($\alpha=0.82$); potential barriers (0.66); negative attitudes (0.78); negative scientific perspective (0.70); negative expectations (0.67). Four of these five factors significantly predicted the response to the statement "if TDM for antipsychotics was readily available, I would use it" and together explained 40% of the variance in a multivariate linear regression model. Increased likely future use of TDM for antipsychotics was predicted by positive attitudes and expectations and

decreased use was predicted by potential barriers, negative attitudes and negative expectations. Alternatively negative scientific perspective and also consultant participant characteristics (gender, age, place qualified, clinical speciality and clinical setting) were not significant predictors.

Discussion: The majority of consultant psychiatrists indicated that they would use TDM for antipsychotics if it were available, thus indicating it is possible that TDM might be used as an additional tool to aid in the optimisation of antipsychotic treatment at the individual level. Clinicians' attitudes, expectations and the perceived potential barriers appear to predict whether or not a clinician will use TDM, whereas consultants' characteristics and their perspectives regarding scientific evidence do not. Consequently, the predictive factors identified here should be targeted when considering putative interventions to promote the use of TDM for antipsychotics in clinical practice.

Poster #S245

LONG-TERM SAFETY AND EFFECTIVENESS OF LURASIDONE IN SCHIZOPHRENIA: RESULTS OF A 22 MONTH, OPEN-LABEL EXTENSION STUDY

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Background: Lurasidone has demonstrated efficacy in the treatment of schizophrenia in a series of short-term placebo-controlled trials. The goal of this study was to evaluate the safety, tolerability and effectiveness of lurasidone in the long-term treatment of patients with a DSM-IV-TR diagnosis of schizophrenia.

Methods: Patients who completed a 6 week, double-blind, placebo-controlled trial received once-daily, flexible-doses of lurasidone, 40–120 mg in a 22 month open-label extension study. An observed case analysis was performed on change from pre-treatment baseline in safety and efficacy parameters.

Results: 250 subjects entered the study; 39.8% completed 12 months and 26.8% completed 22 months of treatment. Lurasidone treatment was associated with a mean endpoint change in weight of +0.7 kg. Median endpoint change at Month 12 and Month 24, respectively, was -1.0 and -9.0 mg/dL for total cholesterol; 0.0 and -1.0 mg/dL for LDL; +1.0 and -11.0 mg/dL for triglycerides; +4.0 and +2.0 mg/dL for glucose; 0.0 and +0.1% for HbA1c; and -1.3 and -1.1 ng/mL for prolactin. The mean PANSS total score was 69.5 at extension baseline. The mean (95% CI) endpoint change from extension baseline in PANSS total score was -0.5 (95% CI: -0.7, -0.3). Overall, 14.7% of patients discontinued due to an adverse event. Adverse events occurring with an incidence $\geq 10\%$ were schizophrenia (12.4%), akathisia (10.8%) and somnolence (10.8%).

Discussion: In this 22 month extension study, treatment with lurasidone was associated with minimal effects on weight, glucose, and lipids. Subjects demonstrated sustained improvement in the PANSS total score for up to 24 months of lurasidone treatment.

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Poster #S246

EFFECTS OF DURATION OF ILLNESS ON THERAPEUTIC RESPONSE TO ADJUNCTIVE TREATMENT WITH N-ACETYL CYSTEINE IN SCHIZOPHRENIA

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Background: Schizophrenia is a chronic and often debilitating disorder in

which stage of illness appears to influence course, outcome, prognosis and treatment response. Current evidence suggests roles for oxidative, neuroinflammatory, neurotrophic, apoptotic, mitochondrial and glutamatergic systems in the disorder; all targets of N-acetyl cysteine (NAC). A double blind, placebo controlled trial suggested NAC to be beneficial to those diagnosed with schizophrenia. The current study aims to investigate duration of the illness as a key factor that may be modulating the response to NAC in the participants who took part in the study.

Methods: A sample of 140 participants were randomized in a double fashion to 24 weeks (placebo=71; NAC=69). Clinical and functional variables were collected over the treatment period. Duration of the illness at baseline was grouped into <10 years, 10-<20 years and >20 years. Mixed Model Repeated Measures Analysis was used to explore the effect of illness duration on response to treatment with NAC.

Results: A significant interaction between duration of the illness and response to treatment with NAC was consistently found for positive symptoms and functional variables, but not for negative or general symptoms or for side effects related outcomes. The pattern of changes suggests a mediator effect of duration of illness in response to treatment more evident in those participants with 20 years or more of illness duration.

Discussion: Our results suggest a potential advantage of adjunctive NAC over placebo on functioning and positive symptoms reduction in those patients with chronic schizophrenia. This has potential for suggesting stage specific treatments.

Poster #S247

A RANDOMIZED, ACTIVE-CONTROLLED RATER-BLINDED 2-YEAR STUDY OF PALIPERIDONE PALMITATE VERSUS INVESTIGATORS' CHOICE OF ORAL ANTIPSYCHOTIC MONOTHERAPY IN PATIENTS WITH SCHIZOPHRENIA (PROSIPAL)

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Background: Recent metaanalyses have reported conflicting results on the efficacy of long-acting injectable antipsychotic treatment (LAT) compared to oral antipsychotics in the prevention of relapse in patients with schizophrenia [1,2]. The objectives of this study was to evaluate time to relapse, relapse rates and other clinically relevant outcomes in recently diagnosed (1–5 years) patients with schizophrenia treated with paliperidone palmitate (PP) LAT monotherapy compared to investigators' choice of one out of the six most frequently prescribed oral antipsychotics (oAPs), i.e. aripiprazole, olanzapine, quetiapine, paliperidone ER, risperidone or haloperidol.

Methods: 2-year international randomized controlled, open-label, rater-blinded study. Initially, acutely ill patients with schizophrenia were randomized in a 1:1 ratio to PP or oAPs. For the first two weeks patients in the two arms were treated either with paliperidone ER or one of the 6 oAPs, respectively. Responders were then treated with PP or oAPs over 2 years or until prespecified relapse criteria according to Csernansky et al were met. Primary endpoint was time to relapse. Other endpoints included relapse rates, changes in psychotic symptoms (PANSS) and patient functioning (PSP) from baseline to endpoint and treatment-emergent adverse events (TEAEs).

Results: 764 patients were randomized and entered the initial 2-week acute treatment phase. Of these, 715 responded to acute treatment and entered the 2-year study period (352 PP, 363 oAPs). Most patients were male (58.4%), mean age (\pm SD) was 32.5 ± 10.4 years and the majority had paranoid schizophrenia (86.2%). There were no significant differences in demographics or baseline characteristics. Time to relapse was significantly longer with PP compared to oAPs (mean \pm SE: 616 ± 10.9 vs 603 ± 13.1 days,

$p=0.019$). Relapse rates were significantly lower with PP vs oAPs (14.8% vs 20.9%; $p=0.032$), reflecting a relative risk reduction of 29.2%. Reduction of psychotic symptoms in PANSS was significantly superior with PP at treatment day 8 ($p=0.021$) and showed a trend in favor of PP at endpoint ($p=0.074$). At endpoint, improvement in patient functioning was also numerically, but not statistically significantly, better with PP vs oAPs (mean change from baseline 9.8 vs 8.7, respectively; $p=0.28$). TEAEs reported in $\geq 5\%$ in any group (PP vs oAPs) were: weight increase (15.9% vs 17.4%), headache (11.1% vs 8.5%), insomnia (9.7% vs 8.0%), schizophrenia (8.2% vs 9.6%), nasopharyngitis (7.1% vs 5.0%), injection site pain (6.8% vs 0%), anxiety (5.7% vs 4.4%), tremor (5.1% vs 2.2%) and suicidal ideation (4.5% vs 5.5%).

Discussion: In this randomized controlled 2-year study PP was significantly delaying time to relapse and reducing relapse rates compared to investigators' choice of oral APs. The observed relative relapse risk reduction of 29.2% is clinically relevant and in line with some previous metaanalyses and naturalistic studies comparing long-acting antipsychotics and oAPs [1,3]. Recent data suggest that patients with schizophrenia may benefit from minimizing time in a relapse state and at the same time from a lower exposure to antipsychotics [4]. Therefore, given the significant reduction of relapse rates and the relatively lower exposure to long-acting compared to oral antipsychotics, PP may represent a valuable treatment option to achieve both objectives.

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Poster #S248

FLEXIBLY DOSED PALIPERIDONE PALMITATE IN NON-ACUTE PATIENTS WITH SCHIZOPHRENIA PREVIOUSLY UNSUCCESSFULLY TREATED WITH CONVENTIONAL DEPOT ANTIPSYCHOTICS

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Background: To explore tolerability, safety and treatment response of flexibly dosed paliperidone palmitate (PP) in adult non-acute patients with schizophrenia previously unsuccessfully treated with haloperidol decanoate (Hal), flupentixol decanoate (Fpt), fluphenazine decanoate (Flu) or zuclopentixol decanoate (Zuc).

Methods: International, prospective 6-month open-label multicenter study. Outcomes were clinical response (percentage of patients with $\geq 20\%$ improvement based on Positive and Negative Syndrome Scale (PANSS) total score change at endpoint), Personal and Social Performance scale (PSP), Extrapyramidal Symptom Rating Scale (ESRS) and treatment-emergent adverse events (TEAEs).

Results: The intent-to-treat population comprised n=53 Hal, n=35 Fpt, n=44 Flu and n=42 Zuc patients. Subgroups somewhat differed in baseline demographics: Mean age (ranging from 42.1 ± 10.7 [Zuc] to 44.4 ± 9.4 years [Hal]), male gender (ranging from 57.1% [Zuc] to 69.8% [Hal]), and BMI (ranging from 27.3 ± 5.9 [Hal] to 30.8 ± 8.5 kg/m² [Zuc]). Between 70.5% [Fpt] and 85.7% [Flu] of patients completed the 6-month study. The median mode dose of PP was 100 mg eq across all subgroups. Mean baseline PANSS total scores ranged from 73.7 ± 14.1 [Fpt] to 75.7 ± 13.2 [Hal]) and decreased significantly by -7.5 ± 19.4 [Flu] to -10.6 ± 21.5 points [Zuc] at endpoint ($p < 0.003$ for each subgroup). At endpoint, between 53.7% [Zuc] to 61.8% [Fpt] of patients had improved $\geq 20\%$ in their PANSS total score. Patient functioning (mean PSP baseline scores between 48.7 ± 12.5 [Hal] and 59.6 ± 11.2 [Fpt]) improved by 5.2 ± 13.0 [Hal] to 6.4 ± 15.2 points [Zuc] (all $p \leq 0.0071$). TEAEs reported at least once in all and in $\geq 5\%$ in any subgroup were insomnia (max 11.5%), psychotic disorder (max 9.5%) and injection site pain (max 9.1% of subjects). Extrapyramidal symptoms in ESRS significantly improved from baseline to endpoint (all subgroups $p < 0.01$).

Discussion: These data suggest that paliperidone palmitate was associated with a clinically meaningful treatment response and well tolerated in

non-acute schizophrenia patients previously unsuccessfully treated with conventional depot antipsychotics.

Poster #S249

IS ONCE DAILY DOSING OF PERPHENAZINE CLINICALLY FEASIBLE?

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Background: Many antipsychotic drugs, including perphenazine, are routinely administered in a divided dosage regimen because of their relatively short plasma half-lives. Whether this is actually necessary has never been extensively investigated. The objective of this study was to evaluate the impact of once vs. twice daily dosing of perphenazine on clinical outcomes in patients with schizophrenia.

Methods: Data from phase 1 of the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) were used. Patients with schizophrenia randomly allocated to treatment with perphenazine were also randomly assigned to once daily (N=133) or twice daily (N=124) dosing and followed over 18 months. These two groups were compared regarding the following outcomes: Effectiveness – discontinuation rate and time to discontinuation (primary outcomes); Efficacy – Positive and Negative Syndrome Scale, Clinical Global Impression – Severity scale, Calgary Depression Scale for Schizophrenia, and Drug Attitude Inventory; Safety/Tolerability – Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, Simpson-Angus Scale, body weight, treatment emergent adverse events, and concomitant psychotropic medications; Medication Adherence – Pill count and clinician rating scale.

Results: No significant differences were found in any outcome measures between the once daily and twice daily dosing groups, which remained the same when using the average dose of perphenazine as a covariate.

Discussion: The present findings indicate that despite a pharmacokinetic rationale supporting dosing of perphenazine at least twice daily, once daily dosing produces similar clinical outcomes. These findings also suggest it may be necessary to revisit the longstanding axiom that antipsychotic dosing be established based on peripheral pharmacokinetics.

Poster #S250

PRESCRIPTION PATTERNS PRIOR TO CLOZAPINE INITIATION IN FIRST-EPIISODE PSYCHOSIS

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Background: Treatment-resistance is fairly common in first-episode psychosis (FEP), with studies reporting ranges between 16-25%. Clozapine is the antipsychotic of choice in treatment-resistant schizophrenia, and its superiority has been well-established. In clinical practice, there is often a hesitancy to start clozapine given its side-effect profile, need for regular haematological monitoring, and perceived position as treatment of "last resort". In light of an increasing number of studies suggesting that restrictions on the use of clozapine be reassessed given the risk-benefit ratio, the question arises as to whether there is a role for the early use of clozapine in patients with FEP. In this study, we sought to first understand the prevalence of clozapine use in our Asian population, and prescription patterns prior to clozapine initiation.

Methods: In our naturalistic study, clinico-demographic data from all consecutive patients who had been accepted into the Singapore Early Psychosis Intervention Programme (EPIP), from April 2001 to June 2012, and were prescribed clozapine during the course of their follow-up with the programme were included. Clinical data extracted include the names of antipsychotic drugs used prior to clozapine initiation, as well as their corresponding maximum dosage, duration of treatment, and reasons for discontinuation.

Antipsychotic drugs were included so long as there was a prescription of a regular dose of an antipsychotic drug for at least 24h. An "adequate antipsychotic treatment episode" was defined as the prescription of a regular dose of an antipsychotic drug at or above the minimum therapeutic dosage given the patient's age, and dosing schedule for at least 6 weeks. Depot dosages were converted to chlorpromazine equivalents.

We analysed the total number of different antipsychotic drugs used prior to clozapine initiation; the number of patients who fulfilled the criteria for treatment resistance (defined as an inadequate response to treatment with 2 different antipsychotic drugs at adequate dose and duration); and the theoretical delay in clozapine initiation (i.e. time from the end of the 2nd adequate antipsychotic treatment episode to clozapine use).

Results: Of the 2089 patients that were accepted into EPIP from April 2001 to June 2012, 44 had missing data. 70 (3.4%) patients were prescribed clozapine during the course of their follow-up with the programme. Complete records were available for 68 patients. The mean total number of different antipsychotic drugs used prior to clozapine initiation was 3.4 (s.d.=1.2; range 2-7). Majority of the antipsychotic drugs were discontinued due to a lack of efficacy (53.4%). 46 (67.6%) patients fulfilled the criteria for treatment resistance. Of these, the mean theoretical delay in clozapine initiation was 18.4 (s.d.=27.1; range 0-117) weeks.

Discussion: Although treatment-resistance is fairly common in FEP, the prevalence of clozapine initiation in our study population was only 3.4%. Furthermore, clozapine initiation was delayed by a mean of 18.4 weeks, with the longest delay being 117 weeks. Delays were not because patients were offered but refused clozapine. Adherence was also not a major problem since patients in EPIP were each assigned a case manager who provided regular counselling and psychoeducation. In patients whom adherence were identified as poor, depots were prescribed. In addition, majority were switched to a different antipsychotic due to psychiatrist-determined lack of efficacy. These findings suggest that the delay was a true reflection of actual delay by psychiatrists in initiating clozapine. It is also quite likely that clozapine is under-utilized and delayed for longer than is clinically desirable.

Poster #S251

PROGNOSTIC FACTORS FOR TREATMENT RESISTANCE IN SCHIZOPHRENIA

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Background: Treatment-resistant schizophrenia (TRS) affects approximately 30% of patients with schizophrenia (SZ). Clozapine (CLZ) is recommended in TRS, but is considered to be underused. Early identification of patients with TRS is important to improve treatment decisions and thereby improve quality of life and lifetime for patients with SZ. The objective of this study is to determine baseline factors predictive of TRS.

Methods: Danish population-based cohort study on patients with incident SZ between 1996 and 2006 followed until 2010. We analyzed time to TRS, defined as initiating CLZ or meeting the eligibility criteria for CLZ. Sensitivity analyses were performed for a narrower definition of TRS (CLZ initiation only) and a broader definition of TRS (including AP polypharmacy). We report hazard rate ratios (HR) and 95% confidence intervals (CI) from Cox proportional hazards regression analysis including the following socio-demographic and disease-related candidate prognostic factors: sex, age at first diagnosis of SZ, family history of SZ, marital status, education, employment, place of living, psychiatric hospitalization and psychotropic medication, assessed at or in the year prior to first SZ diagnosis. Prior psychiatric diagnoses, suicide attempts and violent offences were counted as ever registered or not prior to first SZ diagnosis.

Results: Among 8,632 patients with SZ, 34.3% fulfilled the criteria of TRS during follow-up (median follow-up was 9.1 years, IQR: 6.3-11.9). For the narrower and broader TRS definitions these percentages were 13.2% and 46.7%, respectively. In a multivariable model including all factors, factors associated with significantly increased rate of TRS were: living in rural area compared to capital, HR=1.8 (95% CI: 1.6-2.1), hospitalization, HR=1.6 (1.4-

1.7), benzodiazepines, HR=1.5 (1.3-1.6), anti-depressants, HR=1.4 (1.3-1.5), SZ affective disorder, HR= 1.4 (1.2-1.7), suicide attempt, HR=1.4 (1.2-1.5), and early retirement pension, HR=1.4 (1.2-1.6). Other factors significantly associated with increased HR were lower age, personality disorder, paranoid subtype, substance abuse, other SZ spectrum disorders, and female sex. A clear dose-response relationship was detected between decreasing urbanicity and increased rate of TRS. Applying the broader TRS definition showed similar results, whereas the narrower TRS definition revealed additional associations, such as violent offence, HR=1.5 (1.1-2.0), antipsychotic redemptions, HR=1.4 (1.2-1.6), and low education level, 0.8 (0.7-1.0). Prior diagnosis of autism and ADHD indicated increased and decreased rates of CLZ initiation with HR=1.5 (0.9-2.3) and HR=0.3 (0.1-1.1), respectively.

Discussion: Several disease-related factors, such as prior psychiatric hospitalization and comorbidity, were associated with increased rates of TRS. Among patient-related factors, lower age, female sex, place of living, and early retirement pension were associated with increased TRS. Overall, associations were similar regardless of definitions of TRS. However, prior violent offence was significantly associated with CLZ initiation as expected. The factor with the highest effect estimate for TRS found in this study was place of living. Urbanicity is an established risk factor for SZ incidence and is associated with TRS in opposite direction, potentially due to a higher threshold of SZ diagnoses in less urban areas, resulting in a higher severity of disease for these patients at first SZ diagnosis. Other reasons could be differences in quality of treatment in less urban areas. The predictive factors identified in this study could be included in a prognostic model to detect TRS early after diagnosis, which should be validated in subsequent studies.

Poster #S252

OBJETIVE MEASUREMENT OF COMPLIANCE AND ATTITUDE TOWARD TREATMENT IN PATIENTS WITH SCHIZOPHRENIA

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Background: Medical compliance is defined as the degree to which a patient's behavior coincides with medical and/or health advice. Non-compliance is still a major problem in the treatment of schizophrenia and about 50% of patients with schizophrenia are non-compliant. These patients are frequently admitted to hospital compared to compliant patients and have worse health outcomes. The current longitudinal study investigated whether the ratio of observed and expected plasma levels of antipsychotic drugs, as an objective measurement of compliance, correlates with the patients' attitudes toward treatment.

Methods: We included both in- and outpatients between 18 and 65 years of age suffering from schizophrenia according to ICD-10 criteria, who started monotherapy with a new-generation antipsychotic. Antipsychotic medication was chosen by the attending psychiatrist and dosing followed clinical needs. Visits were done at baseline as well as after 2, 4, and 12 weeks of treatment. At each visit, a blood sample was taken and the concentration of the antipsychotic medication in the blood plasma was measured. Expected plasma concentrations were calculated by using Autokinetic® software. Subsequently, the ratio of effective and expected plasma levels was established (approximate value: 0-0.5 too low, 0.5-2 expected range, >2 too high). The patients' attitudes toward antipsychotic treatment were assessed by using the Drug Attitude Inventory (DAI), medication side effects were evaluated by using the Udvalg for Kliniske Undersøgelser Side Effect Rating Scale (UKU).

Results: 93 patients (63.8% male) with a mean age of 36.5 ± 10.3 years were included into the study. The mean duration of illness was 7.6 ± 7.3 years and the most common antipsychotic medication used was amisulpride followed by ziprasidone and olanzapine. The ratio of effective/expected plasma levels had a median of 0.7. The DAI total score at Weeks 2, 4, and 12 of treatment showed a positive attitude toward treatment with antipsychotic medication (mean values of 76.9, 77.4 and 77.8 on a scale of 0 to 100). We identified weak negative correlations between the DAI and ratio; however, they were insignificant following Bonferroni correction. Side effects (UKU), examined

as potential intervening variables between DAI and ratio, showed no effect. There was also no association between the ratio of effective/expected plasma levels and the side effects (UKU).

Discussion: Our results suggest that higher ratios may be associated with a negative attitude toward treatment but they do not provide clear evidence for an association between the ratio of effective/expected antipsychotic plasma levels and the patient's attitude toward antipsychotic treatment. However, further research is required to clarify in more detail the various relationships between plasma level, attitude toward treatment, treatment compliance as well as efficacy and side effects of antipsychotics.

Poster #S253

SHOW ME THE MONEY REVISITED: MONETARY REINFORCEMENT VERSUS INTRINSIC REWARD FOR LEARNING IN SCHIZOPHRENIA

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Background: Recent studies show that diminished hedonic experience may affect the representation of information about reward, and the subsequent motivation for goal-directed behavior. We sought to (a) examine how experimental provision of intrinsic and extrinsic rewards would impact learning performance and subjective evaluations of learning, and (b) identify patient characteristics related to better learning outcome in the context of internal or external rewards.

Methods: Eighty-two adults with schizophrenia were enrolled in a computer-based arithmetic learning program. The arithmetic training phase consisted of ten 30-minute sessions over the course of 6 weeks. Participants were randomized into learning conditions with 4 cells that manipulated (a) intrinsically rewarding (IR) learning cues, and (b) cash payment as an external reward (ER) for performance. In the two IR conditions, the arithmetic learning program was made into an intrinsically-rewarding and enjoyable game, with and without cash payment for performance immediately after each session. In the two ER conditions, the same arithmetic learning program was void of all intrinsically-rewarding game elements to create an austere learning experience, with and without cash payment immediately after each session.

Results: Overall, ER was related to greater learning compared to IR ($F[2,80] = 5.19$, $p=0.014$) and this improvement in arithmetic was associated with greater hedonia and perceived therapeutic value. There was a decline in experienced pleasure and intrinsic motivation—irrespective of IR—when ER was removed but no associated decline in self-efficacy or learning. Furthermore, for those with low baseline motivation, ER was related to greater learning, greater hedonia, and greater perceived therapeutic value. IR was modestly associated with greater learning only in patients with high baseline motivation. Baseline symptom of amotivation predicted learning outcome by accounting for a total of 53% of the variance in the entire sample ($R^2=0.53$, $F[3,78] = 5.95$; $p=0.008$).

Discussion: In contrast to the non-psychiatric literature, IR had no impact on learning outcome when a highly desirable ER was available for reinforcing performance. The extent of learning taking place, irrespective of IR, was associated with greater hedonic experience and perceived therapeutic value. IR had minimal impact on those with a low degree of motivation to learn, especially when ER was available. IR offered some benefit but only to those who were already highly motivated. Amotivation was found to predict learning outcome more than other patient factors. We will discuss how these findings highlight two forms of motivation and reward, both of which carry important implications for behavioral intervention programs aimed at ameliorating amotivation and its functional consequences.

Poster #S254**INFANCY-TO-ADOLESCENCE FUNCTIONAL DETERIORATION IN EARLY ONSET PSYCHOSIS: ARE THERE DIFFERENCES BETWEEN SCHIZOPHRENIA AND AFFECTIVE PSYCHOSIS?**

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Background: Studies conducted in adult patients generally show that schizophrenia is a more deteriorating disorder than affective psychosis. However, early onset may yield a different prognosis and may be a specific marker of a different course. In this study we explore the course of global adjustment since infancy (retrospective assessment) to 2 years after a first episode of schizophrenia or affective psychosis.

Methods: 86 adolescents with a first episode of schizophrenia or affective psychosis (12-17 years of age) were followed up for 2 years after recruitment. Socio-academic adjustment in infancy (up to 11 years of age) was retrospectively assessed (infancy-Premorbid Adjustment Scale, i-PAS). Global adjustment was assessed 2 years after the first episode of psychosis (C-GAS). I-PAS and 2-year GAS were transformed in order to make them comparable by devising 3 levels of adjustment for each scale; and by making a z-score values in relation to a control group of 92 healthy adolescents from the same schools and catchment area, matched for age ($T276=-1.85$; $p=0.07$) and gender ($\chi^2=0.46$; $p=0.83$). Deterioration was defined as a downward change in the level of adjustment.

Results: 29.4% of patients (n=15) with schizophrenia and 26.5% (n=9) of patients with affective psychosis had a deteriorating course between infancy and two year after the first episode of psychosis (FEP). Gender ($\chi^2=0.69$; $p=0.41$), age at onset of FEP ($T84=-0.26$; $p=0.79$), intelligence ($T84=0.67$; $p=0.53$), duration of untreated psychosis (DUP) ($T81=0.08$; $p=0.93$), severity of the baseline psychotic episode (CGI score) ($T84=-1.81$; $p=0.076$) or cumulative doses of antipsychotic through the follow-up ($T84=0.45$; $p=0.65$) did not predict a deteriorating course. Diagnosis was not a predictor of a deteriorating course ($\chi^2=0.87$; $p=0.81$). A multivariate linear regression model showed that DUP and CGI explained a 10% of the variance of downward change in adjustment ($F84;2=4.891$; $p=0.01$).

Discussion: A 28.2% of adolescent patients suffer a deteriorating course over the 2 first years after the first psychotic episode, irrespective of the specific diagnosis. After two years of follow-up, longer DUP and greater severity of psychotic episode were the only baseline variables that significantly predicted a deteriorating course. The main result derived from this study is that after two years of follow-up, the same percentage of patients within schizophrenia and affective psychosis groups showed a deteriorating course, notwithstanding diagnosis, gender, age at onset or cumulative dose of antipsychotics. The second main result showed that around 30% of the patients with a first episode of schizophrenia or affective psychosis in adolescence display a lower social functionality 2 years after a FEP than they did in infancy (up to 11 years of age). However, in around 70% of adolescent patients with schizophrenia or affective psychosis, functionality did not suffer a deteriorating course after an episode of psychosis. Our findings strengthen the importance of the introduction of early detection programs which would allow shortening DUP in adolescent patients. This evidence supports the importance of developing prevention and early detection programs that focus in adolescent population.

Poster #S255**COMPARATIVE STUDY OF SCHIZOPHRENIA PATIENTS ACCORDING TO THEIR FUNCTIONALITY**

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Background: According to the World Health Organization, schizophrenia is among the ten most disabling diseases (WHO, 2012). The functionality is described as individual adaptation to different needs from the perspective of a productive adult (Geopte, 2012). There are many factors associated with the performance of patients with schizophrenia; among those are include the severity of positive and negative symptoms and substance use (Suzuki et al 2008). The severity of positive symptoms affects the outcome and functionality but only during the acute episode of the illness, the clinicians focus all their attention on this stage of the disease (Schenkach R, 2012). The functionality is usually determined by the GAF Scale (Scale of Global Functionality) (APA, 1994), the problem with this measure is that is very vague and is rarely used in clinical trials; Functional Assessment Scale for Comprehensive Treatment of Schizophrenia (FACT-Sz) was created only for patients with schizophrenia (Suzuki et al 2011). This scale is easy to apply and is based on the GAF scale, this scale is designed to provide relevant information and to be simple and brief for wide application. This FACT-Sz divided the patients in acceptable or unacceptable functionality. (Suzuki et al 2011) That is why we decided to classify the patient in terms of psychosocial functionality using the FACT-Sz scale and compare these groups with substance abuse prevalence and the severity of symptoms measured by the PANSS (Scale of Positive and Negative Symptoms of Schizophrenia).

Methods: We recruited subjects who met the criteria for chronic paranoid schizophrenia (DSM IV TR) and we used the following scales: PANSS, the Global Assessment of Functioning (GAF) and the Functional Assessment Scale for comprehensive treatment of schizophrenia (FACT-Sz.). The substance use was measured by the CIDI (Composite International Diagnosis Interview) a standarized diagnostic interview.

Results: The patients were classified regarding the score of the FACT-Sz: Unacceptable functionality (group 1) vs. acceptable functionality (group 2) FACT-Sz and GAF: The scale of global functioning was the basis for the subsequent construction of the scale of psychosocial functioning in schizophrenia; correlation between both was positive ($r=0.739$ $p=0.01$). Sociodemographic: The total sample consisted of 100 subjects in which 63% were male and 37% female, mean age was 36 ± 9 years. The 80% were single, and 60% of the sample had less than 12 years of scholarity, 80% were unemployed at the moment of the study. Functionality and drug use: We compared FACT-Sz groups regarding the substance use. The 20% of the sample had substance use (excluding nicotine). There were no differences between groups ($df = 1$, $\chi^2=1.43$, $p=0.231$). Functionality and PANSS: We found differences on total PANSS score and positive subscale between groups. Thre group 1 (unacceptable functionality) had higher scores on total PANSS score vs. group 2 (acceptable functionality) ($X=83.2\pm 11.86$ vs. $X=67.2\pm 14.4$, $t=4.9$, $df=98$ $p=0.006$)

Discussion: The sample was taken from ambulatory service of the National Institute of Psychiatry where the patients have more control of all the symptoms domain. The sample associated with substance abuse and dependence is smaller than reported in others studies however it seems that those with substance dependence had significantly lower PANSS negative subscale scores compared to those without dependence (Compton et al 2004), perhaps associated with the theory of self-medication or the strategies required to gain access of substances. Both the negative and positive symptoms were associated with social and occupational impairment; the positive symptoms with poor self-care and impersistence at work (Addington et al 1991).

Poster #S256**LONGITUDINAL FOLLOW-UP OF CRITICISM AND DEPRESSION AMONG FAMILIES OF FIRST EPISODE PSYCHOSIS PATIENTS**

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Background: The role of a family is widely acknowledged in the man-

agement of psychosis, and the family environment may alter the outcome of psychosis. Although high expressed emotion, particularly criticism, is believed to develop in the first few years after the onset of psychosis, little is known about when and how criticism develops. Additionally, some family members may show psychiatric symptoms themselves; however, the early stages of emotional distress of family members of patients with psychosis have not been fully studied. In this study, we longitudinally followed up first episode psychosis (FEP) patients and their families and made a preliminary assessment of criticism and depression in the families.

Methods: FEP patients and their families were recruited through the Sendai ARMS and first episode clinic, which is a specialized clinic in the Department of Psychiatry, Tohoku University Hospital in Sendai, Japan. Nineteen FEP patients and their families were followed up for 6 months. Psychopathology and global functioning of the patients were assessed using the Positive and Negative Syndrome Scale (PANSS) and the Global Assessment of Functioning (GAF). Criticism and depressive symptoms in the families were assessed using the Japanese version of the Family Attitude Scale (FAS) and the Beck Depression Inventory, 2nd edition (BDI-II). This study was approved by the ethics committee of Tohoku University Graduate School of Medicine and Tohoku University Hospital; all families and patients provided written informed consent.

Results: Mean PANSS and GAF scores of the patients were improved at follow-up compared with baseline. The mean BDI-II score of the families at follow-up (mean = 9.2, SD=9.2) was lower than that at baseline (mean = 12.7, SD=9.1). Although the mean FAS score of the families was comparable between baseline (mean = 29.8, SD=20.6) and follow-up (mean = 29.0, SD=20.6), the direction of change during the 6-month follow-up varied. FAS score was reduced in 13 families but increased in 6 families. Two critical families at baseline remained critical at follow-up. Reduction in total PANSS scores correlated with improvement of FAS scores. Depressive symptoms of the families correlated with GAF scores of the patients at follow-up but not at baseline.

Discussion: Depressive symptoms were improved in most family members of FEP patients during 6-month follow-up. However, psychopathology and functioning of the patients appear to be associated with depression in families at follow-up. Although the average FAS score of the families did not differ between baseline and follow-up, the direction of change during the follow-up varied. Some families became more critical at follow-up. The change of symptoms and global function of patients appear to affect the level of criticism of families. More attention is required for the dynamic course of expressed emotion and distress in the families; personalized care and intervention appear necessary for the families of FEP patients.

Poster #S257

TOUCHING BY HAND HOW PSYCHOTIC FEATURES TRANSLATE INTO WORSE LIFE CONDITIONS: THE RELATION OF KEY PSYCHOSOCIAL ISSUES WITH CLINICAL VARIABLES IN NON-PSYCHOTIC, PSYCHOTIC RESPONDER, AND PSYCHOTIC NON-RESPONDER PATIENTS

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Background: Psychotic symptoms predispose to poor psychosocial functioning in multiple social domains. Poor psychosocial conditions and treatment response may influence each other. We assessed psychosocial functioning and multiple clinical variables in psychotic patients not responding to treatments (PNR), psychotic responders (PR) and non-psychotic patients (NP) as a first step to develop targeted interventions in each subgroup

Methods: We included all patients afferent to our Outpatient Unit from May to September 2013. Patients were divided in NP, PR and PNR according to the following criteria: i) diagnosis within the psychotic-spectrum; ii) having or not responded to antipsychotic (AP) treatments, according to American Psychiatric Association guidelines. Psychosocial variables evaluated were: occupational status; housing conditions; need and type of economic support. Demographics and clinical variables were recorded for all patients, including Positive and Negative Syndrome Scale (PANSS), Drug

Attitude Inventory (DAI), and Personal and Social Performance (PSP) rating scales, and cognitive tasks.

Results: NPs were mostly in-search of job (29.5%) or professional freelancers (16%). PRs were mostly unemployed (33%) or in-search (28.5%). PNRs were mostly either unemployed (35%) or being granted legal disability (29%). Compared to other groups, PNRs were less frequently in-search of job ($p=0.0099$) and more frequently granted legal disability ($p=0.02$). NPs were more frequently student ($p=0.037$) and professional freelancers ($p=0.0031$) compared to both PRs and PNRs. The occupational status was related to several variables in the whole sample: age, antipsychotic (AP) doses, school years, previous hospitalizations, age of first treatment, disorganization, verbal fluency performances, PSP total score. In PNRs, occupational status was associated with AP doses, score on PANSS general psychopathology (GP) subscale, PSP total score, and working memory (WM) performances. Most NPs lived with their spouse (43%) or in their origin family (36%). PRs lived with their origin family (62%) or with their spouse (24%). Almost all PNRs lived with their origin family (82%). NPs more frequently lived with the acquired family ($p<0.0001$) or with their partner ($p=0.037$) compared to both PRs and PNRs. However, PRs were more frequently married compared to PNRs. Living conditions in the whole sample were associated with age, AP doses, educational status, age of disease onset, age of first treatment, negative symptoms, WM performances. In PNRs, living conditions were associated with AP doses, negative symptoms, GP, disorganization, PSP score. NPs needed familial economic support (59%) or did not need any economic support (36%). PRs and PNRs needed familial economic support (62% and 53%, respectively) or were granted legal disability (24% and 41%, respectively). No need for economic support was more frequent in NPs compared with both PRs and PNRs ($p<0.0001$), and was more frequent in PRs compared with PNRs. Economic status in the whole sample was associated with: AP doses; previous hospitalizations; previous compulsory hospitalizations; positive and negative symptoms; GP; disorganization; performances on cognitive tasks; PSP score; current remission. In PNRs, the variables associated with the economic status were: AP doses; number of hospitalizations; positive symptoms; GP; problem solving performances.

Discussion: Among the patients screened, PNRs show the worst psychosocial adaptation, with poor outcomes in occupational status, living conditions, and economic income. Multiple clinical variables were associated with psychosocial adaptation. In PNRs, the most relevant ones were AP doses, GP and PSP scores.

Poster #S258

TEACHING AND LEARNING THE DISCOURSE OF SCHIZOPHRENIA: DEVELOPMENT OF A STANDARDIZED PATIENT TRAINING PROGRAM

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Background: Treatment of patients with schizophrenia can be improved by precise administration of rating scales. The Positive and Negative Syndrome Scale (PANSS) is a commonly used tool to assess symptoms of TD (Kay et al. 1987). In order to develop a participatory learning program that aims to enhance raters training and increase inter-rater reliability we trained five actors to serve as standardized patients (SP). By studying the development of this program – through which healthy adults (actors) were trained to portray symptoms of schizophrenia through discourse – important knowledge can be gained about a number of important aspects related to the genesis of symptoms and overall psycho-social functioning of individuals diagnosed with schizophrenia, such as the impact of semantic and discursive practices on interpersonal interactions.

Methods: A training program for SPs was constructed using a narrative analysis scheme (Labov, 1972; Peterson & McCabe, 1983; Bruner, 1986; Daiute, 2010) in the following manner: 1) Seven transcripts of SCI-PANSS interviews were analyzed and subdivided into thematic chapters including: symptom frequency, intensity, complexity, interference and impairment; 2) Script/story analysis of transcribed interviews were conducted where we identified scripted elements common among all seven interviews and storied elements that deviate from the script and have a function to individuate each of the interviews; 3) Linguistic markers (words, phrases, or discursive patterns indicative of symptoms and their severity) that are often seen as hallmarks of aetiology of schizophrenia were identified; 4)

Symptoms were divided into two severity levels, moderate and severe, and three full SCI-PANSS interview scripts were built; 5) A workshop for five professional actors was conducted under the supervision of an expert PANSS interviewer.

Results: Findings of this project indicate that: 1) narrative analysis can be effectively utilized to develop teaching tools for symptomatology of schizophrenia 2) rater training programs can be enhanced through participatory learning methods.

Discussion: Review of literature suggests that this is the first attempt to develop a SP program for schizophrenia. By studying the development of this program – in addition to enhancing rater training – important knowledge was gained about the effects of semantic and discursive practices which accompany schizophrenia on interpersonal interactions.

Poster #S259

FFM PERSONALITY TRAITS AND ADULT ATTACHMENT STYLES IN PATIENTS WITH PSYCHOSIS, THEIR SIBLINGS AND HEALTHY CONTROLS

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Background: The aim of this study was to assess the role of two constructs that have gained increasing attention in psychosis research: Five Factor Model (FFM) personality traits and Adult Attachment styles. We explored the relationship between FFM personality traits, attachment style, illness characteristics and dimensional liability for psychosis. Second, we investigated the relation between these constructs and childhood maltreatment in patients with psychosis, their healthy siblings and controls. Third, we assessed the relative contribution of symptoms, FFM personality and attachment style to different domains of Quality of Life (QoL).

Methods: Positive, negative and depressive symptoms (PANSS, CAPE), Five-Factor model personality traits (Neuroticism, Extraversion, Openness, Altruism and Agreeableness), Attachment style dimensions (Psychosis Attachment Measure; anxious and avoidant attachment styles), Childhood maltreatment (Childhood Trauma Questionnaire (CTQ)) were assessed in 217 patients with psychotic disorders, 281 of their siblings and 176 healthy controls that took part in the Genetic Risk and Outcome of Psychosis (GROUP) study.

Results: Patients differed from siblings and controls on four of the five FFM traits, all but Openness. Siblings reported higher levels of Neuroticism than controls, but lower levels than patients. Lower Agreeableness, higher Neuroticism and lower Extraversion were associated with more severe symptoms in patients. Furthermore, higher Neuroticism and higher Openness were associated with higher levels of subclinical psychotic experiences. Differences between patients and siblings in levels of anxious and avoidant attachment were confounded by (subclinical) negative symptoms. In both samples, more negative symptoms were related to higher levels of insecure attachment. In patients and siblings but not in the control group, Childhood Maltreatment (ChM) predicted levels of positive and negative symptoms. In both groups, attachment style accounted for part of the relation between ChM and positive symptoms. Only in siblings attachment explained a substantial part of the variance accounted for by ChM in negative symptoms. FFE personality also accounted for part of the relation between illness characteristics and ChM. Both attachment and FFE personality factors were associated with QoL, when symptom severity was controlled for. Different domains of QoL were differentially related to specific attachment styles, personality and symptoms dimensions.

Discussion: Our findings shed more light on the role that Adult Attachment styles and FFM personality traits play in relation to onset, illness characteristics and outcome of psychosis and psychotic like experiences in patients with psychosis, their siblings and healthy controls. Group differences regarding both attachment and FFM traits were found between patients, siblings and controls. Also, associations between specific attachment styles and personality characteristics vs specific symptoms of (subthreshold) psychosis were found. Furthermore, attachment and personality may both provide more insight in understanding the relation between childhood maltreatment and illness characteristics. Especially in persons with an increased genetic risk for developing psychosis, insecure attachment is an important factor with regard to the relationship between ChM and development of (subthreshold) psychotic symptoms, being most pronounced for negative symptoms. Finally, both constructs may be important for outcome

domains such as subjective QoL. Results will be discussed in relation to future clinical and treatment implications.

Poster #S260

ADDRESSING DEFEATIST BELIEFS IN WORK REHABILITATION

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Background: People with schizophrenia in vocational rehabilitation programs may struggle with expectations of failure. Research has not addressed if global or specific defeatist beliefs, and any changes therein, are dynamically related to functional outcomes. Indianapolis Vocational Intervention Protocol (IVIP; Lysaker et al., 2005) is a CBT intervention used to address expectations of failure, improve work performance, and maintain self-esteem. We examined the relationships between global and work-specific defeatist beliefs, self-esteem, social functioning, and work behaviors after IVIP.

Methods: Adults with schizophrenia (n=42) completed a four-month transitional work therapy program that included IVIP. Assessments were conducted at baseline and program conclusion.

Results: Only a decline in work-specific defeatist beliefs rather than global beliefs was associated with better social functioning ($r=0.39$, $p<0.01$), self-esteem ($r=0.29$, $p<0.05$), and more successful work behaviors ($r=-0.34$, $p<0.05$). Furthermore, only baseline defeatist beliefs about work performance predicted work readiness at the end of the 4-month program, even when accounting for baseline positive and negative symptoms, attitudes about employment, and global defeatist beliefs ($R^2=0.42$, $F=4.23$, $df=2,40$, $p=0.004$).

Discussion: Explicit beliefs about work performance governed the relationship between attitudes, work-related skills, and productive social behavior. Performance-specific defeatist beliefs may be more amendable to change than the more trait-like global beliefs and hence dysfunctional beliefs about work performance may be a more appropriate target of interventions such as IVIP.

Poster #S261

INVESTIGATING THE ROLE OF BETACELLULIN IN THE PLASMA OF SCHIZOPHRENIA PATIENTS TREATED WITH THE ANTIPSYCHOTIC CLOZAPINE

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Background: Schizophrenia is a complex neuropsychiatric disorder of unknown aetiology however recent studies have implicated epidermal growth factor (EGF)/ErbB-system dysfunction. Betacellulin (BTC) is an EGF family ligand for ErbB1 and ErbB4 receptors and has been demonstrated to be elevated in the serum of schizophrenia patients. Furthermore our previous in-vitro, in-vivo and clinical data support clozapine's augmentation of deficient ErbB1 signalling suggesting a mechanism for its therapeutic efficacy. We therefore postulated that BTC levels are altered in schizophrenia and that they may be influenced by clozapine treatment. In this study we sought to prospectively evaluate plasma BTC levels in a clozapine-treated schizophrenia cohort over a 26-week treatment period and in healthy control subjects.

Methods: We used an ELISA assay to measure plasma concentrations of BTC in schizophrenia patients prior to (n=39), 2-weeks (n=22), 6-weeks (n=21) and 26-weeks (n=38) after clozapine treatment and also in age/gender matched healthy controls. The Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI) were administered at baseline, 6 and 26 weeks of treatment.

Results: Mean BTC levels were significantly lower in patients at baseline (2280 ± 3496 pg/ml, mean \pm SD), 2-weeks (1782 ± 2749), 6-weeks (1938 ± 2939) and 26-weeks (2195 ± 3938) compared to controls (2536 ± 1585). Post-treatment BTC levels at 26-weeks significantly correlated with PANSS positive score ($r^2=0.176$; $p<0.05$; $N=35$) and with PANSS

change % ($r^2=0.143$; $p<0.05$; $N=38$). Furthermore at 26-weeks there was a significant difference in BTC levels between responders ($n=19$) (symptom improvement of $\geq 20\%$) and non-responders ($n=19$; $p=0.034$).

Discussion: Schizophrenia patients on antipsychotic drugs have significantly lower BTC levels compared to healthy controls. It would appear that the lower the BTC value the greater the treatment response in particular with reference to positive symptoms. This suggests that BTC activation of ErbB1 and/or ErbB4 may adversely impact on treatment response. Given our previous clozapine findings, we hypothesize that adverse BTC effects may be principally mediated through ErbB4.

Poster #S262

IMPACT OF OBESITY ON QUALITY OF LIFE IN PATIENTS WITH SCHIZOPHRENIA

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Background: Schizophrenia is associated with a 2-fold increased risk of obesity, and obesity increases the risk of cardiovascular morbidity and mortality. A lesser known impact of obesity in schizophrenia is how it might impair the quality of life (QOL) of patients. Therefore, this study aims to examine the burden of obesity on the quality of life of patients with schizophrenia. It is hypothesized that obese patients have poorer quality of life compared to the non-obese.

Methods: Outpatients diagnosed with schizophrenia aged 21-69 years old were recruited from the Institute of Mental Health, Singapore. Only participants who were able to provide informed consent were recruited. Height and weight were measured for all participants and obesity was defined as a BMI ≥ 30 kg/m². QOL of participants were assessed on the RAND36 and the Impact of Weight on Quality of Life-Lite (IWQOL-lite). RAND36 is a 36-item instrument commonly used to measure the general Health Related Quality Of Life (HQOL), and the IWQOL-lite is a 31-item instrument that measures weight related QOL. These instruments were chosen as they have been demonstrated to be reliable and valid measures of QOL in schizophrenia. One sample t-test was used to compare the sample QOL scores with the population norms in Singapore. Group comparisons of the QOL subscale scores were performed using Man-Whitney U tests and linear regressions were used to examine the associations between obesity and QOL scores. A p-value <0.05 was considered to be statistically significant.

Results: 105 participants were recruited into the study and 32 (30.5%) participants were found to be obese. There were no significant differences in the demographic and clinical variables between non-obese and obese participants except for higher rates of alcohol consumption ($p=0.026$) and metabolic comorbidities ($p=0.008$) in the obese group. Participants with schizophrenia reported significantly lower HQOL in all RAND36 subscales compared to the general Singapore population. Obese participants reported lower HQOL scores on all RAND36 subscales when compared to the non-obese group, but this difference was not statistically significant. Obese participants reported lower scores on total and all subscales of the IWQOL-lite. After adjusting for interviewers, mode and language of administration, and symptoms severity, significant associations were observed between the obese and non-obese groups on all IWQOL-lite subscales and total score with an average reduction of 20.0 points in the obese group.

Discussion: Participants with schizophrenia reported lower HQOL when compared to the general population. Obese participants reported lower RAND36 scores but this difference was not statistically significant. On the IWQOL-lite, significant impairments were observed in obese participants on all subscales and total score of the IWQOL-lite. IWQOL-lite is more sensitive than the RAND36 in detecting impairments in weight related QOL. This finding suggests that prevention and management of obesity is important to improve the QOL of patients with schizophrenia.

Poster #S263

DOES ROUTINE OUTCOME MONITORING IN SCHIZOPHRENIA IMPROVE THE IMPLEMENTATION OF EVIDENCE BASED CARE?

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Background: Is there a gap between identified clinical problems of patients with schizophrenia and the offered evidence based treatment? Patients with schizophrenia show a serious reduced life expectancy, which is related to cardiovascular problems. Approximately 60% of the patients report sexual dysfunctions, mainly related to the use of antipsychotics. Additionally, many patients have severe impairments in social functioning. Data out of Routine Outcome Monitoring (ROM) give insight in unmet needs on these three domains. This study investigates the gap between clinical problems and offered care in patients with schizophrenia.

Methods: The ROM-PHArmacotherapy Monitoring and OUtcome Survey (ROM-PHAMOUS) protocol assesses annually the physical, psychological and psychosocial situation of the patient in the Netherlands. Psychiatric symptom severity (PANSS), quality of life (MANSA), sexual functioning (SRA), psychosocial functioning (HONOS/PANSS), and cardiovascular risk factors (e.g. physical examination, laboratory testing, smoking) are assessed. All patients with a psychotic disorder living in the province of Groningen in the Netherlands are eligible to participate. Out of 1123 patients, a random sample of 100 patients was selected. We investigated three domains: cardiovascular, sexual, and psychosocial functioning. Electronic patient files were examined whether the offered care was in line with the Dutch Guideline for Schizophrenia. Also, the annual letter reporting the present clinical condition and offered treatment, to the general practitioner (GP) was screened. A treatment gap is defined in case there is no correspondence of the identified unmet need (out of ROM) with an intervention from the guideline.

Results: The majority of the patients in our sample were male (63%), 44 years, diagnosed with schizophrenia (76%), used one antipsychotic and had a long duration of illness (18 years). The three most common cardiovascular risk factors were smoking (72%), obesity (70%) and dyslipidaemia (61%). Approximately 50% (38%-66%) of the patients remain untreated with regard to any cardiovascular risk factor. Sexual dysfunction as assessed with the SRA was found in 53% of the patients. Specific treatment goals with regard to sexual dysfunction and/or dissatisfaction were not formulated in any treatment plan. The HONOS demonstrated that 15% of the patients had unmet needs on daily activities, and 8% on living conditions. About 39% suffered from severe positive and/or negative symptoms (PANSS; score ≥ 3). Offered interventions were: psycho-education 38%; cognitive behavioural therapy 19%; individual rehabilitation treatment 11%; psychomotor therapy 12%; individual placement support 4%; social skill training 4%; and family support 1%. The analysis of unmet needs and offered interventions is still in progress.

Discussion: ROM is an useful instrument in detecting risk factors in different domains. However, our study demonstrates that ROM does not necessarily lead to offering evidence based care. Cardiovascular risk factors are treated in 50% of the cases; sexual dysfunctions were not managed according to clinically records. The gap between unmet needs and offered care in the psychosocial domain is still under study. Treatment history should be added for the right interpretation of the data. Translation of ROM data into clinical practice is challenging. Education and automated systems connecting ROM data to evidence based care are needed to optimize the provided care.

Poster #S264

EVALUATION OF A COMMUNITY CASE-MANAGEMENT PROGRAM FOR PATIENTS WITH SCHIZOPHRENIA-SPECTRUM DISORDER: A PROSPECTIVE 1-YEAR CASE-CONTROL STUDY

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Background: The Personalized Care Programme (PCP) is a government-funded community psychiatric service in Hong Kong. PCP, which was

launched in three pilot districts in 2010, adopts intensive case-management and multi-disciplinary approaches involving community partners to deliver individualized, recovery-oriented care to adult patients with severe mental illness, in particular psychotic disorders. This study aimed to systematically evaluate the effectiveness of PCP in community-dwelling patients with schizophrenia-spectrum disorder (schizophrenia, schizophreniform disorder or schizoaffective disorder) using concurrent case-control design.

Methods: This prospective 1-year follow-up study compared patients receiving PCP (n=81) with those managed by non-PCP community psychiatric care (control treatment, n=80). The two groups were matched in terms of age, sex and DSM-IV diagnosis. Comprehensive evaluation on multiple outcome domains encompassing symptom (Positive and Negative Syndrome Scale, PANSS; Calgary Depression Scale, CDS), psychosocial functioning (Social and Occupational Functioning Assessment Scale, SOFAS), needs (Camberwell Assessment of Need, CAN), subjective quality of life (WHO-QoL Brief version) and service satisfaction (Patient Satisfaction Questionnaire, PSQ) was conducted at study entry and at 12 months of follow-up.

Results: There were no significantly differences between the two groups in socio-demographics, past illness history characteristics, baseline clinical and functional ratings. At 12 months, Patients in PCP group had significantly fewer number of unmet needs ($t=3.9$, $p<0.05$) (in particular social needs of care: $t=7.2$, $p<0.01$) and greater degree of service satisfaction than those in non-PCP group ($t=0.7$, $p=0.50$). No significant between-group differences were noted in 12-months outcome on symptoms severity, functioning and subjective quality of life. Longitudinal analysis revealed a trend (though statistically non-significant) suggesting that patients in PCP group had greater improvement in depressive symptom (CDS) and general psychopathology (PANSS) ratings, and various domains of WHO-QoL measures than those in non-PCP group over 1-year follow-up period.

Discussion: This study provided supportive evidence to the 1-year pilot implementation of PCP for patients with schizophrenia-spectrum disorder in HK with regard to improvement in unmet need management and service satisfaction. Further research is required to evaluate the longer-term effects of this community-oriented case-management service on clinical and functional outcomes.

Poster #S265

THE ASSOCIATION BETWEEN WORKING ALLIANCE AND CLINICAL AND FUNCTIONAL OUTCOME IN A COHORT OF 400 PATIENTS WITH FIRST EPISODE PSYCHOSIS: A CROSS-SECTIONAL STUDY

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Background: Working alliance between patients with a first-episode psychosis and their case manager is regarded as a key element in specialised early intervention services. The impact of this patient-case manager dyad on functional and clinical outcome is unknown. We aimed to investigate if a strong working alliance was associated with fewer clinical symptoms and better social functioning.

Methods: In a cross-sectional design, patients with first-episode schizophrenia spectrum disorders were included after 18 months of treatment (n=400). Symptoms were assessed using Scale for the Assessment of Positive and Negative Symptoms (SAPS, SANS), General Assessment of Functioning (GAF), and Brief Assessment of Cognition in Schizophrenia (BACS), Working Alliance Inventory (WAI), and General Self-efficacy (GSE). Linear regression analyses were adjusted for age, sex, cognition, and self-efficacy.

Results: Results revealed significant associations between working alliance and fewer negative ($\beta=-0.12$; 95% CI, -0.19 to -0.04), and disorganized symptoms ($\beta=-0.06$; 95% CI, -0.11 to -0.01), and between working alliance and better social functioning ($\beta = 1.45$; 95% CI, 0.55 to 2.36). General self-efficacy mediated the effect of working alliance, explaining 14% to 18% of the variance in associated outcomes. Global level of cognitive functioning, compliance and self-efficacy influenced clinical and functional outcome more strongly than working alliance.

Discussion: Better working alliance was weakly associated with fewer negative and disorganized symptoms and better social functioning. Working alliance may be prerequisite for adherence to treatment, providing the basis for positive treatment outcome

Poster #S266

VIRTUAL REALITY JOB INTERVIEW TRAINING

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Background: The return to employment is a major goal of recovery for individuals with chronic mental illness. The job interview is a key component to obtaining employment, however, individuals with chronic mental illness (e.g., schizophrenia, bipolar disorder) are characterized by impaired social skills that may interfere with successfully navigating the job interview. There are few evidence-based interventions design to improve job interview skills that are available to this population.

Methods: This study assessed the preliminary feasibility and efficacy of Virtual Reality Job Interview Training (VR-JIT). This intervention is comprised of up to 10 hours of simulated job interviews with a virtual human resources representative and includes a didactic learning component. VR-JIT uses behavioral learning principles to provide a personalized learning experience, constant reward and feedback, a progressive degree of difficulty, and repetitive practice in a game-like format. In a randomized single-blind controlled trial with 39 adults with chronic mental illness (i.e., schizophrenia, bipolar disorder, major depression) aged 18–65 years were randomized to VR-JIT (n=27) or to a treatment as usual (TAU) control condition (n=12). The primary outcome measures were performance on standardized job interview role-plays and a measure of job interview self-confidence. Our secondary outcome measure included the average performance scores across each simulated interview trial.

Results: Regarding feasibility, participants found the training easy-to-use, helpful, enjoyable, increasing their confidence, and prepared them for future interviews and 90% of VR-JIT training sessions were attended. Regarding efficacy, we found a significant interaction between group and time for the role-play measures suggesting that the intervention group had significantly higher role-play scores at follow-up compared to baseline, while the control group did not differ ($F=5.13$, $p\leq 0.05$). A similar pattern was observed with regards to self-confidence ($F=4.14$, $p\leq 0.05$). We also found a linear increase in simulated interview scores as the simulations progressed in difficulty as the number of trials increased ($R^2=0.64$).

Discussion: There is a major gap in services available to adults with chronic mental illness that target the improvement of job interview skills. Our findings suggest there is preliminary support for the feasibility and efficacy of the VR-JIT intervention, which uses an internet-based platform that can be widely used by families, support groups, and service providers. Virtual reality training is an efficacious and highly accessible strategy for improving community-based outcomes, and the field appears to be moving in this direction. Future research is needed to evaluate the implementation of VR-JIT in a community setting.

Poster #S267

IMPROVING SOMATIC HEALTH OF OUTPATIENTS WITH SEVERE MENTAL ILLNESS

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Background: Patients with severe mental illness (SMI) experience a 13- to 30-year reduction in life expectancy compared with the general population. The majority of these deaths can be attributed to somatic health problems. The risk on somatic health problems is partly increased due to a reduced

ability to request care and the fact that the current health care organisation is unable to fulfil the needs of these patients. Our previous work shows that a health check intervention can bypass the inability to request help of patients with SMI by detecting somatic health problems that were not detected previously [1]. The aim of this research project is to develop a policy recommendation on how to improve physical health based on consensus by the major stakeholders: patients, family carers, general practitioners, and mental health care staff.

Methods: We used a three round Delphi method. The first round consisted of an inventory of potential policy recommendations, in two consecutive rounds consensus was sought on a selection of recommendations.

Results: The policy recommendations described improvement in collaboration among health care professionals; the need to educate involved professionals regarding the specific medical risks associated with patients with SMI; and defining the differences between GPs and mental health care professionals regarding their responsibilities to provide adequate care for the physical health of SMI patients. Examples of consensus based policy recommendations on collaboration are:

- The GP is the professional with overview and direction of the complete (general and specialist) treatment of patients.
- The professional (MHP or GP) who diagnoses a new somatic complication should notify the other professional (MHP or GP) providing them with relevant medical information. – o The results from cardiovascular risk screening need to be known by the GP and MHP. The performer of the screening should inform the other party in writing.
- For the policy on new physical symptoms, MHP should always consult the GP.
- Consultation with the GP is necessary before referral to a medical specialist by MHP.
- Changes in medication should always be reported in writing between MHP and GP.
- The psychiatrist can delegate the performance of the necessary screening required for some medications used in the treatment of psychiatric disease to the GP, if the patient agrees.
- Direct personal contact between MHP and GP is an important prerequisite for improving cooperation. Sharing of direct (cell)phone numbers can contribute in facilitating direct contact.

Discussion: Currently there are multiple barriers to optimal health care which can be overcome by implementing the suggested policy recommendations. Part of these recommendations can be implemented directly in current health care.

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Poster #S268

DECREASED BRAIN CANNABINOID RECEPTOR (CB1R) AVAILABILITY IN CANNABIS DEPENDENCE RAPIDLY NORMALIZES WITH ABSTINENCE

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Background: Cannabinoids, either natural or synthetic, are one of the most widely used recreational drugs in the world. Understanding and characterizing the functional effects of long term use of cannabinoids is important. Animal studies have shown that chronic exposure to Δ9-THC and other cannabinoid agonists leads to a reduction in the number and function of brain cannabinoid receptors (CB1R). Furthermore, this downregulation and desensitization has a distinct regional and temporal course, and is related to the duration and magnitude of exposure, with greater downregulation in cortical compared to subcortical regions. With prolonged abstinence there is normalization in the number and function CB1Rs over 2 weeks with quicker recovery in subcortical compared to cortical regions. A recent PET study of heavy cannabis users demonstrated reversible and regionally selective downregulation of CB1Rs. CB1R density returned to normal levels after 4 weeks of confirmed inpatient abstinence. We sought to characterize

the temporal course of reversal in CB1R downregulation by measuring CB1R availability while smoking as usual, and after 2 days and 4 weeks of abstinence.

Methods: Using positron emission tomography (PET) with the High Resolution Research Tomography (HRRT) and the CB1R selective radiotracer 11C-OMAR, we determined volume of distribution (VT) values, a measure of CB1R density, in several regions in men with cannabis dependence (n=11) and matched healthy controls (n=19). Cannabis users were scanned at three time points: at baseline (n=11), after 48 hours of abstinence (n=10), and after four weeks of abstinence (n=8). Control non-users were scanned at baseline and a subset were scanned again 4 weeks later.

Results: Relative to healthy nonusers, cannabis dependent subjects showed significant reductions in CB1R availability (VT) in the amygdala ($p=0.08$), centrum semiovale ($p=0.035$), caudate nucleus ($p=0.056$), anterior cingulum ($p=0.001$), posterior cingulum ($p=0.013$), frontal lobe ($p=0.007$), hippocampus ($p=0.007$), hypothalamus ($p=0.051$), insula ($p=0.002$), pallidum ($p=0.051$), parietal lobe ($p=0.006$), putamen ($p=0.012$), and temporal lobe ($p=0.007$) at baseline. These differences ranged in magnitude from medium to large (effect sizes $r=0.310$ to 0.559). However, within 48 hours of abstinence, at a time when withdrawal symptoms peaked in cannabis dependent subjects, except for the anterior cingulate cortex (ACC) ($p=0.02$) and the insula ($p=0.039$), there were no other significant group differences in CB1R availability. With 28 days of abstinence, there were no significant group differences in CB1R availability in any brain region. Finally, there were no significant differences in CB1R availability between scans 4 week apart in healthy nonusers.

Discussion: Cannabis dependence is associated with CB1R downregulation in specific brain regions. In most brain regions CB1R downregulation normalizes within 72 hours, even though withdrawal symptoms take longer to resolve. The dissociation between the resolution of withdrawal symptoms and recovery of CB1R downregulation suggests that withdrawal symptoms and craving are a consequence of long-lasting downstream effects. The persistence of reductions in CB1R density in the ACC and the insula during acute abstinence is consistent with the preclinical literature of region specific recovery of CB1R. By 4 weeks, there appears to be complete normalization of CB1R availability in cannabis dependent subjects.

Poster #S269

DEXTROMETHORPHAN AND PSYCHIATRIC MORBIDITY: A SINGAPORE PERSPECTIVE

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Background: Dextromethorphan is a common over-the-counter antitussive agent. It is often prescribed by general practitioners (GPs) and specialists as an alternative to codeine containing cough mixtures. Though considered safe, it may cause dissociative symptoms and hallucinations through N-methyl-D-aspartate receptor antagonism when taken in excess. We are seeing a rising trend of DXM abuse in Singapore due to existing strict laws against illicit drugs such as cannabis, heroin etc. As a result number of dextromethorphan related psychiatric presentations to hospitals are increasing.

Methods: We reviewed the existent literature on DXM abuse and its psychiatric manifestations in Singapore.

Results: We found that there are 4 cases of dextromethorphan related psychiatric presentation reported since 2009 in Singapore. 2 patients presented with predominantly psychotic symptoms, 1 with altered consciousness and 1 with manic symptoms. All of them recovered quickly and were discharged without long term medications. Central Narcotics Bureau (CNB) of Singapore website mentions a death possibly related to overdose of dextromethorphan and has identified dextromethorphan as an easily accessible addictive substance and has included information about it in its preventive drug education material. The Health Sciences Authority of Singapore also found dextromethorphan as an undeclared component in a traditional Chinese medicine in 2011. We will describe the case series of 4 patients in the poster.

Discussion: The reports do indicate a necessity of raising awareness about the abuse potential and psychiatric adverse effects of this seemingly safe

cough suppressant among the physicians and members of the general public and to consider dextromethorphan as a probable causative agent in patients presenting with mood or psychotic symptoms.

Poster #S270

DOES SUBSTANCE ABUSE INCREASE THE RISK OF PSYCHIATRIC ILLNESS?

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Background: The Danish National Health Board estimates, that 60-70% of people with substance use disorders in Denmark have psychiatric comorbidity. Some studies have already postulated a causal link between cannabis and psychosis, suggesting that adolescence exposure to cannabis increases the risk of later psychotic illness. Cannabis has been found to impact negatively on dimensions related to psychosis (e.g. symptom levels, psychiatric hospitalization rates and antipsychotic medication compliance). A lot of evidence shows that substance use can complicate the course of a psychiatric illness, but we still only know a little about the risk factors concerning this matter. We are interested in investigating whether the substance use disorder is preceding the psychiatric disorder to evaluate a possible causal link. The aim for the study is to examine if people with a diagnosis of substance use disorder or people having received treatment for substance use disorder are more frequent diagnosed with psychiatric illness than the background population. To our knowledge, the association has never been examined in an unselected nationwide register-based cohort, nor has Danish figures ever been published. This study will have the opportunity and seek to examine possible causal links directly from the available data from the Danish nationwide registers.

Methods: The study population will consist of all people living in Denmark and born since 1955. Data from several different Danish registers will be extracted and combined. We will have information on the patients from following registers: the Psychiatric Central Register, the Central Persons Register, the National Patient Register, the Register over People with Substance Abuse in Treatment, the Danish Medicinal Products Register and Statistics Denmark. People with psychiatric disorders before the substance use disorder diagnosis will be excluded to secure the longitudinal effect. The statistics program SPSS and Cox regression models will be used.

Results: The data analyses are not run yet. Results will be ready for the conference in the spring.

Discussion: We are expecting that the substance use disorder diagnosis is underreported in the registers. This can be due to patients either hiding their abuse, or patients not acknowledging that they have a problematic use and consequently not seeking help. A problem could also be that a substance use disorder is firstly recognised when the patient contacts the Mental Health Services due to psychiatric comorbidity. These individuals will be excluded in the study. The spread of the problem can therefore unfortunately be expected to be an underestimation of the reality. If substance abuse is shown to be a significant risk factor for developing psychiatric diseases, it indicates the need for reevaluation and improvement of the future treatment, early intervention plans and national drug policies.

Poster #S271

SCHIZOPHRENIA AND DISORDERED GAMBLING: QUALITATIVE FEATURES OF DUAL DIAGNOSIS

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Background: Disordered gambling may affect as many as 1 in 5 individuals with schizophrenia. Despite this, little research has examined the association between disordered gambling and psychosis. Additionally, clinicians treating schizophrenia rarely screen for or treat gambling problems. Thus, the effects of disordered gambling on symptoms of schizophrenia and vice versa, such as stress-precipitated acute psychotic episodes, exacerbation of gambling fallacies due to cognitive deficits of schizophrenia, and bias in the perception of gambling risk remain largely unexplored and unidentified in clinical practice. Due to the above shortcomings in the literature, the aims of the present study were to qualitatively explore the reciprocal associations between schizophrenia and disordered gambling through content and functional analyses.

Methods: Twenty-one participants who met DSM-IV criteria for schizophrenia were screened for gambling disorders. All participants completed questionnaires assessing gambling cognitions, impulsivity, and gambling habits. Eight of these participants additionally met DSM-IV criteria for disordered gambling and were invited for a qualitative interview. These eight participants were asked open-ended questions focusing on key antecedents associated with their gambling, as well as perceived functional consequences of gambling. Open-ended responses to the qualitative interview questions were transcribed and independently coded by two researchers via content analysis to derive general categories of responses based on domains of problem gambling (e.g., motivations for gambling, interaction between schizophrenia and gambling behaviour). The final categories were compared to previously reported literature in the area of gambling to ascertain key differences between important correlates of gambling among the general population versus those identified in persons with schizophrenia.

Results: The average lifetime score of the eight dual diagnosis participants on the Problem Gambling Severity Index was 11.75 ($SD = 8.58$), indicating a relatively severe level of problems across the sample. The most frequently played gambling activities were lottery, instant win/scratch tickets, and video lottery terminals other than in casinos. Quantitative comparisons of questionnaire data are ongoing. A number of patterns of responses specific to the eight individuals with a dual-diagnosis were derived via the content analysis. Notably, in addition to endorsing typical motivations for gambling (e.g., escape from negative emotions, making money, excitement), individuals with both schizophrenia and disordered gambling also endorsed the following: 1. Gambling as filling the "need for activity". 2. Gambling as a means to achieve a sense of accomplishment. 3. Gambling as a means of "connecting with society/world". Furthermore, in addition to several individuals denying any interaction between aspects of their gambling and symptoms of schizophrenia, other participants endorsed direct exacerbation of psychotic symptoms by gambling and greater involvement in gambling due to psychotic symptoms.

Discussion: The current study is the first in-depth qualitative exploration of the complex reciprocal interactions between schizophrenia and disordered gambling. The results shed light on these interactions and highlight the need for improved awareness of these processes among healthcare professionals and researchers. Specifically, these findings suggest that the impact of comorbid disordered gambling should not be overlooked in individuals with schizophrenia. Future research should expand on these findings via quantitative methodology.

Poster Session

MONDAY POSTER SESSION

Poster #M1

CHILDHOOD MALTREATMENT, THE BDNF-VAL66MET POLYMORPHISM AND HIPPOCAMPAL VOLUME: FURTHER EVIDENCES FROM A MRI-TWIN STUDY

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Background: Evidence from animal studies indicates that stress influences hippocampal neurogenesis and plasticity (Woolley et al 1990). However, individuals can be differentially susceptible to the same environmental factors, depending on their genetic background. Stress and childhood trauma in interaction with BDNF-Val66Met polymorphism has been reported to lead to reduced hippocampal volumes in psychosis (Aas et al 2013; Mondelli et al 2011), major depression disorder and controls (Carballido et al 2013). It has been pointed out that the experience of psychopathology may mediate the effect of childhood maltreatment on hippocampus and amygdala growth (Whittle et al 2013). Several studies examine the impact of childhood maltreatment on adult hippocampal volume in depression (Edmiston et al 2011; Frodl et al 2010; Vytilingam et al 2002) but studies in healthy individuals are still relatively scarce (Dannlowski et al 2012; Edmiston et al 2011). The current study was aimed to explore how childhood adversity and the BDNF Val66Met polymorphism affect the volumetric measures of the hippocampus in healthy MZ twins and lifetime affected MZ twins for anxiety and depression.

Methods: MRI scans and genomic DNA were obtained from 53 MZ twins from the general population. Childhood physical, emotional and sexual abuse and physical and emotional neglect were assessed using Childhood Trauma Questionnaire (CTQ; (Bernstein & Fink 1998). These 5 types of childhood adversity were defined as binary variables (high and low) according to median split allowing the classification of the participants as exposed to low or high rates of childhood adversity (Frodl et al 2010). MRI scans were processed and analyzed using FreeSurfer. Measures of left and right hippocampal volumes were obtained for each twin. Multiple linear regression analyses were conducted to test main and interaction effects of the five types of childhood trauma and the BDNF-Val66Met polymorphism on left and right hippocampal volumes separately. All analyses included sex, age and total subcortical gray matter volume as covariates. Of note, in the present study the individual was the unit of analyses. The non-independence of clustered twin data was corrected for by using tests based on the sandwich or Huber/White variance estimator.

Results: Main effects of emotional ($\beta=-233.4$; SE=107.6; $p=0.048$) and sexual abuse ($\beta=462.9.5$; SE=200.3; $p=0.029$) were found in right hippocampus. A significant interaction effect between emotional neglect and the BDNF-Val66Met polymorphism was detected ($\beta=-866.5$; SE=298.3; $p=0.007$) in left hippocampus. The interaction effect accounted for 12.8% of the variance of left hippocampus.

Discussion: Our findings are in line with previous research indicating that childhood adversity influence adult hippocampal volume (Dannlowski et al 2012; Edmiston et al 2011; Teicher et al 2012). Nevertheless, while most research indicates that childhood adversity leads to decreased hippocampal volume, we found that sexual abuse was positively associated with right hippocampal volume. Interestingly and largely in agreement with a previous study (Carballido et al 2013), a gene-environment interaction effect was found indicating that Met carriers exposed to emotional neglect were more likely to present reductions in hippocampal volume compared to Val/Val genotype carriers.

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Poster #M2

INVESTIGATION OF THE ROLE OF ALLELIC VARIANTS OF MULTIDRUG RESISTANCE GENE (MDR1) ON CLOZAPINE RELATED LEUKOPENIA/AGRANULOCYTOSIS

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Background: The risk factors and the pathophysiology of clozapine related leukopenia/agranulocytosis are yet unclear. It is suggested that this adverse event could be immune mediated or due to toxic or apoptotic effects mediated by clozapine or its metabolites which are affected by genetic factors. It has been proposed that clozapine and possibly its metabolites interact with the multidrug resistance transporter (MDR1) gene product, P-glycoprotein (P-gp). P-glycoprotein is a membrane protein functioning as an exporter of xenobiotics from cells, and is highly expressed in various tissues, including the white blood cells. Among various P-gp genetic polymorphisms, a nucleotide change in exon 26 (C3435T) and another in exon 21 (G2677T) have been frequently implicated for changes in pharmacokinetics and pharmacodynamics of many substrate drugs. We had earlier reported a case of agranulocytosis related to clozapine in monozygotic twins diagnosed with schizophrenia, who were heterozygote for both MDR1 C3435T and G2677T polymorphisms. We had proposed that existence of both polymorphisms could be linked to an additive functional loss in P-gp action, resulting in toxic metabolite accumulation of clozapine in leukocytes and thereby agranulocytosis. The aim of the present study was to further investigate the role of MDR1 polymorphisms and their possible impact on leukopenia/agranulocytosis related to clozapine.

Methods: Twenty three patients with a history of leukopenia/agranulocytosis related to clozapine and 47 control patients without such a history despite 10 years of continuous clozapine were included in the study. All of the patients included, who either had a diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV, gave informed consent. Leukopenia was defined as leukocyte count $<3000/\text{mm}^3$ or absolute neutrophil count (ANC) $<1500/\text{mm}^3$, and agranulocytosis as ANC $<500/\text{mm}^3$. Patient and blood sample recruitment was conducted at Hacettepe University Faculty of Medicine, Department of Psychiatry and various psychiatry clinics in collaboration with members of the Schizophrenia and Other Psychotic Disorders Section of the Psychiatric Association of Turkey. Exclusion criteria consisted of history of any other medical condition or drug use which could be linked to leukopenia/agranulocytosis. After DNA extraction from peripheral blood lymphocytes, genotyping of MDR1 C3435T and G2677T polymorphisms were performed using polymerase chain reaction and endonuclease digestion.

Results: No significant differences were found among the leukopenia/agranulocytosis and control patient groups regarding age, gender and age of illness onset. Patients with a history of leukopenia/agranulocytosis had significantly shorter illness duration and older age at clozapine initiation. There were no significant differences in genotype or allele distributions of MDR1 C3435T and G2677T variants between the control and leukopenia/agranulocytosis patient groups. There was only 1 subject with a history of leukopenia (4.3%) out of 23 leukopenia/agranulocytosis patients with the TT-TT haplotype, compared to 7 subjects (15.2%) in the control group. Therefore, there was a tendency for a lower frequency of homozygous mutant subjects in the leucopenia/agranulocytosis patients ($\chi^2 = 1.77$, $p=0.09$).

Discussion: This study did not reveal a positive finding regarding the role of MDR1 polymorphisms on leukopenia/agranulocytosis related to clozapine. However, a possible protective effect of being a homozygous mutant for MDR1 C3435T and G2677T variants (TT-TT haplotype) regarding this hematological adverse event could be further explored in a larger sample of patients receiving clozapine treatment.

*CRLA-SG Collaborators: Vesile Altintayazar, Memduha Aydin, Berna B. Kivircik Akdede, Koksal Alptekin, Ayten Esen Danaci, Bilge Cetin Ilhan, Semra Ulusoy, Haldun Soygur, Hatice Ozdemir, Mustafa Celik, Fatma Ozlem Orhan, Hasret Ozan, Ismet Kaygisiz

Poster #M3

PREDICTION OF SUICIDAL BEHAVIOURS IN YOUNG PEOPLE PRESENTING WITH FIRST-EPISEDE PSYCHOSIS IN HONG KONG: A 3-YEAR FOLLOW-UP STUDY

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Background: Suicide behaviours are common in the early stage of psychotic disorders. The present study aimed to examine the rate and predictors of suicidal behaviours in the initial 3 years of treatment for patients presenting with first-episode psychosis to a territory-wide specialized early intervention program, namely EASY (Early Assessment Service for Young people with psychosis) in Hong Kong.

Methods: Seven hundred patients aged 15–25 years presenting with first-episode psychosis (based on ICD-10 criteria) to EASY program between July 2001 and August 2003 were included in the study. Of the initial cohort, 546 completed the 3-year follow-up and thus constituted the final study sample. Demographics, past history of suicidal attempts, substance abuse, baseline and follow-up clinical and functioning variables were collected via systematic medical record review based on standardized protocol. Suicidal behaviour was defined as either attempted or committed suicide. A series of univariate logistic regression analyses were performed to examine the relationship of suicidal behaviour (yes/no in 3-year follow-up) with potential predictor variables, followed by multivariate regression model to determine independent predictors of suicidal behaviours.

Results: There were no significant differences between completers and non-completers in socio-demographics, past suicidal attempt, baseline clinical and functional measures with the exception that completers were significantly more likely to have schizophrenia diagnosis. By the end of 3-year follow-up, 11.2% (n=61) of patients exhibited suicidal behaviour over the study period, including 1.3% (n=7) committing suicide. Univariate analyses revealed that hospitalization at intake ($OR=0.45$, $p<0.05$), past history of substance abuse ($OR=0.43$, $p<0.05$), pre-treatment suicidal attempt ($OR=0.38$, $p<0.01$), and baseline social functioning ($OR=0.97$, $p<0.01$) were identified as the risk factors for suicidal behaviours. Multivariate regression demonstrated that only pre-treatment suicidal attempt, past history of substance abuse and baseline functioning independently predicted the occurrence of suicidal behaviours during 3-year follow-up period (Nagelkerke R² = 0.064, chi-square= 21.8, $p<0.0001$).

Discussion: In a large representative cohort of Chinese young patients with first-episode psychosis, we found that 3-year prevalence rate for suicidal behaviours and suicide was 11.2% and 1.3%, respectively. Pre-treatment suicidal attempt, past history of substance abuse and baseline functioning were shown to independently predict suicidal behaviours in the initial 3 years of treatment for first-episode psychosis in EASY program.

Poster #M4

TREATMENT OF CLOZAPINE-INDUCED HYERSALIVATION WITH AMISULPRIDE: A SYSTEMATIC REVIEW

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Background: Clozapine is an atypical antipsychotic indicated for treatment resistant schizophrenia. Hypersalivation is a frequent and bothersome side effect, leading to social withdrawal and potentially life-threatening situations (e.g., choking, aspiration pneumonia). Several treatments are proposed for clozapine-induced sialorrhea, including atropine, botulinum, biperiden among others. Amisulpride is a benzamide derivate with high affinity on D2/D3 receptors, similar to sulpiride which is reported to be an option in sialorrhea treatment.

Methods: A systematic review of the treatment of clozapine induced hypersalivation (CIH) with amisulpride. Medline and Embase were researched

with the search terms “clozapine”, “amisulpride”, “hypersalivation”, or “sialorrhea”. No language- or publication date restriction.

Results: A total of 296 abstracts were found. After exclusion of duplicates, 6 abstracts remained. These were fully read by both authors, to obtain relevant data. Four were case reports, 2 were RCTs, one against placebo and one comparing amisulpride with moclobemide. In all reports (case reports and RCTs) there was a reduction of sialorrhea with amisulpride. This drug also showed additional benefits in reducing symptoms as measured by the PANSS.

Discussion: Hypersalivation is a frequent and unpleasant side effect that interferes in the adherence to treatment by the patients. As the pathophysiology of clozapine mechanism of hypersalivation remains unclear, possibly involving both cholinergic and adrenergic receptors, different types of drugs have been tried, but their effectiveness is controversial. Other explanations include an interference in the mechanism of swallowing and an alteration in circadian rhythm with increased salivation at night. The perception of the amisulpride effects on CIH is evidenced in 4 published case reports. During the last few years, there have been 2 RCT that confirmed the reports, and associated with additional benefits on symptoms treatment, showing an increasing of interest in this drug action. However, the pathophysiology of amisulpride hypo salivation caused by clozapine use is still unknown. In experiments with rodents, no clear evidence of its effects was observed. Amisulpride, per se, caused no flow of saliva, had no effect on blood flow and there was no support for any inhibitory action at central level, but potentiated the actions of agonists by mobilizing intracellular pathways, supporting the view that amisulpride acts at gland level. In fact, in a posterior study, amisulpride induced ultrastructural signs of secretory activity, hypothesizing that may provide an overall readiness for secretion, resulting in augmented responses to agonists, contrasting with the clinical observations. In another hand, amisulpride, as an atypical antipsychotic alone, appears in the first line treatment of schizophrenia (Harvard Project, Osser DN, 2013) and a recent meta-analysis showed that is effective in partial responders when associated with clozapine (Porcelli, 2012; Pani, 2008). Additionally, it has been suggested that this combination could permit a decrease of the amount of clozapine use, reducing dose-dependent side-effects. (plasma clozapine concentration >0.25 mg/l increase the chances of appearance of side effects). Although amisulpride, because of its profile in enhance therapeutic use of clozapine and it's a well tolerated drug, seems to be an interesting option on treating sialorrhea, there is only a small studies to confirm this initial observation and, until know, the experimental findings in rats are unexpectedly against clinical experience.

Poster #M5

CLOZAPINE-INDUCED SEIZURES, EEG ABNORMALITIES, AND CLINICAL RESPONSE IN JAPANESE PATIENTS WITH SCHIZOPHRENIA

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Background: Clozapine is effective against treatment-resistant schizophrenia and was introduced to Japan in 2009. Clozapine-induced seizures are more frequent than agranulocytosis (Karper et al., 1992), and electroencephalography (EEG) abnormalities are even more common. Because clozapine efficacy varies among individuals and races, there is a need to determine the predictive factor of treatment-response and side effects of clozapine in a Japanese population to establish safe treatment practices. Here, we describe EEG abnormalities and seizures associated with clozapine treatment in Japanese schizophrenia and compare EEG results and total score of positive and negative syndrome scale (PANSS (T)) before and after treatment.

Methods: Twenty patients with treatment-resistant schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria were enrolled in this study, including 4 males and 16 females. Their average age was 34 years old. EEGs were obtained prior to clozapine treatment, when seizures occurred, and every 4 weeks. PANSS (T) were used to determine clozapine treatment outcome and were compared at baseline and last observation.

Results: All patients had normal baseline EEGs, and 10 patients (50%) later

showed EEG abnormalities. There were no significant differences between the EEG normal and EEG abnormal groups in mean age, gender, mean clozapine dose, or length of treatment with clozapine. Six patients (30%) experienced seizures; one with both tonic-clonic and myoclonic, one with tonic-clonic and four with myoclonic seizures. The mean baseline PANSS (T) scores were not significantly different between the EEG normal and EEG abnormal groups, but the mean score in the EEG abnormal group was significantly lower than that in the EEG normal group at the final follow-up. The response rate was not significantly different between the two groups.

Discussion: The incidence of seizure in this study was higher than other reports in the literature. These results suggest that clozapine is more likely to cause seizures in the Japanese population. However, this study involved a small number of patients, so we cannot be certain that Japanese patients with schizophrenia have a higher risk of seizure with clozapine use; additional studies with larger samples are needed to verify our observation. All patients who experienced seizures in this study were successfully treated with valproate or lamotrigine without clozapine discontinuation. Cott (2007) described the treatment of clozapine-associated seizures with dosage reduction and/or the addition of an antiepileptic drug. It has been reported that clozapine-induced EEG abnormalities occur in a dose-dependent manner and correlated with serum level of clozapine. However, Centorrino et al. (2002) reported that clinical factors associated with EEG abnormalities included hypertension and age over 40 years old; they described no relationship between dose and EEG abnormalities. In this study, the mean dose of clozapine was no significantly different between the EEG abnormal and EEG normal groups. In half of the patients with EEG abnormalities, the clozapine dose was <300 mg. The relationship between clozapine dosage and EEG abnormality remains controversial. The baseline PANSS (T) was not significantly different between patients with normal and abnormal EEGs. However, the PANSS (T) from the last observation was significantly lower in the EEG abnormal group, indicating that EEG abnormalities appeared after clozapine treatments were associated with a good clinical response to clozapine.

Poster #M6

CARDIOMETABOLIC RISKS OF BLONANSERIN AND PEROSPIRONE IN THE MANAGEMENT OF SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: The present study aimed to evaluate cardiometabolic risks [weight gain, blood lipid levels (total cholesterol and triglycerides), blood glucose levels, hemoglobin A1c (HbA1c) levels, and corrected QT interval (QTc) prolongation] associated with the use of blonanserin and perospirone versus other antipsychotics in the management of patients with schizophrenia.

Methods: We conducted a systematic review and meta-analysis of patient data from randomized controlled trials comparing blonanserin or perospirone with other antipsychotics.

Results: In total, 4 blonanserin studies (n=1080) were identified [vs. risperidone (2 studies, n=508); vs. haloperidol (2 studies, n=572)]. Blonanserin produced less weight gain compared with risperidone (weighted mean difference = -0.86, 95% confidence intervals = -1.36 to -0.36, p=0.0008; 2 studies, 480 patients). However, no significant differences were observed in blood lipid, glucose, and HbA1c levels or QTc prolongation between blonanserin and risperidone or haloperidol. For perospirone studies, 5 studies [562 adult patients with schizophrenia randomized to perospirone (n=256), olanzapine (n=20), quetiapine (n=28), risperidone (n=53), aripiprazole (n=49), haloperidol (n=75), or mosapramine (n=81)] were identified. Perospirone did not differ from other antipsychotics with regard to weight gain and total cholesterol levels.

Discussion: Our results suggest that blonanserin is associated with a lower of weight gain compared with other antipsychotics. Because the number of studies was small, additional controlled clinical trials with larger number of patients are indicated.

Poster #M7

NEGATIVE SELF AND OTHER SCHEMAS AND INSECURE ATTACHMENT MEDIATE THE ASSOCIATION BETWEEN CHILDHOOD INTERPERSONAL ADVERSITY AND THE NONCLINICAL PSYCHOSIS PHENOTYPE

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Background: There is mounting evidence indicating that interpersonal adversity in childhood is associated with psychotic phenomena in clinical and nonclinical populations. Among the psychological mechanisms that have been suggested to underlie this association, negative self and other schemas and insecure attachment styles have received increasing theoretical attention. However, there is scant empirical research investigating these predictions, particularly in regards to insecure attachment. The present study investigated the associations of childhood interpersonal trauma with nonclinical psychotic phenomena, and the role of negative self and other schemas and insecure attachment styles as potential mediators of the associations between early trauma exposure and nonclinical psychotic phenomena.

Methods: At the initial assessment, 547 Spanish young adults completed a battery of self-report questionnaires, including measures of schizotypy, suspiciousness, psychotic-like experiences, traumatic childhood experiences, self and other schemas, and attachment style. At the second assessment, a subset of these participants (n=214), oversampled for high schizotypy and psychotic-like experiences, completed interview measures of prodromal symptoms, schizophrenia-spectrum personality disorders, childhood trauma, and attachment style.

Results: At the initial assessment, physical/emotional trauma was significantly associated with positive and negative schizotypy, suspiciousness, and psychotic-like experiences. Results from the bootstrapping analyses indicated that negative self-schemas, negative other-schemas, and fearful attachment significantly mediated these associations. At the second assessment, physical/emotional trauma was significantly associated with positive and negative prodromal symptoms and schizophrenia-spectrum personality traits. Bootstrapping analyses indicated that insecure attachment was a significant mediator of these associations.

Discussion: Childhood physical/emotional trauma was associated with the nonclinical psychosis phenotype across two time points and with both self-report and interview measures. These associations were mediated by theory-driven psychological mechanisms. Although the present study cannot determine causality, the findings are consistent with theoretical accounts suggesting that interpersonal childhood trauma may contribute to the formation of negative cognitive schemas and insecure attachment patterns, which, in turn, may impact upon the development and expression of the extended psychosis phenotype.

Poster #M8

POSITIVE ALLOSTERIC MODULATION OF MGLUR5 REVERSES THE AKT SIGNALING DEFICITS IN SERINE RACEMASE KNOCKOUT MICE, A GENETIC MODEL OF SCHIZOPHRENIA DUE TO NMDA RECEPTOR HYPOFUNCTION

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Background: There is substantial evidence that hypofunction of the N-methyl-D-aspartate receptor (NMDAR) is a core pathophysiological mechanism underlying schizophrenia. We have previously demonstrated that serine racemase knockout (SR^{-/-}) mice exhibit neuroanatomical and behavioral similarities to schizophrenia, as well as reductions in hippocampal Akt/glycogen synthase kinase 3 (GSK3)/mammalian target of rapamycin (mTOR) signaling that can be reversed with three weeks of D-serine treatment. Traditional metabotropic glutamate receptor 5 (mGluR5) positive allosteric modulators (PAMs) enhance NMDAR activity through circuits that are regulated by NMDARs and are currently being developed to ameliorate

the NMDAR hypofunction associated with schizophrenia. However, a novel mGluR5 PAM, VU0409551 (VU551), has been developed that can selectively modulate coupling to some, but not all signaling pathways.

Methods: Wild-type (WT) mice were given once daily (q.d.) intraperitoneal injections (10ml/kg) of vehicle (20% β -cyclodextrin in sterile water) or the mGluR5 PAM VU551 (10, 30 mg/kg) for 5 days. A separate cohort of WT and SR $^{-/-}$ mice were given q.d. injections of either vehicle, D-serine (150 mg/kg), or VU551 (30 mg/kg) for 5 days. All mice were sacrificed \sim 2 hours after the last injection for subsequent analyses. Plasma and cortical levels of VU551 were determined by mass spectrometry, while D-serine brain tissue content was measured using high-performance liquid chromatography. Western blot was used to measure changes in brain proteins.

Results: In WT mice, we found a dose-dependent increase in the plasma and brain levels of VU551 that was accompanied by a dose-dependent increase in the amount of phosphorylated Akt (p-Akt; active state), without affecting the total amount of Akt protein. In addition, the amount of p-GS3K α/β was increased, which is a downstream targets of Akt. Furthermore, administration of D-serine or VU551 for 5 days to SR $^{-/-}$ mice reversed their deficits in TrkB, Akt, GS3K, and mTOR phosphorylation, a measure of their activation.

Discussion: These data demonstrate that impairments in Akt/mTOR signaling caused by a lack of D-serine and consequent NMDAR hypofunction, can be corrected by subchronic administration of D-serine or VU551, an mGluR5 PAM. These results support augmenting NMDAR and/or mGluR5 function as viable mechanisms by which to reverse the deficits in signaling cascades that are known to be perturbed in models of NMDAR hypofunction and schizophrenia. Finally, our findings highlight the utility of a new class of mGluR5 PAMs as potential novel therapeutics for treating the cognitive and negative symptoms of schizophrenia.

Poster #M9

DISC1 MUTATION INDUCED ALTERATIONS IN CEREBRAL METABOLISM AND IN THE RESPONSE TO ACUTE SUBANAESTHETIC KETAMIINE: A COMPARISON OF THREE DIFFERENT DISC1 MUTATIONS

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Background: Disrupted-in-Schizophrenia-1 (DISC1) is strongly implicated in psychiatric disease, as is NMDA receptor hypofunction. How DISC1 dysfunction impacts upon constitutive brain functioning or NMDA receptor functioning is yet to be determined. Here, we characterise the impact of Disc1 gene mutation on brain functioning and on the cerebral metabolic response to the schizomimetic NMDA receptor antagonist ketamine in three lines of Disc1 mutant mice, one a Disc1 truncation (Disc1tr hemizygous mice, Shen et al., 2008. J. Neurosci. 28: 10893) and two ENU-induced missense mutations (Disc1 100P/100P and 31L/31L mutant mice, Clapcote et al., 2007. Neuron. 54: 387) in the gene.

Methods: Cerebral metabolism was determined in Disc1 mutant mice (Disc1tr hemizygous n=20, Disc1 100P/100P n=18, Disc1 31L/31L n=18) and their wild-type littermates (C57BL6JRsccHssd, n=20, n=19 and n=20 respectively) in 58 brain regions by 2-deoxyglucose autoradiography (Dawson et al., 2013. Schizophr. Bull. 39: 366-377). Animals were treated acutely with either 30mg/kg ketamine (i.p.) or vehicle (saline, 2mls/kg). Data were analysed using 2-way ANOVA with genotype (Wt, Disc1 mutant) or treatment (saline, ketamine) as independent variables.

Results: The Disc1 mutation present in Disc1tr hemizygous mice had the most pronounced effect on constitutive cerebral metabolism, inducing a significant hypofrontality (prefrontal cortex hypometabolism), along with hypometabolism in the reticular thalamus and habenula. The Disc1 mutation present in both of the ENU mutant lines failed to induce significant hypofrontality. Rather, the mutation present in Disc1 100P/100P mutant mice induced widespread thalamic hypometabolism, whereas that present in Disc1 31L/31L mutant mice was even more limited, inducing only cingulate cortex hypometabolism. In all three mutant lines there was evidence that the cerebral metabolic response to ketamine was significantly attenuated. Again, this effect was most pronounced in Disc1tr hemizygous mice, which included an attenuation of ketamine induced hyperfrontality.

Ketamine-induced hyperfrontality was not attenuated in either of the ENU Disc1 mutants.

Discussion: Overall, these data suggest that Disc1 mutation modifies cerebral functioning in neural systems strongly implicated in psychiatric disorder. Moreover, the data suggest that the specific molecular nature of the mutation present in the Disc1 gene has a pronounced impact on the emergent properties of altered brain functioning at a systems level. Furthermore, we have shown that Disc1 mutation modifies the cerebral metabolic response to ketamine, supporting NMDA receptor hypoactivation/hypofunction in these animals.

Poster #M10

A NEW "DOUBLE HIT" SCHIZOPHRENIA MODEL IN RAT SHOWS STRUCTURAL AND NEUROCHEMICAL ALTERATIONS OF THE MEDIAL PREFRONTAL CORTEX AND THE HIPPOCAMPUS

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Background: An important risk factors for schizophrenia development are alterations in neurodevelopment and aversive experiences during childhood and adolescence. Animal models reproducing these alterations mimic some of the symptoms, constituting a valid approach to study the etiopathology of this disorder. Among these models, the perinatal injection of N-methyl-d-aspartate receptor antagonists and the postweaning social isolation rearing are among the most widely used. Our aim is to combine them in a "double hit" model, which should produce a wider spectrum of alterations.

Methods: Lister Hooded rats have been subjected to a single injection of MK-801 at postnatal day 7 and have been socially isolated from post-weaning to adulthood in order to combine the consequences of both conditions.

Results: These animals presented increased body weight gain and volume reductions in their medial prefrontal cortex (mPFC) and hippocampus. They also showed an increased number of activated pyramidal neurons and alterations in the number of parvalbumin and calbindin expressing interneurons in the mPFC. The expressions of the polysialylated form of the neural cell adhesion molecule (PSA-NCAM) and GAD67 are decreased in the mPFC. The mRNA level of calbindin was increased, while that of calretinin was decreased in the mPFC. The mRNA level of ERBB4, a gene associated to schizophrenia, was also altered in this region.

Discussion: All these structural and neurochemical alterations, specially in cortical inhibitory circuits, are similar to those found in schizophrenic patients and are more numerous than in each of the single models. Consequently, the present "double hit" model may be a better tool to study the neurobiological basis of schizophrenia and to explore new therapeutic approaches.

Poster #M11

LONG-TERM EFFECTS OF NEONATAL MK-801 TREATMENT ON PROTEIN TRANSLATION SIGNAL PATHWAY IN THE RAT FRONTAL CORTEX

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Background: Treatment of MK-801, a selective NMDA receptor antagonist, on neonatal rat induces long-term neurochemical and behavioral changes, which is suggested as neurodevelopmental rat model of schizophrenia. Proper regulation of protein synthesis is required for neurodevelopment process. Previously, we have reported that neonatal MK-801 treatment induced acute reductions in protein translation activity in the frontal cortex of the developing rat brain. In this study, the long-term developmental effects of neonatal MK-801 on the protein translation signal pathway have been investigated.

Methods: Postnatal 7-day (PN7) rats were treated with MK-801, and the

locomotor activity and prepulse inhibition were investigated at PN60. Their frontal cortices at PN7 (1 h after injection), PN8, PN21, PN42, and PN60 were examined to investigate the long-term effects on the molecules in signal pathway of protein translation.

Results: At PN60, the rats treated with MK-801 at PN7 showed psychotomimetic behaviors, including increased locomotor activity and deficits in prepulse inhibition. Accompanied with the behavioral changes, the phosphorylation level of S6 at S240/244, which promotes protein translation initiation, was increased, and the phosphorylation of raptor at S792, which inhibits the activity of mTOR signal pathway, was reduced in the rat frontal cortex at PN60. The phosphorylation level of S6 in neonatal MK-801-treated group was significantly lower at 1h after injection, higher at PN8, PN21, PN42, PN60 in the rat frontal cortex compared to the vehicle-treated group.

Discussion: Neonatal MK-801 treatment induced acute reduction followed by increase in the phosphorylation of ribosomal S6 protein through developmental process with the long-term psychotomimetic behavioral changes in adult rats. These findings could suggest an important role of aberrant long-term activation of protein translation machinery in the MK-801 neurodevelopmental animal model of schizophrenia.

Poster #M12 REWARD DEFICITS IN THE MATERNAL IMMUNE ACTIVATION MODEL

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Background: Prenatal maternal infection is an environmental risk factor of schizophrenia and disease-associated behavioral abnormalities. Modeling this epidemiological link in animals shows that maternal immune activation is capable of inducing long-term deficits in numerous behavioral and cognitive domains. However, whether maternal immune activation causes deficits in central reward processing thus far remains unknown. Exploring this issue seems highly warranted because impaired reward processing is a core symptom related to the negative symptoms of schizophrenia.

Methods: Pregnant C57BL6/N mice were treated with the synthetic viral mimetic poly(I:C) (5 mg/kg, i.v.) or control (saline, i.v.) solution on gestation day 17. All offspring were subjected to behavioral testing in adulthood (PND70-100) using a running alley paradigm to assess willingness to run for food reward, and a sucrose-driven conditioned place preference (CPP) paradigm. Poly(I:C) and control animals were further compared in conditioned active avoidance and contextual fear paradigms to evaluate their capacities for instrumental learning and context-dependent conditioning. Finally, brains were harvested for immunohistochemical analyses of brain markers of interest, which included dopamine receptors 1 (D1R) and 2 (D2R), tyrosine hydroxylase (TH), and dopamine transporter (DAT) in the nucleus accumbens (NAc) and caudate putamen (CPu).

Results: We found that prenatal poly(I:C) treatment induced deficits in the running alley paradigm, in which the completion speed of poly(I:C) offspring was significantly lower over time as compared to control mice. Such deficits could not be explained by deficient instrumental learning per se because conditioned active avoidance performance was similar in poly(I:C) and control offspring. Hence, the poly(I:C)-induced deficit emerging in the running alley test likely represents a genuine impairment in the willingness to work for food reward. This impression was further confirmed by the CPP test, in which control mice significantly preferred the sucrose-paired (vs. water) chamber while poly(I:C) offspring spent an equal amount of time in both chambers. Such deficits are unlikely to be accounted for by abnormal contextual processing given that the performance of poly(I:C) offspring in contextual fear conditioning was fully intact. The reward-related behavioral manifestations were further accompanied by marked changes in the mesolimbic dopaminergic system, known to represent a major neural contributor to reward-related functions. Our data reveal that striatal DAT and TH levels were significantly decreased and increased, respectively, indicating the existence of an augmented dopaminergic tone at the presynapse. On the other hand, D1R and D2R were reduced in the CPu and NAc, suggesting reduced dopaminergic signaling at the post-synapse.

Discussion: Our findings demonstrate for the first time that in-utero immune challenge results in the emergence of deficits in reward-related behaviors in mice, which are accompanied by abnormalities in several key dopaminergic markers of the mesolimbic system. Such data support the hypothesis that immune-mediated disruption of neurodevelopmental

processes may contribute to the appearance of aberrant reward function. Our etiologically informed model suggests that prenatal immune abnormalities may be a causal environmental factor contributing to behavioral and dopaminergic abnormalities relevant especially to the negative symptoms of schizophrenia.

Poster #M13

CHARACTERIZATION OF A 'TWO-HIT' MOUSE MODEL OF METHAMPHETAMINE-INDUCED PSYCHOSIS: EFFECTS OF BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) DEFICIENCY AND RELEVANCE TO SCHIZOPHRENIA

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Background: Methamphetamine (METH) users have an increased risk of psychosis and schizophrenia, including cognitive and negative symptoms. For this reason animal models of methamphetamine psychosis may aid our understanding of both schizophrenia and psychotic disorders more broadly. Brain-derived neurotrophic factor (BDNF) had been implicated in the pathophysiology of schizophrenia and also the neuronal response to stimulant drugs. However the role of BDNF in METH-induced psychopathology remains unclear.

Methods: We developed a "two hit" animal model where BDNF heterozygous mice (HETs) and wild-type (WT) littermates were treated with METH during young adulthood, from 6-9 weeks of age, using an escalating dosing protocol (Manning & van den Buuse, *Front Cell Neurosci* 2013). Following a two-week break, mice were tested in adulthood in behavioural paradigms relevant to schizophrenia. Specifically, we used amphetamine-induced locomotor hyperactivity as a model of psychosis and prepulse inhibition (PPI) and its disruption by an amphetamine challenge (5mg/kg) as a model of sensorimotor gating deficits in schizophrenia. Social interaction was assessed in a 3-chamber paradigm and short-term spatial memory was assessed in a Y-maze task. There were 8-14 animals per genotype/pretreatment group and data were analyzed using repeated-measures ANOVA.

Results: The effects of young-adult METH treatment were altered in BDNF HETs in a task-dependent and sex-specific manner. As expected, in response to a challenge dose of amphetamine (3mg/kg) in adulthood, METH-treated WT mice showed locomotor sensitization compared to control WT mice. However, this increased hyperactive response following METH pre-treatment was absent in BDNF HETs. This genotype effect was observed in both male and female mice. BDNF deficiency and METH treatment had sex-specific and independent effects on the disruption of PPI by amphetamine. At baseline, BDNF HETs showed reduced PPI compared to WT mice irrespective of METH pre-treatment. In addition, male, but not female BDNF HETs were more sensitive than WT to the effects of amphetamine on PPI, again irrespective of prior METH treatment. In contrast, in female mice, but not male mice, treatment with METH reduced sensitivity to the effects of an acute amphetamine challenge, irrespective of the genotype. There were no differences between the groups in terms of general sociability, measured by interaction time with a "stranger" mouse compared to that with an empty cup. However, in the subsequent social novelty preference phase of the test, male BDNF HETs treated with METH showed no preference to interact with a "novel stranger" mouse over a "familiar stranger" mouse. All other METH treated mice showed normal social novelty preference. Neither genotype nor METH treatment affected short term spatial memory.

Discussion: These studies demonstrate that young-adult METH treatment can induce behavioural changes that are relevant to the symptoms observed in schizophrenia, and that BDNF HETs show an altered response to this treatment in some behavioural paradigms. Several sex differences were also observed in these studies, which may help to provide insight into the sex differences observed in schizophrenia. Ongoing molecular studies will aim to utilize this "two hit" model to address the question of how disruption of BDNF signalling alters the brain's vulnerability to develop schizophrenia.

Poster #M14**USE OF FOLATE TO PREVENT SCHIZOPHRENIA IN ANIMAL MODEL OF KETAMINE INDUCE SCHIZOPHRENIA IN RATS**

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Background: Schizophrenia is a chronic psychiatric disorder affecting about 1% of the population worldwide, whose symptoms cause severe impairment of cognitive and social skills. Treatment with antipsychotics are unable to revert all of these symptoms, and side effects like obesity, glucose intolerance and agranulocytosis in the case of clozapine generates the need to search for novel therapeutic and prophylactic approaches. In this context, vitamins like folic acid are interesting alternatives as an adjuvant to antipsychotic treatment, and the present work investigates the role of folic acid in preventing behavioral and biochemical effects of acute ketamine administration effects, an animal model of schizophrenia.

Methods: Male young adult Wistar rats were subjected to either water or folic acid (5, 10 or 50 mg/kg) p.o. once a day for seven days. In the 8th day, these animals received a single dose of ketamine 25 mg/kg or saline i.p. After the injection, behavioral tasks were performed (covered distance in the open field, latency for first social contact, number of interactions, total time of interactions). The animals were then killed by decapitation and brain structures (prefrontal cortex, hippocampus and striatum) were dissected and homogenized for biochemical analyses (lipid peroxidation levels, protein carbonylation levels).

Results: Our results show that folic acid in the three doses prevented protein carbonylation and lipid peroxidation induced by ketamine in the hippocampus and striatum. In the prefrontal cortex, lipid peroxidation was increased by ketamine and/or folic acid in all doses, and increased carbonylation was partially prevented by folic acid. Folic acid in the three doses prevented the increasing of latency for social contact induced by ketamine, as well as folic acid 50 mg/kg prevented the decreasing of total time of social contact induced by ketamine. However, folic acid was unable to prevent the increasing of locomotion induced by ketamine.

Discussion: Our results show that folic acid prevented ketamine effects regarding oxidative stress in the hippocampus, prefrontal cortex and striatum. Moreover, folic acid prevented increased latency for social contact induced by ketamine, which has relevance for future studies in negative symptoms of schizophrenia. Further studies are necessary in humans and animal models in order to clarify questions like doses, duration and side effects of treatment with of high doses of folic acid in treatment and prevention of schizophrenia.

Poster #M15**PRE-SYNAPTIC LOCALIZATION OF PDE2 ENZYME AND PHARMACOLOGICAL CHARACTERIZATION OF THE PDE2 INHIBITOR PF-999 IN MODELS RELATED TO COGNITIVE SYMPTOMS OF SCHIZOPHRENIA**

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Background: Evidence from numerous clinical and preclinical studies has led to the hypothesis that impaired synaptic plasticity and function related to NMDA receptor hypofunction plays an important role in cognitive impairment of schizophrenia. Second messenger pathways depending on cAMP and/or cGMP are key regulators of synaptic functions and plasticity. Thus, specific cyclic nucleotide phosphodiesterases (PDEs), expressed in cognition relevant brain regions, such as PDE2 are considered interesting targets for cognition enhancement. In fact, it has been shown previously that the PDE2 inhibitor Bay 60-7550 increases synaptic plasticity, as determined by hippocampal long-term potentiation (LTP), and improves memory performance in animal cognition tasks [1]. However, the exact sub-cellular localization of PDE2 enzyme in neurons is not fully established. Thus, in the present study, co-localization studies of PDE2 with pre- and post-synaptic markers were performed by double immunofluorescence staining. Moreover, the PDE2 inhibitor PF-999 [2] was characterized pharmacologically in animals regarding hippocampal LTP enhancement in-vitro, cGMP increase in the brain and memory improvement.

Methods: Brains of adult rats were fixed with formalin and sliced for double immunofluorescence staining of PDE2 with pre-/post-synaptic markers. Analysis of staining was performed by confocal microscopy. Effects of the PDE2 inhibitor PF-999 on synaptic plasticity were evaluated in rat hippocampal slices by using the LTP model. Adult male mice were administered with PF-999, and the increase of cGMP was determined in cognition relevant brain regions (i.e. hippocampus and prefrontal cortex) via ELISA technique. Memory performance in naïve rats was tested after administration of PF-999 in the social recognition test using the natural forgetting paradigm.

Results: Double immunofluorescence analysis revealed co-localization of PDE2 predominantly with pre-synaptic, but not post-synaptic markers and mainly in glutamatergic neurons. PF-999 led to a concentration-dependent enhancement of hippocampal LTP in-vitro and to a dose-dependent increase of cGMP in the hippocampus and prefrontal cortex of mice. Regarding cognition, PF-999 improved memory performance in the rat social recognition test.

Discussion: As demonstrated in this study, PDE2 is predominantly localized pre-synaptically in glutamatergic neurons, which might indicate an involvement of PDE2 in neurotransmitter release via regulating cGMP levels at pre-synaptic terminals. Regarding pharmacology of PF-999, these results corroborate previous findings on preclinical efficacy of PDE2 inhibition regarding enhancement of synaptic plasticity and memory improvement. Thus, our data further supports the use of PDE2 inhibitors as potential approach for the treatment of disorders with cognitive dysfunction such as schizophrenia.

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Poster #M16**EFFECTS OF A NITRIC OXIDE SYNTHASE INHIBITOR ON AN ANIMAL MODEL FOR THE STUDY OF SCHIZOPHRENIA BASED ON THE NEURODEVELOPMENTAL HYPOTHESIS**

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Background: Some animal models used for the study of schizophrenia are based on the theory of neurodevelopmental disruption. The methylazoxymethanol acetate (MAM) model involves neurogenesis interruption, consisting on giving the mitotoxin MAM at the gestational day 17, leading to morphophysiological, neurochemical and behavior changes on the offspring when they reach adulthood. Considering that the atypical neurotransmitter nitric oxide (NO) was found to be increased in schizophrenic patients, the main objective of this work was to investigate if a NO synthase inhibitor (NOS) was able to improve the behavior deficits observed in MAM offspring, specifically on the behavior tests of prepulse inhibition (PPI), social interaction and Y-maze.

Methods: Nine pregnant Wistar rats were treated with i.p. injection of either saline or 22mg/kg of methylazoxymethanol on the 17th day of pregnancy. Male rats of the offspring (N=26) were evaluated when they reached 90 days. Controls and MAM rats were subdivided into treatment groups which received an i.p. injection of either saline or the NOS inhibitor LNOARG 40mg/kg 1 h before testing. Each rat was first tested on PPI and then on social interaction PPI test consisted on 5 minutes of acclimatization, followed by 10 presentations of P (120dB) for habituation and then the PPI test itself consisting on pseudorandom presentations of 64 stimuli: P, PP (69, 73 and 81dB), PP+P and null (no stimuli), with 30 s interval between presentations. %PPI was determined by expressing the PP+P startle response (ASR) as a percentage decrease from P ASR. The social interaction test consisted on the exposure two unfamiliar rats (same treatment) for 5 min at the open field. Registered behaviors were: sniffing, grooming, following and genital inspection.

Results: MAM rats treated with saline presented significant lower %PPI and higher ASR to all stimuli compared to controls and significantly reduced social interaction behaviors (sniffing, following, genital inspection) compared to control animals. MAM rats treated with LNO had no significant difference compared to controls under the same treatment.

Discussion: The present results are consistent to our previous data showing the reversal by NOS inhibitors of dopamine agonists-induced PPI deficits and strongly suggest that NOS inhibitors may have important antipsychotic effects.

Poster #M17

THE MECHANISM OF ACTION OF ANTIPSYCHOTICS AND INTRACORTICAL MYELINATION IN SCHIZOPHRENIA

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Background: Post-mortem and imaging studies suggest that early in the treatment of schizophrenia (SZ), antipsychotics increase myelination and specifically intracortical myelin (ICM). We used MRI to examine whether in SZ, the ICM trajectory is dysregulated, altered by oral antipsychotics, associated with cognitive performance, and whether antipsychotic formulation can modify the ICM trajectory.

Methods: Frontal lobe ICM volume was estimated using a novel dual contrast MRI method. *Study 1:* Seventy-one male SZ subjects taking oral antipsychotics whose medication exposures ranged from 0–333 months were examined in conjunction with 57 healthy male controls (HCs). *Study 2:* Six-month randomized trial of risperidone long acting injectable (RLAI, N=9) versus oral risperidone (RisO, N=13) in first-episode SZ subjects.

Results: *Study 1:* When plotted against medication exposure, the ICM trajectory of SZ subjects was highly quadratic, significantly increasing during the first treatment year and significantly decreased thereafter. Cognitive scores were associated with ICM volume. *Study 2:* Compared to healthy controls, ICM volume increased significantly ($p=0.005$) in the RLAI and non-significantly ($p=0.39$) in the RisO groups. SZ subjects receiving RLAI had better medication adherence and more ICM increases (chi-square $p<0.05$).

Discussion: Oral antipsychotic treatment increased ICM during the first year of treatment followed by declining ICM despite continued treatment. This ICM trajectory resembles antipsychotic response trajectory with high rates of remission (80%) in the first year followed by progressively lower remission rates (<50%). Better adherence and/or pharmacokinetics provided by RLAI may modify this ICM trajectory, possibly through delivering continuous inhibition of the constitutively active enzyme glycogen synthase kinase 3 (GSK3). Dopamine and serotonin receptor blockade provided by antipsychotics inhibit GSK3 and promote myelination. The results support post-mortem evidence that SZ pathophysiology involves ICM deficits and suggest that correction of these deficits through GSK3 inhibition may be a shared mechanism of action of antipsychotics.

Disclosures: Funding for this study was provided in part by NIH grants (MH 0266029; AG027342; MH51928; MH6357; MH037705; P50 MH066286), and by two investigator-initiated grants from Ortho-McNeil Janssen Scientific Affairs, LLC. The NIH and Janssen Pharmaceutical Inc. had no further role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit these data for presentation.

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Poster #M18

OLFACtORY IDENTIFICATION DEFICITS AS A MARKER OF IMPAIRED BRAIN DEVELOPMENT? A CROSS-SECTiONAL STUDY iN PATiENTS WITH SCHIZOPHRENiA AND HEALTHy CONTROLS

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Background: Olfactory identification is a putative vulnerability marker of

schizophrenia and may also be a marker of impaired brain development (Kamath et al., 2011; Turetsky et al., 2009). The current study investigated how current olfactory identification deficit (OID) is linked to performance on developmental measures of premorbid adjustment in childhood and adolescence.

Methods: Group difference on OID and premorbid adjustment between 177 Patients with non-affective psychosis (mean age: 30.20; SD: 6.95; gender ratio male/female: 138/39) and 141 healthy controls (mean age: 31.95; SD: 9.28; gender ratio male/female: 76/65) were assessed with the Sniffin' Sticks olfactory identification test (Hummel, 2001) and the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982) using ANCOVA's, with gender as a covariate. Using random-effect regression analyses we evaluated whether premorbid adjustment was associated with olfactory identification, and whether this association was different for patients and controls.

Results: Patients did score worse on all premorbid adjustment scales than healthy controls ($F=5.86$ (4,305), $p<0.001$). Patients had worse scores on olfactory identification than healthy controls at trend level ($F=3.45$ (1,317), $p=0.064$). In patients, OID was negatively correlated with school performance ($r=-0.214$; $p=0.002$) and school adaptation <12 years ($r=-0.226$; $p=0.001$), and with social adjustment between 12 and 16 years ($r=-0.170$; $p=0.013$). In healthy controls OID was negatively correlated with school performance <12 years ($r=-0.231$; $p=0.003$), and with social adjustment between 12 and 16 years ($r=-0.204$; $p=0.008$).

Discussion: Premorbid adjustment deviates from normal developmental trajectory in children and adolescents who later on in life develop schizophrenia. Interestingly, deviation in social and cognitive development appears to be related to a reduced ability of olfactory identification. However, as this was independent of group status, olfaction appears to be a biomarker for early brain development and not necessarily for schizophrenia.

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Poster #M19

SHARED BRAiN DYSFUNCTION iN SUBTYPES OF SCHIZOPHRENiA AND BIPOLAR DISORDER DEFINED BY POOR WORKiNG MEMORY

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Background: Dysfunctional working memory (WM) is implicated as a shared intermediate phenotype for schizophrenia (SZ) and bipolar-I disorder (BD), to which common susceptibility genes may contribute. We examined WM-related brain activity in SZ and BD patients grouped according to task performance rather than diagnosis, in order to elucidate shared neurocognitive markers of this common endophenotype.

Methods: Participants were 41 SZ, 34 BD, and 34 healthy controls (HC) who underwent functional magnetic resonance imaging while performing a standard (0/2-back) n-back task. Clinical cases performing with less than 50% accuracy were regarded as the Executive Deficit (ED; $n=32$; comprising 23 SZ & 9 BD cases), while those performing above 50% accuracy were termed "Executive Spared" (ES; $n=43$; comprising 18 SZ and 25 BD cases). All HC's performed above 50% accuracy. Functional imaging data were analysed using SPM8, using one-sample t-tests to determine within-group 2-back response relative to an implicit 0-back baseline ($p<0.05$, FWE-corrected), followed by a series of 2-sample t-tests to examine group differences ($p<0.0001$ uncorrected at the voxel-level, and FWE-cluster corrected).

Results: Focal analyses of neural activation according to performance-based groups showed lack of task-related suppression in the posterior cingulate

cortex (PCC)/precuneus, ventral anterior cingulate cortex/medial prefrontal cortex (mPFC) and the right posterior insula/Rolandic operculum in the ED group, compared to the HCs. In addition, the HC group showed activation in regions such as the cerebellum and the right pre/postcentral gyrus that were deactivated by the ED group, as well as increased activation in the right precentral/superior frontal gyrus (BA6) relative to the ED group. There were no differences revealed for ES versus HC comparisons. However, when the ED and ES groups were directly compared, the ES showed activation in regions (including the cerebellum and in the left pre/postcentral gyrus) that were deactivated in ED, as well as greater activation in the right precentral/mid frontal gyrus than the ED group ($p(FWEc) < 0.0005$).

Discussion: Aberrant deactivation of the right posterior insular, PCC and mPFC may be shared brain markers of the working memory deficit proposed as an endophenotype for psychotic disorders. These brain regions may provide common targets for further genetic investigation in subtypes of SZ and BD with severe cognitive deficits.

Poster #M20

INCREASED GLYCOGEN SYNTHASE KINASE-3B (GSK-3B) EXPRESSION IN PLATELETS OF FIRST ONSET PSYCHOSIS NON-AFFECTIVE PATIENTS

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Background: Despite popular assumptions, to date the molecular pathogenesis of psychosis is not fully understood. One consistent finding is the evidence that dopamine signalling, in particular through the D2 receptor, is central mechanism. Recent findings have linked the intracellular pathways that function downstream of the dopamine D2 receptor to glycogen synthase kinase 3B (GSK-3B). This kinase is involved with important neuronal processes such as cell survival, gene regulation, mood and cognitive performance. This enzyme activity is inactivated by phosphorylation at the Ser9 site. There are evidences that GSK3B is altered in schizophrenia, but there is nothing concerning drug naïve first onset psychosis patients. Thus, the aim of this study was to determine the GSK3B and pGSK3B levels in first onset psychosis non-affective patients and healthy controls.

Methods: Twenty-five first onset psychosis non-affective patients (DSM-IV, American Psychiatric Association) were enrolled to this study. The control group comprised 24 age-matched, healthy individuals. GSK3B and pGSK3B levels in platelets were determined by an enzyme immunoassay kit. We used a parametric T-test to access significant differences between first episode patients and healthy controls. To access the influence of duration of untreated psychosis (DUP) and GSK3B levels, we used the correlation. All statistical analyses were done with the software Statistical Package for Social Science (SPSS, Chicago, USA), version 14.0 and significance level was set at $p < 0.05$.

Results: First episode drug naïve patients with non-affective psychosis presented higher GSK3B expression ($p = 0.008$) but no difference regards pGSK3B as compared to control group. Regards to the psychosis, the patients classified as schizophreniform presented a marginally decreased pGSK3B as compared to others psychosis (mostly delusions) ($p = 0.085$). DUP seems to have a positive correlation ($\rho = 0.375$, $p = 0.065$) with the GSK3B levels, but not to the enzyme phosphorylation levels irrespective of psychosis.

Discussion: The findings on GSK3B levels in schizophrenia are inconclusive. The reduction of GSK3B levels has been reported in the frontal cortex, hippocampus, and cerebrospinal fluid of patients with schizophrenia, but any difference was described in lymphocytes. To our knowledge, there is no report in platelets of first onset psychosis patients, but the increased GSK3B levels in drug-naïve patients, without increase in phosphorylation levels, seems to be an attempt to restore cellular homeostasis.

Poster #M21

PREDICTIVE VALIDITY OF COMBINED MINOR PHYSICAL ANOMALIES AND NEUROLOGICAL SOFT SIGNS IN PATIENTS WITH SCHIZOPHRENIA AND THEIR NONPSYCHOTIC FIRST-DEGREE RELATIVES

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Background: The neurodevelopmental hypothesis proposes that schizophrenia is originated from aberrant brain development. Minor physical anomalies (MPA) and neurological soft signs (NSS) are suggested as a biomarker associated with disruptions of fetal development. Numerous studies report an increased frequency of neurodevelopmental impairments in schizophrenic individuals compared with controls. However, since most previous studies were limited in the method of measuring the MPA of neurodevelopmental markers by using qualitative measurements, we used an extended scale of MPA in patients with schizophrenia and their nonpsychotic relatives. The aim of this study was to identify which specific MPA and NSS are more associated with schizophrenia and to determine the optimal predictive value of combined MPA and NSS scores.

Methods: We have developed a new physical measurement scale that includes the mainly qualitative Waldrop scale (Waldrop et al. 1968), which was used in the vast majority of studies and mainly qualitative in nature, and some quantitative measures of the head and face area from two most cited books on anthropometric measurements (Farkas 1981, Hall et al. 1989). For the access of neurological soft signs, we used Neurological Evaluation Scale (NES) established by Buchanan et al. (1989). Group comparisons in MPA and NSS were conducted by using mixed-effect model. These MPA and NSS variables were selected by stepwise logistic regression model, adjusted for sex, age and BMI, to determine whether a specific pattern could be found with greater predictive validities and ROC curve to evaluate predictive accuracy, sensitivity, and specificity of these neurodevelopmental markers.

Results: There were 210 patients with schizophrenia, 109 nonpsychotic first-degree relatives, and 151 normal controls have been recruited in this study. For the MPA, the patients with schizophrenia had more MPA in the areas of eyes, ear, mouth, hands and feet comparing with normal controls, and also had more MPA in the areas of eyes and mouth comparing with their relatives. The relatives had more MPA in the areas of mouth comparing with normal controls. For the NSS, the patients with schizophrenia had more NSS in the tests of motor coordination, sensory integration, sequencing of complex motor acts and others comparing with normal controls. In these tests, the patients tended to have the greatest proportions of having NSS, followed by their relatives, and then the normal controls. For the predictive validity of combined MPA and NSS, the model of patients with schizophrenia vs. controls provided an accuracy of 83.8% (a sensitivity of 84.6% and a specificity of 82.7%); The model of patients with schizophrenia vs. relatives provided an accuracy rate of 83.4% (a sensitivity of 87.5% and a specificity of 75.9%); and the model of the relatives vs. controls provided an accuracy rate of 82.4% (a sensitivity of 75.5% and a specificity of 87.8%).

Discussion: We found that the MPA and NSS are more frequent in patients with schizophrenia and their relatives compared to controls, which are consistent with the hypothesis of abnormal neurodevelopment in schizophrenia. Subjects were most accurately classified when MPA & NSS were considered as a composite endophenotype rather than independently. The composite endophenotype afford greater predictive validity may be used as potential biomarker for schizophrenia, and will be used in further family-based association study.

Poster #M22**CLASSIFICATION OF PEOPLE WITH TREATMENT-RESISTANT AND ULTRA-TREATMENT-RESISTANT SCHIZOPHRENIA USING PERSONALISED COMPUTER MODELLING AND EEG DATA**

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Background: Clozapine (CLZ) is uniquely effective for treatment-resistant schizophrenia (TRS). However, many patients still suffer from residual symptoms or fail to respond at all (ultra-treatment-resistant schizophrenia; UTRS). Electroencephalography (EEG) abnormalities in people with schizophrenia have been reported to both precede and result from treatment with antipsychotic medicines. This study utilised EEG recordings from people with TRS who responded well to CLZ (TRS) or were receiving a combination of two antipsychotics after failing treatment with CLZ monotherapy (UTRS), to build a personalised model of treatment response. **Methods:** This study was conducted as part of a larger cross-sectional study investigating biomarkers of TRS; only participants with TRS (n=20) or UTRS (n=16) were included in this analysis. We collected amplitude and latency measures for event-related potentials (ERPs) during Go/No-Go, auditory oddball and sustained attention tasks in addition to alpha, theta and delta power measures during resting state, using a 40-channel EEG system (Neuroscan). Missing values were replaced with the average of all values for that ERP at that electrode. A personalised model (PM) was then built for every participant using weighted k-nearest neighbours and a leave-one-out cross-validation algorithm. Briefly, a computer-based PM for each person in the study was built using the most important features specific to that person that classified them in their respective class (TRS or UTRS). The features represented an individual's amplitude or latency for each ERP at each electrode during each task.

Results: The PM correctly classified 95% of participants with TRS and 100% of participants with UTRS. Only one participant with TRS was misclassified as UTRS. The features selected as important in >10 participants' PMs included the N200 amplitude during the auditory oddball task, measuring selective attention, the N100 amplitude during the Go/No-Go task and beta power during the rest state with eyes open.

Discussion: These results indicate that ERPs obtained during EEG can be used to accurately classify patients according to their response to antipsychotics during treatment. Future research will be undertaken to determine the accuracy of our PM using ERPs obtained prior to initiating treatment with CLZ in a CLZ-naïve treatment-resistant cohort.

Poster #M23**ANTIPSYCHOTIC TREATMENT DECREASED iPLA2 ACTIVITY IN FIRST EPISODE DRUG NAÏVE PATIENTS WITH SCHIZOPHRENIA**

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Background: One consistent biochemical finding in schizophrenia is an increased activity of the enzymes phospholipases A2 (PLA2). Whereas treatment with anti-psychotic drugs was found to reduce the enzyme activity to levels similar to those observed in control subjects. However the mechanisms underlying this reduction are not yet understood. This family of enzymes is responsible for the metabolism of membrane phospholipids and is composed by three main groups: calcium-dependent cytosolic PLA2 (cPLA2), calcium-dependent secretory PLA2 (sPLA2) and calcium-independent intra-cellular PLA2 (iPLA2). There are so far no investigations of PLA2 groups' activity in first episode drug naïve patients.

Methods: Twelve first episode drug naïve patients with schizophrenia (DSM-IV, American Psychiatric Association) were recruited to this study.

The control group comprised 17 age-matched, healthy individuals. Patients and controls were assessed at baseline. Patients were also assessed after remission with antipsychotic treatment. PLA2 activity was determined in platelets by a radio-enzymatic assay addressing PLA2 groups, ie., cPLA2, sPLA2 and iPLA2. We used a parametric T-test to access significant differences between first episode patients and healthy controls. To test variations of PLA2 activities we used Paired Samples Correlations tests. All statistical analyses were done with the software Statistical Package for Social Science (SPSS, Chicago, USA), version 14.0 and significance level was set at p<0.05.

Results: Our results showed an increased totalPLA2 activity in patients with schizophrenia as compared to controls (p= 0.01) but no difference regards isolated groups (iPLA2, cPLA2 and sPLA2). After remission we found an increased cPLA2 (p= 0.006), sPLA2 (p=0.006) and totalPLA2 (p=0.001) activity as compared to controls. The effect of anti-psychotic treatment in patients with schizophrenia showed a significant reduction in iPLA2 activity (p=0.005). No differences were observed in cPLA2, sPLA2 and total PLA2 activity.

Discussion: Our results confirm the increased totalPLA2 activity in patients with schizophrenia so far reported. The reduction of PLA2 activity with anti-psychotic treatment is regard to iPLA2 group that are the most abundant in neurons and confirm the involvement of this group of enzyme in psychoses. The increased cPLA2 and sPLA2 group activity after anti-psychotic treatment could be explained by their capacity in activate PKC and inflammation process.

Poster #M24**ALTERATIONS IN THE AMPLITUDE OF LOW FREQUENCY FLUCTUATIONS IN REFRACTORY SCHIZOPHRENIA PATIENTS WITH AUDITORY VERBAL HALLUCINATIONS**

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Background: Auditory Verbal Hallucinations are one of the most common symptoms of schizophrenia, which in at least 25% of patients are resistant to pharmacological treatment (Shergill, 1998). Alterations in the BOLD signal of Low Frequency Fluctuations (LFF) measured with Resting State functional magnetic resonance imaging (R-fMRI) have been frequently reported in patients with schizophrenia (Skudlarsky, 2010). Recently, there has been an increasing interest in examining the amplitude of these LFF (ALFF), with studies reporting differences in both ALFF and fractional ALFF values (fALFF) between patients with schizophrenia and healthy controls (Hoptman, 2010; Huang, 2010). With the aim of shedding light on the neural mechanism underlying auditory hallucinations, we examined the amplitude of LFF in schizophrenia patients with persistent auditory verbal hallucinations. We hypothesized the existence of a neurofunctional correlate specific to refractory schizophrenia.

Methods: We collected Resting State Functional Magnetic Resonance Imaging (R-fMRI) and T13D data with a 3T scanner in a group of 19 schizophrenia patients with persistent auditory verbal hallucinations and resistant to pharmacological treatment (AVH), 14 schizophrenia patients without auditory verbal hallucinations (NAVH) and 20 healthy controls (HC) matched in age, gender and educational level. R-fMRI data was preprocessed using FSL and AFNI according to other similar studies (Zuo, 2010). The ALFF and fALFF values were calculated for the most typical frequency range 0.01 – 0.8 Hz. Group-level analyses were conducted using the FSL ordinary least squares (OLS) model implemented in FLAME, which produces thresholded

z-statistic maps of ALFF and fALFF based on Gaussian Random Field theory using clusters defined by $Z > 2.3$ and a corrected cluster threshold of $p = 0.05$. We conducted an ANOVA with the ALFF and fALFF of the three groups (AVH, NAVH, HC) and subsequent post-hoc analysis of AVH vs NAVH vs HC. **Results:** The analyses revealed that both groups of patients showed differences in the ALFF and fALFF values, compared to HC. Also, AVH and NAVH patients exhibited differences between each other in both measures. As we expected, we found ALFF and fALFF alterations specific to AVH patients. In particular in AVH patients, fALFF was increased in bilateral putamen and bilateral insular cortex and fALFF was decreased in bilateral medial frontal cortex, compared to NAVH and HC. ALFF was increased in AVH patients in bilateral thalamus and bilateral parahippocampal gyrus, compared to NAVH patients and HC.

Discussion: Although few R-fMRI studies have examined the correlations of the BOLD signal LFF in patients with auditory verbal hallucinations from the perspective of functional connectivity, none of them have analyzed the intensity of such regional spontaneous brain activity. We identified the thalamus, parahippocampal gyrus, putamen, insular cortex and medial frontal cortex as main altered regions specific to hallucinating patients. As these middle frontal regions are relevant to internally directed thoughts, the dysregulation of these areas might lead to an inappropriate emphasis on internally generated stimuli, as well as confusion as to their source (Whitfield-Gabrieli, 2009). In this sense, Hoptman postulated that the dysregulation of frontal and medial regions might be associated with hallucinations (Hoptman, 2010). Not only are our results in accordance with previous reports suggesting LFF abnormalities in schizophrenia, but they also appear to suggest the existence of a specific aberrant pattern in persistent hallucinating patients. This work has been partly supported by grant 091230/091231 (Marató TV3), and grants FIS 08/0475 and ETES 09/91030.

Poster #M25

SPONTANEOUS BRAIN ACTIVITY AS A BIOMARKER FOR SCHIZOPHRENIA

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Background: One of the most direct ways to get insight into the functional organisation of the human brain is to measure the BOLD-signal with fMRI during rest. This signal is not a random signal but is highly organized in several functional networks. Many of these networks mirrors the functional networks active when interacting with the surroundings and some mirrors the brain networks active during introspection. The Resting State Networks (RSN's) are believed to be a fundamental function of the brain even though their origins are poorly understood at this point. Several studies have investigated RSN's in chronic, long-term medicated schizophrenic patients but very few studies have been done on Antipsychotic Naïve First Episode patients (ANFE). In this study we wanted to investigate the potential of using the RSN's as a biomarker for schizophrenia and for effect of treatment in a cohort of ANFE patients.

Methods: To study this potential we designed a case control study with six weeks follow up after intervention with amisulpride. All patients underwent a diagnostic interview (SCAN) in order to determine the diagnosis. All subjects were scanned and re-scanned with 10 min resting state fMRI in a 3T scanner. At this point the analysis contains 46 patients and 52 controls at baseline and 32 patients and 37 controls at follow up. In addition to resting state fMRI all subjects were examined with a list of structural MR-modalities, psychophysiology, cognition and gene-samples. The methods used to measure the functional connectivity are Amplitude of Low Frequency Fluctuations (ALFF), Independent Component Analysis (ICA) and Functional Network Connectivity (FNC).

Results: As expected, using ICA we were able to detect several significant functional networks at whole group level e.g. auditory network, visual network, sensory motor network and the so-called default mode network. At baseline we discovered a significant difference where patients have a higher

connectivity than controls between the auditory network component and the left parahippocampal gyrus (corr., $p = 0.011$). The functional connectivity between the different networks (FNC) did not show any significant group differences at this point when corrected for multiple comparisons. The analysis is on-going and will be presented in detail at the conference.

Discussion: The fact that we are able to detect a significant difference between our groups at this very early stage of the disease, without any influence of medication, is promising for the potential of using the RSN's as a biomarker for schizophrenia. On the other hand, it is surprising to see, that the differences in functional connectivity between the groups at this point seems to be subtle, when the patients in fact have severe functional difficulties and are seriously ill. Further analysis is needed to give a full picture of the alterations in the functional connectivity of the brain at the debut of the disease, and to determine the effects of medication on the connectivity in this vulnerable group of patients.

Poster #M26

ASSOCIATION OF SCHIZOPHRENIA WITH INDEPENDENT COMPONENTS OF BRAIN CONNECTIVITY DURING ATTENTIONAL CONTROL

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Background: Cognitive processing implicates increased activity in specific brain networks and attenuation of responses in other brain regions included in the Default Mode Network (DMN). Previous studies have demonstrated that schizophrenia is associated with abnormal activity and connectivity in the attentional control brain network, particularly in the Dorsolateral Prefrontal Cortex (DLPFC). Other results have also indicated abnormal DMN activity and connectivity in patients with this brain disorder. In the present study we have investigated association of schizophrenia with brain functional connections of DLPFC and DMN during attentional control.

Methods: 62 NC and 31 SCZ underwent an event-related 3T fMRI scan while performing the Variable Attentional Control task (VAC), which allows to investigate brain activity associated with increasing demands of attentional control. Groups were matched for age, gender, socio-economic status, handedness, IQ. One group spatial independent component analysis (ICA) was performed on fMRI data with the Group ICA of fMRI toolbox (GIFT 2.0c) implemented in SPM8. ICA decomposition resulted in 33 independent components (ICs). Reliability of every IC was tested using spatial correlations within templates encompassing grey matter, white matter, cerebrospinal fluid, DMN and attentional control network. Thus, temporal regressions using the three levels of attentional control load (low, intermediate, high) were performed to identify task related components. Such identification allowed temporal analysis on components of interest using a general linear model with the beta values of temporal correlations of each individual time course (TC) as the dependent variable, diagnosis as the between group factor and increasing attentional demand as within groups factor. Furthermore, a two sample T-test was used to investigate association of diagnosis with strength of connectivity within components. All the results were $p < 0.05$ FWE small volume corrected for functional areas within regions of interest, i.e. DLPFC (BA9) and CC (BA31). Furthermore, Pearson's correlations were performed between the strength of connectivity of significant clusters within the Components of Interest (COIs) and behavior during the VAC.

Results: ICA analysis identified two COIs: COI 1 with greater correlation with the DLPFC template ($R^2=0.02$); and COI 2 having greater correlation with the DMN template ($R^2=0.09$). Analysis on TC of COI 1 revealed a main effect of load ($p=0.006$) (HIGH > INT > LOW) and of diagnosis ($p=0.02$) (NC > SCZ). A similar effect of diagnosis was present on TC of COI 2 ($p=0.03$). Two sample T-test on COI 1 identified a cluster in right BA9 in which NC had greater strength of connectivity compared with SCZ. The same analysis

on COI 2 identified a cluster in BA31 in which NC had increased strength of connectivity than SCZ. Pearson's correlation analysis revealed in NC but not in SCZ a negative correlation between BA9 strength of connectivity within COI 1 and reaction time (RT) at the high load ($r=-0.2607$, $p=0.041$). Furthermore, there was in SCZ but not in NC a positive correlation between BA31 strength of connectivity within COI 2 and reaction time (RT) at the high load ($r=0.393$, $p=0.029$).

Discussion: Our data suggest that patients with schizophrenia have anomalies of patterns of connectivity during attentional control processing, which are particularly elicited in nodes of the attentional control network and of the DMN. Such anomalies may differentially modulate the relationship between brain connectivity and behavior in healthy subjects and patients with schizophrenia.

Poster #M27

SERIOUS OBSTETRIC COMPLICATIONS CONTRIBUTE TO RISK FOR HIPPOCAMPAL DYSFUNCTION DURING RECOGNITION MEMORY

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Background: Abnormalities of hippocampal-parahippocampal (H-PH) function are prominent features of schizophrenia and have been associated with deficits in episodic memory. Early stressful life events such as Serious Obstetric Complications (OCs) may affect H-PH plasticity and may contribute to H-PH dysfunction. Indeed, recent studies in animals indicate that prenatal stress inhibits neurogenesis and impairs hippocampal-dependent learning and memory. In addition, structural magnetic resonance imaging studies (MRI) in humans have reported abnormalities in H-PH volume in subjects with severe OCs. Aim of the present study with functional MRI was to evaluate for the first time in humans, in the context of encoding of recognition memory, the potential effect of OCs on H-PH physiology.

Methods: We recruited 99 healthy subjects (M/F = 39/60; age, years $\pm SD = 26 \pm 5.4$). OCs data were rated using the McNeil-Sjostrom scale (severity score 4, on a scale of 1 to 6). Based on OCs data we distinguished two groups: subjects with absent OCs (N=39) and subjects with severe OCs (N=60). All participants underwent fMRI at 3T (gradient-echo EPI, TE 3000 ms, TR 20 ms) during performance of a block design recognition memory task, that has previously been associated with robust activation of the H-PH. During scanning behavioral performance was recorded in terms of accuracy (% correct responses) and reaction time (ms). SPM8 (<http://www.fil.ion.ucl.ac.uk>) and random effects models were used for imaging analyses. The statistical threshold was set at $p < 0.05$ Family-Wise-Error (FWE) within the bilateral H-PH, identified with the Wake Forest University PickAtlas 1.04. BOLD response was extracted from significant clusters using MarsBar (<http://marsbar.sourceforge.net/>) to further explore relevant effects outside SPM (STATISTICA, StatSoft).

Results: There was no significant difference between the two groups in terms of age, gender, handedness, and socio-economic status index (all $p > 0.4$). ANOVA of behavioral performance data indicated no significant effect of OCs on both encoding accuracy and reaction time (all $p > 0.9$). Unlikely, there was a main effect of OCs on accuracy ($p=0.03$) and reaction time ($p=0.005$) at retrieval, in that subjects with severe OCs showed impaired behavioral performance compared to subjects without OCs. ANOVA of the imaging data demonstrated a main effect of OCs on right H-PH activity (MNI: x 30, y -22, z -16, k=147, Z=3.5, pFWECorr = 0.05) during encoding of recognition memory. More in detail, healthy subjects with serious OCs had greater BOLD signal change in right H-PH compared to individuals without OCs (post-hoc Tukey HSD, $p=1 \times 10^{-5}$), that negatively predicted behavioral

accuracy at retrieval in the same group of subjects (Spearman correlation analysis: $\rho=-0.33$; $p=0.04$).

Discussion: The present study demonstrates for the first time in vivo in humans that severe OCs are associated with abnormal H-PH activity, suggesting a mechanism through which they may contribute to increase risk for schizophrenia. In particular, subjects with severe OCs showed increased right H-PH activity during encoding of recognition memory compared to subjects with absent OCs. Moreover, the increased H-PH activity was predictive of worse behavioral accuracy at retrieval, suggesting inefficient H-PH function in subjects with severe OCs. Further studies in patients with schizophrenia and their siblings may help to disentangle how genetic variation interact with OCs in affecting the intermediate phenotype of H-PH dysfunction in schizophrenia.

Poster #M28

BRAIN ACTIVATION INDUCED BY MENTAL STRESS IN PATIENTS WITH SCHIZOPHRENIA

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Background: External factors act on genetic predisposition to produce active psychotic symptoms in most patients with schizophrenia. It is known that these patients have an abnormal peripheral autonomic response to psychological stress. Such autonomic abnormalities are shared by first-degree-relatives and have been proposed as an endophenotype of the disease. We sought to characterize the brain activity correlates of a paradigm of psychological stress known to evoke robust autonomic reactions.

Methods: We studied the pattern of brain activation in response to a mental arithmetic stress paradigm in 19 patients and 21 healthy subjects aged 18 to 50 years, using 3T-fMRI. A period of 6 minutes of resting state acquisition was followed by a block design with three 1-minute CONTROL task (one digit sum), 1 minute STRESS task (two digit subtraction) and 1 minute rest after task. Data were analyzed with SPM and SPSS software.

Results: Healthy controls showed bilateral activation of anterior cingulum, orbitofrontal cortex, middle and superior frontal gyrus, activation of right parahippocampus and pons, activation of left inferior frontal gyrus, precuneus and thalamus during mental stress compared with control task. In patients, the activation pattern was similar in stress and control tasks. Bilateral anterior cinguli and orbitofrontal cortices remained active shortly after stress in healthy individuals. Patients displayed sustained activation of temporal pole, angular gyrus, precuneus and superior frontal gyrus for the observation period.

Discussion: Present results suggest that abnormal activation of limbic structures could be considered the central correlate of the extensively documented peripheral autonomic abnormalities in patients with schizophrenia. Abnormal fronto-temporal connectivity may be the pathophysiological link for these results. Moreover, failure of frontal activation after stress could be a reason for a sustained autonomic stress pattern in this group.

Poster #M29

BRAIN HARDWARE AND SOFTWARE FOR SELF-REFLECTION ASSOCIATED WITH INSIGHT IN PATIENTS WITH SCHIZOPHRENIA

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Background: Impaired insight into illness, the awareness of being ill or recognizing the need for treatment, is common in schizophrenia and it is associated with worse treatment outcome. Lower insight has been correlated with impaired self-reflection, the process of discerning whether an

occurrence or statement refers to oneself (when contrasted with another person or baseline). Abnormalities in activation of the neural correlates of self-processing, the posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), inferior frontal gyrus, anterior insula, and inferior parietal lobule (IPL) have been associated with insight in schizophrenia patients. In addition, a distinction was suggested between the ventral (v) and dorsal (d) MPFC, hypothesizing that self-referential and other-referential processing relate more to the vMPFC and dMPFC, respectively (cognitive neuropsychiatric self-reflective model; van der Meer et al.). We investigated the effective functional and anatomical connectivities involved in self-reflection in relation to insight into illness in schizophrenia. We hypothesized that the routes from and to the vMPFC (involved in self-processing) would be more affected in patients with impaired insight.

Methods: 19 healthy subjects and 45 schizophrenia patients participated in the study. Insight was determined using the Schedule of assessment of insight-Expanded (SAI-E). Anatomical connectivity was estimated from DTI scans combined with FSL tract-based spatial statistics (TBSS), estimating fractional anisotropy (FA). During an fMRI scan subjects performed a self-reflection task (sentences were presented in 3 conditions: self, other and semantic (baseline)). Effective functional connectivity was estimated using dynamic causal modelling (DCM) between: PCC, vMPFC, dMPFC, anterior insula and IPL. Bayesian model selection and Bayesian model averaging (BMA) were used to identify group (healthy – schizophrenia) and individual differences in brain connectivity.

Results: Schizophrenia patients and healthy controls did not differ in age, gender or education nor effective connectivity (DCM). Patients had decreased FA bilaterally in the anterior thalamic radiation (ATR), IFOF, UF, superior longitudinal fasciculus (SLF, temporal part), corpus callosum, and in the visual cortex. We found no significant associations of FA with insight after correction for multiple comparisons. The best DCM model was the same in both groups; the effects of self-reflection modulated connections to and from the vMPFC, and others-reflection modulated connections to and from the dMPFC. The BMA revealed that the effects of self-reflection modulated connections significantly more from the vMPFC to PCC than from the dMPFC. Insight in illness (SAI-E) was negatively correlated with the intrinsic connections from the IPL, PCC and dMPFC towards the vMPFC, as well as from the IPL to dMPF and PCC (significant at $pFDR < 0.05$), and positively correlated with the connection from the dMPFC to vMPFC. The other-reflection modulatory effect on the dMPFC-PCC decreased with clinical insight ($pFDR < 0.02$), as did the self-reflection modulatory effect on the PCC-vMPFC ($p = 0.01$, uncorr.).

Discussion: We found alterations in functional connectivity associated with clinical insight into illness in patients with schizophrenia. In particular, the finding that higher insight corresponded to decreases in effective connectivity towards vMPFC and from IPL suggests that patients' efforts to understand their illness involve self-reflection processes which balance self-awareness and seeing oneself through the eyes of another. Our finding that the averaged model revealed modulatory increases for self-reflection from vMPFC more than from dMPFC is in line with the self-reflective model. The observed functional alterations were not accompanied with changes in white matter integrity.

Poster #M30

PRESYNAPTIC DOPAMINE MODULATES GOAL-DIRECTED BEHAVIOR AND INTERACTS WITH PREFRONTAL AND STRIATAL GLUTAMATE

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Background: Schizophrenia patients suffer from severe cognitive deficits which have been postulated to be closely linked to a deficit in using environmental reward-indicating stimuli to guide goal-directed behavior. Based on meta-analyses, it is well-known that presynaptic dopamine is elevated in schizophrenia (e.g. Howes et al., 2012, Arch Gen Psychiatry). Nevertheless, a few studies indicate that presynaptic dopamine positively correlates with cognitive 'prefrontal' functioning (e.g. Cools et al., 2008, J Neurosci) while the impact of these measures on goal-directed behavior

and its neural learning signals remain largely unknown. Current biological hypotheses of schizophrenia postulate aberrant dopamine-dependent modulation of glutameric plasticity as a potential key mechanism (e.g. Stephan et al., 2009, Schizophr Bull). In the present study, we aim to disentangle these processes by implementing multimodal functional neuroimaging (fMRI, PET, MRS) and computational models of reinforcement learning.

Methods: We use a novel two-step decision task (Daw et al., 2011, Neuron) that enables the examination of goal-directed behavior in terms of the relative influence of model-free and model-based reinforcement learning on choice behavior. This analysis was complemented by computational modeling of the observed choices. Data was collected in 29 healthy participants that performed the task during fMRI and also underwent FDOPA-PET to assess presynaptic dopamine synthesis capacity. Glutamate MRS (lateral prefrontal cortex and ventral striatum) was acquired in a partially overlapping sample. Additionally, 20 patients diagnosed with schizophrenia underwent the same task behaviorally.

Results: First, we replicate fMRI findings by Daw et al. (2011, Neuron). Second and extending previous work (Schlagenhauf et al., 2013, Human Brain Mapping), we demonstrate that PET-derived ventral-striatal dopamine synthesis capacity differently modulates striatal and prefrontal learning signals. Third, we explore that PET-derived ventral-striatal dopamine synthesis capacity correlates negatively with MRS-derived lateral-prefrontal glutamate but positively with ventral-striatal glutamate. Fourth, schizophrenia patients displayed reduced model-based aspects of reinforcement learning in the two-step decision task.

Discussion: Here, we demonstrate for the first time that presynaptic dopamine differently modulates striatal and prefrontal learning signals during a task that trade-offs the balance of model-free and model-based reinforcement learning. This supports the idea that presynaptic dopamine levels are closely involved in regulating the balance between different modes of cognitive control, namely model-free and model-based control over decision making. In line with the dopamine-glutamate hypothesis of schizophrenia, presynaptic dopamine interacted differently with striatal and prefrontal measures of glutamate as potential surrogate markers of synaptic plasticity. These observations point towards a fine-tuned balance of neuromodulators acting in a narrow window. The demonstrated disruption of model-based control over decision making in schizophrenia patients may be a result from this dysbalance.

Poster #M31

RELATIONSHIP BETWEEN CORTICAL ACTIVATION DURING WORKING MEMORY AND FUNCTIONAL OUTCOMES IN INDIVIDUALS AT HIGH RISK FOR PSYCHOSIS

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Background: Patients with first episode psychosis and schizophrenia experience impairments in working memory that are present in attenuated form in those at high risk (HR) of developing the disorder. Little is yet known, however, about how the early working memory impairments and their neurofunctional correlates present at baseline relate to future clinical functional outcomes in these HR subjects.

Methods: We used functional magnetic resonance imaging (fMRI) and a delayed matching to sample (DMTS) task in 34 HR and 20 healthy subjects (HC). Group differences in regional brain activation associated with the task were identified. 19 of the HR participants were followed-up clinically for a mean of 3.6 years ($SD=2.2$) and subdivided at that time into "functional" and "no functional" recovery subgroups on the basis of their Global Assessment of Function (GAF) at follow-up.

Results: There were no group differences in task performance between the HR and HC and the HR recovery and HR no-recovery groups. Analysis of fMRI baseline data showed that lateral frontal and temporal activation was greater, while medial frontal activation was reduced in the future HR no-recovery subjects compared to HR recovery group.

Discussion: These findings are consistent with evidence implicating frontal and temporal dysfunction in the pathophysiology of psychosis. Functional neuroimaging data obtained at first presentation may provide a means of predicting future functional outcomes in HR subjects, thereby forming the basis of a potentially clinically useful strategy to inform prognosis.

Poster #M32

IMAGING ENDOPHENOTYPIC BIOMARKERS FOR SCHIZOPHRENIC AND AFFECTIVE PSYCHOSES IN KEY NEURAL CIRCUITS

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Background: In order to identify pathophysiological abnormalities in brain circuits of patients with schizophrenic and affective disorders, to test for their possible role as endophenotypes, and to search the genome for genetic factors that may be involved in the occurrence of these endophenotypic markers, we conducted functional MRI studies in healthy subjects, patients with schizophrenia and affective disorders and in their healthy first-degree relatives.

Methods: We applied a battery of recently established experimental fMRI paradigms in order to systematically investigate different core pathophysiological processes and neurophysiological endophenotypes of schizophrenic and affective psychoses. These paradigms included different versions of circuit-specific working memory tasks (Gruber & von Cramon 2003), a combined task-switching, oddball and incongruity paradigm (Gruber et al. 2009), and the "desire-reason dilemma" paradigm (Diekhof & Gruber, 2010), which assesses functional interactions between the reward system and prefrontal control mechanisms.

Results: Endophenotypic brain dysfunctions in schizophrenia were identified in terms of a hyperresponsivity of a saliency/evaluation network (e.g. of the nucleus accumbens) to reward stimuli. In first-degree relatives of patients with bipolar affective disorder endophenotypic brain dysfunctions could be found particularly in the right middle frontal gyrus showing hyperactivation during verbal working-memory performance. Genome-wide association studies for these endophenotypic neuroimaging markers are currently underway.

Discussion: The endophenotypic approach in functional neuroimaging may help to identify genes involved in the pathogenesis of schizophrenic and affective disorders and may provide important information for the development of valid animal models for further research. This line of research may provide more direct insight into pathophysiological brain processes and may pave the way for future diagnostic systems in psychiatry.

Poster #M33

SALIENCE NETWORK IN YOUNG PEOPLE WITH FAMILIAL RISK FOR PSYCHOSIS – THE OULU BRAIN AND MIND STUDY

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Background: The salience network (SAL) is a large-scale brain network that detects external events and internal stimuli that stands out from the rest. Abnormal connectivity in the SAL has been related to psychosis and schizophrenia but it is not known whether this applies to people with familial risk for psychosis (FR).

Methods: We conducted a resting-state functional MRI (R-fMRI) in 72 (29 male) FR young adults with a history of psychosis in one or both parents and 72 (29 male) control subjects without parental psychosis. Both groups

in the Oulu Brain and mid study were drawn from the general population-based Northern Finland Birth Cohort 1986 and were 21–25 year old. Parental psychosis was established using the Finnish Hospital Discharge Register. R-fMRI data pre-processing was conducted using independent component analysis with low and high model orders to probe large-scale networks and sub-systems. A dual regression technique was used to detect between-group differences in the SAL with $p < 0.05$ threshold corrected for multiple comparisons.

Results: FR participants showed statistically significantly lower level of connectivity compared with control subjects in the right inferior frontal gyrus of the SAL corresponding to Brodmann areas 44 and 45. The volume of the lower intensity area with model order 30 was 254 mm³ and with model order seventy 704 mm³.

Discussion: FR for psychosis may be mediated by a loss of connectivity patterns in the right inferior frontal gyrus that could be one of the key regions involved in the pathophysiology of psychosis.

Poster #M34

FUNCTIONAL DISCONNECTION IN THE FIRST EPISODE OF SCHIZOPHRENIA AND IN REMISSION

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Background: Schizophrenia is a brain disconnection disorder with abnormalities of both anatomical and functional connectivity. It is, however, not clear if the functional disconnection recovers with symptomatic remission or remains present on background as a trait feature of the disease. The objective of the present study was to assess the time-course of functional disconnection during one year follow-up of patients experiencing the first episode of schizophrenia (FES) who achieve remission (RMS) one year after it.

Methods: 29 FES patients and 22 healthy controls underwent fMRI activation study during Verbal fluency task during the first episode and in remission one year after. Group independent component analysis was used to extract functional component maps. Analysis of the beta weights of the activation design and functional network analysis (correlations between individual network time-courses) were performed to detect group differences in functional connectivity.

Results: The patients showed lower activation of the left fronto-parietal (FP) network and lower deactivation of the default mode network (DMN) during VFT processing both at FES and RMS. Moreover, schizophrenia patients had smaller negative correlation between left FP and DMN networks. Finally, there were no differences between the FES and RMS in a pair-wise comparison.

Discussion: The functional disconnection is expressed both during the psychotic episode and in remission one year later. It is, therefore a stable trait marker of the disease.

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Poster #M35

DISRUPTIONS IN SMALL-WORLD CORTICAL FUNCTIONAL CONNECTIVITY NETWORK DURING AN AUDITORY ODDBALL PARADIGM TASK IN PATIENTS WITH SCHIZOPHRENIA

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Background: P300 deficits in patients with schizophrenia have previously been investigated using EEGs recorded during auditory oddball tasks. However, small-world cortical functional networks during auditory oddball tasks and their relationships with symptom severity scores in schizophrenia have not yet been investigated.

Methods: In this study, the small-world characteristics of source-level func-

tional connectivity networks of EEG responses elicited by an auditory oddball paradigm were evaluated using two representative graph-theoretical measures, clustering coefficient and path length. EEG signals from 34 patients with schizophrenia and 34 healthy controls were recorded while each subject was asked to attend to oddball tones.

Results: The results showed reduced clustering coefficients and increased path lengths in patients with schizophrenia, suggesting that the small-world functional network is disrupted in patients with schizophrenia. In addition, the negative and cognitive symptom components of positive and negative symptom scales were negatively correlated with the clustering coefficient and positively correlated with path length, demonstrating that both indices are indicators of symptom severity in patients with schizophrenia.

Discussion: Our study results suggest that disrupted small-world characteristics are potential biomarkers for patients with schizophrenia.

Poster #M36

DECREASED ACTIVATION IN SUPERIOR FRONTAL GYRUS IN PATIENTS WITH SCHIZOPHRENIA EXPOSED TO CURSE WORDS: fMRI STUDY

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Background: The contents of idea of reference or auditory hallucinations in patients with schizophrenia are usually negative and contain curse words. Many studies suggest that the brain processes swearing in the lower regions of brain such as limbic system, along with emotion and instinct. Up to now, very few studies have been conducted to explore how and where brain regions are responding to curse words. This study was undertaken to investigate how patients with schizophrenia are responding differently to curse words compared to normal controls using fMRI.

Methods: Thirty nine patients with schizophrenia and twenty normal controls, matched for age and sex, were enrolled. Inclusion criteria for patients were outpatients with clinically stable condition and no change of medication over the last 2 months. Participants were presented with curse and neutral words using block design while in the magnetic resonance imaging scanner. Activation maps in the two groups during the test were compared using SPM8.

Results: A main effect of group was observed with decreased activation in superior frontal gyrus in schizophrenic patients compared to normal controls. A main effect of condition (curse words vs. neutral words) was observed in frontal gyri (superior/middle/inferior/medial), precentral gyrus, cingulate gyrus, insula, superior temporal gyrus, fusiform gyrus, etc. A group-by-condition interaction was seen in the middle frontal gyrus and paracentral lobule.

Discussion: These results indicate that patient's brain with schizophrenia, especially superior frontal gyrus, respond differently to curse stimuli compared to controls. Evidence suggests that superior frontal gyrus is associated with self-awareness and laughter. The implications of decreased activation in superior frontal gyrus in patients need to be explored further with regard to pathogenetic mechanism for idea of reference or auditory hallucinations. In addition, our findings suggest that diverse cortical gyri are involved in emotional processing related to curse stimuli.

Poster #M37

WORKING MEMORY AND BRAIN ACTIVATION IN SCHIZOPHRENIA VS. PSYCHOTIC BIPOLAR I DISORDER ASSESSED WITH FUNCTIONAL MRI

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Background: Working memory impairment is a core neurocognitive deficit

and validated endophenotype for schizophrenia. Yet, other psychotic disorders also show working memory deficits, and it remains unclear whether this might reflect an overlap in endophenotypes across diagnostic borders or whether different brain structural and/or functional substrates might underlie those deficits.

Methods: We used functional MRI at 3 T with a Sternberg task to assess working memory related brain activation in three groups (all of whom provided written informed consent to a study protocol approved by the local ethics committee): 34 patients in remission from DSM-IV schizophrenia (Sz), with >2 year disease course, on stable antipsychotic medication, 17 patients with bipolar I disorder (BD) and previous psychotic symptoms, who were all currently euthymic (no concurrent depressive, manic, or mixed episode, and maximum scores of 7 on the YMRS or HAMD) on stable medication, as well as 34 healthy controls (with no prior medication and no personal psychiatric history). Analysis of fMRI data with SPM (at $p < 0.001$, uncorr.) included both the assessment of overall task-related brain activation, as well as separate modelling of the encoding, delay, and retrieval phases of the task. In addition, the task was presented with two variations: either with or without additional manipulation of memorised information during the delay phase, which area assumed to induce additional prefrontal cortical (PFC) activations.

Results: Effects of diagnosis were found for the overall task-related effect in the right caudate, cuneus, precuneus, and cerebellum bilaterally, for the encoding phase it included dorsolateral and ventrolateral prefrontal cortices (PFC), thalamus, hippocampus, parahippocampus, for the differential delay activity (with or without manipulation) an additional effect in the right DLPFC, and for delay in general the hippocampus and right caudate. Comparison between groups showed that for the overall task effect, schizophrenia (Sz) patients had activation deficits (relative to healthy controls) in the DLPFC and VLPFC bilaterally, as well as anterior cingulate cortices and basal ganglia, while for the bipolar I disorder (BP-I) patients, this was left parahippocampal, SMA, as well as cerebellar and occipital areas. The same comparison for the encoding phase showed similar activation deficits (relative to healthy controls) in Sz patients, while BP-I patients showed deficits mostly in cingulate cortices and cuneus/precuneus. During the delay phase, Sz showed bilateral hippocampal and PFC, but BP-I only left hippocampal activation deficits.

Discussion: Our findings add to previous studies of working memory in schizophrenia and (psychotic) bipolar disorder, in that they provide a direct comparison between Sz and a bipolar disorder subgroup that most closely resembles symptomatology and disease course of Sz patients. Prefrontal, and to some extent also hippocampal activation deficits appear to be more extensive in schizophrenia, and they tend to manifest already at the encoding stage of a working memory task.

Poster #M38

NEURAL CORRELATES OF SELF-REFERENCE PROCESSING AND ABERRANT SALIENCE ATTRIBUTION – IMPLICATIONS FOR PSYCHOSIS

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Background: Self-reference processing concerns stimuli that are experienced as related to oneself in contrast to stimuli that are related to an unknown person [Northoff et al., 2006]. Neuroimaging studies have investigated cortical activations in the anterior cingulate cortex (ACC), the medial prefrontal cortex (MPFC) and the insula relevant to self-specific processing [Murray et al., 2012]. It has been hypothesized that psychotic symptoms are related to aberrant attribution of salience to external objects and internal representations [Heinz, 2002; Kapur, 2003; Heinz & Schlagenhauf, 2010]. The current study examines the relation between neural activation during self-reference processing and aberrant salience attribution in healthy subjects.

Methods: 54 healthy individuals (19 female, 35 male) underwent fMRI scanning while performing a self-reference paradigm [Kelley et al., 2002]. Participants were required to indicate whether the adjectives described themselves ("self"), Angela Merkel ("other") or whether the adjective had two syllables ("syllables"). fMRI data was analyzed using SPM8 computing

the contrast "self > other". To assess aberrant salience attribution, participants completed the Salience Attribution Test [SAT; Roiser et al., 2009] outside the scanner. In order to probe associations between neural activation during self-reference processing and aberrant salience attribution, a one-sample t-test for the contrast "self > other" with aberrant salience as covariate was conducted. Based on previous findings [Murray et al., 2012; Northoff et al., 2006; Araujo et al., 2013] a mask of the ACC and the MPFC was used for small volume correction. Results are reported at $p < 0.05$, FWE corrected.

Results: The task effect for the contrast "self > other" showed activation in a cluster comprising the ACC/MPFC ($-6/41/2$, $t=11.77$, p FWE whole brain corrected <0.05). Aberrant salience attribution was negatively correlated with the activation in the ACC/MPFC ($-3/32/4$, $t=3.68$, p FWE-corrected for ACC/MPFC volume = 0.044) indicating that subjects with higher aberrant salience attribution showed less activation during self-reference processing in the ACC/MPFC.

Discussion: In this study, self-reference processing was associated with activation in the ACC/MPFC. Moreover, the activation in the ACC/MPFC was negatively correlated with aberrant salience attribution. This finding suggests a relation between incorrect attribution of salience to otherwise neutral stimuli and the neural activation underlying the distinction between oneself and others. Our finding is in line with findings of a relation between psychotic-like experiences and the two social-cognitive mechanisms, aberrant salience processing and low self-concept clarity [Cicero et al., 2013]. In psychosis, the basic tone of selfhood appears to be impaired, with subsequent changes in the perceptions of oneself and the environment. A disturbed differentiation between self and others might contribute to mechanisms of positive symptoms like hallucinations and delusions [Walter and Spitzer, 2007]. Aberrant salience attribution was shown to be increased in deluded schizophrenia patients [Roiser et al., 2009]. Furthermore, imaging studies investigating self-reference processing in schizophrenia patients show reduced activation in the self-reference network [van der Meer et al., 2012]. Our finding of an association of self-reference processing and aberrant salience attribution might be involved in the formation and maintenance of psychotic symptoms and is in line with a current phenomenological approach [Nelson et al., 2013].

Poster #M39

SEMI-METRIC ANALYSIS OF THE FUNCTIONAL HUMAN BRAIN NETWORK: RELATIONSHIP WITH FAMILIAL RISK FOR PSYCHOTIC DISORDER

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Background: Dysconnectivity in schizophrenia can be understood in terms of dysfunctional integration of a distributed network of brain regions. Here we propose a new methodology to analyze complex networks based on semi-metric behavior. When two regions in a network are connected through an indirect path representing a more efficient association (i.e. faster information processing) between the regions than the direct path between them, that path is semi-metric. We hypothesized that individuals with (increased risk for) schizophrenia will have less semi-metric paths compared to controls, suggesting aberrant network efficiency.

Methods: Anatomical and resting-state functional MRI scans were obtained from 63 patients with psychotic disorder, 63 siblings of these patients and 63 healthy controls. Groups were matched for age and gender. We measured the proportion of semi-metric paths at the whole brain level, i.e. between 116 brain regions. For each individual, paths between regions were depicted in an association matrix. Subsequently, we calculated the average percentage of semi-metric paths for each individual association matrix. These semi-metric percentages per individual were used as the dependent variable in a multilevel random regression analysis to investigate group differences.

Results: There were distinct differences in semi-metric percentage between the three groups. Patients showed a significant lower semi-metric percentage compared to controls ($B=-0.81$, $p=0.008$). The semi-metric percentage of siblings was intermediate to that of controls and patients ($B=-0.55$, $p=0.068$ and $B=0.25$, $p=0.407$, respectively), but was not significantly different compared to either group.

Discussion: Indirect paths of functional connectivity between brain regions

lend efficiency and robustness to the overall network. This type of connectivity differs between patients, siblings and controls. The reduced number of indirect paths in patients, and a similar tendency in siblings, suggest semi-metricity as a disease or vulnerability marker reflecting aberrant network communication.

Poster #M40

THE RELATION OF ABNORMAL BRAIN CONNECTIVITY AND PSYCHIATRIC SYMPTOM EXPRESSION IN SUBJECTS AT HIGH-RISK FOR PSYCHOSIS

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Background: A key challenge in the early detection of psychosis is to find robust markers to characterize the neural mechanisms underlying the onset of psychosis. It has been proposed that psychosis may be associated not only by changes in focal brain activity, but also by abnormal functional integration of specific brain regions. Indeed, recent evidence has revealed abnormal functional connectivity between frontal and parietal brain regions during working memory processing in patients with schizophrenia and first-episode psychosis. However, it still remains unclear whether abnormal fronto-parietal connectivity during working memory processing is already evident in subjects at high-risk for psychosis and whether the connection strengths are related to psychopathological indices.

Methods: 19 healthy controls and 27 antipsychotic-naïve individuals with an "at-risk mental state" (ARMS) performed an N-back working memory task while undergoing functional magnetic resonance imaging. Cognitive performance during the task was evaluated with signal detection theory (d' prime), whereas effective connectivity between frontal and parietal brain regions during working memory processing was characterized using dynamic causal modeling.

Results: ARMS subjects showed significantly lower task performances as operationalized by the sensitivity index d' prime ($F(1,45)=6.66$; $p < 0.05$) and reduced activity in the right superior parietal lobule ($x=38$, $y=-64$, $z=58$; cluster size 304) and middle frontal gyrus ($x=34$, $y=30$, $z=40$; cluster size 291) relative to healthy controls (FWE cluster-level corrected at $p < 0.05$). Furthermore, the working memory-induced modulation of the connectivity from the right middle frontal gyrus to the right superior parietal lobule was significantly reduced in ARMS individuals ($F(1,45)=8.19$; $p < 0.006$ Bonferroni-corrected), while the extent of this (dys)connectivity was negatively related to the BPRS total score ($r=-0.523$, $p < 0.01$).

Discussion: These findings support the disconnection hypothesis of schizophrenia and extend previous evidence that abnormal brain connectivity is already evident in the high-risk state for psychosis. Moreover, our results provide evidence for a mechanistic relation between the degree of functional network integrity and psychopathological symptom expression. Thus, our results provide further insights into the pathophysiological mechanisms of the psychosis high-risk state by linking functional brain imaging, computational modeling and psychopathology.

Poster #M41

HIGH RESOLUTION BASAL STATE FUNCTIONAL IMAGING REVEALS A SUBCORTICAL-CORTICAL SPREADING PATTERN OF FUNCTIONAL ABNORMALITY IN CLINICAL HIGH-RISK PATIENTS WHO PROGRESS TO PSYCHOSIS

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Background: Our previous studies using high resolution basal state func-

tional imaging have identified abnormalities of basal-state hippocampal CA1/SUB and OFC/DLPFC prefrontal function in schizophrenia. In prodromal stages of disease, basal-state functional abnormalities were limited to the CA1 subfield of the hippocampus. Recent longitudinal follow-up of this prodromal cohort has revealed a spreading pattern of functional abnormality within hippocampus, such that focal CA1 abnormalities "spread" to neighboring subiculum, consistent with the previous findings in schizophrenia (Schobel et al *Neuron* 2013). However, it is unknown whether emergent subiculum dysfunction found at first episode psychosis is also associated with emergent functional and structural abnormalities of linked subcortical and cortical regions, including striatum and prefrontal cortex. The purpose of the present study is to track longitudinal functional changes in these brain regions as well as to test for predictive relationships between hippocampal abnormalities present at baseline and emergence of dysfunction at extra-hippocampal sites upon progression to psychosis.

Methods: We enrolled n=25 patients at clinical high risk for psychosis (n=15 non-progressors; n=10 progressors; mean age (s.d.) 19.3 (3.9) = non progressors; mean age (s.d.) 20.4 (S.D. 3.6) progressors) who were followed prospectively for clinical outcomes over 2.5 years on average. We imaged patients at presentation and at clinical follow-up in n=20 cases or 80% of the baseline sample. Subjects received high-resolution basal-state structural and functional imaging using a gadolinium protocol, which produces whole-brain anatomical maps of cerebral blood volume (CBV) at submillimeter spatial resolution (0.78 by 0.78mm). Regions of interest for the present study included hippocampal subregions along the entire long axis of the structure (EC, DG, CA3, CA1, SUB), striatum (Nucleus Accumbens, Anterior Caudate, Putamen), and prefrontal cortex (OFC BA11 and DLPFC BA 46). Hippocampal and striatal volumes from T-1 weighted images were calculated using ITK-SNAP. Repeated measures ANOVA was used to assess change from baseline in CBV of regions of interest controlling for demographics and follow-up interval. Regression models tested the association of baseline hippocampal CBV to emergence of abnormalities in striatum/PFC upon clinical follow-up, and correlational analysis assessed the functional relationships between regions (HIPP, striatum, and PFC) at baseline split by progression status (progressors vs. non-progressors).

Results: Progression to psychosis was associated with significant longitudinal decreases in DLPFC CBV and longitudinal increases in orbitofrontal CBV, in a seesaw pattern. At baseline, HIPP CBV in CA1/SUB was highly correlated with basal function in striatum selectively in progressors to psychosis (NAcc and AntCaud). Baseline CA1 CBV predicted longitudinal decrease in volume of the anterior caudate selectively in progressors to psychosis. Longitudinal increases in SUB CBV were associated with increases in OFC CBV in progressors to psychosis.

Discussion: The present results provide evidence that progression to psychosis from clinical high-risk stages is associated with a functional and anatomical spread of basal-state functional abnormalities within brain, from hippocampal subregions in prodromal stages of disease to more wide-spread dysfunction of striatum and prefrontal cortex upon clinical progression. The findings also suggest that active pathophysiological processes present during this stage of disease can be interrupted with appropriate targeted therapies. Limitations of the present dataset and findings include the small sample size, and lack of whole-brain analysis of the data to include other brain regions commonly implicated in schizophrenia, such as thalamus.

Poster #M42

A FUNCTIONAL NEUROIMAGING FAMILY STUDY OF FACIAL EMOTION PERCEPTION IN SCHIZOPHRENIA

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Background: A core feature of schizophrenia is impairment in social cognition, an ability that encompasses the affective and cognitive processes necessary to engage in social behaviour, such as accurately perceiving emotional information from faces. Individuals with schizophrenia have reliably been found to display impaired facial emotion perception, and importantly, this impairment is associated with real world outcomes such as social and work attainment. Furthermore, there is evidence that impairments in facial emotion perception are also present in unaffected relatives of individuals with schizophrenia, suggesting that these impairments reflect a genetic

vulnerability for the disorder. Previous research on facial emotion perception in schizophrenia using functional magnetic resonance imaging (fMRI) has demonstrated brain activation abnormalities in regions important for face perception and emotion processing; however, findings are often inconsistent. One interpretation is that traditional facial emotion tasks recruit a variety of additional cognitive mechanisms (e.g., set shifting, working memory) that influence the brain activation patterns reported. Moreover, few fMRI studies of facial emotion perception have included unaffected relatives, reducing the ability to answer important questions concerning the genetic basis of this deficit. The current study aims to 1) clarify the biological basis of impaired facial emotion perception in schizophrenia through a passive viewing fMRI task of facial emotion perception, and 2) investigate the genetic risk for brain activation abnormalities related to facial emotion by using a family study design.

Methods: 28 individuals with schizophrenia, 27 nonpsychotic first-degree relatives, and 27 healthy controls underwent an fMRI scan while performing a passive viewing task of facial emotion perception. Participants were required to attend to images of several categories of facial emotions (happy, sad, fearful, angry, or neutral), as well as images of scrambled faces. Participants also completed a Social Functioning Scale. fMRI data was pre-processed and analyzed using FSL (FMRIB, UK) in order to look at activation differences between groups and between each category of facial emotions.

Results: Preliminary whole-brain analyses reveal activation differences in both individuals with schizophrenia and unaffected relatives compared to controls, for brain regions involved in perceiving faces and emotions. These findings suggest that impairment in facial emotion, and the neural abnormalities underlying the impairment, are associated with the genetic vulnerability for schizophrenia. Analyses are ongoing in order to further characterize the extent of these activation abnormalities. We will also examine the relationship between brain activation differences and a measure of social functioning.

Discussion: The results of this study will improve our understanding of the neural basis of emotion perception deficits in schizophrenia. Linking social impairment to basic neurocognitive processes may help to provide treatment targets for future work designed to improve real world outcomes for individuals with schizophrenia. By comparing both individuals with schizophrenia and unaffected relatives to healthy controls, we will be able to identify activation abnormalities associated with the genetic risk for disorder, potentially identifying biological vulnerability markers that may be useful for future genetic research into the etiology of schizophrenia.

Poster #M43

CEREBRAL BLOOD FLOW CHANGES IN LATE-ONSET SCHIZOPHRENIA USING SPECT WITH THE EASY Z-SCORE IMAGING SYSTEM

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Background: The incidence of schizophrenia peaks during late adolescence or early adulthood. Another peak, particularly among women, occurs in middle or old age. The International Late-Onset Schizophrenia Group proposed the existence of two types late-onset psychotic symptoms: a late-onset schizophrenia (LOS: onset >40 years), and a very-late-onset schizophrenia-like psychosis (VLSP: onset>60 years) groups. However, knowledge about the pathophysiology of LOS or VLSP is still sparse. Investigating regional cerebral blood flow (rCBF) of older schizophrenic patients will be useful to understanding the pathophysiology. The aim of this study is to examine rCBF in a group of LOS using single photon emission computed tomography (SPECT) with the easy Z-score imaging system (eZIS).

Methods: The subjects were recruited at the Toho University Omori Medical Center, Tokyo. All the patients were fulfilled both recent consensus criteria for LOS/VLSP and DSM-IV-TR criteria for schizophrenia. We assessed the psychotic symptoms using The Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression Scale (CGI). The cognitive functions were evaluated using the Mini-Mental State Examination (MMSE), the Rey-Osterrieth Complex Figure (ROCF), the Letter Cancellation Test (LCT),

the Seven-word Learning Test (SLT), the Verbal Fluency Test (VFT) and Digit span. All the measures were administered at baseline, after 3 months, 6 months, 9 months and 12 months. SPECT brain imaging was carried out at baseline and after 12 months. This study was approved by the Ethical Research Committee of Toho University School of Medicine.

Results: A total number of 12 patients (11 female and 1 male, with a mean [SD] age of 64.3 [13.9] years) were assessed. Five (41.7%) of the 12 patients were diagnosed with LOS, and 7 (58.3%) were diagnosed with VLOSLP. A statistically significant improvement on PANSS Positive, PANSS Negative, PANSS General Psychopathology, PANSS Total Score and CGI was observed by the end of the study. At baseline, hyperperfusion was observed prefrontal area and medial frontal area. After 12 months, rCBF in prefrontal area and medial frontal area were decreased.

Discussion: To our knowledge, this study may be the first report in sequential SPECT with eZIS findings of LOS/VLOSLP. The results suggested that the rCBF changes in the frontal lobe of patients with LOS/VLOSLP could be related with psychotic symptoms.

Poster #M44

INTERACTION BETWEEN DIAGNOSIS OF SCHIZOPHRENIA AND DRD2 GENETIC VARIATION ON AMYGDALA ACTIVITY DURING EXPLICIT EMOTION PROCESSING

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Background: Dopamine D2 receptor signaling modulates several phenotypes of relevance to schizophrenia and including emotion processing, which is crucially associated with amygdala activity. A functional single nucleotide polymorphism (SNP) in the gene coding for D2 receptors (DRD2 rs1076560, G>T) alters ratio of expression of D2 short/long isoforms, modulates D2 signaling and has been associated with behavioral and physiological responses to emotionally relevant inputs. Here, our aim was to investigate the interaction between diagnosis of schizophrenia and DRD2 rs1076560 genotype on brain activity during explicit processing of facial emotional stimuli.

Methods: rs1076560 was genotyped in 51 patients with schizophrenia on stable treatment with antipsychotics and in 102 healthy subjects (N=SCZ/T carriers: 12; SCZ/GG: 39; NC/T carriers: 22; NC/GG: 80). Groups were matched for age, sex, socio-economical status and handedness, but not for premorbid IQ ($p > 0.05$). Chlorpromazine equivalents and PANSS scores were equally distributed between genotype groups in patients. All subjects underwent 3 Tesla fMRI during explicit processing of facial emotional stimuli, with angry, fearful, happy or neutral expression. Subjects were instructed to decide whether they would "approach" or "avoid" the faces presented during the task. SPM8 analysis was performed on the imaging data using the amygdala as the region of interest. In particular, contrast of interest were used in a multifactorial ANCOVA, covarying for age, gender, handedness, premorbid IQ, and number of emotional stimuli avoided as variables of no interest.

Results: SPM analysis indicated in left amygdala a main effect of genotype ($p < 0.05$, FWE corrected), with greater activity in subjects carrying the T allele compared with GG subjects during explicit processing of emotionally relevant stimuli. Moreover, there was a genotype x diagnosis interaction in the same brain region, with T carriers patients having greater activity compared with other genotype groups ($p < 0.05$, FWE corrected). Furthermore BOLD activity of the left amygdala in T carriers patients positively correlated with the number of emotional stimuli avoided (Pearson's $r = 0.5926$, $p < 0.05$). No significant correlations were present between amygdala activity and chlorpromazine equivalents or PANSS scores in patients (all $p > 0.05$).

Discussion: These results suggest an interaction between DRD2 rs1076560 genotype and diagnosis of schizophrenia on amygdala response to emotionally relevant stimuli. The differential effect on amygdala elicited in T carriers patients may represent the impact of genetically determined levels of D2 signaling on dysregulated dopamine tone in schizophrenia, which in turn may affect activity in this brain region.

Poster #M45

GABA, GLUTAMATE AND INTELLECTUAL ABILITY

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Background: Intelligence is a measure of general cognitive functioning capturing a wide variety of different cognitive functions. For the intelligent brain it may be that not simply more is better, but rather more efficient is better. To test the hypothesis that minimizing energy resources is beneficial to intelligence in the prefrontal and occipital cortices, GABA (gamma-aminobutyric acid) and glutamate (Glu) levels were measured in the healthy human brain *in vivo*. A combination of higher GABA levels and lower Glu levels suggests a more efficient energy use (Deary, 2012). Performing 1H-MRS at an ultra-high magnetic field strength of 7T results in increased sensitivity and spectral resolution, which are particularly important when measuring Glu and GABA.

Methods: 23 healthy subjects (age 27.7±5.3, M/F 16/7) participated in this study. Participants underwent a general cognitive assessment using the full Wechsler Adult Intelligence Scale (WAIS)-III (Wechsler, 1997). Participants did not have a history of psychiatric or neurological disorders, and did not have first-degree family members with psychiatric or neurological disorders. 1H-MRS experiments were performed on a 7T whole body MR scanner (Philips, Cleveland, OH, US). A birdcage transmit head coil was used in dual transmit driven by 2×4 kW amplifiers, in combination with a 32-channel receive coil (both Nova Medical Inc., Burlington, MA, US). For the assessment of Glu an sLASER sequence (Boer et al., 2011) was used. Non-water-suppressed spectra were obtained for quantification. GABA-edited experiments were conducted using a MEGA-sLASER sequence (Andreychenko et al., 2012). Voxels were located in the medial prefrontal and medial occipital lobe. Fitting of the sLASER spectra was performed with LCModel-based software implemented in Matlab (De Graaf, 1999), which uses a priori knowledge of spectral components to fit metabolite resonances (Govindaraju et al., 2000). To correct for the contribution of gray matter, white matter and cerebrospinal fluid in each voxel, segmentation was performed using the SPM8 software package. Fitting of the MEGA-sLASER spectra was performed by frequency-domain fitting of the GABA and Cr resonances to a Lorentzian line-shape function in Matlab. GABA levels were expressed as the ratios of their peak areas relative to the peak areas of the Cr resonance. Spectra with a CRLB of 20% or more were excluded from the study. Statistical analyses were performed using SPSS 21.0 (2012, Chicago, IL). Pearson correlation coefficients were calculated to evaluate associations between metabolite levels and intelligence measures.

Results: A higher Working Memory Index (WMI) was associated with a significantly lower Glu concentration ($p < 0.004$) and with a higher (but not significantly) GABA/Cr ratio ($p = 0.19$), resulting in a significantly higher GABA/Glu ratio in the occipital cortex ($p = 0.04$). Also, Glu levels and GABA/Cr ratios in the occipital cortex are strongly correlated ($r(7) = -0.85$, $p < 0.01$).

Discussion: The correlation between a higher WMI and a lower GABA/Cr ratios and higher Glu concentrations in the occipital cortex, suggests that individuals with a higher intelligent WMI performance make more efficient use of their brains' energy resources. The strong correlation between Glu concentrations and GABA/Cr ratios in the same brain region suggests that our findings of metabolite levels with cognitive functioning are not working in isolation but are part of a network of connective metabolites.

Poster #M46**ARE THE GLUTAMATERGIC DYSFUNCTION AND MEMBRANE LIPID HYPOTHESIS LINKED? A COMBINED 1H/31P-MR-SPECTROSCOPY STUDY IN NEVER TREATED ACUTE ONSET SCHIZOPHRENIA**

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Background: Glutamatergic dysfunction and deregulated phospholipid turnover are considered as main pathology in schizophrenia, and can be studied in vivo using magnetic resonance spectroscopy (MRS). While animal studies showed a link between deficits in neuronal plasticity and membrane pathology and the level of glutamatergic activation, this association has not been investigated directly in vivo in humans. This study combines 1H- and 31P-MR spectroscopy to cover glutamate (Glu) and glutamine (Gln) as well as markers of membrane lipid metabolism in never treated first onset schizophrenia.

Methods: We applied 3 T chemical shift imaging (3D 31P-MRS, 2D 1H-MRS) and hippocampal single-voxel 1H-MRS in 28 neuroleptic-naïve first-episode patients (FEP) and 28 healthy controls matched for age and gender. ANCOVA with interaction term was used to assess disease effects on Glu or Gln as well as on the correlations between Glu or Gln and phospholipid metabolites (PME, PDE) or high energy phosphates (PCr, ATP).

Results: 1) Glu values were significantly decreased bilaterally in the DLPFC, in the left ACC and left hippocampus in FEP. 2) The physiological Glu/Gln balance was deregulated in patients bilaterally in the DLPFC and related white matter. 3) Positive associations between Glu or Gln and phospholipid metabolites (or high energy phosphates) were focally disturbed in patients in the left ACC, the left thalamus, and white matter adjacent to prefrontal, insular and anterior temporal cortex, and basal ganglia.

Discussion: These findings strongly suggest an association between glutamatergic hypofunction and deregulation of activity depending neuronal and synaptic plasticity, affecting key networks of schizophrenia in the early acute phase of illness.

Poster #M47**WHITE MATTER INTEGRITY AS A CANDIDATE ENDOPHENOTYPE FOR SCHIZOPHRENIA**

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Background: In schizophrenia, white matter integrity is known to be affected [1]. Reductions in white matter integrity are related to a loss of interregional connectivity [2], which is thought to be critical for healthy brain functioning. The question remains whether white matter integrity is primarily affected by the disease process itself, or whether it is part of a genetic liability for the disease. This study addresses this question by comparing the core white matter skeleton of healthy twins to those with a high genetic load for schizophrenia and those with an affected phenotype.

Methods: A total of 236 twins, consisting of 10 monozygotic (MZ) discordant twin pairs, 1 MZ concordant twin pair, 2 singleton MZ co-twins, 1 singleton MZ patient, 16 dizygotic (DZ) discordant twin pairs, 2 DZ singleton co-twins and 3 singleton DZ patients participated in this study. Patients all met diagnostic criteria for a 295.xx disorder according to DSM IV criteria, co-twins did not. Healthy participants did not meet criteria for a major psychiatric disorder. FSL's diffusion toolbox was used to calculate FA maps of each subject, after which a tract based spatial statistics analysis was performed to calculate a white matter skeleton. Subsequently, non-parametric permutation testing with threshold free cluster enhancement (TFCE) was used to study three contrasts. 1: healthy control (HC) > patient (PT) (for

assessment of affected white matter areas in schizophrenia). 2: HC > DZ co-twin and 3: HC > MZ co-twin (for assessment of affected white matter in subjects with genetic load for schizophrenia). Age and sex were added to the analysis as covariates.

Results: Contrast 1 showed widespread areas of reduced FA (corrected p-value <0.05), particularly concentrated in white matter that is part of the corpus callosum, the right arcuate fasciculus, right fornix bundle and bilateral internal and external capsule. Contrast 2 did not show significant differences. Contrast 3 showed significant differences in the right Anterior Limb of the Internal Capsule (ALIC), the right fornix bundle and the right corticospinal tract. Areas constituting genetic risk were defined as the overlap between contrasts 1 and 3. A cluster of significantly reduced FA in both patients and MZ co-twins remained, which is situated in white matter below the dorsolateral prefrontal cortex, in the ALIC and in the fornix bundle. Within twin correlations irrespective of disease indicate genetic influence ($r_{MZ}=0.45^*$, $r_{DZ}=0.20$). Repeated measures ANCOVA including twin 1 as time point 1 (HC or co-twin) and twin 2 as time point 2 (HC or patient) revealed a significant effect of genetic risk by zygosity ($p=0.023$). Independent samples t-tests revealed significant difference in mean FA between groups ($F_{AHC}=0.47$, $F_{ADZco}=0.47$; $F_{AMZco}=0.45$, $F_{APT}=0.44$; $p_{HC>DZco} < 0.49$; $p_{HC>PT} < 0.00$; $p_{HC>MZco} < 0.00$).

Discussion: Both schizophrenia patients and genetically identical non-schizophrenic co-twins of patients showed significant reductions of white matter integrity in the right ALIC, which contains the fronto-thalamic projection fibers. Furthermore, the white matter of the right fornix was affected in both patients and MZ co-twins. We did not observe any significant differences in the DZ co-twin group, suggesting that the genetic load for schizophrenia must be sufficiently high for white matter to be affected. Our findings show that white matter integrity in the right fronto-thalamic circuit and the right fornix are candidate endophenotypes for schizophrenia. To confirm that a genetic correlation between the white matter integrity reductions and schizophrenia liability exists, structural equation modeling will be applied to these data in the near future.

Poster #M48**CHILDHOOD TRAUMA AFFECTS THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS ACTIVITY AND BRAIN STRUCTURE IN INDIVIDUALS AT FIRST EPISODE PSYCHOSIS AND HEALTHY CONTROLS DIFFERENTLY**

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Background: Experiencing physical or sexual abuse during childhood is a major risk factor for psychosis but the mechanisms underlying the increased risk remain unclear. There is increasing evidence that childhood trauma is associated with Hypothalamic-Pituitary-Adrenal (HPA) axis dysfunction and brain abnormalities in psychosis, however, whether these factors are part of the same biological pathway has not been clarified.

Methods: To better understand how childhood abuse increases the risk of psychosis we separately investigated the effect of childhood trauma on the HPA axis (cortisol levels during the day and cortisol awakening response) and on brain structure in patients with psychosis and healthy controls with and without moderate/severe childhood trauma exposure: 1) 102 first episode psychosis (FEP) patients (60 positive for trauma) (mean age: 30.1 SD±9.5 years); and 58 healthy controls (19 positive for trauma) (mean age 32.3, SD±14.5 years).

Results: Results show a linear trend indicating that the exposure of childhood trauma is associated with a reduced cortisol awakening response in FEP patients as well as in controls ($F(1)=9.65$ $p=0.03$ $\omega^2 = 0.59$), possibly lowering the already blunted awakening response present in FEP patients ($t(63)=2.07$ $p=0.021$ $r^2 = 0.25$). There is no difference in grey matter volume between healthy controls exposed and non-exposed to childhood trauma. FEP patients with exposure to childhood trauma had reduced grey matter volume of the left caudate body compared with the healthy control group (irrespective of childhood trauma) while FEP patients negative for childhood trauma exposure showed widespread reduced grey matter volumes in the left anterior cingulate, left pre-central gyrus, left middle temporal gyrus and in the left and right superior parietal lobule compared with

the healthy control group (irrespective of childhood trauma). Interestingly these abnormalities are equivalent to the ones we found comparing cases and controls irrespective of childhood trauma exposure (all $p=0.01$).

Discussion: These preliminary results suggest that exposure to childhood trauma in people with psychosis may worsen their HPA axis response to a mild stressor. Furthermore, the analysis shows differences in brain structure between patients never exposed and patients exposed to trauma, highlighting a potential precocious relationship between childhood abuse and brain structure. Remarkably the effect of childhood trauma on the brain structure seems to be present only in subject with vulnerability for psychosis and not in healthy controls. In order to further investigate this relationship, in future analyses we will explore whether the alterations in HPA we observed in individuals with childhood trauma mediate the brain abnormalities identified in these patients, thus representing a potential biological pathway by which a history of trauma increases the risk of psychosis.

Poster #M49

FUNCTIONAL AND GRAY MATTER ASYMMETRIES IN PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDERS

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Background: It has been reported that patients with schizophrenia exhibit decreased functional hemispheric lateralization while patients with bipolar disorders do not. Few studies have evaluated the relationships between the hemispheric anatomical and functional asymmetry in language networks. The present study aimed to determine whether decreased leftward functional hemispheric lateralization could be related to the gray matter volume asymmetry. This investigation was the first to use an individual structural asymmetry index to analyze the gray matter specifically involved in a language network.

Methods: Thirty-one right-handed patients with schizophrenia and 20 right-handed patients with bipolar disorders underwent a session of functional magnetic resonance imaging (fMRI) with a speech listening paradigm. Each group was matched with healthy subjects on gender, age and level of education. Maps of the Blood Oxygen Level Dependent (BOLD) signal contrast and structural maps (gray matter, white matter and CSF were generated in each participant in the MNI (Montreal Neurological Institute) space. Functional laterality indices (FLI) were calculated (Wilke, M. and Lidzba, K., 2007. LI-tool: a new toolbox to assess lateralization in functional MR-data. *J Neurosci Methods*. 163, 128–136) in each subject from the individual contrast maps. The gray matter volume asymmetry indices (GVAI) were computed in each subject from the gray matter maps masked with the individual functional maps. Anatomо-functional relationships were studied with ANCOVAs.

Results: Patients with schizophrenia exhibited a significant decreased leftward functional hemispheric lateralization and patients with bipolar disorders did not. There was a positive correlation between GVAIs and FLIs ($p<0.0001^*$) in healthy subjects, in patients with schizophrenia and in patients with bipolar disorders.

Discussion: This study reports for the first time a significant relationship between the anatomical and functional asymmetry in healthy subjects, in patients with schizophrenia and in patients with bipolar disorders. While decreased leftward functional lateralization for language was observed in patients with schizophrenia compared to the control group, anatomо-functional relationships were observed in all groups of patients or healthy subjects and did not differ between groups. Thus, the decreased functional lateralization in patients with schizophrenia might not be due to a decreased gray matter volume asymmetry.

Poster #M50

STRUCTURAL GREY MATTER AND WHITE MATTER DIFFERENCES IN INDIVIDUALS WITH PSYCHOTIC LIKE SIGNS FROM AN EPIDEMIOLOGICAL COHORT

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Background: Identifying neuroanatomical correlates of psychotic symptoms in non-clinical population samples promises insights into the underlying neurobiology of psychosis unconfounded by illness and treatment. To explore this, we examined structural differences in the grey (GM) and white matter (WM) of individuals experiencing pre-clinical psychotic-like signs (PLIKS) and healthy controls without such symptoms.

Methods: 252 subjects were selected from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, on the basis of the presence or absence of psychotic experiences based on interviews conducted at 17 years of age. Those whose psychotic experiences were verified by trained researchers as suspected or definite (cases), and subjects with no such experiences (controls) were invited to undergo MRI scanning. At the time of scanning all subjects were 18 years old. All data were acquired on a 3T GE HDx MRI system. Structural data were acquired with a 3D-FSPGR sequence (TR = 7.8 ms, TE = 3.0 ms, FOV = 256×256 mm, 186 slices, voxel size = 1×1×1 mm³). HARDI data were acquired with a cardiac-gated EPI sequence (TE = 87 ms, 60 gradient orientations, b-value = 1200 s/mm², FOV = 96×96 mm, 60 slices, voxel-size = 1.6×1.6×2.4 mm). 3 PLIKS subjects and 1 control withdrew before the HARDI acquisition. GM volume was analysed using voxel-based morphometry (VBM) using the program FSL. GM volumes were tissue segmented, non-linearly registered to the MNI152 template and smoothed with a 2 mm³ Gaussian kernel. General linear model (GLM) analysis compared the PLIKS and control groups while co-varying for total brain volume. Statistics were corrected with cluster-enhanced permutation tests. HARDI data were analysed in ExploreDTI and corrected for motion, eddy current distortions and field inhomogeneities. Fractional anisotropy (FA), axial diffusivity (AD) and radial diffusivity (RD) was derived from a diffusion tensor model fitted using the RESTORE algorithm and corrected for partial volume effects. FA, AD and RD were analysed using tensor based spatial statistics (TBSS). DTI images were non-linearly registered to the FMRIB58_FA template and projected onto the template skeleton. Additional tractography was carried out using the damped Lucy-Richardson algorithm to identify tracts that traverse through statistically significant WM regions.

Results: VBM analyses revealed a significant cluster of voxels with lower GM volumes in the left temporoparietal junction in the PLIKS group compared to controls without PLIKS. TBSS analysis data showed significant decreases in FA, AD and increases in RD in a white matter region in the left medial frontal lobe. Seeding tracts from this region implicate the left cingulum, anterior thalamic radiation and genu.

Discussion: The results suggest some candidate biomarkers relevant to the psychosis spectrum. The lack of overlap in the GM and WM changes points to heterogeneity of processes potentially implicated in the development and pathogenesis of psychotic illness. The GM results may imply dysfunction in language processes while the WM results may implicate executive or motivation abnormalities.

Poster #M51

TEMPORAL LOBE WHITE MATTER ALTERATIONS IN SCHIZOPHRENIA: A DIFFUSION TENSOR IMAGING TRACTOMETRY FAMILY STUDY

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Background: Individuals with schizophrenia consistently show abnormalities in white matter (WM) tracts compared to controls. Evidence also suggests that the non-psychotic relatives of individuals with schizophrenia show WM dysfunction. Given the relevance of the temporal lobe to the pathophysiology of schizophrenia, we investigated three key tracts associated with the temporal lobe: (1) the inferior longitudinal fasciculus, which connects the temporal lobe with the occipital lobe; (2) uncinate fasciculus,

which connects the temporal lobe with the prefrontal cortex; and (3) fornix, which connects the hippocampus with the hypothalamus. Furthermore, most previous studies investigating WM changes in schizophrenia have used voxel-based analysis, typically of a highly restricted WM skeleton (eg TBSS) or whole-tract mean values from tractography, thereby losing anatomical specificity. The goal of this investigation therefore, was to use sophisticated diffusion tensor imaging (DTI) tractometry analysis to examine along-tract microstructural differences in three major temporal lobe WM tracts in a family study of schizophrenia. Inclusion of both patients and family members allowed a better examination of genetic (familial) liability, as well as disease-related processes.

Methods: Twenty-five patients with schizophrenia, 24 non-psychotic healthy relatives, and 27 community controls participated. DTI data were acquired (3T GE) along 60 gradient directions with b-value 1300 s/mm² and corrected for motion and distortion using ExploreDTI. DTI parameters fractional anisotropy (FA) and mean and radial diffusivity (MD, RD) were estimated. A population-based FA-template was constructed, to which all parameter maps were registered. The aforementioned temporal lobe tracts were isolated using targeted tractography. The fornix was further subdivided into left/right anterior columns, body and left/right fimbriae. Parameter values for each subject were calculated at evenly distributed points along the length of the tract masks in template space. ANCOVA was used to investigate the main effect of group membership on mean tract values (between-subject factors: group, gender, covariate: age), whilst the group:position interaction term in a 2-way ANOVA was used to identify group differences at each point along each tract.

Results: Both patients with schizophrenia and non-psychotic relatives demonstrated lower mean and radial diffusivity in their fornix compared to controls using age and gender as covariates. Tract profiles illustrated group differences along the entire length of the fornix rather than localized differences. No other significant differences were found between groups.

Discussion: We found both schizophrenia patients and their biological relatives had differences in two indices associated with WM microstructure, compared to controls along the length of the fornix; however, in an unexpected direction. Possible reasons for this surprising finding could be a true biological difference, volumetric differences present between groups, or methodological issues associated with DTI analyses in typically sized schizophrenia study populations. Further investigation of the relationship between the DTI parameters, white matter volume and anatomical structures bordering the fornix will be presented to understand these findings. The results of this analysis may allow a better understanding of not only these results, but also other findings of fractional anisotropy changes in schizophrenia.

Poster #M52

NEUROLOGICAL SOFT SIGNS AND BRAIN MORPHOLOGY IN PATIENTS WITH CHRONIC SCHIZOPHRENIA

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Background: While neurological soft signs are frequently described in patients with schizophrenia the underlying cerebral changes are rather scarcely investigated especially in patients with a chronic course of the disease.

Methods: Therefore we examined a group of 37 patients with a duration of the disease of 28.7 years (± 11.3 years) and 24 healthy subjects matched for age, gender and education. Neurological soft signs were assessed with the Heidelberg Scale after remission of the acute symptoms and correlated to grey matter volume using optimized voxel-based morphometry (VBM), the preprocessing steps of VBM have been improved with the DARTEL-algorithm.

Results: 18 patients had a NSS sum-score of 10.1 (± 10.3), 19 patients had a NSS sum-score of 28.6 (± 10.6), while the NSS sum-score in the control group was significantly reduced with 4.1 (± 3.5). The NSS low-score patient group had significantly increased grey matter volume than the NSS high-

score patient group in the inferior occipital gyrus, the anterior lobe of the right cerebellum (culmen) and the left thalamus.

Discussion: These preliminary results are similar to those patterns found in patients with a first-episode and support at least partly the model of cognitive dysmetria with a dysfunctional prefrontal-thalamic-cerebellar circuitry in schizophrenia.

Poster #M53

DIAGNOSING SCHIZOPHRENIA USING NEUROIMAGING: A META-ANALYSIS OF MULTIVARIATE PATTERN RECOGNITION STUDIES

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Background: Numerous studies have applied novel multivariate statistical approaches to the analysis of brain alterations in patients with schizophrenia. However, these studies differ with respect to multiple aspects such as the demographical characteristics of the investigated populations or the methodological details of the conducted analysis. As a result, the diagnostic accuracy of the reported predictive models differ largely, making it difficult to evaluate the overall potential of these studies to inform clinical diagnosis.

Methods: We conducted a comprehensive literature search to identify all studies reporting performance of neuroimaging-based multivariate predictive models for the differentiation of patients with schizophrenia from healthy control subjects. A bivariate random-effects meta-analytic model was implemented. The robustness of the results as well as the effect of potentially confounding continuous variables (e.g. age, gender ratio, year of publication) was investigated by adding moderator variables to the bivariate regression model. All computations were performed using the R statistical programming language with the package mada.

Results: The final sample consisted of n=37 studies including n=1491 patients with schizophrenia and n=1488 healthy controls. Meta-analysis of the complete sample showed a sensitivity of 80.7% (95%-CI: 77.0 to 83.9%) and a specificity of 80.2% (95%-CI: 83.3 to 76.7%). There was no evidence for a publication bias and no effect of year of publication. Separate analysis for the different imaging modalities showed similar diagnostic accuracy for the structural MRI studies (sensitivity 77.3%, specificity 78.7%), the fMRI studies (sensitivity 81.4%, specificity 82.4%) and resting-state fMRI studies (sensitivity 86.9%, specificity 80.3%). Moderator analysis showed significant effects of age of patients on sensitivity (p=0.021) and of positive-to-negative symptom ratio on specificity (p=0.028) indicating better diagnostic accuracy in older patients and patients with positive symptoms. There was no significant effect of gender-ratio and no significant difference between different multivariate statistical approaches (all p>0.1).

Discussion: Our analysis indicate an overall sensitivity and overall specificity of around 80% of neuroimaging-based predictive models for differentiating schizophrenic patients from healthy controls. This finding was robust against the inclusion of potential confounding factors. Thus our results underline the potential applicability of neuroimaging-based predictive models for the diagnosis of schizophrenia.

Poster #M54

THE ROLE OF A FOXP2 VARIANT ON BRAIN STRUCTURE AND SPEECH PRODUCTION – A DTI STUDY

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Background: Mutations in the FOXP2 gene have been associated with severe speech disturbances. In addition, several variants within this gene have been associated with schizophrenia in general as well as speech-related psychopathology in patients. The aim of the current study was

to investigate the effect of rs17137124 of the FOXP2 gene on fiber tract integrity and speech production in a sample of healthy subjects.

Methods: A sample of 103 healthy native German subjects was investigated with diffusion tensor imaging (DTI). In addition, they were tested with several verbal fluency tasks outside the scanner to investigate semantic and lexical verbal fluency.

Results: Subjects with the minor allele of the rs17137124 variant displayed lower word production rates in semantic verbal fluency. In comparison to major allele carriers, reduced fractional anisotropy (FA) was found in the left superior longitudinal fasciculus adjacent to Broca's area, as well as the corpus (all results FWE corrected).

Discussion: Results demonstrate that an influence of FOXP2 variation on word production can already be found in healthy subjects. Furthermore, these results shed light on the pathophysiological mechanisms underlying speech disturbance in schizophrenia patients, in particular with respect to dysfunctions in the semantic domain. Finally, the reduced FA within the corpus callosum could explain the often found diminished functional lateralization of networks sub-serving speech production in patients with schizophrenia.

Poster #M55

DURATION OF ILLNESS ASSOCIATED WITH CORTICAL THICKNESS CHANGE IN SCHIZOPHRENIA: A LONGITUDINAL MRI STUDY

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Background: There is consistent evidence for progressive brain changes during the course of the disease, but the underlying mechanisms remain unclear. Several confounding factors have been suggested to play a role, e.g. symptomatic and functional outcome, medication intake, nicotine and cannabis smoking. The current study focused on changes in cortical thickness over time in schizophrenia in relation to the duration of the illness.

Methods: A total of 119 patients with schizophrenia (mean duration of illness at the baseline = 4.07 years, mean age = 26.71) and 128 age-matched healthy controls (mean age = 26.91) were included at baseline, and underwent structural magnetic resonance imaging (MRI) using a 1.5-Tesla scanner. Of them, 58 patients and 65 controls underwent follow-up MRI using the same scanner with a mean interval of 3.26 years. Written informed consent was obtained from all the subjects, and the study was approved by the Medical Ethics Committee for Research in Humans (METC) of the University Medical Center Utrecht. Surface-based analysis with FreeSurfer software (ver5.1.0) was applied to measure global and local cortical thickness (change) in each subject. Yearly cortical thickness change was defined as the percent thickness change per year during the scan interval. First, patients and controls were compared on baseline global and local cortical thickness. Secondly, in the patients only, the correlation between baseline cortical thickness and duration of illness at baseline was examined. Thirdly, in subjects with follow-up MRI data, group comparison of change in global and local cortical thickness was conducted. Finally, in the patients only, the correlation between yearly cortical thickness change and duration of illness at baseline was investigated. Statistical threshold was set at $p < 0.05$, and clusterwise correction was conducted for vertexwise analysis. In all the analysis, age and gender were regressed out.

Results: At baseline, patients had significantly thinner cortex both globally and regionally in widespread regions, in particular bilateral prefrontal and left temporal regions. No significant correlation was found between duration of illness and baseline global thickness ($p=0.12$), while significant negative correlations were found between duration and baseline local thickness, in particular in bilateral frontal and temporal regions. For yearly thickness change, no significant difference was found between the groups. However, in the patient group, duration of illness at the baseline was significantly and positively correlated with yearly thickness change both globally and regionally across the brain, indicating that illness duration is associated with greater yearly cortical thinning in patients.

Discussion: These results suggest that the progressive cortical thinning in schizophrenia might occur most prominently in the earlier stages of the illness.

Poster #M56

SHARED WHITE MATTER DYSCONNECTIVITY IN SCHIZOPHRENIA AND BIPOLAR DISORDER WITH PSYCHOSIS

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Background: There is an appreciable overlap in the clinical presentation, epidemiology and treatment response of the two major psychotic disorders Schizophrenia and Bipolar Disorder. Nevertheless, the shared neurobiological correlates of these two disorders are still elusive. Using Diffusion Tensor Imaging (DTI), we sought to identify brain regions which share altered white matter connectivity across a clinical spectrum of psychotic disorders.

Methods: A sample of 41 healthy controls, 62 patients in a clinically stable state of an established psychotic disorder (40 with schizophrenia, 22 with bipolar disorder) were studied using Diffusion Tensor Imaging (DTI). Tract-Based Spatial Statistics was used in order to study group differences between patients with psychosis and healthy controls using Fractional Anisotropy (FA). Probabilistic Tractography was used in order to visualise the tracts clusters that showed significant differences between these two groups.

Results: The TBSS analysis revealed 5 clusters (callosal, posterior thalamic/optic, paralimbic and fronto-occipital) with reduced FA in psychosis. This reduction in FA was associated with an increase in radial diffusivity and a decrease in mode of anisotropy. Factor analysis revealed a single white matter integrity factor that predicted social and occupational functioning scores in patients irrespective of the diagnostic categorisation.

Discussion: Our results show that a shared white matter dysconnectivity links the two major psychotic disorders. These microstructural abnormalities predict functional outcome better than symptom-based diagnostic boundaries during a clinically stable phase of illness, highlighting the importance of seeking shared neurobiological factors that underlie the clinical spectrum of psychosis.

Poster #M57

LEFT FRONTO-TEMPORAL DISCONNECTIVITY WITHIN THE LANGUAGE NETWORK IN SCHIZOPHRENIA: AN FMRI AND DTI STUDY

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Background: Schizophrenia is a mental disorder characterized both by a functional disconnectivity and a disturbance in the integrity of white matter (WM) fibers implicated in the language processes. Functional neuroimaging studies have posited that, compared to healthy controls, patients with schizophrenia present an altered left fronto-temporal functional connectivity. Likewise, recent studies of tract-based DTI in schizophrenia have revealed alterations in WM integrity within the fiber bundles that are implicated in the language functional networks such as the uncinate, inferior occipitofrontal and arcuate fasciculi. Here, we present the first study that investigates, through several diffusion parameters, the relationship between functional connectivity within a functional language comprehension network and anatomical connectivity using fiber tracking in schizophrenia. We hypothesized that patients with schizophrenia would present an impaired functional connectivity in the language network due to anatomical disconnectivity.

Methods: Twenty patients, diagnosed with schizophrenia based on the DSM-IV, and 20 healthy controls, matched on age, sex, and level of education, were included in this study. Diffusion and functional Magnetic Resonance Images (MRI-3T) were acquired. The experimental paradigm consisted in listening to a factual story in French, the native language of the participants, alternated with the same story in Tamil considered as the reference task. Maps of the Blood Oxygen Level Dependent (BOLD) signal contrast (French minus Tamil) and maps of diffusion (fractional anisotropy (FA), radial diffusivity (RD) and mean diffusivity (MD)) were generated in

each participant in the MNI (Montreal Neurological Institute) space. Likewise, fiber tracking between the left frontal cluster and the left temporal cluster belonging to the language comprehension network (from the mean functional map generated from the individual contrast maps in the whole population using SPM5) was reconstructed for each participant using a probabilistic tractography method. Functional connectivity between these two clusters was individually calculated. Mean FA, RD, and MD values were extracted in left fronto-temporal tracts considered as the left arcuate fasciculus and part of the left inferior occipitofrontal fasciculus. Relationships in anatomo-functional connectivity were studied with ANCOVAs.

Results: Compared to controls, the patients with schizophrenia showed lower functional connectivity between the left frontal and temporal clusters and alterations in WM integrity within the left arcuate fasciculus and part of left inferior occipitofrontal fasciculus. Mainly, an altered relationship in anatomo-functional connectivity was observed in patients; functional connectivity was positively correlated with FA, but was negatively correlated with RD and/or MD, in both the left arcuate fasciculus and part of the inferior occipitofrontal fasciculus.

Discussion: Our findings indicate a close relationship between anatomical and functional disconnectivity in patients with schizophrenia, suggesting that a disturbance in the integrity of the left fronto-temporal tracts might be one cause of functional disconnectivity in the language comprehension network in schizophrenia. This finding strongly supports the hypothesis of a disconnection in the left fronto-temporal neural circuitry. Further research using multimodal cerebral approach should investigate several measures that couple function with the structure like integrity of WM and volume of GM, in order to improve our understanding of the pathophysiology of schizophrenia.

Poster #M58

BRAIN STRUCTURE CHANGES IN FIRST-EPIISODE PSYCHOSIS PATIENTS WITH PERSISTENT APATHY

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Background: Magnetic resonance imaging (MRI) studies have shown structural brain abnormalities in patients with psychosis compared to healthy controls. How these abnormalities relate to the clinical heterogeneity observed in the patients is unknown. Apathy has been associated with poorer functioning in psychosis patients. We have previously shown that apathy is an enduring feature in 30% of patients with first-episode psychosis (FEP). The FEP patients with enduring apathy were predominantly men, with a longer duration of untreated psychosis and poorer general functioning. The aim of the present study was to test if FEP patients with persistent apathy (PA) differed from FEP patients without persistent apathy (NPA) in brain structure measurements early in the course of illness.

Methods: The subject sample consisted of 70 FEP patients participating in the Thematically Organized Psychosis (TOP) Research Project, Oslo, Norway. Apathy was assessed using the Apathy Evaluation Scale clinical version (AES-C) at two time points; upon inclusion (within 12 months from first adequate treatment for psychosis) and at one year follow-up. Patients underwent MRI on the same 1.5 T scanner at time of inclusion. Cortical thickness and subcortical structure volume measures were automatically obtained using FreeSurfer and compared between patients with PA (N=18) and NPA (N=52), using linear regression models while correcting for age and gender. Analyses on subcortical volumes were corrected for intracranial volume. First, we tested the hypotheses that the PA group would show cortical thinning in anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) and/or reduced basal ganglia volumes (caudate, putamen, pallidum, accumbens) and the thalamus. Second, we performed exploratory analyses of cortical thickness across the cortical mantle, and additional subcortical structures (hippocampus, amygdala, ventricles and cerebellum).

Results: The PA group showed significantly thinner cortices in the left OFC ($B=-0.098$, $p=0.004$) and bilaterally in the ACC (Left: $B=-0.138$, $p=0.009$. Right: $B=-0.138$, $p=0.025$), as well as increased caudate volume ($B=517.99$, $p=0.021$). The results remained significant after controlling for depression and antipsychotic medication. Exploratory analyses showed no additional differences in brain structure between PA and NPA patients.

Discussion: First-episode patients with persistent high levels of apathy over the first year of treatment show brain structural alterations compared to first episode psychosis patients without persistent apathy. These alterations are confined to regions that have previously been associated with apathy in patients with Alzheimer's disorder and in lesion studies, and theoretical models on cortical-subcortical circuits involved in motivation support the findings.

Poster #M59

THE "FIBRE" PATH TO PSYCHOSIS? CAN ADVANCED DIFFUSION IMAGING CAPTURE WHITE MATTER BRAIN ANOMALIES IN ADOLESCENTS EXPERIENCING PSYCHOTIC SYMPTOMS?

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Background: White matter changes are frequently described in individuals who fulfil the criteria for At Risk Mental States (ARMS) and DSM IV for schizophrenia and have proved invaluable in our understanding of how the clinical symptomology of the disease relates to associated neuroanatomical alterations. These changes have provided evidence of key affected brain structures, such as targeted frontal abnormalities driven by the disease onset (1, 2), and more recently, have been identified in individuals categorized as ultra-high risk (UHR) (Carletti et al, 2012, Peters et al., 2009). Yet little is known about the genesis of these morphologies prior to the transition to schizophrenia and psychosis. In particular, it remains unclear if adolescents experiencing psychotic symptoms show evidence of early white matter abnormalities. Advancing imaging techniques such as High Angular Resolution Diffusion Imaging (HARDI) may provide researchers with a mechanism to capture these disease related changes during their formative phases and thus provide clinicians with a possible means to identify those individuals with increased vulnerability to the disease and influence early interventional strategies for a better prognosis.

Methods: Twenty-eight young people aged 13–16 years who reported psychotic experiences and twenty-eight young people who did not, matched for age, gender and handedness, featured in the study. HARDI data was acquired and preprocessed using ExploreDTI (<http://www.ExploreDTI.com>). The images were then initially used to conduct whole brain data white matter analysis using Tract Based Spatial Statistics (TBSS) (Smith et al., 2006) followed by Constrained Spherical Deconvolution (CSD) based deterministic tractography and a novel tract resampling technique. Fractional anisotropy, mean diffusivity, axial and radial diffusivity metrics were extracted, to investigate if white matter (WM) differences are present in adolescents with psychotic symptoms.

Results: Whole brain WM analyses identified white matter differences between young people with psychotic symptoms and those without, localised bilaterally in striatal regions in proximity to the putamen ($p=0.01$ FDR corrected). CSD tractography in proximity to these regions identified WM tract anomalies in the frontal projections of the right inferior fronto-occipital fasciculus (IFO) and bilaterally in the Uncinate fasciculus (UNC) ($p\leq0.05$ corrected).

Discussion: These findings provide the first evidence of white matter anomalies in both frontal and fronto-temporal regions in young adolescents experiencing psychotic symptoms in the pre prodromal phase, prior to the transition to psychosis. These anomalies may reflect key brain structures targeted during the developmental surges experienced during adolescence thus associated with heightened vulnerability and possible underlying psychopathology that renders these individuals with increased risk of psychosis.

Poster #M60**MODELLING GENETIC AND ENVIRONMENTAL INFLUENCES ON BRAIN VOLUME IN TWINS WITH SCHIZOPHRENIA**

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Background: Whole brain and grey matter volumes are reduced in schizophrenia. How these pathological abnormalities are influenced by schizophrenia's genetic and environmental risk remains less clear.

Methods: We investigated the relationship between genetic, common and unique environmental risk on brain volumes in monozygotic and dizygotic twin pairs varying in their concordance for schizophrenia, and healthy control twins. Total brain, grey and white matter volumes were established from structural magnetic resonance images using an automated algorithm in SPM8 from 86 twin pairs (n=168). Hippocampal volumes were measured manually in the same sample. Between group differences in brain volumes were tested before full genetic modelling in Mx.

Results: We found that whole brain, grey, white and right hippocampal volumes were smaller in probands with schizophrenia compared to healthy controls. Well co-twins from DZ discordant pairs also had smaller hippocampal volumes compared to the healthy controls. Whole brain, grey and white matter volumes were heritable, while hippocampal volume was subject to significant common environmental effects. All of the brain volumes tested had a significant negative phenotypic correlation with schizophrenia. Lower birth weight and hypoxia were both associated with lower whole brain volumes, and with lower white and grey matter volumes respectively. There were no significant effects in the patients of cumulative antipsychotic exposure.

Discussion: Our data suggest that total brain, grey, white matter and hippocampal volume reductions are associated with schizophrenia. Whole brain and white matter volumes were most strongly linked to genetic effects. Hippocampal volume reductions appear to be particularly sensitive to environmental effects.

Poster #M61**AUDITORY HALLUCINATIONS IN FIRST EPISODE PSYCHOSIS: A LONGITUDINAL DTI STUDY OF THE ARCUATE FASCICULUS**

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Background: Auditory hallucinations occurs with a lifetime prevalence of 60% in patients with schizophrenia. The arcuate fasciculus, a white matter tract, has been implicated in auditory hallucinations, but DTI studies have so far showed contradictory findings, with studies showing increase in FA, an index of white matter integrity, while others reporting a decrease in FA. Furthermore, no study so far has analysed the longitudinal changes in white matter integrity and its relationship to changes in the severity of auditory hallucinations.

Methods: 39 first-episode psychosis patients with auditory hallucinations, 46 without auditory hallucinations and 45 healthy controls were enrolled in this study. All subjects underwent MRI at baseline and 3 months follow-up. The presence and severity of auditory hallucinations was assessed using the PANSS Scale.

Results: We found a reduction in FA in several segments of the arcuate in patients with auditory hallucinations compared to patients without auditory hallucinations and controls. This reduction was still present at 3 months follow-up. Furthermore, there was a significant correlation between changes in the severity of auditory hallucinations and changes in white matter integrity.

Discussion: This is the first study to assess the arcuate white matter integrity in first episode psychosis and its relation with auditory hallucina-

tions, using a longitudinal design. This study highlights the importance of the arcuate for in the etiopathogenesis of auditory hallucinations.

Poster #M62**WHITE MATTER VOLUME REDUCTIONS IN FIRST EPISODE PSYCHOSIS ARE ASSOCIATED WITH CORTISOL LEVELS**

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Background: The hypothalamic-pituitary-adrenal (HPA) axis governs the release of glucocorticoids, such as cortisol, in response to stress. Stress and abnormal HPA-axis functioning have been implicated in the early phase of psychosis and may underlie reported changes in brain structure. This study investigated whether levels of morning cortisol were related to grey and white matter brain volume.

Methods: Blood cortisol and MRI scans were obtained in 22 patients (18M:4F; mean age 20.64, SD=2.38) and 22 matched healthy controls (18M:4F; mean age 22.48, SD=1.95). 13 Patients had a diagnosis on the schizophrenia spectrum. Eight (36%) patients were neuroleptic naïve at the time of assessment. The remaining patients received an average of 4.93 days (SD=2.13) of antipsychotic medication. Images were analysed using the VBM8 toolbox in SPM8. Spatial extent threshold was determined by 10,000 Monte Carlo simulations conducted using 3dClustSim (AFNI), which yielded a cluster extent of 317 voxels for grey matter and 309 voxels for white matter at a voxel-wise threshold of p<0.002.

Results: There were no significant differences (p>0.05) between patients and controls on measures of cortisol, nor in grey or white matter volumes (p<0.05 FWE corrected). Higher levels of baseline cortisol were indicative of smaller white matter volumes in the cuneus (peak voxel [9 -84 8]) and anterior cingulate (peak voxel [12 37 -1]). This relationship was significantly stronger for the patients than the controls. No such relationship was observed for grey matter volumes.

Discussion: These findings support the involvement of stress mechanisms in the pathophysiology of early psychosis and suggest that the first subtle brain changes can be observed in the white matter.

Poster #M63**PROGRESSIVE BRAIN STRUCTURE CHANGE PREDICTS NEGATIVE SYMPTOMS IN FIRST EPISODE PSYCHOSIS AT 3 YEAR FOLLOW-UP**

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Background: First episode psychosis (FEP) is known to be associated with structural brain abnormalities and some evidence suggests that these changes may be used to predict clinical outcome. In a previous study, we identified caudate volume and shape abnormalities and right superior temporal gyrus (STG) thinning in a cross-sectional study of FEP, with no evidence of these brain changes predicting patient outcome. Recent studies however suggest that longitudinal rather than cross-sectional neuroimaging may be better predictors of patient outcome. In this study, we investigate how brain structure (volume, thickness and shape) may change over time in FEP and determine if identified changes may better predict clinical outcome at 3 year follow-up.

Methods: 1.5 Tesla T1-weighted MR images were acquired for 28 patients (18 male, 10 female; mean age 29±9 years) at the time of their FEP and again 3.5 years (SD=0.9) later. Twenty-eight healthy controls (HC) were also scanned at the same time points (14 male, 14 female; mean age 33±9 years). Cerebral cortical thickness change was investigated using FreeSurfer software. Volume and shape of the hippocampus, caudate and lateral ven-

tricles were assessed using manual tracing and spherical harmonics applied for shape description. Linear regression was used to determine the effect of group on brain change (volume, thickness or shape) correcting for age (ICV was controlled for in the case of the volume measures only) and using a false discovery rate (FDR, $p=0.05$) to correct for multiple comparisons. Linear regression was then utilised to determine if identified structural changes were related to Negative Symptom Scale (PANSS) and Global Assessment of Functioning (GAF) at follow-up, a diagnosis of an affective or non-affective disorder, cumulative antipsychotic medication use and illicit psychoactive drug use. Age and ICV (for volume measures) were added as covariates.

Results: A significant increase in caudate volume, left lateral ventricle volume and a decrease in cerebral white matter volume over time in FEP patients was identified when compared to HC. Surface based analysis revealed regional volume increases in the bilateral caudate in FEP. Although superior temporal gyrus (STG) thinning was observed at baseline, this abnormality did not appear to be progressive in FEP compared to HC. Changes in left lateral ventricle volume ($F=2.1$, $p=0.05$) and right STG thickness ($F=-2.2$, $p=0.04$) were predictive of Negative PANSS at follow-up. An increase in caudate volume was associated with FEP patients with no previous psychoactive drug use ($F=5.3$, $p<0.001$). The caudate volume of patients with a history of drug use did not significantly differ from healthy controls at baseline, whereas patients without a drug history had significantly smaller caudate volume at baseline, which then normalised over time. No brain structure change was related to the other clinical measures. **Discussion:** The results support the hypothesis that longitudinal brain changes are better predictors of clinical outcome than baseline brain changes alone. This study supports the growing literature that progressive brain structure volume loss is associated with a poorer outcome and more recent research that suggests patients with and without a history of psychoactive drug use may represent distinct subgroups of psychosis patients.

Poster #M64

CONTINUING GREY MATTER CHANGES IN FIRST-EPISEODE SCHIZOPHRENIA AND AFFECTIVE PSYCHOSIS

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Background: Magnetic Resonance Imaging (MRI) studies have shown that brain abnormalities in psychosis might be progressive during the first years of illness. We sought to determine whether first-episode psychosis subjects show progressive regional grey matter changes compared with controls, and whether those changes are associated with diagnosis, illness course or antipsychotic use.

Methods: The cases for the present study were selected from a sample of 200 first episode psychosis subjects who took part in a population-based incidence and case-control study conducted in São Paulo, Brazil. Inclusion criteria for patients at baseline were age 18–50 years and a diagnosis of psychotic disorders according to DSM-IV criteria. Thirty-two subjects with first-episode schizophrenia-spectrum disorders (including schizophrenia, schizoaffective disorder and schizoaffective disorder), 24 patients with first-episode affective psychoses (16 with bipolar disorder and 08 with psychotic depression) and 34 controls recruited using a population-based design underwent structural MRI scanning at baseline and at 5-year follow-up. Seventeen schizophrenia-spectrum subjects and 11 affective psychosis patients were categorized as fully remitted. Patients were treated at community settings, and thirty-six percent of them remained mainly untreated during follow-up. Regional grey matter volumes were assessed with voxel-based morphometry. Images were processed and analyzed using the statistical parametric mapping (SPM). Repeated-measures analysis of covariance (ANCOVA) was employed for group comparisons and post hoc evaluation of significant between-groups differences was then performed with secondary two-tailed t-tests. We reported significant clusters of voxels

that survived family-wise error (FWE) correction for multiple comparisons ($p<0.05$).

Results: No significant progressive changes in grey matter regional volumes were observed in either schizophrenia-spectrum patients or affective patients compared to controls. However, schizophrenia-spectrum subjects with a non-remitting course showed grey matter decrements in the left superior temporal gyrus and in the left insula relative to remitted patients. Non-remitting affective subjects exhibited grey matter decrease in the dorsolateral prefrontal cortex bilaterally in comparison to remitted subjects. Among schizophrenia-spectrum subjects, antipsychotic use was associated with regional grey matter decrements in the right insula and in the left superior temporal gyrus. We did not analyze the effects of medication on grey matter volumes in the affective psychosis group due to the highly heterogeneous use of medication use in such a relative small sample size. **Discussion:** Our results suggest that the progression of brain abnormalities in first episode psychosis subjects is restricted to those with a poor outcome. Moreover, the pattern of grey matter reductions over time differs according to diagnosis of affective or non-affective psychosis. Our findings are also in accordance with previous MRI studies that showed longitudinal effects of antipsychotics on grey matter in patients with schizophrenia.

Poster #M65

ZNF804A AND CORTICAL STRUCTURE IN SCHIZOPHRENIA – IN VIVO AND POSTMORTEM STUDIES

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Background: Recent evidence indicated that the ZNF804A (rs1344706) risk allele A is associated with better cognitive performance in patients with schizophrenia. Moreover, it has been demonstrated that ZNF804A may also be related to relatively intact gray matter volume in patients. To further explore these putatively protective effects the impact of ZNF804A on cortical thickness and folding was examined in this study. To elucidate potential molecular mechanisms an allelic-specific gene expression study was also carried out.

Methods: MRI cortical thickness and folding were computed in 55 genotyped patients with schizophrenia and 40 healthy controls. Homozygous risk allele carriers (AA) were compared with AC/CC carriers. ZNF804A gene expression was analyzed in a prefrontal region using postmortem tissue from another cohort of 35 patients.

Results: In patients, AA carriers exhibited significantly thicker cortex in prefrontal and temporal regions and less disturbed superior temporal cortical folding, whereas the opposite effect was observed in controls, i.e. AA carrier status was associated with thinner cortex and more severe altered cortical folding. Along with this, our expression analysis revealed that the risk allele is associated with lower prefrontal ZNF804A expression in patients, whereas the opposite effect in controls has been observed by prior analyses.

Discussion: In conclusion, our analyses provide convergent support for the hypothesis that the schizophrenia-associated ZNF804A variant mediates protective effects on cortex structure in patients. In particular, the allele-specific expression profile in patients might constitute a molecular mechanism for the observed protective influence of ZNF804A on cortical thickness and folding and potentially other intermediate phenotypes.

Reference:

- [1] Schultz, CC. et al.; Schizophr Bull. 2013 Sep 27.

Poster #M66**REDUCED REGIONAL GREY MATTER VOLUMES IN OFFSPRING OF SCHIZOPHRENIA PATIENTS RELATIVE TO OFFSPRING OF BIPOLAR PATIENTS AND CONTROLS**

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Background: Neuroanatomic abnormalities are likely to precede onset of clinical illness in both schizophrenia (Sz) and bipolar disorder (Bp), and may serve as candidate markers for early detection and treatment of vulnerable individuals. There is increasing support towards the notion that Sz and Bp share neurodevelopmental underpinnings, although areas of divergence remain. Structural MRI studies have revealed neuroanatomic abnormalities in Sz Offspring (SzO), including whole brain grey matter volume reduction and smaller regional prefrontal, temporal and parietal volumes. Conversely, structural MRI studies in Bp Offspring (BpO) have failed to identify differences relative to controls, although the existing body of evidence has been limited by small sample sizes. No study to date has directly compared the neuroanatomical substrates of Sz and Bp young offspring.

Methods: This study was conducted in the Hospital Clinic of Barcelona and Hospital Gregorio Marañón of Madrid, Spain, and was approved by their local Ethical Review Boards. Subjects: Children and adolescents aged 6 to 17, with a parent with Sz or Bp (DSM-IV-TR), and community controls (no diagnosis of Sz or Bp in 1st or 2nd degree relatives). Exclusion criteria: IQ<70, presence of neurological disorder or antecedents of head trauma with loss of consciousness. All subjects underwent a comprehensive socio-demographic and clinical evaluation. High-resolution magnetic resonance structural images were acquired on a 3T Siemens and 1.5 T Philips Intera scanner. Pre-processing: segmentation (sample specific template), normalization (DARTEL) and smoothing (8 mm FWHM). Voxel-based morphometric (VBM) between group analyses were performed, where age, gender, intracranial volume and center included as covariates (SPM8). Peak-level statistics were employed. Post-hoc mixed-models were performed to explore the effect of lifetime axis I disorders and sibship on the significant results (SPSS). All analyses were repeated excluding subjects receiving psychotropic medications.

Results: 206 subjects underwent assessment (32 SzO vs. 76 BpO vs. 98 CC, mean ages: 10.7 (SD: 3.3) vs. 12.5 (3.1) vs. 11.7 (3.1) F=3.9, p=0.02; gender (%female): 28.1 vs. 43.4 vs. 55.1; χ^2 :7.5, p=0.02). 7 SzO and 6 BpO were receiving psychotropic medications at the time of scanning (p<0.001). 54.8% of SzO, 38.7% BpO and 17.3% CC had a lifetime history of lifetime axis I diagnosis (p<0.001). Whole brain grey matter volume was significantly reduced in SzO (753.3cc) relative to BpO (760.9cc) and CC (761.5cc), F=4.6, p=0.01. No other whole brain volumes differed between groups. VBM analyses revealed significantly reduced grey matter volumes in right supramarginal gyrus (t =4.87, pFWE = 0.040) and trend-level reduction in left superior temporal sulcus (t =4.7, pFWE = 0.074) in SzO relative to CC. BpO showed no area of grey matter differences relative to CC. Relative to BpO, SzO displayed reduced grey matter in left occipital gyrus (t =4.89; pFWE = 0.015) and left inferior frontal gyrus/insula (t =4.51, pFWE = 0.073). BpO exhibited no regions of reduced grey matter volumes relative to CC. These results survived in the medication free group and the differences remained when taking into account the effects of lifetime axis I diagnoses and sibship.

Discussion: SzO exhibited significant whole brain and regional grey matter volume reduction relative to both BpO and CC. This may index what has been postulated as a greater neurodevelopmental impact of risk for Sz relative to Bp (Murray 2004), although such differences may also be associated with different neurodevelopmental trajectories of the two disorders (Demjaha 2012). The longitudinal follow-up of these adolescents will help answer these unresolved issues.

Poster #M67**APATHY IN SCHIZOPHRENIA: ARE STRUCTURAL ABNORMALITIES IN PRIMARY EMOTION PROCESSING AREAS INVOLVED?**

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Background: Apathy, a quantitative reduction in voluntary, goal directed behavior, is a prominent negative symptom in schizophrenia that has been strongly related to an unfavorable course and poor outcome. It has been thought to break into components of 1) behavioral initiation and execution, and 2) coding the rewarding value of (social) events (Levy & Dubois, 2006). This would imply that areas subserving motor, planning and emotional processing could be structurally related to severity of apathy. We aimed to explore the relation of apathy and gray matter volume of regions associated with primary emotional processing (thalamus, caudate nucleus, and amygdala) and associated with cognitive control and motor execution (dorsolateral prefrontal cortex, lateral parietal cortex, anterior cingulate cortex).

Methods: We included 88 patients (69 males, mean age 33.48±11.22) with a diagnosis of schizophrenia. We defined an apathy sum score based on Positive and Negative Symptom Scale (PANSS) items that were shown to strongly load on apathy as measured with the Apathy Evaluation Scale in first episode patients (Faerden et al., 2008). Items included N2 (emotional withdrawal), N4 (apathetic social withdrawal), N6 (lack of flow), G13 (disturbance of volition), G16 (active social avoidance). 3T structural images were acquired of each subject (TR=9 ms, TE=3.5 ms; matrix 256×256; voxel size: 1×1×1mm; 170 slices, duration: 4 min 11s). Images were analyzed using the segment and DARTEL tools implemented in SPM12b (www.fil.ion.ucl.ac.uk/spm). Modulated, normalized (MNI-space) and smoothed (8mm FWHM) gray matter images were then entered in a linear regression model with apathy sum-score as predictor (mean 10.36±3.71, range: 5–20). Age, sex, total negative symptomatology (minus N2, N4, N6) and total generalized symptomatology (minus G13 and G16) were added as covariates. Finally, total brain volume was entered by means of proportional scaling. Significance was set at p<0.05 FWE corrected at the cluster level (height threshold p<0.005) for the extent of either the subcortical or cortical areas of interest. Non-stationarity correction was applied.

Results: A negative relation between apathy severity and volume of the thalamus was observed [MNI-coordinate: x=8 y=−9 z=2, k=2123; p<0.05 FWE corrected]. In addition, reduced nucleus accumbens volume was also associated with apathy, although just subthreshold at p<0.09 FWE corrected (subcortical composite ROI; [MNI-coordinate: x=6 y=11 z=−9, k=55]). An exploratory whole-brain analysis revealed negative associations with volume of the bilateral insula and hippocampus. In cortical areas, negative relationships with volume of the left superior parietal lobe and right inferior frontal gyrus were observed, but these effects did not survive correction for multiple comparisons. No positive associations were observed.

Discussion: Apathy in schizophrenia is associated with lower volume in subcortical areas including the thalamus, nucleus accumbens, insula and hippocampus. The strongest effect was observed in the thalamus, suggesting that gating of motoric and sensory signals may be compromised at an early level of processing. A smaller volume of the nucleus accumbens may further hamper labeling of potential rewarding information. Hippocampal and insular abnormalities potentially link to respectively abnormalities in memory retrieval and integration of signals of bodily arousal. Future studies should study structural correlates in an unmedicated sample, use a well-validated apathy scale, and link structural deficits to functional activation patterns.

Poster #M68**PREVALENCE OF SPES IN CHILD AND ADOLESCENTS WITH ANXIETY AND DEPRESSIVE DISORDERS AND CORRELATION WITH GENERAL FUNCTIONING**

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Background: While early onset psychosis (EOP, onset before the age of 18) represent 10 to 15% of the total amount of First Episode of Psychosis (FEP) and is considered to have a poorer diagnosis than 'adult-onset psychoses' (AOP), less is known about the prevalence of subthreshold psychotic symptoms (SPEs) in child and adolescent clinical samples (i.e. mood disorders and anxiety disorders). Even less is known about the influence of SPEs in these clinical populations on general and neurocognitive functioning. The aim of the present study is to investigate frequency of SPEs and their correlation with level of functioning in a clinical sample of children and adolescents.

Methods: The study was conducted on a sample of 94 individuals (age range: 7-18 years; mean age: 13.3) with mood or anxiety spectrum disorder. SPEs were measured using the Structured Interview for Prodromal Syndromes (SIPS/SOPS). Only patients with symptom scores at SIPS positive sub scale ≤ 2 (i.e. non UHR nor FEP) were included in the present study. Psychiatric diagnoses were made by an expert clinician based on the diagnostic interview Kiddie SADS – Present and Lifetime Version (K-SADS-PL); the severity of depressive symptoms was measured using the Calgary Depression Scale for Schizophrenia and Child Depression Inventory; general functioning was assessed using the Childhood Global Assessment Scale; Neurocognitive functioning (including IQ, EF, social cognition) was measured with a full neurocognitive battery. Participants were recruited from Child and Adolescent Neuropsychiatry Units of the Clinical and Research Hospital Bambino Gesù of Roma and of the Sapienza University of Rome.

Results: The mean age of the sample was 13.3 ($SD \pm 1.6$). About 45% (n=44) of the sample experienced at least one SPEs in the last year (score of 2 or at least one item of SIPS positive scale). No significant differences in term of age and gender were found between patients with and without SPEs. The most frequent SPEs experienced was "Suspiciousness/Persecutory Ideas", followed by "Perceptual Abnormalities/Hallucinations". No significant differences were found in frequency of SPEs between patients with mood and anxiety disorders ($p=0.445$). Patients with SPEs showed significantly higher level of impairment in several neuro cognitive domain (i.e. general functioning; EF; social cognition) compared with patients without SPEs, independently from diagnosis (mood disorders vs anxiety disorders).

Discussion: SPEs are frequent in non psychotic young clinical population and have a significant influence on level of functioning, personal beliefs and self-esteem. These results suggest that SPEs should be investigated on a regular base in child and adolescents clinical population and considered as possible factors which influence negatively level of functioning.

Poster #M69**WHAT LIES BENEATH? A THEMATIC CONTENT ANALYSIS OF SUB-CLINICAL PSYCHOTIC EXPERIENCES AMONG CHILDREN AND YOUNG ADOLESCENTS FROM THE GENERAL POPULATION IN IRELAND AND THE UK**

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Background: The idea that the content of delusions and hallucinations

may have meaning or be symbolically significant is not new. From a psychodynamic perspective, the experience of psychosis has long been conceptualised as a defence against unbearable or unmanageable emotions (Martindale et al 2013) and the content of psychotic experiences is therefore considered to have meaning and relevance for clinical practice (Martindale 2007). In adult samples, the content of delusions and hallucinations has been found to be associated with the experience of trauma and abuse (Raune et al. 2006, Reiff et al. 2012). To the best of our knowledge, no study to date has examined the content of sub-clinical psychotic-like experiences (PLEs) using non-clinical child or adolescent samples. This study aims to identify the presence of themes in the content of PLEs among children and adolescents from the general population and to examine associations between the content of the psychotic experience and adverse or abusive life events.

Methods: A content analysis of qualitative data detailing PLEs from 82 children and adolescents aged 9-13 years is being undertaken to uncover themes within the content of reported PLEs and to determine whether or not the content of PLEs is associated with the experience of trauma or abuse. The data under analysis are reported PLEs from two population-based studies, one based in Ireland and the other in the UK. The Irish sample (N=53) comes from a larger sample of 212 Irish adolescents aged 11-13 years who took part in the Adolescent Brain Development Study (Kelleher and Cannon 2011). The UK sample (N=29) comes from a sample 102 young people aged 9-12 years from the London Child Health and Development Study (Laurens, Hobbs et al. 2012). Both samples were clinically assessed for the presence of PLEs and psychopathology using the Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime Versions (K-SADS) (Kaufman et al. 1997). All young people in both studies who were rated as having definite PLEs were included in the analysis. Transcripts of interviews were examined and detailed descriptions of psychotic symptoms were extracted where present. Qualitative data from the descriptions of PLEs from the young people from each study are being analysed using NVivo 10. Data are being examined to uncover emergent themes within the content of the reported PLEs. The content of PLEs is also being analysed in the context of any reported experiences of trauma or abuse.

Results: Preliminary results from this study reveal that auditory hallucinations are the most prevalent PLE reported within the 9-13 year age range, particularly the experience of voice-hearing. Command hallucinations are infrequent but associated with additional PLEs for young people who experience them. Paranoid and persecutory delusional beliefs, associated with the themes of threat and danger, are relatively common. Religious themes are evident with God and the Devil emerging as central features of more severe PLEs. Preliminary analysis suggests that psychotic experiences manifest potentially unacceptable feelings and urges and are likely to be associated with adversity or past trauma/bullying. Further analysis will consolidate these preliminary findings and identify emergent themes and associations more definitely, including cross-cultural comparisons.

Discussion: This analysis will yield new insights into PLEs among young non-clinical populations that are of relevance to clinical practice. Findings from this study will enhance our understanding of the complex etiology of psychotic psychopathology and inform clinical practice and intervention for young people who report PLEs or who present with emerging psychotic disorders.

Poster #M70**JUVENILE OFFENDERS WITH SEVERE PSYCHIATRIC DISORDERS IN A FORENSIC UNIT: RISK FACTORS OF OVERT AGGRESSIVE BEHAVIORS**

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Background: In juvenile offenders with severe psychiatric disorders, aggressive interaction model is common with peers and adults. Besides of mental illness, abuse during childhood, psychiatric hospitalizations, substance abuse and delinquent behavior are often described as risk factors of aggressive behavior.

Methods: This study was conducted in Brussels, Belgium in a forensic 14-bedded unit of the C.H.J. Titeca. The unit treats adolescents (aged 15 to

18) with early-onset schizophrenia and/or major affective disorders, who are involved in severe delinquency. In order to retrospectively assess risk factors we collected anamnestic data of 72 patients (based on medical records, reports of previous interventions as well as individual and family interviews). To evaluate aggressive behavior during hospitalization, the Overt Aggression Scale (Yudofsky et al., 1987) was completed from patients' files. As violent behaviors are an inclusion criterion for hospitalization, patients were categorized as overtly aggressive by a high weighted cut-off score of 25 points (range 0-60). To ensure validity, patients who scored between 20 and 30 points were re-evaluated by clinical staff. Of patients, 51 presented pervasive overt aggressive behaviors (A+) during their stay, while 21 presented less aggressiveness (A).

Results: When compared to A patients, A+ patients had significantly more frequently been neglected (68.6% vs 42.9%; p=0.04) and sexually abused (41.2% vs 14.3%; p=0.024) during childhood. This was not significant for physical and psychological ill-treatment (respectively, 70.6% vs 66.7% and 74.5% vs 76.2%). Prior psychiatric admission was significantly more frequent among A+ patients than A patients (82.4% vs 47.6%; p=0.003), while age of first admission and number of prior admissions were not significantly different. However, at the beginning of current admission, A+ patients were significantly younger (15.9 years ±1.1) compared to A patients (16.7 years ±0.6) (p<0.001). Rates of substance abuse were not significantly different (88.2% vs 71.4%). Considering delinquent behavior prior to admission, A+ patients committed significantly more often crimes that included physically aggressive acts (without weapon) than A patients (98.0% vs 71.4%; p=0.002). No other delinquent behavior was found to be discriminating between the groups.

Discussion: In juvenile offenders with severe psychiatric disorders, high rates of history of child abuse were observed, illustrating failures in the caregiving environment. Furthermore, A+ patients' environment included more neglect and sexual abuse suggesting a cumulative effect of risk factors for the emergence of overt aggressive behaviors. In regard to the chaotic environment, it is not surprising to observe a higher frequency of a prior hospitalization as well as a younger age of current admission among overtly aggressive patients. Our findings have important implications for developing more comprehensive interventions. One has to also keep in mind that these patients were victims before becoming offenders.

Poster #M71

SUBCLINICAL PSYCHOTIC EXPERIENCES ARE ASSOCIATED WITH ANXIETY, DAILY STRESSORS AND FAMILY FUNCTIONING IN AN ADOLESCENT GENERAL POPULATION SAMPLE

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Background: There is evidence that subclinical psychotic experiences (SPEs) are associated with depression in the general population, but less is known about the association between these experiences and anxiety and stress, and how they might affect daily functioning. The aim of the current study was to examine the association between SPEs and anxiety, stress, daily hassles and general functioning in a large adolescent sample from the general population.

Methods: The sample comprised of 301 adolescents (58% female) recruited through secondary schools in the West Midlands area of the United Kingdom. Participants were aged 14 to 18 years. SPEs were indexed using the CAPE-42.

Results: Increased levels of anxiety ($\beta=0.39$, $p<0.001$) were the strongest predictor of positive psychotic experiences, followed by higher perceived stress ($\beta=0.19$, $p=0.01$) and daily hassles ($\beta=0.16$, $p=0.04$), and lower family functioning ($\beta=-0.12$, $p=0.03$). Depression, and general and peer functioning, were not significantly associated with a total score of positive psychotic experiences after accounting for other covariates. Because females showed significantly higher levels of psychopathology than males, we investigated this association separately for each gender. For females, subclinical psychotic experiences were predicted by higher anxiety ($\beta=0.38$, $p<0.001$) and perceived stress ($\beta=0.18$, $p<0.05$), and lower family functioning ($\beta=0.20$, $p=0.008$). For males, these experiences were predicted by anxiety ($\beta=0.34$, $p<0.001$) and daily hassles ($\beta=0.35$, $p=0.02$), but not any area of functioning. Confirmatory factor analysis was conducted to identify

four subgroups of subclinical psychotic experiences: bizarre experiences, perceptual abnormality, persecutory ideation and magical thinking. Perceptual abnormalities and persecutory ideation were most strongly associated with anxiety, perceived stress and daily hassles, and also associated with significantly decreased functioning.

Discussion: Psychotic experiences in this adolescent general population sample were not associated with depression, but with self-reported anxiety and stress. It is likely that the stress and daily hassles scales are tapping into a similar construct of "daily life stressors" but these are perceived and described differently by adolescent males and females. Perceptual abnormalities and persecutory ideation appear to be more pathological than other psychotic experiences at this level of the extended psychosis continuum. Gender differences and the specificity of experiences may inform school-based interventions.

Poster #M72

DIFFERENTIAL DEVELOPMENT OF THE REWARD NETWORK IN ADOLESCENT OFFSPRING OF SCHIZOPHRENIA PATIENTS

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Background: Adolescence marks a distinct developmental phase during which the brain transforms to its adult state. This transformation occurs at different rates throughout the brain, with subcortical regions as the striatum reaching maturity early, whereas the frontal cortex continues to develop into adulthood. This results in a functional imbalance in the fronto-striatal network. Adolescence is also a time in which psychiatric illnesses such as schizophrenia begin to manifest. Adult schizophrenia patients as well as their siblings show functional and structural abnormalities in the fronto-striatal network (Vink et al. 2006). It has been hypothesized that schizophrenia originates from an abnormal development of the fronto-striatal network during adolescence. Here, we investigate the fronto-striatal network in the context of reward processing in offspring of schizophrenia patients compared to control subjects. These offspring have a ten-fold increased risk to develop a psychotic disorder themselves, and about 70% will develop non-specific psychopathology.

Methods: Thirteen offspring of schizophrenia patients (mean age 13.3, 11 females) and 28 control offspring (mean age 13.3, 10 females) performed a reward task while being scanned with functional MRI (2D-EPI, TR = 1.6s, TE = 23ms). In this task, Participants have to respond to the target as fast as possible, by pressing a button. If this target is preceded by a reward cue, then they can win money. If preceded by a neutral cue, no money can be won. The task was designed so that it allows measuring brain activation associated with reward anticipation during the fixation period, as well as with receiving reward during feedback. The task is tailored to individual capabilities, so that each subject wins the same amount of money, thereby preventing performance confound. 1 euro can be won (shown as a green + 1) during potentially rewarding trials. During feedback, the amount of money won in that trial and the total amount won is displayed. We performed analyses in predefined brain regions, being the bilateral ventral striatum and medial orbitofrontal cortex.

Results: Both groups won the same amount of money (SZ offspring: 6.5 euro, CT offspring: 6.9 euro), while SZ offspring showed a larger reward effect on reaction times (SZ offspring: 24 ms, CT offspring 2 ms). Consistent with our previous findings in controls (Hoogendam et al., 2013), activation in the bilateral ventral striatum increased with age during reward anticipation (versus neutral anticipation) in the control group. No such an increase occurred in the SZ offspring group. During receipt of reward (versus correct neutral feedback), activation in the orbitofrontal cortex was reduced in the SZ offspring group compared to the control group, and this difference remained present across development. No differences were found between the groups in the ventral striatum during receipt of reward.

Discussion: Prior to the presence of major psychopathology, adolescents at familial risk to develop a psychotic disorder already show impaired reward processing during development. These data are in line with results from adult SZ patients showing reduced activation in the ventral striatum during reward anticipation. Also, they are consistent with our recent findings of impaired reward processing in unaffected siblings of schizophrenia patients (De Leeuw et al., submitted). Together, these data suggest that impaired

reward processing is linked to the genetic vulnerability for schizophrenia. We plan to follow these groups longitudinally, so that we can identify how the familial risk for schizophrenia impacts individual developmental trajectories.

Poster #M73

THOUGHT DISORDER IN FIRST-EPIISODE PSYCHOSIS

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Background: Thought disorder is one of the main symptom clusters in schizophrenia. Few studies have investigated thought disorder in the sample of first-episode schizophrenia patients. However in these insufficient number of studies examining thought disorder in first-episode psychosis, thought disorder was evaluated indirectly using the subscales of the other scales, such as BPRS, SAPS, SANS, SADS, in order to evaluate psychotic symptoms. An assessment device which is primarily developed to evaluate thought and language disorder in patients with schizophrenia hasn't been used in previous research. The aim of this study was to examine thought disorder in first episode psychosis by using thought disorder language index.

Methods: Fifty six patients aged between 15–45 and who had a first episode psychosis over the last 2 years were included into the study. All the patients were drug naïve or using medicine less than 6 weeks. First episode patients who had been treated with electroconvulsive treatment were excluded. All the patients were diagnosed as DSM-IV criteria using SCID-I (Structured Clinical Interview for DSM Axis I). 45 normal subjects who had no previous history of mental and neurological disorders were also included as the control group. PANSS was used to rate severity of psychotic symptoms and thought disorder was evaluated by using the Thought and Language Index (TLI) which comprises of impoverishment of thought and disorganization of thought subscales. Impoverishment of thought category includes: poverty of speech, weakening of goal and perseveration. Disorganization of thought category includes: looseness, peculiar word use, peculiar sentence construction, peculiar logic and distractibility.

Results: There were no differences between patient and normal control groups regarding age, gender and education level. First episode patients had significant higher total TLI scores that show worse thought functions ($F=30.65$ $p=0.001$) compared to normal controls. There were significant differences between first episode psychosis patients and normal controls regarding poverty of speech ($F=3.191$ $p=0.001$), weakening of goal ($F=33.071$ $p=0.0010$), perseveration ($F=21.239$ $p=0.001$), peculiar word use ($F=33.061$ $p=0.001$), peculiar sentence construction ($F=50.55$ $p=0.001$), peculiar logic ($F=48.937$ $p=0.001$), thought distractibility ($F=36.525$ $p=0.001$).

Discussion: First episode patients had significantly thought and language abnormalities compared to normal controls. Thought disorder may be evaluated as one of the important symptom domains of schizophrenia requiring further research.

Poster #M74

PROBLEM-SOLVING BASED BIBLIOTHERAPY FOR FIRST-TIME PRIMARY CAREGIVERS OF FAMILY MEMBERS WITH A FIRST EPISODE OF PSYCHOSIS: RANDOMIZED CONTROLLED TRIAL

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Background: First-time primary caregivers of young people with a first episode of psychosis frequently experience significant physical, psychological, social and financial problems as a consequence of their caregiving role.

In this study, we evaluated if caregivers who completed a problem-solving based bibliotherapy intervention (PSBI) manual were able to deal with everyday problems more so than a control group who received treatment as usual (TAU).

Methods: Family caregivers were recruited through case managers at Orygen Youth Health and the Recovery and Prevention of Psychosis Service, both in Melbourne, Australia. Participants were assigned randomly to PSBI or TAU groups. The Social Problem-Solving Inventory-Revised Short Form (SPSI-R:S) (D'Zurilla, Nezu, & Maydeu-Olivares, 2002), a 25 item measure, was used to assess individual's ability to deal with everyday problems. Five standardised scale scores (positive problem orientation, negative problem orientation, rational problem solving, impulsivity/carelessness, avoidance) are derived along with a total score, each of which is measured on a scale with a mean of 100 and a SD of 15 points, with higher scores suggesting "good" social problem solving ability. Intent-to-treat principles were used for the main analyses.

Results: Participant Flow and Sample Characteristics 216 family carers were assessed for eligibility and 57.41% ($n=124$) met inclusion/exclusion criteria and consented to take part in the study. 61 were randomised to the PSBI and 63 to TAU groups. The majority of carers were female, a parent of, and living with, the client. The majority of clients were in the recovery phase. The carers indicated that their support role had adversely influenced their mental (76.4%, $n=94$), physical (59.3%, $n=73$) and social (59.3%, $n=73$) well-being, and employment (62.7%, $n=69$). A significantly longer time had elapsed since diagnosis in the PSBI in comparison to the TAU group, $t(120)=2.15$, $p=0.033$. No other between group differences were detected, at baseline, on any of the demographic variables. 19 participants dropped out of the study (15.3%); 8 from the PSBI group (13.1%) and 11 from the TAU group (17.5%). The dropout rate did not differ significantly between both groups, $\chi^2(1)=0.45$, $p=0.502$. No significant differences in demographic variables were detected between study completers and non-completers. Social Problem-Solving For the SPSI, there was a significant group by time interaction for the impulsivity/carelessness subscale, $F(2,136.6) = 5.76$, $p=0.004$. The rate of improvement in impulsivity/carelessness, from baseline to 6 weeks ($t(157.9) = -3.22$, $p=0.002$) and baseline to 12 weeks ($t(110.1) = -2.65$, $p=0.009$), was greater in the PSBI than the TAU group. Although the two groups appear to differ at baseline, this difference was not significant ($p=0.053$). For the remaining SPSI subscales there were no significant interactions between group and time, between the PSBI and TAU groups, from baseline to 6 weeks and from baseline to 12 weeks. The main effect for time for the rational problem-solving subscale was significant, $F(2,124.3) = 3.74$, $p=0.027$, with significant reductions seen from baseline to 6 weeks ($p=0.018$), and baseline to 12 weeks ($p=0.012$) in both groups.

Discussion: The PSBI group showed significant improvements in their social problem solving in impulsivity/carelessness in comparison to the TAU group, and significant reductions in rational problem-solving. However, there were no significant differences between the groups in social problem solving in positive problem orientation, negative problem orientation, and avoidance. The implications of the findings for caregivers, clinicians and further research are also outlined.

Poster #M75

THE EFFECTS OF MODAFINIL ON COGNITIVE TRAINING: A PROOF-OF-CONCEPT TRIAL IN PATIENTS WITH SCHIZOPHRENIA

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Background: The optimal therapeutic approach for cognitive impairment in schizophrenia may require a combination of cognitive remediation with pharmacological compounds that enhance learning. Our goal was to test the feasibility and cognitive effects of such a combined intervention in patients with schizophrenia.

Methods: 49 participants with schizophrenia or schizoaffective disorder were enrolled in a double-blind, placebo-controlled study across two sites

and were randomised to either modafinil (200mg/day), a compound with known effects on learning and cognition, or placebo. All participants engaged in a broadly-targeted, computer-based cognitive training program daily for 10 consecutive days. The primary outcome measure was the performance on the cognitive training tasks and secondary outcome measures included neuropsychological measures (MATRICS Consensus Cognitive Battery), proxy measures of everyday functioning and symptom measures.

Results: 84% of the participants enrolled in the trial completed all study visits. The performance of all participants in all cognitive training tasks improved over time irrespective of treatment arm assignment. Repeated doses of modafinil did not induce differential enhancement in the performance of the trained tasks nor on the neuropsychological, functional capacity and symptom measures compared to placebo.

Discussion: Interventions combining pharmacological compounds with cognitive training are feasible, though demanding, in schizophrenia. The combination of the particular drug, modafinil, with the cognitive training program used here did not result in differential cognitive enhancement. Issues such as choice of drug, cognitive domains to be trained and cognitive outcome measures remain open for future studies that will combine cognitive training programs with pharmacological compounds for cognitive impairment in schizophrenia.

Poster #M76

AN OPEN-LABEL, FLEXIBLE-DOSE STUDY OF PALIPERIDONE EXTENDED RELEASE IN CHINESE PATIENTS WITH FIRST-ONSET PSYCHOSIS

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Background: Antipsychotic medications facilitate improvement of positive psychotic symptoms in patients with first episode psychosis (FEP). Paliperidone extended-release (pali-ER) is an atypical antipsychotic approved in many countries, including China, for the treatment of schizophrenia in adults. The efficacy and safety of pali-ER in Chinese patients with FEP was examined.

Methods: In this 8-week, open-label, single-arm, multicenter prospective study, patients (aged 18-65 years) with FEP (DSM-IV criteria), and with Positive and Negative Syndrome Scale (PANSS) total score ≥ 70 were treated with flexible-dose pali-ER tablets (3-12 mg/day). The primary efficacy endpoint was percentage of patients with ≥ 8 points increase in personal and social performance (PSP) scale from baseline to day 56 (week 8). The PSP scale scores and its four domains were assessed at baseline, day 28 (week 4) and day 56.

Results: Of the 313 enrolled patients, 308 were included in safety set and 306 in full analysis set. Total 35/308 (11.4%) patients discontinued the study. The percentage of men and women (50%) was similar, with a mean (SD) age of 30.88 (10.4) years; baseline PSP score of 41.39 (12.21) and PANSS total score of 95.3 (18.50). The mean (SD) actual daily dose of pali-ER was 3.65 (2.14) mg at baseline, and 6.53 (1.82) mg at day 56 \pm 3. A total of 283/294 (96.3%) patients achieved a ≥ 8 point increase at endpoint in PSP score (primary endpoint). Secondary efficacy endpoints: 284/306 (92.8%) patients had $\geq 30\%$ reduction in PANSS total score ($P < 0.0001$); 266 (86.9%, 95% CI: 83.2-90.7%) patients achieved a ≤ 3 Clinical Global Impression-Severity (CGI-S) scale score and 218/294 (74.2%, 95% CI: 69.2-79.2%) patients had PSP score ≥ 71 . PANSS Marder factor scores significantly improved ($P < 0.0001$) after 8 weeks of pali-ER treatment, with greatest improvement occurring in "positive symptoms". The mean (SD) changes in PANSS total scores (51.80 [21.60]), CGI-S scores (3.20 [1.21]) and Neuroleptics Scale scores (21.97 [20.38]) from baseline to endpoint were also significant ($P < 0.0001$). There was a significant improvement on Subjective Well-being under Neuroleptics (SWN) scale from (72.67 [16.95]) at baseline to (94.66 [16.70]) at day 56. There was a negative correlation between duration of untreated period and posttreatment PSP score ($r = -0.2019$, $P = 0.0006$) and positive correlation with posttreatment PANSS total score ($r = 0.1952$, $P = 0.0007$). Most common treatment emergent adverse events (TEAEs) were extrapyramidal symptoms (12%), agitation, and somnolence (4% each). Three patients (1%) experienced serious TEAEs: depression, excitement, and extrapyramidal symptoms, of which excitement and extrapyramidal symptoms led to permanent study discontinuation.

Discussion: An 8-week flexible dose (3-12 mg/day) treatment with pali-ER resulted in significant improvement in psychotic symptoms and social functions in Chinese patients with FEP and was generally tolerable. Results were consistent with previous placebo-controlled studies conducted in non-Chinese and Chinese population. The study is limited by the open-label study design and lack of placebo-control, but the flexible-dose treatment simulates current clinical treatment practice.

Poster #M77

HOW DOES THE NSA-4 COMPARE TO THE NSA-16?

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Background: The 16-item Negative Symptom Assessment (NSA-16) is increasingly used as a validated measure to track response to treatment of negative symptoms in clinical trials of schizophrenia. The NSA-16, although reliable, takes up to 30 minutes to administer. As clinical trials have become more complex, a briefer assessment tool would be useful. Alphs et al have proposed a four-item version, the NSA-4, as a reliable and valid alternative to the NSA-16. Four of the 16 NSA items are included: restricted speech quantity, emotion: reduced range, reduced social drive, and reduced interests; in addition, both versions of the scale include an overall global rating of negative symptoms. Alphs et al examined the psychometric properties of the NSA-4 in two randomized clinical trials. The current study is an effort to replicate their findings in two other large schizophrenia trials.

Methods: Data are from two Phase 2 randomized double-blind studies comparing an antipsychotic medication with placebo in the treatment of subjects with DSM-IV-TR schizophrenia with prominent negative symptoms. Subjects were interviewed by live two-way videoconferencing at screen, baseline, and 11 more visits, including end point. Raters were from a centralized independent and blinded cohort who were uniformly trained via initial didactic and applied training, and were monitored throughout the studies to ensure calibration and prevent drift. At each visit, raters administered the PANSS immediately followed by the NSA-16. Correlation coefficients between the NSA-16 and the NSA-4 were calculated for the NSA global rating, the PANSS negative and positive subscales, and the Marder factors for PANSS negative symptoms, anxiety/depression, hostility/excitement, disorganized thought, and positive symptoms. Cronbach's alpha and interrater reliability (calculated as an ICC) were determined for the NSA-16 and NSA-4.

Results: The NSA-16 was administered a total of 2804 times by 29 Central Raters, to a total of 483 subjects enrolled in two clinical trials. Overall, the correlation between the total scores of the NSA-4 and NSA-16 was high (0.86). Good convergent validity of the NSA-4 was demonstrated by correlations between the NSA-4 and the NSA global rating ($r = 0.67$), as well as the PANSS negative subscale ($r = 0.73$) and the PANSS negative symptoms Marder factor ($r = 0.73$). Divergent validity in our sample was demonstrated by low correlations between the NSA-4 and the following PANSS Marder factors: anxiety/depression ($r = -0.11$), disorganized thought ($r = 0.29$), hostility/excitement ($r = 0.03$), and PANSS positive symptoms ($r = 0.13$). Cronbach's alpha was lower for the NSA-4 ($\alpha = 0.65$) compared to the NSA-16 ($\alpha = 0.87$). Finally, the interrater reliability estimates for the NSA-4 and NSA-16 were 0.94 and 0.97, respectively.

Discussion: The PANSS and NSA-16 in this study were not administered independently of one another, so the usefulness of the NSA-4 alone can only be evaluated in the context of its pairing with the PANSS. Overall, these results were very similar to those obtained by Alphs et al. In the hands of highly trained and calibrated Central Raters, the NSA-4 had very good overall agreement with the NSA-16, and even higher convergent and divergent validity with the selected PANSS subscales and interrater reliability than was demonstrated by Alphs et al.

Poster #M78**EFFECTIVENESS OF THREE ATYPICAL ANTIPSYCHOTIC-INITIATED TREATMENTS IN CHINESE FIRST-EPIISODE SCHIZOPHRENIA: AN OPEN RANDOMIZED CLINICAL TRIAL**

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Background: It was well known that different atypical antipsychotics had similar efficacy for acute phase treatment in first-episode schizophrenic patients. The troublesome problem for clinicians is how to keep the patients in their treatment as long as possible until full recovery. We compared the effectiveness of three atypical antipsychotic-initiated treatments (risperidone-, olanzapine- or aripiprazole-initiated) on treatment discontinuation for all cause during 12 months of follow-up.

Methods: We did an open randomized controlled trial of three atypical antipsychotic-initiated treatments in 6 sites located in 4 cities of China. Eligible patients were aged 16–45 years, and fulfilled DSM-IV diagnostic criteria for schizophrenia ascertained by SCID-I/P. A total of 600 unselected first-episode patients were randomly assigned to risperidone (2–6 mg per day; n=200), olanzapine (5–20 mg per day; n=200), or aripiprazole (10–30 mg per day; n=200); for those patients with poor efficacy or intolerable side effects (including obvious weight gain), they will be changed into second single-drug stage using another different drug from risperidone, olanzapine or aripiprazole; and then the third stage using any other antipsychotics including clozapine, add-ons or combinations; follow-up was at 1 year. The primary outcome measure was treatment discontinuation for any cause. Analysis was by intention to treat.

Results: The proportion of patients (Kaplan-Meier estimate) who discontinued treatment after three stages within 12 months was 25.1% for risperidone-initiated group, 26.5% for olanzapine-initiated group, and 31.1% for aripiprazole-initiated group, but without no significant difference.

Discussion: This trial suggests that whatever the types of initiated atypical antipsychotic, a clinically satisfactory treatment retention rate for first-episode schizophrenic patients is achievable for at least 1 year.

Poster #M79**EFFECTS OF COGNITIVE REMEDIATION ON COGNITION IN YOUNG PEOPLE AT CLINICAL HIGH RISK OF PSYCHOSIS**

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Background: Onset of psychotic disorders such as schizophrenia typically occurs during late adolescence or early adulthood often resulting in chronic social and occupational disability. Deficits in cognition and functional outcome (e.g. social and occupational functioning) often precede the onset of full-blown psychosis although to a lesser degree than observed in schizophrenia. Progress in risk identification methodology has enabled reliable detection of persons thought to be putatively prodromal for psychosis, that is, at clinical high risk (CHR) of developing a psychotic disorder. Since CHR individuals evidence cognitive deficits, which increase around the time of conversion, cognition is an excellent treatment target. There is evidence, in schizophrenia and in CHR samples, that deficits in cognition are related to poor functional outcome. Thus, treatments targeting cognition may consequently improve functional outcome. The primary aim of the project was to reduce cognitive deterioration in CHR individuals using cognitive remediation training (CRT) and test the efficacy of the PositScience Brain Fitness (BF) auditory training program in improving cognition of these individuals.

Methods: This is a longitudinal, single blind, randomized controlled pilot trial of CRT in 32 CHR persons between the ages of 14 and 35 years.

Participants were randomised to either the BF treatment or a control treatment consisting of commercial computer games (CG). The 40 hours of BF intervention or computer game activity was expected to occur 4 days a week, for an hour each day, over a period of 10–12 weeks. Participants were recruited from an ongoing longitudinal study of CHR individuals. The primary outcome was cognitive function assessed using the MATRICS consensus cognitive battery. The secondary outcome was social and role functioning assessed with Global Functioning: Social and Role scales. All clinical and cognitive assessments using symptom, functioning and cognitive measures were performed at baseline, post-treatment (at 3 months) and at 6-month follow-up.

Results: Half of all participants completed between 20–40 training sessions. There were no significant baseline differences between the two groups on demographics, functional outcome or attenuated symptoms. Mixed effects modelling demonstrated no differences between the groups on cognitive domains at baseline or either follow up assessment. For the BF group, there was a trend towards improvement in speed of processing at 6-months ($LSM=46.59$, $SE=2.91$) compared to baseline ($LSM=39.88$, $SE=2.16$; -2.91 (29), $p=0.06$) and post-training follow-up ($LSM=40.6$, $SE=2.46$; -2.99 (29), $p=0.05$). In the CG group, significant improvements in working memory were observed between post-training ($LSM=41.33$, $SE=3.14$) and 6-month follow-up (47.48 , $SE=2.90$; -6.14 (29), $p<0.05$). Additionally, there were significant improvements in social functioning in the BF group at 6-month follow-up ($LSM=7.32$, $SE=0.54$) compared to baseline ($LSM=5.80$, $SE=0.43$; -1.51 (28), $p<0.05$).

Discussion: Although improvements in the BF group were on a trend level, this finding is potentially significant from a clinical standpoint as it suggest that cognitive remediation intervention may have some benefit after 20 training sessions. Similarly, working memory benefits noted in the CG group indicate that there are some possible benefits to cognitive function from engaging in computer games that consisted of word puzzles and strategy games. Despite improvements in social functioning in BF group this was not significantly associated with improvements in cognition. Lack of significant findings may be due to underpowered study resulting from small sample size and high attrition rate.

Poster #M80**SCHIZOTYPY IS ASSOCIATED WITH A “REVERSAL INFERENCE” DEFICIT BUT NO “JUMPING TO CONCLUSIONS”**

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Background: Can a single factor account for both the formation and persistence of delusional beliefs, or are more required? Delusion formation has been modelled as a tendency to “jump to conclusions”, based on the well-replicated finding that schizophrenic subjects make decisions using less evidence than controls in the classic “beads” task. However, this model has difficulty explaining the persistence of delusions as schizophrenics show a greater decrease in certainty than controls when presented with disconfirmatory evidence in the same task. Delusional persistence has been modelled more successfully in schizotypal subjects, in whom a bias against disconfirmatory evidence (“BADE”) has been demonstrated in a scenario-based task but never in the beads task itself. We investigated whether schizotypal subjects either form or maintain beliefs in an abnormal way.

Methods: We tested 96 non-psychiatric subjects on a beads task, using a ratio of 85:15 beads per jar. Subjects viewed 50 draws and rated their certainty about the identity of the jar on a sliding scale. Subjects knew the jar could change during the task. Each subject saw the same sequence, in which the jar changed after 25 draws. Subjects completed schizotypy ratings questionnaires: the Unusual Experiences (UE), Cognitive Disorganization (CD) and Impulsive Nonconformity (IN) short scales from the O-LIFE, and the Referential Thinking Scale (REF). We assessed “draws to certainty” (the number of beads subjects saw before they were certain) from the start of the experiment and from the change of the jar. We also assessed subjects’ responses to disconfirmatory evidence (the average change in certainty caused by a bead of the opposite colour to the subjects’ belief about the majority in the jar).

Results: There were no statistically significant correlations between any of the schizotypy questionnaires and the “draws to certainty” in the first half of the task. Following the jar change, however, there were significant

positive correlations between the "draws to certainty" and the UE ($r=0.25$, $p=0.018$) and CD ($r=0.25$, $p=0.019$) and REF ($r=0.21$, $p=0.046$) subscales. There were also significant negative correlations between the average responses to disconfirmatory evidence and the IN ($r=-0.38$, $p=0.0002$) and CD ($r=-0.21$, $p=0.045$) subscales.

Discussion: This study is the first to demonstrate a process which could lead to delusional persistence in the beads task in schizotypal subjects. Subjects with high schizotypy subscale scores took longer to be certain about a change in the jar (a deficit in "reversal inference"): indeed, some high scorers took more than 20 draws (of 17 blue beads and 3 red) before they were certain the jar was now "blue". Subjects with high scores also showed smaller decreases in certainty when presented with disconfirmatory evidence. One may therefore speculate that there are two – partially opposing – processes at work in the formation and persistence of delusions. One, a deficit in "reversal inference" or "bias against disconfirmatory evidence" (as it is characterised in the scenario-based task), is present in schizotypal subjects: it seems likely that schizophrenic patients also possess a "reversal inference" deficit given their poor performance on reversal learning tasks. The other, a tendency to "jump to conclusions", perhaps as a result of a noisier decision-making process, is present in schizophrenic patients, but is not reliably found in schizotypal subjects. The deficit in reversal inference might explain why schizophrenics who "jump to conclusions" do not jump to new conclusions. Interestingly, both inferential processes can be explained by neuronal attractors encoding categorical beliefs that are unduly attractive or "sticky".

Poster #M81

HOW FRAMING OF THE RESPONSE AND METAMEMORY SELF MONITORING AND CONTROL ALLOW PATIENTS WITH SCHIZOPHRENIA TO IMPROVE THEIR MEMORY REPORTING FOR GENERAL KNOWLEDGE

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Background: Current findings place cognitive and introspection disturbances at the very heart of schizophrenia. Understanding cognitive and state-of-consciousness disturbances is crucial for understanding the pathophysiology and developing new therapies. How consciousness guides behaviour is part of the metacognitive approach. Metamemory refers to what we know about memory, including our awareness of our cognitive ability, and strategic control of a memory task in progress. In real life, a person is usually free to choose which aspects of an event to relate to, how much detail to volunteer, and what degree of confidence to impart. To increase their report accuracy, rememberers may either withhold information that they feel unsure about or provide relatively coarse information that is unlikely to be wrong. The decision will depend on a variety of situational and personal goals. The purpose of this study was to investigate memory and metamemory processes in patients with schizophrenia further, under more natural conditions, and to pave the way for metamemory-based memory remediation. We explored whether patients with schizophrenia are able to achieve a compromise between accuracy and informativeness when reporting information from memory.

Methods: 25 Patients and their healthy matched controls answered 45 general knowledge questions of various difficulties whose answers are numerical (what is the average price of a baguette?), first freely and second through a metamemory-based control. They first answered each question at their self-paced own level of coarseness. Afterward, they gave two answers for each question at two pre-defined intervals, one narrow (fine grain answer), one wide (coarse grain answer), then attributed a confidence-level judgment to both answers. In the next step, they had to select one of these two answers, to provide the best information they could, as if they were helping one of their best friends potentially earn money in a TV show.

Results: Patients were less accurate (27% correct) than healthy participants (36% correct) when reporting information at a self-paced level of precision. However, they benefited remarkably firstly from the framing of the responding (48% correct), and moreover when allowed to rely on their metamemory judgments, patients were able to further raise the accuracy level of their memory performance to that of the healthy participants (respectively 54% and 56% correct). More specifically, the improvement in

accuracy, irrespective of coarseness, occurs almost only with the group of questions for which the fine grain answer was incorrect and the coarse grain answer accurate. The results show a high proportion of correct answers chosen in these cases (healthy: 70.7%; patients: 64.6%).

Discussion: In spite of their memory deficit in the free report, following accurate monitoring, patients strategically regulated the grain size of their memory reporting and proved to be able to manage the competing goals of accuracy and informativeness. They were helped with that by the framing of the recall, in that they were asked to answer in predefined intervals, and by metamemory monitoring and control. These results lead to some optimism regarding the patients' possible adaptation to everyday life situations, as day-to-day situations do not necessarily have to be strikingly specific but allow for coarse answers.

Poster #M82

LINK BETWEEN FACIAL EMOTION PERCEPTION AND SCHIZOPHRENIA TOWARDS A CLINICAL AND COGNITIVE STUDY AMONG A SAMPLE OF 83 SCHIZOPHRENIC PATIENTS

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Background: Impairments in social functioning seen in schizophrenia are thought to be mediated by deficits in the domains of social cognition (Brown and al, 2013). However neurocognitive deficits and clinical symptoms impact functioning. To investigate and to help to develop cognitive remediation programs, it would be interesting to study the link between some neurocognitive specific domains, sub-domains of social cognition and clinical symptoms. We decided to explore facial emotion perception and its link with clinical symptoms, poor outcome and neurocognitive functions. Indeed previous studies report: 1) an hypothesis of a link between facial emotion perception and attention (Combs and al., 2008); 2) poor outcome schizophrenia (defined by Keefe's criteria) is characterized by dysfunction in social interactions (Keefe and al, 1987; Bralet and al., 2002). The aim of this study was first to compare 2 groups of schizophrenic patients, kraepelinians and no kraepelinians, using clinical and cognitive assessments (including a measure of facial emotion perception); then to explain facial emotion perception towards clinical symptoms, outcome and cognitive measures towards a sample of schizophrenic patients.

Methods: Between 2010 and 2013, we recruited 83 schizophrenic patients from the psychiatric departments in Picardie area (France), according to DSM-IV criteria and using Keefe's criteria. Several socio-demographical, pharmacological, clinical, cognitive [French version of the BACS (Bralet and al., 2007), Facial emotion discrimination task (Erwin, 1992)] data were collected for each patient. To compare the 2 groups, kraepelinians and no kraepelinians, we first used anovas adjusting on age and duration of illness; then we did linear regressions to explore the link between facial emotion perception with the other variables.

Results: We found significative differences between 41 kraepelinians and 42 no kraepelinians, regarding PANSS sub-scores: kraepelinians patients had more disorganized ($p<4.3$. 10-6), negative ($p<2.10-4$), general ($p<0.01$) and positive ($p<0.01$) symptoms. Kraepelinian patients had more neurocognitive deficits in all the domains with the most significant differences regarding attention and speed of processing ($p<2.10-4$) and working memory ($p<2.10-4$). Kraepelinian patients had more deficits in facial discrimination emotion ($p<0.01$) and in facial identification emotion ($p<0.01$). Linear regressions showed a significant relation between disorganization and facial emotion discrimination ($p<0.007$) and between attention and speed of processing and facial emotion identification ($p<0.002$); the link between attention and speed of processing with facial emotion discrimination is almost significant ($p<0.051$).

Discussion: Kraepelinian sub-type refers to a distinct etiopathogenetic subgroup of patients (Mitelman and al., 2007). These results confirm the link between attention, speed of processing, facial emotion perception and disorganization. Cognitive remediation programs must be integrative (including social and neurocognitive training) and personalized (depending on the sub-type of the patients).

Poster #M83**DO PATIENTS WITH SCHIZOPHRENIA USE PROSODIC FOCUS MARKING TO ATTRIBUTE MENTAL STATES IN A CONVERSATION SITUATION?**

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Background: Many previous studies have established that individuals with schizophrenia (SZ) experienced deficits in social cognition including Theory of Mind (ToM) disorders (Brüne 2005, Green et al. 2008). Very few studies have investigated these impairments in schizophrenia during natural communication situations (McCabe et al. 2004, Champagne-Lavau et al. 2009). However, to fully characterize ToM ability in schizophrenia, we need to understand several components of this ability that specifically appear during social interactions. In the present study, we were interesting in focus marking as a linguistic marker of ToM. We know that speakers use prosody to encode the difference between the given/contrastive statuses (i.e. focus marking) of discourse referents in accordance with their beliefs about the hearers' knowledge state. Specifically, in French, the contrastive information shows a tendency to be produced in a separate prosodic phrase from the rest of the utterance. In this study we tested whether the prosodic encoding of contrast is altered in SZ speech during social interaction and whether this alteration reflects ToM impairment.

Methods: Ten individuals with a DSM-IV diagnosis of schizophrenia (SZ) and ten healthy control (HC) participants matched for age and educational level were recruited. They were all native French speakers. They were assessed on their ToM ability with the hinting task (Corcoran et al. 1995). Then, they were asked to play a collaborative game with an experimenter. During this game, the aim of the participant was to transfer a given route from his/her map to his/her interlocutor. To do so, he/she had to indicate to the interlocutor 32 pairs of noun-adjective fragments (e.g. You have to go between {the purple CANDLES} 1st fragment {and the purple CANDIES} 2nd fragment). For each pair, the noun of the second fragment could be either identical relative to the first one (e.g. candies vs. candies) or could contrast with it (e.g. candles vs. candies). This interactive task enabled us to measure acoustic correlates of prosodic phrasing to determine whether the same target noun was parsed separately from the adjective in the two focused conditions (unfocused: given vs. focused: contrastive).

Results: A mixed effects logistic regression modelling including the 323 observations obtained from the participants' speech was performed to test the effect of focus condition (unfocused: given vs. focused: contrastive) on the prosodic phrasing produced by participants. The main results showed that SZ participants did not produce more separate nouns when the target noun was contrastive than when it was given ($z=1.543$, $p=0.123$). By contrast, HC participants produced more separate nouns when the target noun was contrastive than when it was given ($z=3.830$, $p<0.0001$). Such pattern of performance in the SZ group was significantly correlated with their ToM abilities.

Discussion: These findings showed that SZ participants were unable to use prosody to indicate to their interlocutor which information is part of a contrastive focus, in relation with their difficulties to attribute knowledge to the person with whom they interact. Their production of prosodic phrasing reflecting attribution of knowledge during conversation is impaired. Thus, the interactive task we used appears to be an original option for studying ToM ability in schizophrenia since it is close to what happens in real-life interactions. Linguistic prosody seems to be a good target for cognitive remediation aiming to increase social cognition ability.

Poster #M84**REWARD LEARNING IMPAIRMENT IN PATIENTS WITH FIRST-EPISTODE SCHIZOPHRENIA-SPECTRUM DISORDER**

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Background: Accumulating evidence indicated that schizophrenia patients exhibited reward learning impairment. Nonetheless, most previous studies focused on chronically-ill patients who had longstanding exposure to antipsychotic medication treatment which may interfere with reward processing. In this study, we aimed to investigate reward learning impairment (gradual reinforcement learning) in patients with first-episode schizophrenia-spectrum disorder with particular focus on its relationship with a key negative symptom sub-domain, namely avolition.

Methods: Thirty-one patients with first-episode DSM-IV schizophrenia, schizopreniform disorder or schizoaffective disorder (treated with antipsychotic for 3-6 months) and 33 healthy controls matched with age, sex and educational level were recruited. Each subject completed a computerized Go/No Go task, in which they had to decide whether or not to choose each stimulus which had different reinforcement probabilities. The task comprised 3 training blocks and 1 transfer phase presenting novel combinations of previously learned stimuli. A battery of cognitive assessments was administered to patients and HC. Patients were assessed with symptom severity using PANSS and SANS (for negative symptoms). Data on antipsychotic medication treatment was obtained. Omnibus repeated measures ANOVA and one-way ANOVAs were used to compare gradual reinforcement learning performance of patients and HC. Spearman's correlational analyses were used to examine the association between reinforcement learning deficit and symptom dimensions.

Results: Patients did not differ from HC in terms of age (P: mean: 24.81, SD: 7.42; HC: mean: 23.68, SD: 7.49), sex (P: male: 42%; HC: male: 47%) and years of education (P: mean: 12.48, SD: 2.67; HC: mean: 12.70, SD: 2.73). HC had significantly higher IQ estimate and better overall cognitive functions than patients. Regarding gradual reinforcement learning performance, patients had significantly lower accuracy in positive stimuli in training blocks 2 ($F(1,62) = 6.25$, $p<0.05$) and 3 ($F(1,62) = 8.00$, $P<0.05$). Patients also had longer reaction time to positive stimuli in training blocks 2 ($F(1,62) = 9.22$, $P<0.05$) and 3 ($F(1,62) = 4.70$, $P<0.05$). Avolition score (derived from Avolition-Asociality global sum score of SANS) negatively correlated with positive stimuli's accuracy in transfer phase ($r(31)=-0.48$, $p<0.01$).

Discussion: The findings of this study indicated that gradual reinforcement learning deficit (esp. positive reinforcement dysfunction) was found in the initial stage of schizophrenia and was associated with severity of volitional impairment. Further prospective research is required to clarify longitudinal course of reward leaning impairment and its relationship with outcome on symptoms and functioning.

Poster #M85**VERBAL EPISODIC MEMORY IMPAIRMENT ALONG THE COURSE OF SCHIZOPHRENIA AND BIPOLAR DISORDER**

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Background: Episodic memory (EM) is an independent declarative memory system responsible for storage and conscious recall of past personal experiences that contains details about the spatial and temporal context of these occurrences – what/when/where happened. EM is highly sensitive to aging and to neurodegenerative diseases, and its performance is thought to be impaired long before the expression of psychological and behavioral symptoms. In severe psychiatric chronic diseases, it is also a domain commonly compromised. In schizophrenia (SZ) and bipolar disorder (BD) that have similar cognitive deficits profiles although their severities are different, memory impairment is shown to be one of the core impairments. There is a correlation with EM and functional outcomes in everyday life; however, the performance of EM across the progression of SZ and BD is still not yet clearly explained. The aim of this study was to compare the performance in an episodic verbal memory and learning neuropsychological task in individuals at recent onset of SZ (RO), chronic patients with SZ (CP); early-stage patients with BD and late-stage patients with BD.

Methods: The double case-control design included 23 RO patients (within first 5 years of SZ diagnosis), 20 CP (minimum of 20 years after the diagnosis of SZ), 16 early-stage patients with BD (well established periods of euthymia and absence of overt psychiatric morbidity between episodes), 14

late-stage patients with BD (individuals who present a clinically relevant pattern of cognitive impairment) and their respective matched controls for age, gender and level of education (27 early-stage controls and 26 late-stage controls). Subjects underwent a psychiatric evaluation to confirm diagnosis, and to verify euthymia or stability. Subsequently, they were assessed with the Hopkins Verbal Learning Test – Revised (HVLTR) a word-list task widely used in psychiatric diseases that measures verbal learning and episodic memory.

Results: Either for immediate ($p<0.0001$, $F=12.060$, RO/early-stage controls = CP/late-stage controls = early-stage BD > RO = late-stage BD = CP) or delayed recall ($p<0.0001$, $F=13.914$, RO/early-stage controls = CP/late-stage controls = early-stage BD > RO = late-stage = CP) performance was different between groups.

Discussion: Results are in accordance with the literature, where patients with BD usually present a milder and more confined cognitive impairment while SZ patients a more severe and pervasive. In SZ, memory impairment may result from failure of strategic processing at encoding. The 1st trial of immediate recall was responsive to progression of BD and SZ. The early-stage BD group individuals remembered similar number of words compare to both control groups; however, the number of words remembered by other groups decreased in the following order: RO SZ, late-stage BD and SZ CP with no significant difference. Our results are in line with the evidence that EM is directly associated with psychosocial functioning, i.e. better memory and learning potential is associated with higher social functioning and quality of life. Therefore, it seems that the severity of the EM impairment follows the progression of BD and SZ, and this could help to address the focus of clinical interventions.

Poster #M86

DECREASING PARANOIA LEVELS THROUGH CLASSICAL CONDITIONING: AN EXPLORATORY ESM NON CLINICAL STUDY

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Background: Self-esteem is frequently targeted in psychological approaches to paranoia. Discrepancies between explicit and implicit measures of self-esteem in paranoia have been interpreted as an indicator for the defensive function of delusions. Applying basic learning principles to target self-esteem discrepancies could have potential benefit to decrease defensiveness.

Methods: 45 individuals were studied using Experience Sampling Methodology. Psymate devices were used to administer a structured self-assessment diary which was programmed ten times a day on 6 consecutive days to assess paranoid thinking severity and the level of self-esteem in daily life. Participants with high level of paranoia were randomized into two conditions; experimental condition and control condition (repeatedly pairing self-relevant information with smiling, angry or neutral faces) and then, they were compared to participants with low level of paranoia and control condition. After two days using Psymate device, participants received either the experimental (i.e. pairing self-relevant information with smiling faces) or control condition (i.e. pairing self-relevant information with smiling, angry or neutral faces).

Results: Participants with low levels of paranoia and who were trained under control condition showed significant higher levels of paranoia than participants with high levels of paranoia who were trained with the computer game that repeatedly pairs self-relevant information with smiling faces and participants with low levels of paranoia and control computer game condition. There were not significant differences between participants with high levels of paranoia under experimental condition training and participants with low levels of paranoia and control computer game condition after training in paranoia levels.

Discussion: This exploratory study demonstrated that level of paranoia could be decreased using a Classical Conditioning intervention

Poster #M87

FOLATE PHARMACOGENOMICS, ENDOTHELIAL FUNCTIONING, AND NEUROCOGNITION IN SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Potentially at the core of the metabolic complications seen in patients diagnosed with schizophrenia spectrum disorders (SCZ) is dysfunction of the endothelium. Our research group has shown that alterations in the pharmacogenomically regulated folate metabolism may place individuals at risk for endothelial dysfunction. As part of the AldoMet Cycle, both the methylenetetrahydrofolate reductase (*MTHFR*) 677C/T and Catechol-o-methyl transferase (*COMT*) 158 Val/Met variants are crucial to folate metabolism. Previous reports have also linked *MTHFR* and *COMT* with neurocognition (e.g., working memory). Yet few studies have examined the relationship between folate metabolism enzymes, endothelial functioning, and neurocognition in SCZ. Thus, the purpose of the current study is to explore the relationship between *MTHFR* and *COMT* genotypes, endothelial dysfunction, and their effect on neurocognitive measures in SCZ.

Methods: Participants with schizophrenia spectrum disorders were assessed and screened for endothelial functioning (RHI assessment using the EndoPAT2000), a fasting metabolic laboratory panel was obtained, and a DNA sample was genotyped for *MTHFR* C677T and *COMT* Val158Met. Participants were grouped according to their *MTHFR* 677 T allele and *COMT* 158 Val allele status, and those with an RHI <1.67 met criteria for endothelial dysfunction. Neurocognitive performance was determined using the Brief Assessment of Cognition in Schizophrenia (BACS). Baseline differences in genotype were assessed using standard t-test for continuous variable and chi squared for nominal variables. The relationship between BACS total scores and subscales was examined using a regression model using, age, race, gender, education, folate, and genotype as well as interactions as the independent variables and BACS scores and subscales as the dependent variable.

Results: A total of 95 participants with SCZ were included in this analysis with a mean age of 45 and 56% male. Additionally the participants' average duration of illness was 19 years, 44% were Caucasian, and 38% met metabolic syndrome criteria. All analyses were controlled for race, gender, and education since there were genetic differences in these baseline demographics. Both genotypes were in Hardy Weinberg equilibrium. Overall the BACS composite scores were predicted by level of education, as well as *MTHFR* genotype and an interaction between *MTHFR* and *COMT* genotypes ($p=0.02$). Additionally an interaction between genotype groups and endothelial dysfunction was found ($p=0.03$). For participants not meeting endothelial dysfunction (RHI ≥ 1.67), education best predicted BACS composite scores ($p<0.0001$), while for those meeting endothelial dysfunction criteria (RHI <1.67), poorer overall neurocognition was associated with the *MTHFR* 677 T and *COMT* 158 Val alleles ($p=0.03$).

Discussion: The presence of at least one *MTHFR* T and/or *COMT* Val allele in schizophrenia is associated with poor performance on assessments of general neurocognition. This line of research parallels our previous findings by showing a relationship between *MTHFR*/*COMT* genotypes and risk for metabolic syndrome in schizophrenia. CVD and endothelial dysfunction, in particular, is a specific concern, as it is a CVD risk factor and may have a greater impact of neurocognition in schizophrenia than previously thought. Assessment for overall CVD risk or endothelial functioning is rarely done in clinical practice, but may be an exceedingly important assessment as it is treatable condition. Accordingly, efforts should be made to identify and treat those at high-risk, as treatment may not only reduce CV burden, but also improve neurocognitive outcomes.

Poster #M88

SPREADING DEPOLARIZATION EFFECT ON BEHAVIORAL TEST OF SCHIZOPHRENIC RAT

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Background: Schizophrenia is a complex brain disorder characterized by positive, negative and cognitive symptoms. Unusual levels of glutamate in schizophrenic individuals have been reported. Six week social isolation have used in some research as a model of Schizophrenia.in addition, NMDA

receptor hypofunction has been hypothesized for schizophrenia in preclinical models. Therefore positive modulation of NMDA receptor considered to be important candidates for ameliorate or treatment of schizophrenia. On the other hand, NMDA receptors activation play role in various neurodegenerative diseases. Spreading depression (SD) play a pivotal role in glutamate release and its action on the NMDA receptor. Repetitive SD is concomitant with glutamate receptor expressions up regulation in hippocampal region.

Methods: In the present study 21 Wistar juvenile rats (65-80 gr) were used. Animals were classified in three groups as SD treated with Social isolation, social isolation, and Sham groups. Social isolation was carried out for six week post weaning, which followed by four consecutive weeks SD induction in SD-social isolation group. Prepulse inhibition (PPI) test and anxiety test have been done at the end of experiment.

Results: Our result from behavioral test suggested that SD induction during for week after six week social isolation may be able to help to calm schizophrenia symptoms. Significant changes in cognition tests were seen in SD induced group in comparison with social isolation group. However, there was also significant changes in behavioral and cognition in socially isolated rats in compare to Sham group.

Discussion: Present data demonstrated that NMDA receptor hyperactivation as well as its expression following SD induction perhaps decrease some neurological characteristics of schizophrenia, which could reveal NMDA protective role on schizophrenic patient.

Poster #M89

PSYCHOSIS PRONENESS, ANXIETY, DEPRESSION AND INTERPRETATION BIAS: THE TWINS SCAN CHINA STUDY

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Background: Previous studies have found consistent results that psychosis symptoms and mood disorders, such as depression and anxiety, were all related to a negative interpretation bias, both in the clinical and non-clinical population. Different studies on interpretation bias also showed that negative interpretation bias was a reliable predictor for psychosis proneness and depression.

Methods: The present study investigated the interrelationship among psychosis proneness, depression and anxiety symptoms and interpretation bias in young people from a non-clinical Chinese population from. The Community Assessment for Psychic Experiences (CAPE) and Symptoms Checklist-90 (SCL-90-R) were used as the assessment tools for assessing symptoms including psychosis proneness, depression and anxiety. The Scrambled Sentence Task (SST) with cognitive load was used to measure the index for healthy and unhealthy interpretation bias.

Results: We found a strong correlation between psychosis proneness, depression, anxiety and interpretation bias. Further analysis suggested that the prediction effect of psychosis proneness on interpretation bias was mediated by anxiety, but not depression.

Discussion: In light of the results from the previous studies and the results from the present study, we suggest that the relationship between psychosis proneness, mood disturbances and interpretation bias is interrelated forming a vicious cycle that reinforces the development and persistence of each other. The findings offer insight on how cognitive training and modulation could be used to break the cycle to intervene and treat psychosis and mood disorders.

Poster #M90

CALIBRATION AND CROSS-VALIDATION OF MCCB AND COGSTATE IN SCHIZOPHRENIA

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Background: The Measurement and Treatment Research to Improve Cog-

nition in Schizophrenia (MATRICS) Battery (MCCB), the "gold standard" cognition measure in schizophrenia, covers seven cognitive domains determined to be most relevant to schizophrenia clinical trials. Its test-retest reliability has been demonstrated but concerns have been raised about ease of administration, reliance on language based tests and possible practice effects. Maruff and colleagues developed the CogState Schizophrenia Battery (SB), a computerised cognitive battery designed to minimise the effects of extraneous factors, minimise practice effects, use culture free stimuli (e.g. playing cards) and avoid language-based tasks to minimise problems of culture and experience with testing that can impact performance. Our analysis aimed to examine the convergent validity and reliability of the MCCB and CogState SB in the face of repeated testing.

Methods: 3 studies' data were combined. 1) Single centre, randomised, parallel group study. 40 schizophrenia patients completed the SB and MCCB at baseline 1 and 2 (consecutive days, randomised order), and follow-up 4 weeks later. 2) 2-centre, double-blind, randomised, placebo-controlled proof of concept trial. 41 schizophrenia patients received 12 days of 200mg modafinil or placebo during cognitive training after baseline 1 and 2 MCCB and SB (consecutive days), with 4 week follow-up. 3) Randomised, placebo-controlled, single dose study to evaluate the effects of a putative cognition enhancer on cognitive function in chronic schizophrenia. Patients performed MCCB and SB at baseline, one day later following single administration of study medication and after a 21 day washout period. We used mixed effects models with full information maximum likelihood estimation, including fixed effect terms for site and the stratification factors (sex and smoking status). Linear regression models were used separately to compare the measures at baseline 2 with baseline 1 and follow-up respectively.

Results: – Test-retest correlations between baseline visits for individual SB tasks involving visual learning and memory, attention, and speed of processing were $r=0.91-0.96$. Correlations for the social-emotional task ($r=0.75$) and verbal learning and memory, planning and executive function, and working memory were lower ($r=0.49-0.60$). MCCB domain correlations were lower for speed of processing ($r=0.90$), attention ($r=0.85$) and visual learning and memory ($r=0.72$) than for all others. – Correlation between baseline 2 and follow-up for composite score across all SB domains were $r=0.65-0.80$. MCCB domains were similar: $r=0.62-0.87$. – Correlation at baseline between SB's and MCCB's analogous domains was significant but the strongest correlations in these samples were with different domains, often working memory and attention. – Practice effects on MCCB ($d=0.04-0.40$) exceeded those on the SB ($d=0.07-0.22$).

Discussion: Reliability of the MCCB tasks was more consistent across tasks than the SB but learning effects were larger between baseline 1 & 2. SB composite scores were more reliable and generally exhibited minimal practice effects, so SB tasks may be more suitable to measure change without repeated baselines to ameliorate practice effects. Experiments hinging on generating improvement in these tasks might benefit from initial practice sessions, especially for the MCCB. MCCB and SB domains did not match as expected but we will examine measures of interpersonal function to compare validity.

Acknowledgements: We acknowledge the support of Novartis who provided major in-kind contributions of clinical data sets for this study.

Poster #M91

THE MATRICS CONSENSUS COGNITIVE BATTERY (MCCB): PERFORMANCE AND FUNCTIONAL CORRELATES

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Background: Impaired neurocognition is widely documented in schizophrenia and substantially associated with poor social functioning and independent living skills, low levels of educational attainment and poor occupational functioning. Employment is an essential facet of functioning and there is ample evidence linking occupational measures to neurocognition, specifically to executive functions, working memory, processing speed and attention/vigilance. Associations between MCCB domains and different aspects of functioning such as employment and social functioning have been presented in some recent studies. However, data are still relatively sparse with regard to how the MCCB relates to functional measures. Hence, we

aimed to describe neurocognition as measured with the Norwegian version of the MCB in a sample of patients with psychotic disorders entering a vocational rehabilitation program compared to age and gender matched healthy controls. In the patient group, we further examined the relationships between MCB performance and education, employment history and social functioning.

Methods: One hundred and thirty seven patients and 137 healthy controls completed the MCB. Education- and employment history as well as social functioning as measured with the Social Functioning Scale (SFS), were further assessed in the patient group.

Results: Patients displayed significant impairments on all domains relative to healthy controls. Multivariate analyses of variance yielded substantial main effects for group ($F_{1, 272} = 139.11, p < 0.001$) and for the MCB ($F_{6, 267} = 11.4, p < 0.001$). Patients also performed poorer on all subtests, except on the WMS ($t = -0.61, p = ns$). In the patient group, the MCB differentiated between levels of education with neurocognitive performance increasing with higher level of education ($F_{2, 134} = 11.24, p < 0.001$). Approximately 85% of the patients had previously been employed. The average employment history was 16.3 months part-time, 43.4 months full-time and 4.7 months in work placement. Months of previous employment correlated significantly with processing speed ($\rho = 0.28, p < 0.01$), attention/vigilance ($\rho = 0.27, p < 0.01$), working memory ($\rho = 0.35, p < 0.01$) and visual learning ($\rho = 0.22, p < 0.01$) as well as with the composite score ($\rho = 0.31, p < 0.01$). A multiple regression analysis was statistically significant ($F_{5, 129} = 26.52, p < 0.001$), with age, IQ and employment history as significant predictors of the MCB composite score. The total model explained 51% of the variance. The MCB was further significantly associated with several SFS subscales. The independence- competence subscale yielded the most significant associations with MCB domains (Working memory: $\rho = 0.26, p < 0.05$; Verbal learning: $\rho = 0.19, p < 0.05$; Visual learning: $\rho = 0.20, p < 0.05$ and the MCB composite score: $\rho = 0.25, p < 0.01$).

Discussion: Patients with psychotic disorders, relative to healthy controls, displayed significant impairments on all MCB domains. Our results further confirm the functional validity of the Norwegian version of the MCB and add to findings that the MCB co-varies with different aspects of function, both self-rated measures such as the SFS and objective measures such as education and previous employment. The findings underline the importance of assessing neurocognitive function as this may provide important information about work capacity and the need for task adaptation for patients entering vocational rehabilitation. This may in turn guide employment specialists in tailoring rehabilitation programs.

Poster #M92

PREDICTING FUNCTIONAL CAPACITY AND REAL-WORLD FUNCTIONING IN SCHIZOPHRENIA: THE ROLE OF COGNITION AND NEGATIVE SYMPTOMS

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Background: "Functional Deficits", such as reduced ability to work or have close relationships, are core aspects of Schizophrenia that make it one of the world ten most disabling conditions. "Functional Deficits" may be assessed in two different ways: 1) Functional Capacity, a test that simulates real everyday situations and 2) Real-World Functioning, objective data about patient life. These are different but complementary constructs designed to target interventions to reduce disability in schizophrenia. The aim of this study was determine the factors that best predict functioning as measured by these two kinds of assessment.

Methods: We assessed 48 stabilized patients with Schizophrenia or Schizoaffective Disorder, with mean age of 41 (SD 13.4) years, mean educational level of 9.4 (SD 3.5) years of formal school frequency and mean length of disease of 14.9 (SD 11.8) years. Overall, 64.6% of patients were men and 37.5% were being treated with second-generation antipsychotics. Individuals had their symptoms and Real-World Functioning assessed by PANSS and Personal and Social Performance (PSP) scales respectively. Functional Capacity was evaluated by the UCSD Performance-Based Skills Assessment (UPSA-1), while we used the Brief Assessment of Cognition in Schizophrenia (BACS) for Cognitive performance; a composite z score was calculated averaging individual z scores of each primary measure. Multiple regression was performed using the SPSS (v.20) software, in order to obtain the predictors of Functional Capacity and Real-World Functioning in our

sample. The independent variables used to predict Functional Capacity were Cognitive performance, years of education and Negative Symptoms. When predicting Real-World Functioning, the independent variables were Functional Capacity and Negative Symptoms.

Results: Cognitive performance ($\beta = 0.57, p < 0.01$) was a significant predictor of Functional Capacity, but years of education ($\beta = 0.09, p = 0.45$) and Negative Symptoms ($\beta = -0.16, p = 0.18$) were not. Cognitive performance was able to account for 51% of the variance in Functional Capacity ($F_{3, 43} = 15.00, p < 0.01, R^2 = 0.511$). On the other hand, Negative Symptoms ($\beta = -0.76, p < 0.01$) and Functional Capacity ($\beta = 0.18, p = 0.04$) were significant predictors of Real World Functioning. The two predictor model was able to account for 73% of the variance in Real-World Functioning ($F_{2, 45} = 61.25, p < 0.01, R^2 = 0.731$). Cognition was intentionally suppressed in this last prediction due to its close relationship with Functional Capacity.

Discussion: Confirming previous studies, our findings found a strong relationship between Cognitive performance and Functional Capacity. This is consistent with the idea that Functional Capacity is less influenced by the environment and more sensitive to changes in Cognition. Our findings also established Negative Symptoms as the most important construct on Real-World Functioning, leaving for Functional Capacity a secondary role. A possible explanation for these findings is the idea that, whenever a patient is sufficiently motivated for functioning (lower negative symptoms scores), he may be able to do so in spite of his cognitive status, possibly succeeding through ways that still last to be explored.

Poster #M93

THE ROLE OF COGNITION IN METABOLIC DISTURBANCE IN PEOPLE WITH PSYCHOTIC ILLNESS: NOVEL DATA FROM A LARGE POPULATION PREVALENCE SURVEY

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Background: General population studies, predominantly in older samples with diabetes, have reported an association between metabolic disturbance and cognitive dysfunction. Few studies have examined this association in people with psychosis. Some, but not all, support the association, but the direction of causality in a disorder where cognition may be impaired early in the course of the illness remains indeterminate. The 2010 Australian National Survey of Psychosis was unique in its contemporaneous assessment, within a national epidemiological framework, of symptomatology, medication use, cognitive function and physical health in a large, unbiased sample of people with psychosis. Our aim is to examine cognitive function in people with psychotic illness, and to assess its relationship with (i) metabolic syndrome and (ii) lifestyle risk factors for cardiometabolic disease.

Methods: The survey used a two-phase design. It covered 1,500,000 people aged 18-64 years, 10% of the Australian population in this age group: 7,955 eligible people were screened positive for psychosis in Phase 1 and 1,825 randomly selected and interviewed/assessed in Phase 2. Our results are for 1642 people meeting full ICD-10 criteria for psychosis. Premorbid IQ was measured using NART-R and current cognitive function was measured using RBANS Digit Coding Task, a speed of processing task.

Results: Mean estimated premorbid IQ was 98.0 (SD = 11.3), approximately 0.5 SD below the population mean of 107.4 (SD = 17.1). Current cognitive function was markedly impaired: participants had a mean score of 38.3 (SD = 10.6), 1.6 SDs below the population mean of 54.2 (SD = 9.8). Of participants who provided fasting blood samples, 61% met harmonised criteria for metabolic syndrome. The proportion meeting thresholds for metabolic syndrome were: increased abdominal adiposity, 84%; reduced high density lipoproteins, 58%; elevated triglycerides, 56%; elevated blood pressure, 54%; and elevated glucose, 35%. Many had potentially modifiable lifestyle risk factors for cardiometabolic disease: 66% were smokers, 47% were obese, 32% were sedentary and a further 64% recorded low levels of activity. Fruit and vegetable consumption was low. Lower current cognitive function was significantly associated with having metabolic syndrome

and meeting thresholds for each of its criteria. It was also significantly associated with body mass index, smoking and level of physical activity, but not with fruit and vegetable consumption. Lower premorbid IQ was significantly associated with smoking only. Further analysis was undertaken to assess the independent contribution of cognition and modifiable lifestyle risk factors to metabolic syndrome. In the unadjusted multivariate model, current smoking, body mass index and current cognitive function were significant (ORs and CIs: 1.8 (1.3-2.6), 4.8 (3.1-7.5), 15.8 (10.1-24.6) and 0.98 (0.96-0.99) respectively). After adjustment for sex, age, illness duration, socioeconomic status, diagnosis and medication use, cognition was no longer significant.

Discussion: Our data support a reported association between metabolic disturbance and cognitive deficits, including speed of processing deficits, in schizophrenia. Current but not premorbid cognitive function was associated with metabolic syndrome and its component risks in people with psychotic illness. However, the effect size was small relative to the impact of modifiable lifestyle risk factors. We were unable to explore directionality in our cross-sectional data. Further investigation is warranted of underlying mechanisms and possible bidirectionality in psychosis where cognitive impairment antedates the onset of metabolic disorders.

Poster #M94

ARE THE RELATIONSHIPS OF COGNITIVE PERFORMANCE TO PSYCHOSOCIAL FUNCTIONING AT FIVE YEAR OUTCOME MEDIATED BY DISORGANIZATION SYMPTOMS?

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Background: Recently published meta-analyses show that cognitive functioning in early psychosis can predict aspects of psychosocial functioning at later follow-up; and also suggest that this relationship may be mediated by level of negative rather than positive symptoms. It has been noted, however, that there is little evidence available on the possible role of disorganization symptoms in mediating the relationship of cognitive performance in early psychosis to later psychosocial functioning. In the current paper, based on 113 first episode psychosis patients, we examine the role of cognitive performance as assessed at entry into treatment and one year later in predicting symptoms and weeks of employment and weeks on a disability pension at five year follow-up.

Methods: Global IQ, as well as measures of specific functions, such as speed of processing, verbal and visual memory, working memory and verbal fluency, were assessed soon after admission to treatment and one year later. Weeks of full-time occupation in competitive employment or as a student, as well as use of a disability pension, were assessed in the fifth year of follow-up.

Results: In general, global IQ was the best cognitive predictor of level of disorganization symptoms, occupational activity and use of disability pension at five years. Cognitive functioning was not significantly related to negative symptoms or reality distortion at follow-up. Disorganization symptoms did not fully mediate the relationship of cognitive preference to psychosocial functioning.

Discussion: We found early cognitive performance to be more strongly related to disorganization than negative symptoms at follow-up, but disorganization did not fully mediate the relationship of cognition to psychosocial functioning at five years.

Poster #M95

A RANDOMIZED CONTROLLED TRIAL OF COGNITIVE REMEDIATION AFTER A FIRST EPISODE OF SCHIZOPHRENIA: IMPROVING COGNITION AND WORK/SCHOOL FUNCTIONING

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Background: Work/school functioning is often the outcome domain with

the greatest continuing impairment after a first episode of schizophrenia. The level of cognitive deficit during this period is a strong rate-limiting factor in work recovery. Interventions that can improve cognitive functioning early in the course of schizophrenia are essential if we hope to prevent or limit long-term disability in this disorder.

Methods: We completed a 12-month randomized controlled trial of cognitive remediation with 67 patients with a recent first episode of schizophrenia, using healthy behavior training as an active comparison group. The cognitive remediation approach combined computer programs emphasizing repeated practice with elementary cognitive processes (processing speed, attention, immediate memory) and more complex, life-like situations (higher-order memory and problem solving). Two hours/week of computerized cognitive training at the clinic was supplemented with a weekly bridging group to encourage transfer of learning to work and school situations. Patients assigned to healthy behavior training had an equal amount of treatment time that involved instruction and practice in good nutrition habits, light physical exercise, and stress reduction. Supported education/employment was provided to both treatment groups to encourage return to competitive work or schooling.

Results: Consistent antipsychotic medication adherence was found to increase cognitive improvement in this period after a first psychotic episode, so medication adherence and protocol completion were covaried to examine cognitive remediation effects. Compared to healthy behavior training, cognitive remediation produced significant improvement in the Overall Composite score and the Attention/Vigilance domain from the MATRICS Consensus Cognitive Battery. Cognitive remediation also produced significantly greater improvement in work/school functioning than healthy behavior training. The amount of cognitive improvement was also significantly correlated with the degree of work/school functional improvement, suggesting that the cognitive gains were a notable factor in this functional improvement.

Discussion: Our results indicate that cognitive remediation can significantly improve cognitive deficits after a first episode of schizophrenia. When combined with supported education/employment, cognitive remediation shows an impact on work/school functioning that goes beyond the facilitating effect of that compensatory work rehabilitation approach. Additional research should focus on treatment conditions that can produce even larger gains in cognition in this initial period of schizophrenia and that facilitate further generalization of learning from cognitive training sessions to everyday functioning.

Poster #M96

METACOGNITIVE ABILITIES IN FIRST EPISODE PSYCHOSIS: A CONTROLLED EXPERIMENTAL STUDY

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Background: Metacognition is the capacity to "think about thinking", or reflect upon one's thoughts and behaviours. Metacognition operates across various domains, such as perception and memory. Relationships between impaired metacognition and neuropsychiatric disorders, such as first episode psychosis (FEP), have also been suggested. So far this relationship has been investigated in "social" metacognition, how we think about ourselves and other people, and how this is related to insight and neurocognition. This preliminary study investigated if "objective" measures of metacognition, that quantify perceived vs. actual performance on perceptual and memory tasks, differed between healthy controls and FEP patients. We also investigated the relationship between cognitive insight and objective metacognition.

Methods: This study included 35 healthy adults (HA; 18-39 years) and 14 FEP patients (22-34 years). Memory was measured using a computerised 2-alternative forced choice (2AFC) recognition test. Perception was measured using a computerised 2AFC perceptual task, where participants were asked to discriminate between two sets of Gabor patches regarding their brightness. Both tasks required a confidence rating to be made after each trial. Type-II signal detection theory was used to calculate meta-d'/'d, a measure of metacognitive accuracy (MA). Meta-d'/'d values around 1 represent "ideal" metacognitive accuracy. Cognitive insight was measured using the Beck Cognitive Insight Scale (BCIS) self-reflection (SR) and self-certainty (SC) sub-scales.

Results: Results indicated a significant difference between Patient and Control scores on the BCIS SR ($t=-2.21$, $p<0.05$), but not SC ($t=-1.64$, $p=0.20$). Differences between healthy adults and FEP patients approached significance in memory ($t=1.88$, $p=0.069$) and perceptual ($t=1.78$, $p=0.084$) MA. When adjusting for executive function, however, the difference became significant for memory ($F=4.37$, $p<0.05$) but not perceptual ($F=0.32$, $p=0.57$) MA. FEP: There was no direct correlation between cognitive insight and memory (SR $r=-0.27$, $p=0.30$; SC $r=-0.16$, $p=0.89$) or perceptual (SR $r=0.38$, $p=0.40$; SC $r=-0.06$, $p=0.89$) MA. HA: A linear regression predicting perceptual MA from BCIS subscales indicated main effects of SR and SC, and an interaction between gender and BCIS subscales. Females showed a positive relationship between SR and MA, and males a weaker negative relationship (SR ($t=-2.45$, $p<0.02$)). Females showed a negative relationship with SC and MA, and males showed a positive relationship (SC ($t=-2.94$, $p<0.005$)). There were no significant correlation or interaction effects between BCIS and memory MA.

Discussion: Preliminary results indicate that adults with FEP tend to have lower SR abilities and reduced MA about perception and memory than healthy adults, however these differences are more pronounced for memory metacognition. There was no correlation between patients' metacognitive accuracy in either domain and BCIS sub-scales; however, healthy controls showed a relationship between BCIS and MA that was moderated by gender.

Poster #M97

EFFECTS OF INTIMACY ON THE SOCIAL DECISION IN PATIENTS WITH SCHIZOPHRENIA

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Background: Intimacy generally refers to the feeling of being in a close personal association and belonging together. It is a familiar and very close affective connection with another as a result of a bond that is formed through knowledge and experience of the other. Dysfunction of social relationship in schizophrenia patients is well-known, but the effects of the intimacy to social decision in real life situation in schizophrenic patients have been understudied. The aim of this study was to elucidate the behavioral characteristics of schizophrenic patients to the effects of intimacy on the social decision in everyday workplace using virtual reality.

Methods: Twenty-five patients and 40 healthy controls that were between the ages of 30 and 40 years old were participated in this study. Behavioral data were gathered while participants performing the virtual reality task. Fear of Negative Evaluation Scale (FNE), Liebowitz Social Anxiety Scale (LSAS), Self Esteem Scale (SES) were performed to reveal the personal characteristics that would be influenced to the social decision. In the task, there were four avatars. Two avatars were constructed to be familiar, and the others were made to be unfamiliar with the participants. Appearance, tone of voice, and politeness of their way of talking were carefully constructed based on their characteristics. In pre-session, avatars spoke something to participants depending on their level of intimacy for five times each, and after then, participants estimated levels of intimacy with the avatars. The aim of pre-session was to build and estimate intimacy with virtual avatars before performing the main task. After pre-session, avatars requested the participants to do something for 27 times each. Their requests consisted of three levels of difficulties: easy, medium, and hard. During the main task, the participant asked to decide whether they would comply with the request depending on intimacy with the avatar and difficulties of the requests they received. Acceptance rates and reaction time were estimated.

Results: There were no significant differences in age, score of FNE, LSAS and SES between two groups. During pre-session, patients felt closer to unfamiliar avatars than healthy control significantly. In main session, acceptance rate of hard requests from familiar avatars was significantly lower than those of control groups. And patients accepted easy requests from unfamiliar avatars more than controls significantly.

Discussion: During the pre-session, patients felt closer to unfamiliar avatars than healthy control significantly. It might suggest that patients have difficulty in emotional perception. And there were significant differences in acceptance rates between two groups when the social situations were more complex (hard requests from familiar avatars, easy requests from unfamiliar

avatars). This finding provides additional evidence suggesting that deficits in social perception is more prominent when social relationship is more complex in patients with schizophrenia.

Poster #M98

OPTIMISING THE DELIVERY OF COGNITIVE REMEDIATION FOR SCHIZOPHRENIA – RESULTS FROM A FEASIBILITY RANDOMISED CONTROLLED TRIAL OF A NEW COMPUTERISED PROGRAMME, CIRCUITS

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Background: Cognitive remediation therapy (CRT) is an intensive psychological treatment for schizophrenia which is effective in improving cognitive skills such as concentration, memory and problem solving and leads to benefits for general functioning. New directions in CRT research and dissemination emphasise identifying optimum delivery methods and key treatment components. We report preliminary results from a single blind randomised controlled trial investigating a new computerised CRT programme (CIRCuITS) which is highly applicable for these challenges, having a clear theoretical underpinning and being developed with considerable service user input. It offers the potential for reduced therapist demand, easy translation across languages and cultures, and within-therapy tracking of process measures.

Methods: 93 people with a diagnosis of schizophrenia and cognitive and social functioning problems were randomised to receive up to 40 sessions of therapist-led CIRCuITS plus treatment-as-usual (TAU) ($n=46$) or TAU alone ($n=47$). All participants were assessed at baseline, post-therapy and three months later on a battery of neuropsychological, social functioning and symptom measures.

Results: 15% people dropped out of therapy (all but one of them did so before the third session) and 20% completed at least one session independently. CRT led to improvements in non-verbal long-term memory and visuo-spatial executive function. Improved executive function was associated with increased constructive activity levels. Further analyses will explore the moderating effects of within-therapy factors, such as number and content of sessions, within-session improvements and participant characteristics.

Discussion: CIRCuITS is a feasible and effective new computerised CRT programme which can be delivered by a therapist but can also be carried out independently by patients. Its ability to track within-session changes allows it to inform our understanding of how the process of therapy affects outcome in CRT. Consistent with findings from other studies of CRT, improved functional outcomes were associated with improvements in executive functioning. Executive functioning may thus make an important cognitive target if we are to maximise the transfer of new cognitive skills to everyday life.

Poster #M99

AN EXAMINATION OF AUDITORY PROCESSING AND AFFECTIVE PROSODY IN RELATIVES OF PATIENTS WITH AUDITORY HALLUCINATIONS

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Background: Many cognitive models over the last 30 years have been proposed to explain auditory verbal hallucinations (AVH). AVH are known to be emotive in nature, leading to distress and disability for the voice hearer. Research on cognitive models of AVH has emphasised that affective information exacerbates abnormal patterns of responding in AVH patients. One line of research has shown that AVH schizophrenia patients show greater abnormalities on tasks that require the recognition of affective prosody (AP) than non-AVH patients. Detecting AP requires the accurate perception of manipulations in pitch, amplitude and duration. Additional research has established that schizophrenia patients have a range of difficulties detecting these acoustic manipulations; with a number of theorists speculating that AVH patients have exacerbated difficulty in pitch, amplitude and duration discrimination. This study aimed to examine whether relatives of

patients with AVH compared to matched healthy controls demonstrated (1) a reduced ability to perform an AP task and (2) reduced performance on pitch, amplitude and duration discrimination tasks. Also, (3) whether AP performance was related to pitch, amplitude and duration discrimination, and hallucination proneness.

Methods: We recruited 19 relatives of patients with AVH, whom did not have a psychotic diagnosis themselves and 33 healthy controls. They were administered three tasks that examined auditory processing abilities: pitch, amplitude and duration, and a task that examined AP ability. They additionally completed detailed demographic and AVH proneness questionnaires.

Results: The data established (1) Relatives were slower at identifying emotions on the AP task ($p=0.002$), with follow up analysis showing this was especially so for happy ($p=0.014$) and neutral ($p=0.001$) sentences. (2) There was a significant group by deviation level interaction for pitch discrimination ($p=0.019$), and relatives performed worse than controls on amplitude discrimination at deviation levels from 2 to 10%, and on duration discrimination at 25%. (3) AP performance for happy and neutral sentences was significantly correlated with amplitude perception. Lastly, AVH proneness was significantly correlated with pitch discrimination performance ($r=0.44$) and pitch perception performance was shown to predict AVH proneness ($p=0.005$).

Discussion: In sum, this data suggests that basic impairments in auditory processing are present in relatives of AVH patients; they potentially underlie processing speed in AP tasks, and predict AVH proneness. This indicates auditory processing deficits are a core feature of AVH in schizophrenia, potentially representing an endophenotype for AVH.

Poster #M100

INVESTIGATING FACIAL AFFECT PROCESSING IN PSYCHOSIS: A STUDY USING THE COMPREHENSIVE AFFECTIVE TESTING SYSTEM

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Background: Facial affect processing (FAP) deficits in schizophrenia (SZ) and bipolar disorder (BD) have been widely reported; although effect sizes vary across studies, and there are limited direct comparisons of the two groups. Conversely, no study has directly examined how schizoaffective disorder (SZA) patients perform on FAP tasks. Further, there is debate as to the influence of both psychotic and mood symptoms on FAP. This study aimed to address these limitations by recruiting groups of psychosis patients with either a diagnosis of SZ (N=54), BD (N=41; all type I) or SZA (N=11) and comparing them to healthy controls (HC: N=112).

Methods: All participants completed a detailed demographic and clinical interview as well as the facial affect tasks. Four tasks were selected from the Comprehensive Affective Testing System, these included: affect discrimination, name affect, select affect and match affect.

Results: Overall, SZ patients performed poorly on all four subtests, with SZA patients performing similarly, although group comparisons between SZA and HC were not significant on all subtests due to limited sample size. The BD patients showed impaired performance specifically on the match affect subtest, a task that had a high cognitive load. FAP performance in the psychosis patients was correlated with severity of positive symptoms and mania.

Discussion: This study confirmed that FAP deficits are a potential social cognitive endophenotype for SZ and SZA, independent of the specific methodology of the task; whilst deficits in BD are more subtle, and requires future research to elaborate on the role of neurocognition on FAP performance in this cohort.

Poster #M101

COGNITION AMONG SCHIZOPHRENIA IN SUPPORTED EMPLOYMENT PROGRAM IN HOSPITAL PERMAI MALAYSIA

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Background: Schizophrenia is a chronic and severely disabling neurodevelopmental illness, characterized by positive symptoms, negative symptoms and decline in social and occupational functioning. Cognitive impairment is the core deficit of schizophrenia. It is present persistently over time and not affected by changes in the positive or negative symptoms. Cognitive symptom with functional disability is a cause of economic burden and this is directly and indirectly due to the cost of treatment. According to Malaysia National Mental Health Registry (NMHR) Report 2003-2005, only 19% patients with schizophrenia were employed full time. The unemployment was due to cognitive impairment that interfered with their ability to obtain competitive work. There are evidences that vocational rehabilitation could improve cognition. But patient in vocational rehabilitation has less probability of obtaining competitive employment. The Supported Employment Program was developed to help patient with schizophrenia to get into competitive employment. It is proven to be more effective than vocational training in getting patient into employment. The main objective of this study was to study the cognitive functions of patient with schizophrenia in Supported Employment Program in Hospital Permai Johor Bahru and their job outcome after 3 months.

Methods: This is a prospective study carried out from 1st June 2012 until 31st December 2012. A total of 101 patients with schizophrenia in Supported Employment Program in Hospital Permai Johor Bahru who fulfilled the inclusion and exclusion criteria were included in this study. Sociodemographic characteristics of the respondents were gathered. MATRICS Consensus Cognitive Battery (MCCB) were used at baseline. Trail Making Test A (TMT-A), Brief Assessment of Cognition in Schizophrenia (BACS) - Category Fluency and Symbol Coding, Wechsler Memory Scale-Third Edition (WMS-III): Spatial Span and Hopkins Verbal Learning Test-Revised (HVLT-R) at 3-month follow-up. Their job outcome at 3-month follow-up was obtained.

Results: The overall prevalence of cognitive impairment among patients with schizophrenia in Supported Employment Program in Hospital Permai Johor Bahru is 99% with no significant difference between the employment status and type of job. There are no significant association of demographic data with cognitive impairment. There are significant change in cognitive scoring in speed of processing ($P = 0.037$), working memory ($P < 0.001$), verbal learning ($P = 0.010$) and visual learning ($P = 0.007$) in employed patient. Comparing the group of patient in competitive job and social enterprise, those in competitive job had significant cognitive score change in working memory ($P < 0.001$), verbal learning ($P = 0.009$) and visual learning ($P = 0.022$). There is no significant effect of cognition on job outcome.

Discussion: Patients who are employed had improvement in cognition but cognition does not affect the job outcome most probably due to effect of supported employment itself that allow patient to enter employment. Patient that enters competitive employment showed more significant changes in cognition than those who are in social enterprise. A different outcome in cognition may be seen in patients who are not in supported employment. Implication of this study is recommendation of implementing Supported Employment Program nationwide as part of rehabilitation.

Poster #M102

TRANSCRIPTOME ANALYSIS REVEALS DOWN-REGULATED SIGNAL TRANSDUCTION PATHWAYS IN PERIPHERAL BLOOD MONONUCLEAR CELLS FROM SCHIZOPHRENIA PATIENTS WITH COGNITIVE IMPAIRMENT

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Background: Schizophrenia is a severe psychotic disorder often associated with the presence of significant cognitive impairment. While previous studies have successfully used peripheral blood mononuclear cells (PBMCs) as an alternative to brain tissues to identify gene expression signatures associated with schizophrenia, few have focused on patients with cognitive impairment or considered the cognitive status in controls. In this study, we investigated gene expression associated with schizophrenia patients with

significant cognitive impairment compared with non-psychiatric controls displaying normal cognitive performance.

Methods: Transcriptome analysis of PBMCs from 47 participants meeting ICD-10 criteria for schizophrenia or schizoaffective disorder (referred to as SZ) and 49 healthy control (HC) participants from Australian Schizophrenia Research Bank was performed using Illumina HT-12 microarray. An initial set of ASRB participants (comprising 617 cases and 659 HCs) were subject to Grade of Membership (GoM) analyses, using 9 cognitive performance indicators (including all subscales from the Repeatable Battery for the Assessment of Neuropsychological Status, the Controlled Oral Word Association Test and the Letter Number Sequencing Test, and estimates of premorbid and current intelligence quotient). The 47 SZ cases included here fell into "cognitive deficit" (n=22) or "cognitively spared" (n=25) subtypes (combined for subsequent SZ analyses); all 49 HCs had "normal" cognitive performance (HCs who showed evidence of cognitive impairment were excluded). Differentially expressed genes (DEGs) were identified between SZ cases and HCs using limma package in R/Bioconductor followed by qPCR validation. At pathway level, generally applicable gene-set enrichment (GAGE) analysis was used to identify dysregulation associated with biological pathways.

Results: Differential expression analysis revealed altered expression of 799 genes (fold change >1.1 and FDR <0.05; 332 up-regulated and 467 down-regulated) in PBMCs from patients with SZ compared to HCs. GAGE analysis revealed that 19 and 8 pathways were significantly up- and down-regulated in SZ versus HC, respectively. The 19 up-regulated pathways were comprised of several pathways for human disease including Parkinson's and Alzheimer's disease; six metabolic pathways; four pathways for genetic information processing including DNA repair, ribosome, proteasome, and SNARE interactions in vesicular transport; and two immune system pathways, antigen presentation and complement cascades. In the down-regulated pathways in schizophrenia, 4 out of the 8 were involved in signal transduction, including WNT, Hedgehog, JAK-STAT, and ERBB signaling pathways. The remaining down-regulated pathways were olfactory transduction, taste transduction, aminoacyl-tRNA biosynthesis, and prostate cancer.

Discussion: The transcriptome profiling in schizophrenia was characterized by the up-regulated pathways involved in immune system, genetic information processing and metabolism as well as the down-regulated pathways involved in nervous system signaling and development. While the up-regulation of immune pathways may implicate an immunological component in schizophrenia etiology, the down-regulation of signaling pathways, in line with previous studies on brain tissues, demonstrated the critical connections between peripheral parameters and the pathology of schizophrenia in central nervous system.

Poster #M103

A NEW METHOD OF ASSESSMENT OF THOUGHT DISORDERS (SCHIZOPHRENIA SPECTRUM) USING THE STANDARD FOR CLINICIANS' INTERVIEW IN PSYCHIATRY (SCIP)

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Background: The existing diagnostic criteria for schizophrenia spectrum lack validity and reliability (1-4). Current criteria do not identify homogeneous populations and patients with different presentations satisfy the official criteria (5, 6). Not surprisingly, decades of research in clinical neuroscience and genetics have failed psychiatry (7, 8). Renowned researchers opine that the current systems of the Diagnostic and Statistical Manual (DSM) and International Classification of Diseases (ICD) hinder progress in understanding the etiology of the illness and call for new conceptual frameworks that match the advances in neuroscience (1, 2, 9-11). The author introduces new diagnostic criteria for Thought Disorders (TD) that create homogeneous populations. The author describes a valid and reliable descriptive psychopathology database that matches the new advances in neuroscience and genetics.

Methods: The Standard for Clinicians' Interview in Psychiatry (SCIP) is a method of assessment of psychopathology, administered by clinicians (psychiatrists and experienced mental health professionals) and includes the SCIP interview and the SCIP manual. The SCIP provides diagnoses according to the DSM, ICD or any new system criteria. The SCIP pro-

vides dimensions for generalized anxiety, posttraumatic stress, obsessions, compulsions, depression, mania, suicidality, suicidal behavior, delusions, hallucination, disorganized thoughts, agitation, disorganized behavior, negative symptoms, catatonia, drug addiction, attention, and hyperactivity. The SCIP is a valid and reliable tool and was tested in an international multisite study in three countries (USA, Canada and Egypt) between 2000 and 2012. The total sample size for all sites was 1,003 subjects, making the SCIP project the largest validity and reliability study of a diagnostic tool (12-22). The SCIP data will be used to reclassify patients with schizophrenia spectrum according to the new criteria.

Results: New criteria for Thought Disorders (TD) are proposed based upon essential features (delusions, hallucinations and disorganized speech) and associated features (disorganized behavior, negative symptoms, catatonia, depression, mania, mood swings and cognitive deficits). The following subtypes are proposed: Thought Disorders with Delusions, Thought Disorders with Hallucinations, Thought Disorders with Disorganized Speech, Thought Disorders Mixed (with Delusions and Hallucinations), Thought Disorders Mixed (with Delusions and Disorganized Speech), Thought Disorders Mixed (with Hallucinations and Disorganized Speech), Thought Disorders Mixed (with Delusions, Hallucinations and Disorganized Speech) and Thought Disorders Unspecified. The SCIP data includes 269 patients diagnosed with schizophrenia spectrum according to the DSM-5. The SCIP database for these patients includes symptoms, signs and psychological dimensions. These patients will be reclassified according to the new criteria. The sensitivity and specificity of the new criteria subtypes will be measured against the DSM-5 diagnoses.

Discussion: The new criteria of Thought Disorders and the DSM-5 criteria will be discussed with participants.

Poster #M104

SETTING PSYCHOPATHOLOGY IN MOTION: A NETWORK PERSPECTIVE

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Background: In the light of the recent publication of the DSM-5, there is renewed debate about the relative merit of categorical diagnosis, as laid down in DSM and ICD diagnostic manuals. Issues like validity, usefulness and acceptability of the diagnoses in this manual are increasingly debated.

Methods: Future research and clinical practice may be served by three recent and exciting developments, namely that (i) psychopathology may be best represented by networks of causal influences, rather than as categories or dimensions, (ii) diagnosis in mental health may be based not only on mental symptoms, but also on motor signs, given evidence of cross-diagnostic alterations in motor function in psychiatry, which are thought to represent indicators of neurodevelopmental liability, and (iii) repeated ambulatory assessment of mental experience and motor function may enhance the diagnostic process in psychiatry.

Results: Although 'mental' signs and symptoms to date have been core in the conceptualization of mental disorders, motor dysfunctions represent a possibly underrepresented area in psychiatric diagnosis, as (neurological) motor signs can be linked more directly to brain processes, and research shows that motor and mental signs are strongly interrelated. Therefore, it may be argued that motor signs should become more prominent in the psychiatric diagnostic process, facilitating examination of links between brain alterations and mental disorders.

Discussion: We suggest that novel systems of diagnosis are likely to rely more on continuous monitoring of both mental and motor signs in daily life, possibly providing a diagnostic framework combining the two, complementing symptom criteria in DSM and ICD. Patients and their families are likely to benefit from these projects, as novel models of diagnosis based on daily life information may be linked more strongly to treatment needs and prognosis.

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Poster #M105**SCHIZOTAXIA REDUX**

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Background: In 1962 Paul Meehl introduced the term schizotaxia to refer to a genetically determined neural integrative defect predisposing to schizophrenia. On interaction with the social environment and "polygenic potentiators", schizotaxia was proposed to lead to a pattern of psychological organisation called schizotypy, as a necessary precondition for "true" schizophrenia (as opposed to phenocopies emerging via alternative means). Meehl's schizotype was characterised by "cognitive slippage", interpersonal aversiveness, anhedonia, and ambivalence, with neurological soft signs thought to be caused by the core neural integrative defect. The concept of schizotaxia is difficult to define, and its manifestations in the form of schizotypy similarly difficult to operationalize (but it is not equivalent to DSM schizotypal personality, nor conceptualizations based on positive psychotic-like experiences). Using Meehl's descriptions and attempts by others to measure schizotaxia, we sought to identify individuals with these characteristics and determine the utility of this concept for future study in a large sample of healthy individuals and schizophrenia patients from the Australian Schizophrenia Research Bank (ASRB).

Methods: Participants were 659 healthy controls and 617 schizophrenia or schizoaffective disorder cases in the ASRB. A series of Grade of Membership (GoM) analyses were conducted separately for healthy control and case samples, using putative indicators of schizotaxia including specific neurocognitive measures (attention, immediate memory, executive function), self-reported asociality and constricted affect (from the Schizotypal Personality Questionnaire), and neurological soft signs (NSS). The emergent "pure types" were compared in terms of other cognitive, personality, and socio-demographic features, as well as illness-related variables for cases.

Results: Each GoM analysis produced similar three-type solutions: the first subtype was relatively unimpaired on all variables, the second was characterised by predominant NSS and mild executive dysfunction. The third subtype, arguably reflecting "schizotaxia", was characterised by significantly impaired cognitive functioning, asociality, constricted affect (in controls), and poor NSS sensory integration (in controls) or motor control (in SZ). Post-GoM comparison of resulting subtypes reported high levels of social anxiety, suspiciousness, cognitive-perceptual schizotypal features, and a greater level of childhood adversity in schizotaxic controls (5.7% of the sample). In contrast, SZ cases belonging to the putative schizotaxic type (29.8% of cases) were characterized by more severe negative symptoms, and a lower level of childhood adversity.

Discussion: These findings provide preliminary evidence supporting a putative "schizotaxic" profile evident in both clinical and non-clinical groups, in accord with a population base-rate predicted by Meehl's model. Future study of potential neurobiological differentiation of the schizotaxic subtype is warranted.

Poster #M106**THE CLINICAL OVERLAP BETWEEN AUTISM AND PSYCHOSIS**

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Background: Schizophrenia spectrum disorders (SSD) and autism spectrum disorders (ASD), currently conceptualised as separate, have been reported to co-occur at elevated rates. Additionally, the diagnostic criteria of each disorder have areas of overlap and recent research suggests that the disorders share multiple phenotypic similarities. As SSD and ASD are both thought to exist on extended phenotypic continua, it is important to consider not only co-occurrence at the diagnostic level, but also to investigate evidence of overlap in traits. Research of this type is underrepresented in the field. Investigation at the trait level will aid the development of a fundamental understanding of the disorders and their joint impact on quality of life and functioning.

Methods: Young people presenting with a first episode of psychosis to Early Intervention Services in Birmingham were invited to take part in the research. The positive and negative symptom scale (PANSS) was used to

measure positive, negative, and general symptoms of psychosis, and the schizotypal personality questionnaire (SPQ) used to measure underlying schizotypal traits. The Autism Quotient (AQ) was used to measure traits of ASD. The authors of the AQ suggest that scores of above 32, although not diagnostic, may indicate that ASD is present, and that an individual with ASD is unlikely to score less than 26.

Results: Preliminary results from 32 participants suggest that traits of ASD are found at elevated rates in individuals experiencing a first episode of psychosis. Participants (24 male) were aged between 18 and 36 (mean age 26). Of these initial 32 participants, 4 participants scored higher than 26 on the AQ, including 3 scoring higher than 32. Associations between current psychotic symptoms, schizotypal personality, and autism traits were examined. ASD traits were found to have a moderate to strong positive correlation with both state (PANSS) and trait (SPQ) measures of SSD. In particular, strong positive correlations were found between the SPQ subscale of interpersonal deficit and AQ subscales, and between general current symptoms and AQ subscales. Traits of ASD and SSD, as well as current symptoms of psychosis, also had significant negative correlations with participants' quality of life and current levels of functioning. In particular, current general symptoms of psychosis were highly correlated with overall quality of life and functioning, as well as the quality of life subscale of engagement with life. Similarly current negative symptoms of psychosis showed strong correlations with overall quality of life and engagement in life. In addition, current positive symptoms of psychosis, total AQ score, and the schizotypal subscale of interpersonal deficits were negatively correlated with quality of life and functioning. Data will be collected from 100 participants with first episode psychosis. With the full dataset, we will also discuss the association between traits of ASD and childhood trauma, as well as premorbid adjustment.

Discussion: This remains an important topic for investigation to improve understanding of areas of dissociation and overlap between the disorders. We will present a more definitive conclusion with a larger data set.

Poster #M107**CLINICAL IMPLICATIONS OF SCREENING FOR NMDA ENCEPHALITIS IN FIRST EPISODE PSYCHOSIS**

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Background: The diagnosis of Schizophrenia is based clinically on characteristic positive symptoms (e.g. delusions, hallucinations), negative symptoms and social deterioration. Identifying particular aetiologies in specific patient groups may be important in advancing diagnostics and therapeutics. Anti-N-Methyl-D-Aspartate (NMDA) encephalitis is associated with auto-antibodies to the NR1 heteromeric of the NMDA Receptor. Based on recent literature, Anti-NMDA receptor encephalitis could be implicated in approximately 10% of psychotic presentations. Patients with florid NMDA encephalitis e.g. those with initial psychotic symptoms followed by subsequent catatonia, seizures and autonomic dysfunction are usually referred for treatment with immunotherapy. However mild or incomplete forms of the disorder could potentially occur with psychiatric features in isolation. Electroencephalogram (EEG) and Magnetic Resonance Imaging (MRI) of the brain can aid diagnosis. The aim of this ongoing study is to screen a prospective sample of patients with a first episode of psychosis presenting to our service for NMDA antibodies to establish the prevalence in this group. For identified cases, we aim to collaborate with neurology colleagues on treatment decisions and clinical care pathways. We report findings of the first 9 months of the study.

Methods: Following ethical approval, we invited psychiatry teams within the defined catchment area of our service to refer all patients with a first episode psychosis who met entry criteria from January 2013. Recruitment involved a structured clinical interview for DSM-IV (SCID) diagnosis which incorporated the Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS). Phlebotomy for a serum sample for NMDA antibodies was also taken and sent to John Radcliffe Hospital, Oxford, a tertiary referral centre for the diagnosis of immunological disorders.

Results: 4/31 (13%) samples were identified as being NMDA positive. Average age of NMDA-positive cases was older than other first-episode cases

(mean 45 vs 37 years). Duration of untreated psychosis in NMDA-positive cases was slightly less compared to other first-episode cases (8.25 vs 9 weeks). All NMDA-positive cases were admitted as inpatients via emergency services. Case 1 was female, 55. She presented with a week long history of behavioral change, paranoia and abnormal perceptions followed by an episode of collapse. MRI brain was normal. Initial CSF was normal. EEG suggested altered bilateral cerebral dysfunction. Treatment was commenced with plasmapharesis followed by plasma exchange which is ongoing. She has been unable to complete SCID interview to date. The remaining NMDA-positive cases (n=3) were male. Diagnosis was Major Depressive Episode with Psychotic features (n=2) and Bipolar I disorder single manic episode with psychotic features (n=1). MRI brain and EEG were normal in these 3 cases and all showed clinical improvement following standard psychiatric care. Average SAPS and SANS scores were slightly higher for the NMDA-positive cases compared to other first episode cases however this difference was not significant ($p>0.05$) using unpaired t-test.

Discussion: We identified a slightly higher prevalence of NMDA-receptor antibodies in our study sample, although sample size was limited. Increased awareness of NMDA encephalitis has lead to rapid treatment of florid cases in our service. Cases that test positive for NMDA-antibodies but appear to respond to standard psychiatric care should be closely monitored for any signs of deterioration. We aim to develop guidelines for NMDA-encephalitis screening in first-episode psychosis which may help inform early intervention services.

Poster #M108

MEASURING STIGMA - AN OVERVIEW OF AVAILABLE INSTRUMENTS

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Background: The stigma of mental illness has more and more become a research focus in the last decade. Within the field of mental illness, the subtypes public stigma and self-stigma are widely used concepts. Public stigma refers to the way the general public stigmatises people with a mental illness, self-stigma is the internalisation of public stigma, and refers to stigma experienced by people with personal experience of mental illness. The outburst of research on public and self-stigma brings along a variety of instruments to assess stigma, and calls for a (renewed) review of these instruments. The most recent review on public stigma has been performed in 2004, while for self-stigma the most recent review dates from 2010. Current review of instruments to measure stigma will focus on public stigma as well as self-stigma, and besides self-report measures, we will also include implicit measures, such as the Implicit Association Test.

Methods: The following search terms were entered in the online databases MEDLINE, Embase, and PsychINFO: ("psychiatry" OR "mental health" OR "mental illness") AND ("stigma" OR "discrimination" OR "social distance" OR "social exclusion" OR "prejudice" OR "attitude") AND ("instrument" OR "rating scale" OR "questionnaire" OR "interview" OR "measure" OR "assessing" OR "assessment") AND ("psychometric" OR "reliability" OR "validation" OR "validity" OR "reproducibility"). The search was carried out in November 2013. 92 articles were retrieved. All retrieved studies were screened on title and abstract. Possibly eligible studies will be fully examined for relevance, focussing on: 1. Description of an instrument, 2. Presence of relevant psychometric properties, 3. Relation with stigma, 4. Relation with mental health problems.

Results: The search resulted in 92 articles (MEDLINE (13); Embase (16); PsychINFO (63)). Of these 92 articles, 10 were doubles and were removed from the file, leaving 82 articles. These 82 articles were first screened on title and abstract, thereby excluding 28 non-relevant titles. The remaining 54 articles will be fully read and be included or excluded from the review based on the full text. Complete results will be presented at the conference.

Discussion: The results will be discussed at the conference. Based on the results of the review recommendations will be made regarding measuring stigma in research as well as in the clinical practice.

Poster #M109

COMPARING DIAGNOSTIC STABILITY IN TWO FIRST EPISODE FOLLOW UP STUDIES WITHIN A SINGLE GEOGRAPHICAL AREA BETWEEN 1992-2007

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Background: Over the last 21 years, there have been two cohort studies of first episode psychoses with baseline diagnosis and a follow up diagnosis conducted in the same catchment area, the city of the Nottingham in the UK, between 1992 and 2007. This study considers how the diagnostic stability of psychotic disorders has changed over time.

Methods: The SIN (Schizophrenia in Nottingham) study commenced in 1992-1994 and followed 167 subjects after three years, until 1997. The AESOP (Aetiology of Schizophrenia and Other Psychoses) study subjects (N=203) were recruited in Nottingham between 1997 and 1999, and followed at eight years, to 2007. Both the SIN and AESOP studies used the same diagnostic methodology (SCAN assessments, ICD-10 diagnoses and diagnostic consensus meetings of senior clinicians), excluded organic psychoses and included subjects aged 16-65. Positive Predictive Value (PPV) was calculated and used as the measure of diagnostic stability in each study. For the purpose of this comparison 7 diagnostic groupings were used schizophrenia, schizoaffective disorder, depressive illness, mania/bipolar disorder, acute and transient psychotic disorder and drug induced psychosis.

Results: In the SIN study, after three year follow up, greatest diagnostic stability is seen in bipolar disorder/mania followed by schizophrenia, drug induced psychosis and then depressive disorder. The lowest diagnostic stability was seen in schizoaffective disorder, followed by acute and transient psychotic disorder and then delusional disorder. In the AESOP study after 8 year follow up, greatest diagnostic stability is seen in drug-induced psychosis, followed by bipolar disorder/mania, schizophrenia and depressive psychosis. The lowest diagnostic stability was seen in acute and transient psychotic disorder, followed by delusional disorder and then schizoaffective disorder. The diagnostic stability (PPV) of drug-induced psychosis increased in the AESOP study relative to the SIN study (80% cf 69%). Whereas, the stability of a diagnosis of an acute and transient disorder decreased in AESOP compared to SIN (13% cf 37%). A paired t-test showed no significant difference in diagnostic stability between the two studies ($p=0.84$). A Mann-Whitney U test showed no significant difference between the rankings of diagnostic stability in the two studies ($p=0.95$).

Discussion: This comparison has demonstrated that the diagnostic stability is consistent in two studies in one geographical area for the disorders shown to have high stability such as schizophrenia and bipolar affective disorder. We must conclude that drug induced psychoses have become a stable diagnosis over time, when seen in the context of a first episode of psychosis. Those people with a delusional disorder, schizoaffective disorder or acute and transient psychotic disorder at first presentation are more likely to change diagnostic categories over time than remain the same.

Poster #M110

P3 ABNORMALITIES IN NEUROLEPTIC-NAIVE FIRST-EPIISODE SCHIZOPHRENIA PATIENTS AND IN THEIR HEALTHY SIBLINGS

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Background: Previous studies showed the P3 event-related potential, elicited during continuous performance test (CPT), was abnormal in schizophrenia. Our aim was to investigate the P3 in neuroleptic-naive first-episode schizophrenia patients and in their healthy siblings, to find out whether it could be used as an indicator of vulnerability to schizophrenia.

Methods: Electroencephalogram was recorded from 19 neuroleptic-naive patients with first-episode schizophrenia, 19 of their healthy siblings and 27 control subjects during a cued CPT. P3 potentials to Go ($p=0.1$) and NoGo trials ($p=0.1$) were measured.

Results: Reaction times were longer and miss rates were higher in schizophrenia patients compared to their siblings ($p=0.054$, $p=0.024$) and controls ($p=0.001$, $p=0.002$). Schizophrenia patients showed P3 amplitude reduction, which was greater on NoGo than on Go trials ($p=0.041$), com-

pared to the siblings ($p=0.044$) and controls ($p=0.002$). Although, the P3 amplitude was maximal over central and parietal regions in all groups ($p=0.001$), schizophrenia patients ($p=0.001$) and their siblings ($p=0.015$) showed a more frontally distributed P3 compared to controls.

Discussion: Finding of P3 reduction in first-episode schizophrenia patients but not in their siblings suggests that reduced P3 amplitude is related to the onset of psychosis. The more frontally distributed P3, which was observed both in schizophrenia patients and in their siblings, might be an indicator of genetic vulnerability to schizophrenia.

Poster #M111

ADOLESCENT VTA NEURONS RETAIN NEURONAL CORRELATES OF REWARD OPPORTUNITY AFTER EXTINCTION

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Background: An understanding of the neurobiology of adolescent brains is fundamental to our comprehension of the etiology of schizophrenia, the symptoms of which often manifest during this developmental period. Dopamine neurons in the ventral tegmental area (VTA) are strongly implicated in adolescent behavioral and psychiatric vulnerabilities, but little is known about how adolescent VTA neurons process reward and other behaviorally relevant information.

Methods: We recorded daily from VTA neurons in adolescent and adult rats during learning and maintenance of a cued reward-motivated instrumental task. In brief, a discriminative cue was presented, during which an action (nose-poke) was reinforced with a single sugar pellet. After task acquisition, rats were given extinction training during which actions were not longer reinforced with an outcome.

Results: Both age groups similarly learned the task and quickly adapted their behavior to the absence of reward during extinction. There was no difference in baseline firing rate or phasic responses to task-related events during learning and maintenance of the task in adolescents compared to adults. During extinction, however, a critical difference emerged. Whereas adult VTA neurons rapidly diminished their response to the cue, adolescent VTA neurons remained activated by the cue similar to pre-extinction levels.

Discussion: These data indicate that adolescent VTA neurons maintain neuronal correlates of reward opportunity even after extinction. This may present a unique mechanism for increased reward-seeking behavior, as well as psychiatric vulnerabilities in adolescents.

Poster #M112

ELECTRODERMAL ACTIVITY AS POSSIBLE NEUROPSYCHIATRIC BIOMARKER

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Background: Search of biomarkers for the objectification of mental disorders is one of the significant problems of modern scientific psychiatry. The possible biomarker may be the gene or gene sequences, protein or other macromolecule, morphological, metabolic, physiological and laboratory parameters. One of the areas of research is the study of electrodermal abnormalities. Along with existing biomarkers, electrodermal activity (EA) is complex, dynamic and multi-component indicator of the functional status of the nervous system, reflecting the processes of physiological and psychological arousal in health and disease states. Studies of EA in the field of endogenous psychoses (schizophrenia, affective disorders), have detected abnormalities in 40-50% of patients with schizophrenia compared to 5-10% in controls. Current data reveal some specific changes in affective, organic, personality and psychogenic (stress, panic, anxiety) disorders.

Methods: The electrodermal activity were examined with "AMSAT" system in 3 bilateral body regions (head, hands, legs leads) among 441 patients with mental disorders of different origin and 83 healthy controls. The Endogenous group includes Schizophrenia (positive, negative, latent), Schizophrenia Spectrum Disorders (Schizotypal, Schizoaffective, Acute Polymorphic Psychotic Disorder) and Affective Disorders (Major and Recurrent

Depression, Bipolar Affective Disorder of both types). The Exogenous group includes Organic Psychotic Disorders, Organic Depression and Anxiety, Organic Personality Disorder, Organic Asthenia and Substance Abuses (Alcohol, Opiates). The Psychogenic Disorders group includes Anxiety Spectrum Disorders (Panic, Mixed Anxiety-Depressive Disorder), Stress-Related Disorders (Acute Stress and Post-Traumatic Stress Disorder (PTSD), and Neurasthenia.

Results: Most severe changes of EA were found in the Endogenous group: patients with Acute and Latent Schizophrenia demonstrated significant depression of Skin Conductance (SC) level in all leads. Changes in the Negative Schizophrenia were much less noticeable, which could refer to autonomous hyperactivity in that group. Patients with Acute Polymorphic Psychotic Disorder showed significant depression of EA in the head leads. In the Organic Personality Disorder, we found significant depression of SC in the head leads, which may refer to comorbid to the clinical manifestation of personal regression and frontal brain lesions. In PTSD SC level was higher than normal at 9 - 22 conv. un., that apparently reflect sympathetic hyperactivity and increased level of physiological response in a subjective experience of long-term effects of stress. Patients with an Acute Stress Disorder, by contrast, were characterized by a severe (25 to 40 conv. un.) decrease in the electrical conductivity of the skin mainly in the head regions. Reduced electrical conductivity in response to acute stress may reflect the psycho-physiological protective inhibition, which is accompanied, in a clinical level, with the states of narrowing of attention, partial disorientation. Panic disorder were also characterized by a decrease in the SC level of the head leads.

Discussion: EA characteristics vary significantly depending on the etiology and nosological origin of examined mental disorders, giving grounds for the development of approaches to the clinical application of the results of study. According to fast and non-invasive techniques, evaluation of electrodermal parameters can be used as possible biomarker within the complex diagnostic systems.

Poster #M113

THREATENING AND INTRUSIVE LIFE EVENTS AS PRECURSORS TO PSYCHOTIC DISORDERS

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Background: The role of life events in psychosis is still conjectural due to a lack of robust research studies and a limited consideration of contextual influences, such as event type and severity. Research suggests that intrusive life events may show specificity for the onset of psychotic disorders but this has not been thoroughly explored. Therefore, we aimed to investigate the impact of recent experiences on psychosis onset by considering the wider context in which they occur.

Methods: Preliminary data from 171 first-presentation psychosis cases and 193 unaffected population-based controls were available from an ongoing case-control study in London, UK. The impact of life events and chronic difficulties one year prior to psychosis onset (cases) or interview (controls) was assessed using a modified version of the Life Events and Difficulties Schedule. Associations between the severity, intrusiveness and type of recent life events and difficulties, and case status were assessed using logistic regression. Analyses were adjusted for age, gender, ethnicity and years of education.

Results: Psychosis cases reported more moderate and severe threatening life events (Adjusted odds ratio [Adj. OR] 4.7, 95% Confidence Interval [CI] 2.65-8.34) and difficulties (Adj. OR 6.31, 95% CI 3.2-12.43) and also more intrusive and threatening life events (Adj. OR 3.6, 95% CI 2.13-6.08) and difficulties (Adj. OR 10.2, 95% CI 2.82-36.89) in the one year prior to onset compared with controls. Exposure to two or three threatening events led to around a three-fold increase in the odds of psychosis (Adj. OR 3.48, 95% CI 1.95-6.2) and exposure to at least four threatening events increased odds by around six-fold (Adj. OR 6.45, 95% CI 2.73-15.25). Certain types of threatening events showed particularly strong associations with case status

e.g. crime (Adj. OR 18.18, 95% CI 4.85-68.14), health (Adj. OR 10.74, 95% CI 3.58-32.24), work (Adj. OR 7.55, CI 3.01-18.92), housing (Adj. OR 7.33, CI 2.66-20.23), and relationship (Adj. OR 4.65, 95% CI 2.12-10.2) events. Gender and age did not appear to modify the association between the type and severity of recent events and the onset of psychosis.

Discussion: Individuals with psychosis report more severe, chronic, and intrusive events in the year prior to onset than unaffected individuals over a similar time period. There may also be certain events, especially severe crime and health events, which are more likely to increase the odds for psychotic disorders. These findings have significant implications for the prevention and intervention of psychosis.

Poster #M114

SHARED RISK FACTORS BETWEEN SCHIZOPHRENIA AND OTHER NEURODEVELOPMENTAL DISORDERS

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Background: There is accumulating evidence that various neurodevelopmental and neuropsychiatric disorders may not have distinct etiologies but are in fact different phenotypic outcomes of common underlying aberrant processes. Here we investigate familial vulnerability to a range of neurodevelopmental and neuropsychiatric disorders in a family population-based study and examine risk factors that are shared across these disorders.

Methods: The base study population comprised all individuals born in Helsinki, Finland between 1975 and 1976. From the Finnish Population Register we linked these individuals with their parents and all siblings. Diagnostic outcomes were ascertained for all parents and offspring from the Finnish Hospital Discharge Register.

Results: From the national registers we identified 6,401 families comprised of 6,468 individuals born between 1975 and 1976; 9,891 of their siblings and 12,560 parents. Individuals with schizophrenia had an almost 6-fold increase in the odds of having a family member, in most cases a sibling, with intellectual disability; an almost 4-fold increase in the odds of having a family member with an autism spectrum disorder; an almost 3-fold increase in the odds of having a family member with broadly defined developmental delay and an almost 2-fold increase in the odds of having a family member with major depressive disorder. Families with fathers who were younger than 24-years and older than 35-years when the index case was born were more likely to have one or more offspring with a neurodevelopmental disorder compared to families with fathers who were 25-34 years-old when the index case was born.

Discussion: These findings support recent evidence of overlapping etiological factors between neurodevelopmental disorders especially recent evidence of genetic overlap. Considering schizophrenia as one of a number of etiologically linked disorders, all of which have some degree of neurodevelopmental impairment at their core, may provide our studies with greater power to explain the variance in risk for schizophrenia and other complex neurodevelopmental disorders.

Poster #M115

SCHIZOPHRENIA AND VIOLENCE: A COMPARISON BETWEEN FORMERLY AND NEVER VIOLENT PATIENTS LIVING IN RESIDENTIAL FACILITIES

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Background: Since the 80s many studies have attempted to investigate the relationship between psychiatric disorders and violence, investigating whether illness severity, comorbidity, the condition of hospitalization and other factors such as age, sex, co-existence of organic diseases, number of

psychiatric hospitalizations might be predictors of future violent acts. To date, several variables have been identified that appear to be related to an increased risk of committing violent acts in patients with mental disorders. An history of violent behavior, a diagnosis of schizophrenia, especially early onset, the severity of psychiatric symptoms, a diagnosis of comorbid substance abuse, and the number of previous psychiatric admissions have been shown to be risk factors for aggressive behavior in patients with severe mental disorders. Aims: (1) to investigate the sociodemographic, clinical, and treatment-related characteristics of a sample of male patients with schizophrenia, living in 23 Residential Facilities (RFs) with an history of violent behavior against people (so called "violent patients"); (2) to compare the characteristics of violent patients with age-, sex- and diagnosis-matched never-violent residents; (3) to analyse the associations between aggressive behavior (e.g., verbal, physical and sexual) displayed in two years of observation by these two groups (violent vs never-violent); and (4) to assess the predictors of aggressive and/or violent behavior.

Methods: This study is part of a prospective observational cohort study which involved 23 RFs in Northern Italy. All male patients staying in these medium-long term RFs in September 2010, with a diagnosis of schizophrenia and younger than 65 years of age were recruited. Exclusion criteria were being aged 65 years or older, and a primary diagnosis of organic mental disorder (i.e. dementia or mental retardation). The sample was divided into two groups: non-violent patients and "violent" patients. The violent group included patients ever admitted to a Forensic Mental Hospital for violent crimes, patients ever arrested for violent crimes, and patients with a life history of violent acts against persons. For each inpatient was filled out a "Patient Schedule", which included a specific section to assess aggressive behaviors lifetime and in the year prior to inclusion in the study; this evaluation was repeated at the 1-year follow-up, with a total of two years of observation. Aggressive behavior was grouped into the following three categories: verbal, physical and sexual aggressive behavior.

Results: The study involved 182 male patients with schizophrenia: 55 violent and 127 never-violent. There were no statistically significant differences in their socio-demographic characteristics; violent patients had a higher number of lifetime compulsory admissions. With regard to psychopathological dimensions, violent patients showed higher scores on the BPRS suspiciousness item, and lower scores on the same rating scale in conceptual disorganization and motor slowing. Furthermore, violent patients showed a better psychosocial functioning. In our study, the occurrence of aggressive behavior by violent patients during the two years of observation was significantly higher than among the never-violent patients. Even the results of the logistic regression show that committing violent acts in the past increases the likelihood of committing new violent acts in the future.

Discussion: People with schizophrenia and a history of violence are often seen as a difficult-to-manage segment of the population. Our study shows that the presence of a history of violent behavior in the past significantly increases the probability of committing aggressive acts in the future, even in a population living in RFs, that is a supervised environment. Consequently, it is very important to better identify dynamic risk factors which can give us the possibility to effectively prevent and treat aggressive behavior.

Poster #M116

SOCIAL INEQUALITY AT BIRTH AND RISK OF FIRST EPISODE PSYCHOSIS IN RURAL IRELAND: A CASE-CONTROL STUDY

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Background: The past decade has witnessed revival in interest in the role of socio-environmental factors in the aetiology of mental disorders. Socioeconomic status at birth is an important individual-level variable that has been implicated in the aetiology of psychotic disorders. However, little is known about associations between the social environment and risk for psychosis within rural settings. In this study, we set out to investi-

gate the relationship between socioeconomic status at birth, as measured at individual-and neighbourhood-level within a wholly rural context in Ireland using a dataset of unusual epidemiological completeness.

Methods: Study cohort Cases were identified from the Cavan-Monaghan first episode psychosis study (CAMFEPS). This is a prospective study that seeks the closest approximation to identification of "all" incident cases presenting with a first episode of any psychotic disorder in two rural counties in Ireland, Cavan and Monaghan, since 1995. Study design A matched case-control design was used. Birth certificates of subjects who were born in Ireland were obtained from the general register of births. For each case, the two same-sex entries above and the two below on the birth register were selected as controls. Two measures of socioeconomic status at birth were examined: father's occupation was extracted from the birth certificate and a social class was assigned according to the census of population classification of occupations, which consists of six categories; the second socioeconomic indicator was the social characteristic of the area of residence at birth, which was ascertained from the "dwelling-place of father" in the birth certificate. Neighbourhood-level indices of material deprivation, social fragmentation and urban-rural classification were obtained from census data.

Results: Of 335 cases of first episode psychosis, birth certificates were obtained for 256 cases and 975 controls. Preliminary analyses do not indicate a link between socioeconomic status at birth and risk for psychosis. Additional analyses are ongoing and involve a range of socio-environmental factors.

Discussion: This epidemiologically complete, rural cohort presents an opportunity to examine the relationship between individual- and neighbourhood-level socio-environmental factors at birth and risk for first episode psychosis. Our preliminary findings do not support an association between adverse socio-environmental factors proximal to birth and increased risk for psychosis in this rural region. This is in contrast to our recent report of an association between socio-environmental factors proximal to onset and risk for first episode psychosis in the same region.

Poster #M117

EVIDENCE THAT CHILDHOOD URBAN ENVIRONMENT IS ASSOCIATED WITH BLUNTED STRESS REACTIVITY ACROSS GROUPS OF PSYCHOTIC PATIENTS, RELATIVES AND CONTROLS

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Background: Psychosis is associated with urban upbringing, and increased emotional reactivity is associated with psychosis. The aim of this study was to examine to what degree urban upbringing impacts emotional reactivity, and how this may be relevant for psychotic disorder and familial risk of psychotic disorder.

Methods: Patients with a diagnosis of non-affective psychotic disorder (n=58), 59 first degree relatives of patients and 75 healthy comparison subjects were studied with the Experience Sampling Method (a random time sampling technique to assess affective experience in relation to fluctuating stressors in the flow of daily life), to measure a change in negative affect in relation to a stressful event. Urban exposure was defined at 5 levels, considering the population density and the number of moves between birth and the 15th birthday, using data from the Dutch Central Bureau of Statistics and the equivalent database in Belgium.

Results: Multilevel random regression analyses showed that urban upbringing was consistently and strongly associated with a reduced increase in negative affect in relation to a stressful event in adulthood in a dose-response fashion in all three groups, particularly in patients and in first-degree relatives of patients. Regression coefficients in the patient group decreased from 0.148 ($p<0.001$) in the lowest urbanicity level to 0.094 ($p<0.001$) in the highest urbanicity level.

Discussion: The findings suggest that urban upbringing may occasion "habituation" rather than "sensitization" across groups, which may or may not be relevant for the onset of psychotic disorder.

Poster #M118

A POPULATION-BASED LONGITUDINAL STUDY OF ATOPIC DISORDERS AND INFLAMMATORY MARKERS IN CHILDHOOD BEFORE PSYCHOTIC EXPERIENCES IN ADOLESCENCE

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Background: Schizophrenia is associated with infection (such as, antibodies to Toxoplasma gondii, prenatal maternal infection, childhood infection), and abnormalities in various components of the immune system. These include increased levels of systemic inflammatory markers (innate immune response), autoantibodies against various brain regions and ion channels, increased prevalence of autoimmune and atopic conditions (adaptive immune response). Atopic disorders such as asthma, eczema, urticaria and allergic rhinitis are underpinned by adaptive immune response following exposures to non-infectious antigens. An increased prevalence of asthma in schizophrenia has been reported. Recently, a population-based longitudinal study has reported increased risk of adult schizophrenia among individuals with early-life atopic disorders. The effects of systemic inflammatory makers on the developing brain have been proposed as one mechanism that may underlie the association between atopic disorder and later psychosis. However, empirical data on this topic is limited. Early-life psychotic experiences (PE) may be important antecedents of schizophrenia. They are associated with the risk of adult psychosis as well as a number of risk factors for schizophrenia. Therefore, it has been suggested that studies of early-life PE may be helpful to elucidate the pathophysiology of adult psychotic disorders. Using data from the population-based Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, we report associations between early-life atopic disorders, serum inflammatory markers (interleukin 6 or IL-6, C-reactive protein or CRP) at age 9 years, and the risk of PE at age 13 years. We predicted that atopic disorders will be associated with (1) increased levels of inflammatory markers, and (2) risk of PE. We also predicted that inflammatory markers will be associated with subsequent risk of PE, and finally, that they will explain the association between atopic disorders and PE.

Methods: PE were assessed at age 13 years by the face-to-face semi-structured psychotic-like symptoms interview (PLIKSi) (n=6,785). The presence of clinician-diagnosed atopic disorders (asthma, eczema) was determined from parent-completed questionnaires at age 10 years (n=7,814). IL-6 and CRP levels were measured in non-fasting serum samples collected at age 9 years (n=5,076). Logistic regression examined the association between (1) atopy and PE, (2) inflammatory markers and PE, (3) mediating effects of inflammatory markers on the atopy-PE association. Linear regression examined the association between atopy and inflammatory markers. Age, gender, social class, ethnicity and body mass index were included as potential confounders.

Results: At age 10 years, about 14% of the sample was reported to have asthma, 12% eczema, and 7% both asthma and eczema. Compared with children with no atopy, the risk of PE at age 13 years were increased for all of these groups. The adjusted odds ratio (95% CI) for PE was 1.39 (1.10-1.77) for asthma, 1.33 (1.04- 1.69) for eczema, and 1.44 (1.06- 1.94) for both asthma and eczema. Atopy was associated with increased serum IL-6 and CRP; however, this did not mediate association between atopy and PE. Inflammatory markers at age 10 years were not associated with the risk of PE at age 13 years.

Discussion: Childhood atopic disorders are associated with the risk of PE in early-adolescence. Follow-up of these individuals will be useful to determine the effect of atopy and inflammation on different trajectories of early-life PE.

Poster #M119

PREGNATAL AND POSTNATAL EXPOSURES TO MAXIMUM ADVERSITY AMONG HOLOCAUST SURVIVORS AND THE COURSE OF SCHIZOPHRENIA: A POPULATION-BASED STUDY

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Background: The effects of prenatal and postnatal exposure to protracted

maximum adversity (e.g., the Holocaust) on the course of schizophrenia have not been studied. The current study aims to examine the effects of early age exposure to the Holocaust (prenatal and postnatal, and postnatal only) compared to non-exposed controls on the course of schizophrenia.

Methods: Israeli Jews born in Nazi occupied or dominated European nations who had a diagnosis of schizophrenia in the National Psychiatric Case Registry were examined (N=4933). The study groups comprised of subjects who (1) migrated after WWII and who had (1a) both postnatal and prenatal exposure (n=584, 11.8%) and (1b) postnatal exposure only (n=3709, 75.2%), as well as (2) non-exposed subjects (n=640, 13%) who had migrated prior to Nazi persecution. Descriptive statistics and Generalized Estimating Equations were computed to examine psychiatric re-hospitalizations risk of the three study groups, unadjusted and adjusted for age of onset of the disorder.

Results: The group with combined prenatal and postnatal exposures was at statistically significantly ($p < 0.05$) greater risk of psychiatric re-hospitalizations (OR= 1.4 [1.23, 1.58]) than the non-exposed group. This result replicated following stratification by sex, Poland-originated survivors, and at least 10 years of follow-up, until year 2000.

Discussion: Combined prenatal and postnatal exposures to the protracted maximum adversity of the Holocaust is a consistent risk factor for a worse course of schizophrenia, possibly due to maternal stress and neurodevelopmental disruption.

Poster #M120

TAXOMETRIC ANALYSIS OF MULTILEVEL MULTIMODAL RISK DATA FROM SIBLINGS OF PROBANDS WITH NONAFFECTIVE PSYCHOTIC DISORDERS

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Background: The current holy grail in respect of the latent structure of schizophrenia is evidence of taxonicity within multilevel multimodal indicator distributions. In the absence of this, most existing evidence is readily discounted by reference to psychometric and other artefacts. Therefore, we tested for the latent taxonicity of schizophrenia risk using multilevel multimodal data from biological siblings of probands with psychosis in the Genetic Risk and Outcome of Psychosis (GROUP) study.

Methods: Data from n=498 brothers and sisters of individuals with a DSM-IV nonaffective psychotic disorder were careful cleaned. Five symptom expression scores were obtained from principal components of self-report and interview items (Community Assessment of Psychic Experiences, Structured Interview for Schizotypy-Revised, Scale for the Assessment of Negative Symptoms, Scale for the Assessment of Positive Symptoms): negative-asocial features; grandiosity-magical thinking; sensitivity-reference-suspiciousness features; paranoia-asocial features; and a count of other psychosis symptoms. Twelve cognitive functioning scores were obtained: continuous performance test reaction time variability, accuracy and 2 error scores from the Degraded Facial (affect) Recognition Task, Benton Facial Recognition Task accuracy, Response Shifting Task set shifting cost, verbal recognition and recall, and Wechsler Adult Intelligence Scale Digit-Symbol, Arithmetic, Block Design, and Information scores. Skewness was corrected using Box-Cox transformation and multivariate outliers were removed. Taxonicity was tested using maximum covariance (MAXCOV) analysis (slab width = 0.25 SD, slab n≥10) and the maximum eigenvalue (MAXEIG) inchworm consistency test (10 to 120 windows, 90% overlap).

Results: The indicator correlation matrix was nonmonotonic. Cognitive variables were positively correlated ($M = 0.183$, range 0.002 to 0.884) as were symptom variables ($M = 0.349$, range 0.130 to 0.524); correlations between cognitive and symptom variables tended to be negative ($M = -0.013$, range -0.192 to 0.151). Therefore, MAXCOV analysis was applied iteratively, first to symptom data and then cognitive data. Symptom data yielded a peaked covariance curve (base rate = 0.125, GFI = 0.863, K = 1.86), with n=44 (8.8%) in the taxon. These were corroborated by MAXEIG findings (base rate = 0.104). MAXCOV and MAXEIG analyses of the cognitive data provided no evidence of taxonicity but suggest these variables tapped a latent continuous structure that was unrelated to the classification obtained with the symptom data.

Discussion: Evidence of nonmonotonicity within the correlation matrix is logically inconsistent with a simple two-class latent structure for schizophrenia risk, as defined using the indicators assessed here. Moreover, when cognitive variables were removed iteratively, there was no evidence that the few remaining (monotonically related) variables could be combined with the symptom variables for a multilevel multimodal identification of a schizophrenia risk class. Additionally, it is difficult to reconcile the evidence on the base rate of the risk class obtained using symptom data. More robust multilevel multimodal examinations of the latent taxonicity of schizophrenia risk are urgently needed. If evidence obtained from such studies fails to show signs of taxonicity, categorical models of schizophrenia liability must be questioned.

Poster #M121

INCIDENCE, ILLNESS CHARACTERISTICS AND EARLY OUTCOME IN AN IRISH FIRST EPISODE PSYCHOSIS SERVICE

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Background: Psychosis incidence, illness characteristics and outcomes may vary across populations. Study of these variables in different population based samples can assist comparison across geographical regions as well as informing service planning strategies tailored to a specific area. The current study describes (i) the incidence of first episode psychosis in a defined catchment area of Ireland, (ii) the illness characteristics of a sample of individuals presenting to a first episode psychosis service, and (iii) early outcomes for a first episode psychosis sample.

Methods: All individuals aged 16-65 years presenting with suspected psychosis between 2007 and 2011 in a defined catchment area (population of 390,000) were assessed using the Structured Clinical Interview for DSM IV to determine the presence of a psychosis diagnosis. Assertive strategies were used to increase detection of individuals with psychosis including liaison with local Community Mental Health Teams, General Practitioners and other professionals within the catchment area. Individuals with confirmed psychosis were assessed with standardised instruments to determine illness characteristics and early outcomes both at first presentation and one year follow-up.

Results: The incidence of confirmed first episode psychosis in the catchment area was 17.2 per 100,000 population per year. The incidence for broadly defined schizophrenia (SCID schizophrenia and schizophreniform disorder diagnosis) was 7.2 per 100,000 population per year and for narrowly defined schizophrenia (SCID schizophrenia diagnosis only) was 5.4 per 100,000 population per year. Mean age of the entire sample was 32 years and thirty six percent of the sample were aged over 35 years. Forty percent of the sample were female, 65% were inpatient at first assessment, and 44% had a schizophrenia spectrum diagnosis. Median duration of untreated psychosis was three months and median duration of untreated illness was 12 months. At one year follow-up 5% of the sample were inpatient and 48% were working. Ten percent of the sample had depressive symptoms at follow-up while 24% had positive symptoms. Negative symptoms were present in 37% at follow-up while negative symptoms persisted at both first presentation and at follow-up for 24%.

Discussion: Incidence of psychosis was at the lower end of previous estimates which may reflect the absence of a leakage study to identify cases that may have presented outside the catchment area. While most individuals were managed in the community at follow-up, a substantial portion continued to present with debilitating symptoms. These individuals may require a "second wave" of intensive intervention with treatments targeting deficits such as negative symptoms.

Poster #M122**PREVALENCE OF INFECTIONS IN PATIENTS WITH SCHIZOPHRENIA:
A PILOT STUDY**

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Background: Schizophrenia is associated with increased premature mortality, whereas the average decrease in lifespan is 15-20 years. Excess mortality from diseases and medical conditions among persons with schizophrenia is higher, compared to other psychiatric disorders like bipolar or depression. Side effects of pharmacological treatment, unhealthy diet, as well as inadequate provision of health care have been pointed out as important possible reasons for the excess mortality from natural causes within persons with schizophrenia. The presence of medical comorbid conditions is high. Several studies show an increased prevalence of cardiovascular diseases, obstetric complications, respiratory, endocrinologic, and metabolic disorders in schizophrenic patients. Regarding to infections, human immunodeficiency virus, hepatitis, and other infections are common and associated with substance abuse, homelessness and sexual risk behavior. Known problem among persons with schizophrenia is poor dental status, which can be source of infections and endocarditis. There are several lines of evidence that schizophrenia is associated with immune abnormalities. Abnormal blood levels of cytokines, C-reactive protein and changed immune cell functions were found among persons with schizophrenia. Furthermore, schizophrenia and infectious diseases have been associated with genetic markers in the human leukocyte antigens which can give susceptibility for genetic vulnerability in these individuals. Despite these immune abnormalities and many factors that can suppress the immune system, prevalence of infectious diseases among persons with schizophrenia has not been sufficiently revealed. To contribute to the discussion about prevalence of infections in individuals with schizophrenia, we investigated the prevalence of different infections among persons with schizophrenia living in the South Jutland County.

Methods: Data source and study population: We conducted a register-based study using psychiatric hospital data from January 1, 2007 to December 31, 2012. This data is composed of inpatient and outpatient claims submitted by psychiatrics health care providers in the South Jutland County and includes International Classifications of Diseases (ICD-10) diagnostic for patients with schizophrenia; F20.0 –F20.9 and patients with schizophrenia and substance abuse; F10.0-F19.9. We included alcohol and substance abuse/dependence conditions as comorbidities, given the likelihood of these conditions to increase frequency of infections. Data of 694 patients with schizophrenia was linked with microbiological register MADS from January 1, 2000 to December 31, 2010. We conducted the analysis about prevalence of diverse infectious diseases among those patients, reasons of admitting to Infectious Disease Department, the analysis of microbiological agents, which have caused infections.

Results: Preliminary results: Overall, 266 women (38%) and 428 men (62%) were identified with schizophrenia. In percentages, 31% men with schizophrenia and 37% women with schizophrenia had infectious diseases. For individuals under 30 year old prevalence of infections was further increased – 39%. We have found 21% schizophrenia persons with substance abuse, and 29% had infections. Skin infections, gynecological infections and cystitis were common comorbidities. *Staphylococcus Aureus* and *Hemolytic Streptococcus* occurred to be common microorganisms found in those patients. 82% of patients were admitted to the Infectious Disease Department from General Practitioners

Discussion: This study is established as a 3-month pilot study with a thought of developing it to the large cohort population- based nationwide study. The strength of this study is that data on the presence or absence of infections were based on analysis of biological material. Interestingly, we found that young individuals under 30 years old have been more likely to have infections compared to whole study population with prevalence of 39%. Previous studies have revealed that skin infections and urogenital infections were common co-morbidity prior to the diagnosis of schizophre-

nia, where our study can suggest that they are also common after diagnosis. There are many limitations. This study is designed as a observational and descriptive study with limited time of follow up on a homogeny selected population. Due to the time limitation of the study control population has not been chosen. This retrospective observational study reveals that persons with schizophrenia are often admitted to the Infectious Diseases Department and they have increased co-morbidity with skin infections, gynecological infections and cystitis which is consistent with results from previously studies.

Poster #M123**DO PERSONS WITH SCHIZOPHRENIA SELECTIVELY MIGRATE TOWARDS CITY AREAS?**

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Background: Background: It has been hypothesized that person with schizophrenia migrate towards larger cities due to the development of their disorder or its prodromata or fail to participate in the general movement of mentally healthy persons away from larger cities (Freeman H. Schizophrenia and city residence. Br J Psychiatry Suppl 1994;39-50). Such selective migration of persons with schizophrenia would tend to increase the occurrence of persons with schizophrenia in urban areas. However, no study investigated this hypothesis in a nationwide population. We investigated if persons with schizophrenia spectrum disorders (ICD10: F20-F29) more often moved towards larger cities compared to healthy controls.

Methods: Methods: The study population consisted of all persons born in Denmark 1973-1997 and whose both parents were also born in Denmark. Within this population, we identified persons who had their first diagnosis with schizophrenia spectrum disorder from 1971 to 2007. To account for the general mobility of the Danish population, for each case we identified 10 controls with same sex, born within 15 days from the case, born in the same degree of urbanization as the case, and who was alive, residing in Denmark and not diseased at the time the case became case. For the cases and controls separately, we contrast their degree of urbanization of place of residence two years prior to the time the case became case with the degree of urbanization five years after the case became case.

Results: Results: During the period of observation a total of 12,394 persons were diagnosed with schizophrenia spectrum disorder for the first time in their life. Among cases alive and resident in Denmark 5 years after onset, 77.2% stayed in the same degree of urbanization, 11.2% moved to a higher degree of urbanization, and 11.7% moved to a lower degree of urbanization. Among the 127,453 healthy controls alive and resident in Denmark 5 years after the corresponding case became case, 81.1% remained in the same degree of urbanization, 8.7% moved to a higher degree of urbanization, and 10.2% moved to a lower degree of urbanization. We also observed that persons with schizophrenia more often died and were less likely to emigrate from Denmark.

Discussion: Conclusions This is the first nationwide study to investigate the hypothesis that persons with schizophrenia selectively migrate towards urban areas as a consequence of their disorder or its prodromate. Although, we found support for selective migration of persons with schizophrenia spectrum disorder, we found no support that persons with schizophrenia were more likely to migrate towards urban areas compared to healthy controls. Patients with schizophrenia more often drift towards rural areas as compared to healthy controls.

Poster #M124**FORMAL THOUGHT DISORDER: A SYSTEMATIC EPIDEMIOLOGICAL REVIEW**

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Background: Formal thought disorder (FTD) is a core diagnostic symptom of schizophrenia and yet much remains unknown about it. The clinical im-

portance of FTD lies in helping to differentiate between different psychiatric diagnoses although it has been documented in those without any mental illness. Much research has examined possible biological markers associated with FTD, with varying results. The association between functional capacity and FTD is also unclear and this may be due to a lack of clear clinical conceptualisation of this symptom. We aimed to carry out a clinically-oriented review of FTD, to clarify its basic epidemiology and impact on outcome in mental illness.

Methods: A systematic review of the literature on FTD, using PRISMA guidelines to source all relevant articles published in the English language cited on PubMed, Medline and Embase between the 1978–2013. Search terms included "formal thought disorder", "epidemiology", "factor analysis" and "outcome".

Results: We reviewed 401 abstracts, of which 130 articles met inclusion criteria. Articles reporting on FTD prevalence and longitudinal course (n=29), influence on outcome (n=36), role in diagnosis (n=25), association with age (n=26) and factor structure (n=14) were included. A range of different scales are used to assess FTD in the research setting. Researchers refer to "negative FTD", a construct that clinicians would describe as "alogia". Prevalence estimates for FTD range from 27% to 91% in psychotic conditions, with a rate of 6% quoted for normal controls. Lower rates are found in schizoaffective disorder, mania, depression and personality disorders. FTD in mania may be more severe than that seen in schizophrenia. It appears to be less prevalent in children and is very rarely found in late-onset psychotic illness (~5%). FTD tends to remain stable over time: the point prevalence rate in elderly patients with early-onset psychosis is similar to that of their younger counterparts. Factor analysis has shown that FTD is comprised of up to six different factors. The disorganized domain corresponds most closely to the construct of FTD described in the DSM. The type, severity and longitudinal course of FTD can help distinguish between different diagnostic categories with a high degree of accuracy. Co-morbid anxiety disorders appear to be less likely when FTD is present whilst co-morbid cannabis abuse is associated with greater severity of FTD. FTD may follow a remitted, episodic or continuous course and it is associated with a number of adverse outcomes. It is associated with longer hospital admissions, greater likelihood of relapse, poorer insight and increased risk of transition to psychosis in the at-risk mental state (OR 2–4). Poorer social functioning and worse occupational outcomes have been predicted by measures of "bizarre idiosyncratic thinking" and "negative FTD" however the construct of "disorganized thinking" does not show this association to as significant an extent.

Discussion: FTD is a common symptom of mental illness and may be considered a marker of illness severity. A detailed assessment of FTD can clarify differential diagnosis considerably and may help predict prognosis to a degree. Existing literature is limited by the lack of a coherent conceptualisation of this symptom. The majority of FTD research to date has been performed on inpatient samples, or chronically institutionalised populations, thereby restricting the generalizability of results. There is a need to perform detailed epidemiologic research of FTD using standardised clinical assessment tools with mixed diagnostic populations which may help to establish its impact on functional outcome.

Poster #M125

THE EFFECTS OF CANNABIS ON RELAPSE IN PSYCHOSIS

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Background: The association between cannabis use and psychotic disorders like schizophrenia is well-established in the literature (Arseneault et al. 2004). Although more than half of the patients experience a relapse after the onset of the disorder (Caseiro et al., 2012), with cannabis representing one potential factor that predicts relapse rates (Linszen et al., 1994), a summary of the current evidence has yet to be conducted. For this reason, a meta-analysis was conducted in order to estimate the magnitude of the effects of cannabis on risk of relapse and symptoms in individuals with a psychotic disorder.

Methods: 25 studies met the criteria for inclusion following a systematic literature search. By using the statistical software R 3.0.1, the effect of cannabis use in individuals with a psychotic disorder on rates of relapse (n=

4217 patients) and symptoms (n=3881 patients) was computed employing established meta-analytic techniques.

Results: Random-effects analyses revealed moderate to large effects sizes for the effects of cannabis on relapse ($d=0.46$, $p<0.0001$) and for cannabis on positive symptomatology ($d=0.56$, $p=0.0035$), indicating that those patients using cannabis are at a higher risk of relapse and characterized by more severe positive symptomatology compared to those who never used or stopped using the substance. The analysis further revealed a substantial degree of statistical heterogeneities among studies for the effects of cannabis on outcome ($I^2 = 75\%$ for relapse and $I^2 = 88\%$ for pos. symptoms), indicating that results vary across studies and that other, as yet unidentified factors are likely to impact on the link between cannabis and outcome.

Discussion: The results implicate adverse effects of cannabis when uncontrolled for confounders and at a cross-sectional level. However, differences in sample characteristics and methodological diversity across studies appeared to impact on the effects of cannabis on outcome. Therefore, a more systematic and prospective investigation of a larger cohort of patients with a pre-existing psychotic disorder would help to estimate the precise magnitude of the effects of ongoing cannabis use when controlled for potential confounders.

Poster #M126

ATTITUDES TOWARDS PATIENTS WITH PSYCHOSIS AND DEPRESSION IN THE GENERAL POPULATION: EFFECTS OF LABELING

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Background: Good mental health literacy is thought to improve help-seeking and compliance. Yet it was cautioned in psychosis that it might also increase the desire for social distance, especially when linked to biological causal explanations. Therefore, we investigated attitudes towards patients with psychosis and depression in a general population sample in relation to labeling.

Methods: 1'184 German-speaking participants of a telephone survey (age 16 to 40) were asked to answer a questionnaire on mental health literacy and attitudes whose two versions vary in their diagnostically unlabeled case vignette (schizophrenia or depression). 1'061 (89.6%) agreed to participate, 645 (60.8%) questionnaires were returned: 331 with a schizophrenia, 314 with a depression case vignette.

Results: The type of the depicted mental problem (case vignette) had significant small to moderate effects on the desire for social distance (Rosenthal's r : 0.115 (colleague) to 0.373 (looking after children). Both effect of the vignette and desire for social distance increased with increasing closeness of the suggested relationship for both vignettes, although persons depicted by the depression vignette were generally much better received than persons depicted by the schizophrenia vignette. Furthermore, the higher the wish for social distance, the larger tended to be the effect of the vignette. Correctly labeling the case vignette or adopting a biological illness model had hardly any and, if any, only small effect on the desire for social distance. As regards the effect of a biological causal attribution, no effect was found in case of the depression vignette. For the schizophrenia vignette, only a small, not quite significant effect towards an increase in the desire for social distance in case of a biological illness model emerged when the care of one's own children was concerned ($U=6647.0$, $p=0.077$; Rosenthal's $r=0.101$).

Discussion: While good mental health literacy seems to improve social acceptance of persons with depression, it seems to extend an opposite effect on psychoses irrespective of a possibly biological main causal attribution. This has major implications for public information campaigns in psychoses that will have to be most carefully designed to avoid converse effects.

Poster #M127**CHARACTERISTICS OF A CATCHMENT AREA IN THE STATE OF SÃO PAULO, BRAZIL, FOR CONDUCTING AN INCIDENCE STUDY OF SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS**

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Background: Schizophrenia and other psychotic disorders are highly prevalent conditions associated with significant morbidity and mortality. However, data on the incidence and progression of these disorders across the globe are still scarce, especially in low- and middle-income countries. Urbanicity and migration have been consistently associated with higher incidence of psychotic disorders in European studies, the incidence being twice as high in urban areas than in rural or less urbanized areas, and three times higher among migrants and ethnic minorities, as compared to native Europeans. The present proposal is part of the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI). We aim to describe the region of Ribeirão Preto, in Southeastern Brazil, in terms of its levels of urbanization and migration, where a study of the incidence of schizophrenia and other psychotic disorders is taking place and may contribute to the present knowledge on the aetiology of such disorders.

Methods: Characteristics of the region of Ribeirão Preto in terms of population distribution and migration was performed by consulting the database of the Brazilian Institute of Geography and Statistics (IBGE) for the year 2010 (census data).

Results: The region of Ribeirão Preto has a land area of 9,300 km², comprising 26 municipalities, with a population of 1,300,000 inhabitants. It is a very heterogeneous region with regards to the general characteristics of the 26 municipalities. The average population density of the region is 132 inhabitants/km², ranging from 886 inhabitants/km² in Ribeirão Preto to 12 inhabitants/km² in Santa Cruz da Esperança. The rate of urbanization in the region is 97.4%, with the highest percentage of urbanization in the city of Pontal (98.4%) and lowest in the city of Santa Cruz da Esperança (67.7%). The region's economy is characterized by agribusiness, having as main activity the culture of cane sugar. This productive activity is responsible for an internal seasonal migration process that occurs through the migration of workers from northeastern Brazil and southern Minas Gerais state to work in the fields of cane sugar. A net migration rate for the region of 6.5 migrants per 100,000 inhabitants is estimated.

Discussion: It is speculated that the incidence of schizophrenia and other psychotic disorders has increased in low- and middle-income countries due to demographic and economic changes, which have led to increasing urbanization and migration from rural areas to large urban centers. The region of Ribeirão Preto has demographic characteristics, such as a wide variation in population density between its component municipalities, which allow to test some hypotheses identified in European studies regarding environmental risk factors for the development of schizophrenia and other psychotic disorders. The inclusion of Brazil as part of the EU-GEI European consortium may be very timely and should in the near future bring relevant contribution to the limited evidence produced so far in low- and middle-income countries.

Poster #M128**TESTING ØDEGAARD'S SELECTIVE MIGRATION HYPOTHESIS: A LONGITUDINAL COHORT STUDY OF RISK FACTORS FOR NON-AFFECTIVE PSYCHOTIC DISORDER AMONG PROSPECTIVE EMIGRANTS**

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Background: The selection hypothesis posits that the increased rate of psychotic disorder among migrants is due to selective migration of predisposed people. To test this hypothesis, we examined whether risk factors for psychosis are more prevalent among future emigrants.

Methods: A cohort of 50 087 Swedish military conscripts was assessed at age 18 on cannabis use, IQ, psychiatric diagnosis, social adjustment, history of trauma and urbanicity of place of upbringing. Through data linkage we examined whether these exposures predicted emigration out of Sweden. We also calculated the emigrants' hypothetical risk for developing a non-affective psychotic disorder.

Results: Low IQ (odds ratio (OR) 0.5, 95% confidence interval (95% CI) 0.3-0.9) and "poor social adjustment" (OR 0.4, 95% CI 0.2-0.8) were significantly less prevalent among prospective emigrants, whereas a history of urban upbringing (OR 2.3; 95% CI 1.4-3.7) was significantly more common. Apart from a non-significant increase in cannabis use among emigrants (OR 1.6, 95% CI 0.8-3.1), there were no major group differences in any other risk factor. The hypothetical risks for developing non-affective psychotic disorder were 1.3% (95% CI 1.1-1.7) and 1.0% (95% CI 0.7-1.3) for non-emigrants and emigrants, respectively.

Discussion: This study adds to an increasing body of evidence that does not support the selection hypothesis.

Poster #M129**GENETIC VARIABILITY IN THE FKBP5 AND NTRK2 GENES AND CLINICAL RESPONSE TO CLOZAPINE**

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Background: Clozapine is an atypical antipsychotic highly effective on patients with poor response or resistance to treatment (Lieberman et al., 1994; Kane 1992). Approximately 50% of patients who do not respond to typical antipsychotics benefit from clozapine (Reynolds GP, 2012). However, the mechanism of action of clozapine and the reasons for its success are still unclear. Numerous studies have demonstrated that atypical antipsychotics may suppress hypothalamic-pituitary-adrenal (HPA) activity which may contribute to their therapeutic action (Walker et al., 2008). The aim of this study was to investigate the influence of genetic variants in the HPA axis (FKBP5 ad NR3C1 genes) and in neurotrophic factors (BDNF and NTRK2 genes) on clinical response to clozapine treatment.

Methods: The sample consisted of 590 unrelated patients (32.2% females) with a DSMIII-R diagnosis of schizophrenia. All patients were British Caucasians recruited in hospitals in London, Cambridge and Burnley (UK). Clinical response was retrospectively assessed based on medical notes using the GAS scales (Endicott et al., 1976). A 20-point improvement in GAS scores after a minimum of 3 months treatment was considered as cut-off for response. According to these criteria, the sample was divided into 436 responders (Rp) and 154 non-responders (n-Rp). Ethical approval was obtained for these studies. Genomic DNA was extracted from blood samples from each participant, according to standard protocols. A total of 16 polymor-

phisms were genotyped at the FKBP5 (rs1360780, rs3777747, rs17542466, rs2766533), NR3C1 (rs2963156, rs1837262, rs4634384, rs4912910), BDNF (rs11030076, rs11030096, rs6265, rs1552736) and NTRK2 (rs1619120, rs1778929, rs10465180, rs4388524) genes were genotyped using KASPTM (Kompetitive Allele Specific PCR) technology by Design (LGC Genomics). Single marker analyses were performed using the SPSSv18 and EpilInfo statistical packages. Linkage disequilibrium between markers was tested with Haploview v.4.1. Haplotype analyses were conducted using the "R" software (v.2.2.1) from the "haplo.stat" package.

Results: Significant differences were observed for genotype ($P=0.02$) and allele ($P=0.03$) distributions of the FKBP5 rs1360780 polymorphism between Rp and n-Rp. Individuals who were homozygous for the rs1360780 T allele presented 2.11 times higher risk of non-response than individuals who were C-carriers [$P=0.006$; OR= 2.11; 95%CI (1.22-3.64)]. Haplotype analysis showed that the A-T-A-G allele combination (rs1360780-rs3777747-rs17542466-rs2766533) was more frequent in Rp ($P=0.03$). Regarding the NTRK2 gene, significant differences were found for genotype and allele distributions for both rs1778929 (genotype: $P=0.03$; allele $P=0.01$) and rs10465180 (genotype: $P=0.009$; allele: $P=0.01$) polymorphisms. Individuals with rs1778929 T/T genotypes were 1.7 times more likely to respond poorly to clozapine treatment than than C-carriers [$P=0.008$; OR=1.7 95%CI (1.13-2.59)], while rs10465180 CC-homozygous presented 2.15 times higher risk of non-response than T-carriers [$P=0.002$; OR= 2.15 95%CI (1.3-3.55)]. Haplotype analysis showed that the C-T allele combination (rs1778929-rs10465180) was more frequent in Rp ($p=0.007$) while the T-C allele combination was more frequent in n-Rp ($p=0.02$). No other significant results were found between any of the other analyzed polymorphisms and clozapine response.

Discussion: Genetic variability in the FKBP5 and NTRK2 genes may partially explain clinical response to clozapine. However, more studies are needed in order to clarify the involvement of these genes in the clinical response to atypical antipsychotics. The detection of individual genetic differences in the response to clozapine may provide new strategies for the treatment of schizophrenia.

Poster #M130

EFFECTS OF GENETIC VARIATIONS IN NRG1 ON COGNITIVE DOMAINS IN PATIENTS WITH SCHIZOPHRENIA AND HEALTHY SUBJECTS

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Background: Neuregulin 1 gene (NRG1) has been widely investigated as a candidate susceptibility gene for schizophrenia. A number of association studies have also explored a genetic effect of NRG1 on cognitive deficits related to schizophrenia, and generated inconsistent results. The current study aimed to determine whether genetic variations in NRG1 are associated with cognitive domains in schizophrenia patients and healthy subjects.

Methods: One hundred thirty-five patients with schizophrenia and hundred nineteen healthy volunteers were recruited. Comprehensive neuropsychological tests were administered which composed of six cognitive domains of the MATRICS consensus battery. Based on previous reports of positive association, six SNPs (rs35753505, rs62510682, rs6994992, rs3924999, rs2439272, rs10503929) were selected and genotyped. In testing the genotype effect on cognitive domains, we used repeated measure analysis regarding six cognitive domain scores of each individual as values of repeated measurement.

Results: Rs6994992 noted significant association with the performance of "verbal learning and memory" domain, "reasoning and problem solving" domain and general cognitive ability in the patients group. Rs2439272 showed significant associations across multiple cognitive domains in both patients and control groups. A significant association of rs3924999 with "reasoning and problem solving", and rs35753505 with general cognitive ability were observed only in the control group. For rs6994992, rs3924999, and rs2439272, more than one of those SNP-cognitive domain association remained statistically significant even after the Bonferroni correction.

Discussion: This study suggests that NRG1 might be involved in the sus-

ceptibility for developing cognitive deficits in schizophrenia patients. For some cognitive domains, its genetic effect was also significant in generating inter-individual variability within the normal functional range.

Poster #M131

EPIGENETIC SIGNATURES IN IGF2 AND RELATED GENES AND THEIR LINK TO BIRTH WEIGHT, WORKING MEMORY AND PSYCHOTIC EXPERIENCES: A STUDY BASED ON INFORMATIVE MZ TWINS

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Background: Epidemiological evidence demonstrates that neurodevelopmental disruptions caused by obstetric complications play a role in the etiology of schizophrenia and attenuated psychotic experiences in the general population (Kelleher and Cannon, 2011, Matheson et al., 2011). Importantly, it has been noticed that epigenetic processes may mediate associations between environmental insults very early in life and several health alterations across the human lifespan (Burdge and Lillycrop, 2010). In this regard, there is evidence indicating that DNA methylation levels of the insulin-like growth factor 2 (IGF2) and related developmental genes are linked to human prenatal insults (Heijmans et al., 2008, Wehkamp et al., 2013) and correlate with neuroanatomical features (Pidsley et al., 2010); in addition, this gene has also been related to neurodevelopmentally-influenced cognitive and psychopathological traits (Chen et al., 2011, Mikaelsson et al., 2013).

Methods: Peripheral blood DNA methylation levels were examined in 34 healthy adult monozygotic (MZ) twins (17 pairs, from the UB-Twin Registry), at IGF2 and in three genes codifying for allied mRNA binding proteins (IGF2-binding proteins 1-3, IGF2BP1-3). Data was extracted from the Illumina Infinium HumanMethylation450 (450K) BeadChip, which includes methylation levels at 248 CpG sites across the four genes of interest. Associations were tested between methylation and: i) birth weight (BW), ii) adult working memory (WM) performance and iii) subclinical psychotic experiences (PEs). Using MZ twins allowed the study of methylation changes and their putative phenotypic correlates controlling for confounding factors common to both twins (i.e. genes and shared environment). Multivariate linear regression models were applied to test for associations between methylation levels and the phenotypes of interest.

Results: A link was detected between DNA methylation levels at a region in IGF2BP1 and both BW ($p = 0.033$) and adult WM performance ($p = 0.009$), but not PEs. The BW-IGF2BP1 methylation association seemed due to non-shared environmental factors influencing BW, whereas the relationship between WM and IGF2BP1 DNA methylation levels seemed mediated by both genes and environment.

Discussion: Considering previous reports indicative of an association between some intrauterine events and DNA methylation marks in adulthood (Reynolds et al., 2013), one could speculate that methylation of IGF2-related genes may serve as a proxy for some traits of interest in neurodevelopmental psychiatric conditions. As long as this study is exploratory, results should be interpreted with caution. Replication of the findings is needed in larger and independent samples.

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Poster #M132**STRESS AND VARIATION IN THE GLUCOCORTICOID REGULATING ENZYME 11- β -HYDROXYSTEROID-DEHYDROGENASE TYPE 2 IN CHILDREN WHO LATER DEVELOP SCHIZOPHRENIA**

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Background: Studies have associated maternal stress during pregnancy with CNS disorders including schizophrenia. In Danish register data we showed that the loss of a close relative during and after pregnancy was associated with offspring schizophrenia risk. It has been speculated that stressful life events enhance production of glucocorticoids that adversely affect neurodevelopment in the immature brain, increasing the risk of mental illness in adolescence or adult life. The authors hypothesized that the effect of bereavement was mediated via cortisol, and in part could be explained by variation in the gene HSD11B2 encoding the glucocorticoid regulating enzyme 11- β -hydroxysteroid-dehydrogenase type 2 (11 β HSD2). **Methods:** A matched case-control study with 716 schizophrenia cases and 782 controls, matched on sex, exact date of birth, born in Denmark, alive and with no history of schizophrenia on the date of first diagnosis of schizophrenia of the matched case, and also including all their first-degree relatives. We used information from national registers and, to determine whether the effect of bereavement could be explained by variation in HSD11B2. Two single nucleotide polymorphisms (SNPs) from the locus of HSD11B2 were genotyped (rs5479 and 56303414), and one from a neighboring gene (rs9922624), and the data was analyzed with conditional logistic regression.

Results: We found a significant protective effect of each of the variant alleles for rs9922624 (odds ratio (OR) 0.60, [95% confidence interval (CI), 0.42–0.88]) and rs5479 (OR 0.55 (95% CI 0.34–0.90)). When stress at the age of 3–9 years co-occurred in individuals with the variant allele, we found that the risk of schizophrenia was increased, though not significant. The interaction between stress at the age of 3–9 years and the allele however was significant with (OR 3.02 (95% CI 1.32–6.93)) and (OR 3.92 (95% CI 1.46–10.54)) for rs9922624 and rs5479 respectively.

Discussion: Our results suggest that functional variation in 11 β HSD2 might be a predisposing factor for schizophrenia after stress exposure, since we found interaction between the SNPs in the gene and stress. However, maybe due to lack of power, we were not able to show any significant risk of having the allele after stress exposure in regard to schizophrenia.

Poster #M133**ASSOCIATION BETWEEN RS2267641 IN THE A2RE SEQUENCE OF THE DDR1 GENE WITH COGNITIVE PROCESSING SPEED IN PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS**

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Background: Several lines of evidence have implicated oligodendrocytes in schizophrenia spectrum disorders. Variants of the discoidin domain receptor 1 (DDR1) gene, which is a key protein in oligodendrocyte myelination, are associated with schizophrenia. SNP rs2267641 is located in an A2RE sequence of the DDR1 gene that is involved in the alternative splicing of the DDR1c and DDR1b isoforms and the transport of their mRNA prior to protein translation. Our group observed in a pilot sample that cognitive processing speed was associated to rs2267641CC genotype. Here, we examine the association between the rs2267641 in the DDR1 gene and processing speed in a larger sample of patients with schizophrenia spectrum disorder.

Methods: Peripheral blood DNA from 207 patients with schizophrenia spectrum disorder was used for the genotyping. The Trail Making Test (TMT) A was used to assess cognitive processing speed and T-score was calculated. The sociodemographic and clinical characteristics of study par-

ticipants were analysed. We conducted an ANCOVA using as covariates years of education, years of evolution and antipsychotic potency.

Results: Most of patients were male (N=139, 67.1%) with a mean age of 35.06 (SD= 10.13), single (N=76.9, 76.9%), with a mean of 10.47 years of education (SD=3.05), diagnosed as paranoid schizophrenia (N=86, 41.5%) with \geq 5 years of evolution (mean=10.47 SD=9.92). The rs2267641 genotype was associated to TMT-A score. Carriers of the CC genotype showed lower cognitive processing speed than CA and AA genotype carriers (AA genotype: mean=41.84 SD=10.29, AC genotype: mean=42.93 SD=11.52 and CC genotype: mean=29.00 SD=6.16; F=3.01 p=0.052).

Discussion: Our results indicate that, in addition to being involved in myelination, DDR1 may have a role in cognitive processing speed in schizophrenia. Further studies are needed to confirm these findings.

Poster #M134**ASSOCIATION OF IMMUNE GENE POLYMORPHISMS WITH SCHIZOPHRENIA IN A NORTH INDIAN COHORT**

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Background: Immune system dysfunction in Schizophrenia (SZ) may be a consequence of genetic variation, environmental factors, or the interaction of both. Early infection by microorganisms possessing antigens that have similarity to those present in CNS tissues resulting in antibodies which act against the brain have been reported. These observations invoke theories of autoimmune aspects of SZ. Infections may also act indirectly through activation of systemic cytokines and stress factors, whose differential expression are known to modulate cognitive functioning. In this study we aim to establish the association if any, of a few immune related genes with SZ as well as with cognition.

Methods: A trio (n=600) as well as case-control (n=600 cases, 486 controls) study design was used to evaluate association of a total of 29 SNPs from four candidate genes namely MHC class I polypeptide-related sequence B (MICB), IL-18 receptor (IL18R1), receptor accessory protein (IL18RAP) and Mannose-binding lectin 2 (MBL2) by SNplex and SNaPshot assays. A subset of the samples (n=260 cases; 302 parents) were analysed for cognitive variable using Trail Making test (TMT). Infection load of Toxoplasma gondii (TOXO) and Cyto Megalo Virus (CMV) was estimated in another subset of the samples (n=210 cases and 387 parents).

Results: rs2523651, an intronic SNP from MICB was found to be associated with SZ in the trio analysis. A trend of association was seen for rs11465732 (p=0.06) of IL18RAP in both case-control and family data set. Of note, two different SNPs namely rs2534671 in MICB and rs887972 in IL18RAP showed association with TOXO infections. Two other markers namely rs7084554 in MBL2 and rs2523666 in MICB showed associations with CMV infections. Five SNPs namely rs1420100, rs3755268, rs2272127, rs887972, rs11465702 out of eight SNPs in IL18RAP; rs930507 and rs7084554 in MBL2 and rs3131639, rs2534671, rs3131636 in MICB were associated with B task of TMT which controls the working memory.

Discussion: The markers showed negligible association with SZ but were modestly associated with cognition and infection status. These preliminary findings warrant additional investigations in a larger sample set.

Poster #M135**A GENOME-WIDE ANALYSIS ON ANTIPSYCHOTIC-INDUCED WEIGHT GAIN USING REFINED CRITERIA IN THE CATIE SAMPLE**

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Background: Antipsychotic drugs frequently cause marked weight gain in genetically susceptible individuals. Previous GWAS data analyses in the CATIE trial was limited by several important factors such as use of patients

with different ethnicities and medications with different propensities to cause weight gain. This prompted us to conduct a new set of analyses using rigorous inclusion criteria in order to obtain a more homogeneous sub-sample.

Methods: Our refined subsample of patients consisted exclusively of individuals who were not exposed to high risk medication for weight gain prior to study inclusion, who did not show marked obesity (BMI >40) at baseline (T0) or were exposed to low risk medication for weight gain during the CATIE trial (e.g. ziprasidone). This refined sample (n=358) was used for mixed models analyses on 328,733 SNPs analyzed in each individual.

Results: None of the SNPs was significant at the genome-wide threshold of $p=5\times 10^{-8}$. The top hit of the GWAS was one SNP ($p=1.06\times 10^{-5}$) located downstream of the SAL-1 gene on chromosome 16. The sal-like-1 gene functions as a zinc finger domain containing transcriptional repressor and is associated with developmental syndromes. The second hit, ($p=1.91\times 10^{-5}$), is ~ 194 kb upstream of IRS2 gene (insulin receptor substrate 2). IRS2 mediates effects of insulin and several cytokines and has been associated with insulin resistance, coronary artery disease and cancer in the general population. The third hit, ($p=2.4\times 10^{-5}$), is located ~ 59 kb upstream of the Neuropeptide S gene. The 20 amino acid peptide coded by this gene has been shown to influence food intake, anxiety, locomotion, memory, and drug addiction.

Discussion: Our analyses did not detect an association when considering the commonly applied genome-wide correction threshold for multiple testing. However, our analysis presented here using stringent inclusion and exclusion criteria on the CATIE GWAS data has revealed interesting new genes that may be associated with antipsychotic induced weight gain. Two of our top hits, IRS2 and NPS, were previously shown to be involved in regulation of insulin sensitivity and food intake in other populations. Direct functional effects of the identified SNPs are yet unknown and functional studies as well as replication in independent samples are required. Beside the main limitations given by the relatively small sample size, other limitations include previous antipsychotic exposure in most patients and heterogeneous medication. Nonetheless, our findings are an important contribution to understanding genetic mechanisms of AIWG by using a genome-wide approach.

Poster #M136

INVESTIGATION OF THE RELATIONSHIP BETWEEN SCHIZOPHRENIA AND KREMEN1 GENE

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Background: Schizophrenia is a chronic, debilitating psychotic and a serious disorder that affects about 1 percent of the world's population and has symptoms that generally begin in late adolescence or early adulthood and usually continue throughout life. It is thought to be a neurodevelopmental disorder. The Wnt signaling pathway plays a critical role in regulating this neurodevelopmental process. KREMEN1 Gene A modulates a transmembrane protein KREMEN1 which has been also found to play an important role in Wnt signaling. The aim of this study was to examine the prevalence of KREMEN1 Gene abnormality in schizophrenia patients compared to normal controls.

Methods: Our subjects comprised 155 individuals, with 104 patients with schizophrenia and 51 healthy volunteers with no personal or family history of psychiatric illness. KREMEN1 gene region in question was cloned by PCR and DNA sequence of this region was analyzed in order to investigate the SNPs, rs713526, rs116100643 and rs201088346 in the aforementioned gene, and then, genotypes were determined.

Results: As a result of genetic analysis, heterozygous rs713526 G>A polymorphism was detected %26 and %12 in patients with schizophrenia and healthy controls respectively. There is a statistically significant difference between the two groups ($p=0.042$). Homozygous form of this polymorphism was not detected. In addition, the SNPs, rs116100643 and rs201088346 were not observed in our case and control subjects.

Discussion: KREMEN1 gene modulate the wnt signaling pathway and

may play an important etiological factor in schizophrenia as a neurodevelopmental disorder. Results of this study suggest that rs713526 G>A polymorphism in KREMEN1 might be associated with risk of schizophrenia and contribute to susceptibility to disease. Although our results are suggestive of an association with schizophrenia at this locus, further studies with schizophrenia and KREMEN1 will be necessary to confirm this association with a larger sample group.

Poster #M137

HYPOTHESIS-DRIVEN GENOME-WIDE ASSOCIATION STUDY (GWAS) ANALYSIS HIGHLIGHTS THE ROLE OF IMMUNE GENES IN THE EXTENDED MAJOR HISTOCOMPATIBILITY COMPLEX IN SCHIZOPHRENIA

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Background: Schizophrenia is considered a neurodevelopmental disease, with the causative insults occurring early in brain development before clinical manifestations of the disease are seen in adolescence. Converging evidence from epidemiological studies and animal models suggests that early-life infections alter brain development leading to increased risk of schizophrenia. Although genetic susceptibility has been shown to modulate the risk of developing schizophrenia following exposure to early-life infection, the underlying genetic determinants are not known. In the present study, we evaluated the contribution of 953 known immune genes to schizophrenia.

Methods: The Psychiatric Genomics Consortium schizophrenia genome-wide association study (GWAS), N=9,394 cases and 12,462 controls, was analyzed using a univariate approach where all single-nucleotide polymorphisms (SNPs) received equal weighting. Hypothesis-driven analysis of the GWAS data was then performed using the stratified false-discovery rate (sFDR) method to upweight 15,070 SNPs in 953 genes that had an immune response annotation in three out of four annotation databases (Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), Immunology Database and Analysis Portal (ImmPort), and Ingenuity Systems).

Results: None of the immune SNPs achieved genome-wide significance in the univariate GWAS analysis ($p>5\times 10^{-8}$). After upweighting immune gene SNPs using the sFDR approach, SNPs in UBD (rs404240, $p=1.1\times 10^{-6}$, qSFDR=0.02), CFB (rs1270942, $p=5.7\times 10^{-6}$, qSFDR=0.02), HLA-DQA1 (rs2187668, $p=4.4\times 10^{-6}$, qSFDR=0.02), and HLA-DQB1 (rs2854275, $p=4.8\times 10^{-6}$, qSFDR=0.02) were significantly associated with schizophrenia.

Discussion: In the univariate analysis, no immune SNPs were associated with schizophrenia. Incorporating prior biological evidence improved the ability to identify immune genes important in schizophrenia; in the immune hypothesis-driven analysis, SNPs in the UBD, CFB, HLA-DQA1, and HLA-DQB1 genes of the extended major histocompatibility complex (xMHC) were identified. The xMHC is an 8Mb region of chromosome 6p previously associated with schizophrenia (reviewed by Kodavali et al., Am J Med Genet B, 2013). Ubiquitin D (UBD) and complement factor B (CFB) may contribute to schizophrenia through their roles in innate immunity and complement system activation, respectively. Interestingly, the class II HLA genes identified in this analysis, HLA-DQA1 and -DQB1, have been previously associated with autoimmune diseases including multiple sclerosis (Lincoln et al., PNAS, 2009). Our results further highlight the importance of the xMHC in schizophrenia, and suggest there may be some degree of overlap between the immune genes involved in schizophrenia and those involved in autoimmune diseases.

Poster #M138**P250GAP A NEW CANDIDATE GENE FOR SCHIZOPHRENIA AND PSYCHOSIS-PRONENESS?**

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Background: Hypofunction of the glutamate N-Methyl-d-Aspartate (NMDA) receptor has been strongly implicated in the pathophysiology of Schizophrenia (SZ) (du Bois and Huang, 2007). The p250GAP is a brain-enriched NMDA receptor-interacting RhoGAP. This gene is involved in spine morphology, which has been shown to be altered in the post-mortem brains of schizophrenia patients (Zavitsanou et al. 2002). In a previous study (Ohi et al., 2012) have suggested that a genetic variation in the p250GAP gene might increase susceptibility not only for schizophrenia (rs3796668 and rs2298599) but also for schizotypal traits in a Japanese population (rs2298599). Endophenotypes are measurable components along the pathway between the genetic infrastructure and presentation of the disorder (Gottesman and Gould 2000). Recent studies have suggested schizotypal traits as good candidate endophenotype useful for the dissection of genetic components of schizophrenia. Additionally, significant correlation in linkage signals from genome-wide scans of schizophrenia and schizotypy suggest that at least a subset of schizophrenia susceptibility genes also affects schizotypy (Fanous et al. 2007). The aim of our study was to examine schizotypy in a sample of healthy individuals and to study the association between positive and negative dimensions of schizotypy and the genetic variability of the candidate gene p250GAP involved in the plasticity of glutamatergic neurons.

Methods: We analyzed four SNPs (Single Nucleotide Polymorphisms) in the p250GAP gene (rs2298599, rs546239, rs3740829, rs3796668) in a sample of 547 healthy individuals of the general population that completed a psychometric battery of self-reported questionnaires (The Wisconsin Schizotypy Scales, WSS).

Results: We found that individuals carrying the G allele for the SNP rs3796668 (GAP4) had higher scores for the negative schizotypy dimension compared with the individuals that do not carry this allele ($F=7.98$; $p=0.005$). However we do not replicate the association between rs2298599 and schizotypy reported in the original study.

Discussion: Our results are in accordance with the continuum hypothesis that suggests that some of the risk factors for schizophrenia are common with those associated with a more homogenous phenotype or endophenotype (i.e. schizotypy). Additionally, according to our results the gene p250GAP is still a good candidate for schizophrenia and further studies should be conducted studying the variability of this gene.

Poster #M139**INVESTIGATION INTO AN ASSOCIATION BETWEEN GENETIC RISK FACTORS FOR SCHIZOPHRENIA AND BIPOLAR DISORDER AND DIMENSION-SPECIFIC PSYCHOTIC EXPERIENCES IN ADOLESCENCE**

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Background: Evidence suggests that a considerable amount of variance in liability for schizophrenia and bipolar disorder in adults can be accounted for by common genetic variants. Our aim was to test the hypothesis that these variants associated with schizophrenia and bipolar disorder also influence the full range of variation in psychotic experiences measured dimensionally in adolescence in a general population sample. We tested whether polygenic risk scores (PRS) from schizophrenia and bipolar disorder genome-wide association studies (GWAS) and specific single nucleotide

polymorphisms (SNPs) previously identified as risk variants for schizophrenia were also associated with dimension-specific psychotic experiences in adolescence.

Methods: The sample included 2,152 16-year-olds from Twin Early Development Study (TEDS). Dimension-specific psychotic experiences were assessed using the Specific Psychotic Experiences Questionnaire (SPEQ); self-reported measure of paranoia, hallucinations, cognitive disorganisation, grandiosity, anhedonia, and parent-rated negative symptoms. First, PRS were calculated using estimates of the log of odds ratios from the Psychiatric Genomics Consortium (PGC) GWAS mega-analysis of schizophrenia and bipolar disorder and polygenic risk analyses were conducted for the six measures. Second, individual SNP analyses were performed to test for associations between the SPEQ measures and 28 SNPs previously associated with schizophrenia. Two associations were tested for replication in an independent sample of 3,427 16-year-olds drawn from The Avon Longitudinal Study of Parent and Children (ALSPAC). Here psychotic experiences were assessed using the Psychotic-Like Symptoms Questionnaire (PLIKS-Q), a measure of a range of positive psychotic experiences.

Results: Polygenic risk analyses yielded no significant associations between schizophrenia and bipolar disorder PRS and the SPEQ measures. Single SNP analyses yielded significant associations with two SNPs in TCF4 and the SPEQ Paranoia dimension only, rs17512836 (p -value = 2.57×10^{-4}) and rs9960767 (p -value = 6.23×10^{-4}). These paranoia-specific SNP associations were not replicated when tested in the ALSPAC sample on the PLIKS-Q measure.

Discussion: These preliminary results do not provide support for the hypothesis that the same common variants that are associated with clinical diagnosis of schizophrenia or bipolar disorder in adults are also predictive of specific dimensions of psychotic experiences in adolescence. It remains to be seen how the complex phenotypes that comprise diagnosed schizophrenia and bipolar disorder are linked etiologically with specific dimensions of psychotic experiences, such as paranoia, in adolescence. Further research with larger sample sizes and with replication samples with more directly equivalent measures would be fruitful.

Poster #M140**COST EFFECTIVENESS OF THE JOB MANAGEMENT PROGRAM (JUMP)**

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Background: Although the majority (50–90%) of people with schizophrenia wish to work, unemployment rates remain high (75–95%). Employment holds several economic, social and psychological benefits for people with schizophrenia and is associated with reduced need for mental health services. Overall costs associated with schizophrenia are high due to the long-term disabling effects of the illness. Primary cost drivers include treatment costs, supported accommodation and lost income with consequential requirements for welfare benefits. The purpose of the JUMP (Job Management Program) study is to explore the feasibility of vocational rehabilitation for people with psychotic disorders in a Scandinavian welfare society, and to examine the cost effectiveness of the intervention.

Methods: Participants (n=149) were enrolled in a 10 month vocational rehabilitation program offering close collaboration between health- and vocational services, competitive or sheltered work and either cognitive remediation (CR) or cognitive behavioral therapy (CBT) techniques focusing on work related issues. At two-year follow-up participants' usage of mental health services over the two-year period is compared to service use registered in the two-year period prior to participating in the JUMP study. Housing, employment- and income status were assessed at baseline, after ten months and at two-years. Based on a cost of illness study for schizophrenia in Norway, the cost effectiveness of the JUMP study is examined by identifying effects on primary cost drivers during the follow-up period.

Results: At baseline, 13% of the participants were employed but none had paid work as their main income. At 10 months, 9% had gained competitive employment and an additional 68% were working for welfare benefits in both competitive and sheltered work settings. Follow-up data will be available in February 2014, but preliminary analyses of a small sample indicate a trend towards increased rates of competitive employment and paid work.

Our hypothesis is that employment will reduce the use of mental health services and welfare benefits, and that investing in vocational rehabilitation for people with schizophrenia will reduce the overall economic burden of schizophrenia.

Discussion: Due to the long-term disabling effects of the illness, low employment rates and high treatment and welfare costs, the economic burden of schizophrenia is high. Our preliminary analyses suggest that people with psychotic disorders are willing and able to work, both in competitive and sheltered settings, when given access to vocational rehabilitation and adequate support. Previous cost of illness studies for schizophrenia in Norway are outdated and to our knowledge there are no studies examining the cost effectiveness of programs aimed at helping people with schizophrenia back to work. Thus the current study will provide valuable information for decision makers in resource allocation and service planning.

Poster #M141

RISK REDUCTION AND NUMBERS NEEDED TO TREAT TO AVOID METABOLIC SYNDROME: 12-MONTH CARDIOMETABOLIC PARAMETERS CHANGES AMONG SCHIZOPHRENIA SUBJECTS TREATED WITH LURASIDONE OR QUETIAPINE XR

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Background: Atypical antipsychotics are associated with various degrees of risk for weight gain and metabolic disturbances including metabolic syndrome. Lurasidone, an atypical approved for schizophrenia and bipolar depression may potentially have a lower risk for metabolic syndrome and a lower number of subjects needed to treat (NNT) to avoid one subject developing metabolic syndrome. Differences in metabolic syndrome status based on cardiometabolic parameter changes among subjects with schizophrenia treated with lurasidone or quetiapine XR were examined.

Methods: Data from a 12-month, double-blind, parallel-group, multiregional comparison study of lurasidone (40 to 160 mg/day, flexibly dosed) vs quetiapine XR (200 to 800 mg/day, flexibly dosed) in subjects previously treated with lurasidone or quetiapine XR for 6 weeks were evaluated in this post-hoc analysis. Increased cardiometabolic risk was defined as: BMI >30kg/m², triglycerides (\geq 150 mg/dL), fasting plasma glucose ((FPG) \geq 100 mg/dL), blood pressure (systolic BP \geq 130 or diastolic BP \geq 85 mm Hg) and HDL cholesterol (<40 mg/dL in males and <50 mg/dL in females). Metabolic syndrome was defined by the International Diabetes Federation (IDF) as those with a BMI >30kg/m², plus \geq 2 of the above four factors. Cardiometabolic parameters and presence of metabolic syndrome were assessed at study baseline (BL) and endpoint (12 months). Absolute risk reduction (ARR) in metabolic syndrome and the number of subjects needed to treat (NNT) to avoid one patient developing metabolic syndrome on the IDF formula was calculated.

Results: From the ITT population of 256 subjects, data from 111 subjects (lurasidone N=78; quetiapine XR N=33) with a baseline (BL) and a 12 month assessment were included. At BL there were 2 (2.6%) lurasidone and 0 (0.0%) quetiapine XR subjects with metabolic syndrome. At month 12 there were 2 (2.6%) lurasidone and 3 (9.1%) quetiapine XR subjects with metabolic syndrome. The 12-month change from BL showed no additional subjects developing metabolic syndrome with lurasidone whereas 3 subjects with quetiapine XR did. Absolute risk reduction (ARR) in metabolic syndrome with lurasidone was 6.5% and the NNT to avoid a case of metabolic syndrome with lurasidone was 15. Examination of the individual cardiometabolic parameters indicated an ARR ranging from -9.4% to 9.0% and NNT ranging from -12 to 46. Among subjects with BMI>30, 7 (9.0%) lurasidone and 5 (15.2%) quetiapine XR (NNT=16, ARR=6.2%). Subjects who had raised triglycerides (\geq 150), 10 (14.5%) lurasidone and 5 (16.7%), (NNT=46, ARR=2.2%). Reduced HDL cholesterol was 18 (26.1%) lurasidone and 5 (16.7%) quetiapine XR (NNT=-11, ARR=-9.4%). Raised blood pressure was observed in 19 (24.4%) lurasidone and 11 (33.3%) quetiapine XR (NNT=11, ARR=9.0%) and raised fasting glucose was 24 (35.3%) lurasidone and 8 (26.6%) quetiapine XR (NNT=-12, ARR=-8.6%).

Discussion: Post hoc analysis from this study showed that treatment with lurasidone is associated with improvement in cardiometabolic parameters and a low NNT to avoid one patient developing metabolic syndrome versus quetiapine XR.

Poster #M142

DEPRESSIVE DISORDERS IN PSYCHOSIS RISK SYNDROME IN A CHILD AND ADOLESCENT SAMPLE

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Background: Psychosis Risk Syndrome (PRS) is characterized by the presence of several clinical indicators that reflect the patient vulnerability for developing a psychotic disorder. Previous studies have evaluated clinical criteria to help identify subjects with PRS, showing that about 35% of subjects with clinical high risk (HR) criteria developed a psychotic disorder at 12 months after completing any of the HR criteria, although the percentages vary in the different studies. In other studies we've found that the most prevalent DSM-IV diagnoses among clinical HR subjects at baseline were anxiety and mood disorders, with the majority of subjects having at least one of these diagnoses. In this article, we examine the processes underlying the symptoms related to mood disorders by investigating the affective deficits in adolescents at risk for schizophrenia. We have focused on these symptoms for the following reasons. First, affective deficits are considered a central part of the negative symptom syndrome. A second reason is that, as we explain previously, the mood disorders are one of the most frequent diagnoses in HR patients. The aim of this study is to determine the affective disorders in PRS subjects in a child and adolescent sample (age 10 to 17) from a preliminary phase of a longitudinal multicenter study.

Methods: Preliminary data were available from the initial phases of a longitudinal multicenter study, which evaluated the clinical, cognitive and neuroimaging results of patients with PRS compared with a control group. In this paper we analyze the scan data from a neurocognitive baseline patient group. Inclusion criteria for PRS patients are: age between 10 and 17 years, one or more of the criteria for PRS, as assessed by the SIPS interview, no diagnosis of psychotic disorder, autism spectrum disorder, neurological disease and/or mental retardation. We evaluate the subjects with the Kiddie-Sacks Scale, the Hamilton Depression Rating Scale (HDRS) and the Structural Interview for Prodromal Syndromes (SIPS) and Scale of Prodromal Symptoms (SOPS). We performed a descriptive analysis of the data by SPSS 20.0 statistic program.

Results: 46 PRS subjects (15.2±1.8 years, range: 11-17 years; 39% males) and 20 healthy controls (15.2±1.8 years, range: 11-17 years; 25% males) were included. A 84% of the sample of PRS subjects (n=30) present a DSM IV diagnosis From these, depression was present in 60% of the patients (18subjects). This is the most prevalent disorder in our sample. We've found high scores in the HDRS compared to control group (mean result 11,61±6,57). This score represents a mild depression. We've found positive correlation between the scores of the HDRS and the scores of the global SIPS ($p=0,038$, correlation: 0,357), and general symptoms ($p=0,005$, correlation: 0,474) showing that with a higher score of the HDRS we also have higher scores in general symptoms and in SOPS total scores. There is no correlation between the positive, negative and disorganized scales of the SOPS. However, we can find different correlations between HDRS and the SOPS items: Experience of Emotions and Self N4 ($p=0,005$; correlation 0,473); Ideational Richness N5 ($p=0,014$; correlation -0,423); Dysphoric Mood G2 ($p=0,023$; correlation 0,388); Impaired Tolerance to Normal Stress G4 ($p=0,043$; correlation 0,349).

Discussion: Up to date, the analysis of the depressive diagnoses of a sample of PRS patients shows that it is one of the most prevalent diagnoses in Axis. Moreover, it shows that there is a correlation between the affective and prodromal symptoms, and consequently it could be a possible target for the study of the non-converters subjects and also as the comorbidity of the converters.

Poster #M143**PSYCHOSIS RISK SYNDROME IN CHILDREN AND ADOLESCENTS: CLINICAL CHARACTERISTICS AND TREATMENT IN HELP-SEEKERS VS. CONTROLS**

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Background: The ultra-high risk of psychosis, also known as the prodromal phase or psychosis risk syndrome (PRS) is the first step in the progression to a psychotic disorder. During this phase, the progression towards psychosis could be aborted or delayed with different types of interventions. In fact, in PRS samples one-year transition to psychosis has decreased during the last ten years from 40 to 10%. Previous studies of PRS include mainly subjects over the age of 18 years, while a few studies include subjects as young as 14. However, the psychosis threshold and attenuated symptoms could be different in a younger population. Thus, it is important to study children and adolescents with this syndrome. Objectives To compare the clinical characteristics and treatment of a sample of adolescents with PRS and age and gender matched healthy controls (HC).

Methods: A prospective longitudinal study in which help-seeking subjects who met PRS criteria were recruited from the Child and Adolescent Psychiatry and Psychology departments of Hospital Clinic and Hospital Sant Joan de Déu (Barcelona, Spain). Inclusion criteria were: 1) Attenuated positive or negative symptoms in the previous 12 months; 2) Brief intermittent psychotic symptoms; 3) First or second degree relative with schizophrenia or schizotypal disorder plus impairment of functioning; age: 10-17 years. Exclusion criteria: IQ<70 and a diagnosis of neurodevelopmental disorder. The Structured Interview for Prodromal Syndromes and Scale of Prodromal Symptoms (SIPS/SOPS) were administered. A clinical scale battery (GAF, Young, Hamilton, etc) was also administered, including the diagnostic interview Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL). Types of treatment, and dosages were also registered. A sample of HCs were also included. Exclusion criteria: 1st or 2nd degree familiar with a psychotic disorder; a diagnosis of neurodevelopmental disorder; and IQ<70. The same assessment was performed in the HC sample.

Results: 46 PRS subjects (15.2±1.8 years, range: 11-17 years; 39% males) and 20 HC (15.2±1.8 years, range: 11-17 years; 25% males) were included. In the PRS sample, 77.5% met criterion 1 for inclusion. 52.5% had familiar history of psychotic disorder. All the SOPS, GAF, Hamilton and Young scores were significantly higher in PRS than in HC: 84% of PRS vs. none CC subjects ($p<0.001$) met DSM-IV criteria for a present diagnosis: mood disorder: 41.7%; ADHD: 11%; social phobia: 8.3%; OCD: 2.8%; other anxiety disorders: 8.3%; oppositional-defiant disorder: 8.3%, eating disorders: 2.8%. 61.3% of subjects met criteria for a second diagnosis. 97% of subjects received some type of treatment: 41.7% only psychological, 29.4% only pharmacological and 34.3% combined. Regarding pharmacological treatment, 62% subjects took a selective serotonin reuptake inhibitor (50% combined with an antipsychotic) and 20% only antipsychotics. 85.7% of subjects took more than one drug.

Discussion: PRS subjects presented mainly attenuated positive symptoms, meeting 84% of them current DSM-IV diagnostic criteria. Mood disorder was the most common diagnostic category, similar to other another study with mainly adolescents (Lencz et al., 2004). HC did not meet criteria for any DSM-IV diagnosis. PRS scored higher than HC in all the psychopathological scales. The majority of patients received some type of treatment, as Cornblatt et al., 2007 reported. More than 65% psychological treatment, while pharmacological treatment was used in 43% of the cases. A selective serotonin reuptake inhibitor combined with an antipsychotic was the most frequently prescribed medication.

Poster #M144**NEUROPSYCHOLOGICAL CHARACTERISTICS OF CHILD AND ADOLESCENT OFFSPRING OF SCHIZOPHRENIA OR BIPOLAR DISORDER PATIENTS**

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Background: A growing number of authors have defended that both schizophrenia and bipolar disorder need to be studied jointly (Craddock et al. 2006). Few studies have compared neuropsychological characteristics of offspring of patients with schizophrenia (SZoff) and bipolar disorder (BDoff) (Maziade et al, 2009; Diwadkar et al 2011). These studies showed that BDoff and SZoff shared several difficulties in IQ, Verbal episodic memory and visual episodic memory. Nevertheless they also found significant differences between both groups, specifically Maziade et al (2009) showed that BDoff had higher difficulties in executive functions than SZoff. Moreover Diwadkar et al. (2011) observed lower scores on attentional tests in the BDoff and higher difficulties in working memory in the SZoff. Nevertheless, the first study included densely affected by SZ and BD families and the second only assess working memory and attention. The aim of this study is to compare neuropsychological characteristics in child and adolescent offspring of bipolar and schizophrenia patients with a complete neuropsychological battery.

Methods: This research is part of The Bipolar and Schizophrenia Young Offspring Study (BASYS). Subjects: Three groups of child and adolescent SZoff (N=41), BDoff (N=90) and CC group (N=107) were included. Measures: The cognitive assessment includes the following domains: intelligence quotient (IQ), working memory, processing speed, verbal memory and learning, and executive functions. Statistical analysis: Differences between SZoff, BDoff and CC were evaluated via MANOVA and significant results were confirmed with a multilevel analysis (mixed model) using sibship as the random effect.

Results: Socio-demographic characteristics of the sample: Significant differences were found between groups in terms of age ($F=6.06$; $p=0.03$) and socio-economic status ($F=28.23$; $p<0.001$). Thus, both variables were included in the statistical analysis as covariates. Neuropsychological assessment: Significant differences were observed between groups in working memory ($F=7.39$; $p=0.001$), processing speed ($F=9.906$; $P<0.001$), verbal learning delayed recall ($F=4.19$; $p=0.016$), visual memory immediate ($F=10.92$; $p<0.001$) and delayed recall ($F=4.54$; $p=0.012$) and the copy of the Complex Rey Figure ($F=8.36$; $p<0.001$). Specifically SZoff obtained lower scores than BDoff and CC in working memory and Complex Figure of Rey. Both high risk groups, SZoff and BDoff showed significantly lower scores than CC in processing speed and visual memory immediate recall. And finally, in some neuropsychological variables (verbal learning and visual memory delayed recall) SZoff scored significantly lower than the CC group but no significant differences were found between the SZoff group and the BDoff or between the BDoff and the CC. All significant differences remain stable after controlling for lifetime psychopathology and the presence of siblings in the same study.

Discussion: Conclusions Impairments in working memory and perceptual organization were found in both high risk samples compared to the CC group; nevertheless these difficulties were significantly more severe in the SZoff group. Problems in processing speed and visual memory were also shared by SZoff and BDoff, and both groups scored significantly lower than the CC group. No significant differences were found in these variables between both offspring groups. Finally there were some neuropsychological variables, specifically verbal learning and visual memory delayed recall where only the SZoff showed significant impairments compared to the CC.

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Poster #M145**FOCUSED INTERVENTIONS IN 258 SUBJECTS AT HIGH CLINICAL RISK FOR PSYCHOSIS: OASIS 6-YEARS NATURALISTIC STUDY**

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Background: Randomized controlled trials suggest some efficacy for focused interventions [FI] in subjects at risk for psychosis [HR]. However their effectiveness in the real-world setting is unknown and it is hindered by several practical problems. The present naturalistic study addresses these issues in the OASIS HR sample. The OASIS clinic, established in 2001, is one of the largest prodromal clinic worldwide. Our first aim was to describe the type of FI offered in a prodromal clinic and to test their association with baseline socio-demographic and clinical data. Our second objective was to assess their longitudinal associations with clinical and functional outcomes. **Methods:** All subjects referred to OASIS and diagnosed with a HR state for psychosis in the period 2001-2012 were included (N=258). Patients were followed up for an average period of 6 years (SD=2.5) and repeated measures were collected (Comprehensive Assessment of At Risk Mental State, Global Assessment of Functioning). The cross-sectional associations between demographic and clinical characteristics of the sample and the type of FI were assessed with ANOVA or Chi-square test (Bonferroni correction). Cox regression analyses tested longitudinally the link between FI and clinical (transition to psychosis) and functional (good GAF>61 or poor GAF<61) outcome. The regression model was then corrected for baseline between groups differences.

Results: The mean age of the sample was of 22.9 years (sd=4.5). 33% of the sample was treated with cognitive behavioural therapy (CBT) only. 17% of subjects received Antipsychotics (AP) in addition to CBT. Another 17% of subjects were prescribed with Antidepressants (AD) in addition to CBT. 20% of the sample received other types of interventions (Other) which included: CBT plus both AP and AD, medications only, monitoring. There were baseline between-groups differences in gender, Negative Symptoms CAARMS domain and Avolition CAARMS subscale. In a mean follow-up time of 6 years a transition risk of 18% was observed. There was a significant correlation between FI and psychosis transition (-2LL=365.472, $\chi^2(3)=13.08$, p=0.004). Post-hoc analyses indicated an opposite relationship of CBT+AP vs CBD+AD interventions (p=0.007). CBT+AP intervention was associated with a higher transition risk (-2LL=370.777; $\chi^2(1)=9.509$, p=0.002; $\beta=0.991$, OR=2.694, CI95%=1.403-5.174). CBT+AD intervention was linked with a reduced risk of psychosis transition (-2LL=371.912, $\chi^2(1)=5.242$, p=0.022; $\beta=-1.514$, OR=0.22, CI95%=0.053-0.913). The model survived correction for baseline between-groups differences in gender (p=0.019) and in severity of Negative Symptoms CAARMS domain (p=0.033) and of Avolition (p=0.023). There was no correlation between FI and functional outcomes (p=0.330).

Discussion: Our results are in line with recent guidelines discouraging the use of AP in HR patients. Another recent long term follow-up study found indirect evidence supporting a potential beneficial effect of AD in preventing psychosis. Despite these promising beneficial effects, we cannot exclude that the differential relations of AD and AP with psychosis transition may be secondary to core underlying features of the HR state. The HR diagnosis may include different subgroups: a "true prodromal" endophenotype later transiting to psychosis together with a "clinical noise" HR endophenotype. The AP vs AD effects may not reflect a better preventative efficacy but simply a lower level of psychosis risk in the HR subgroup with anxiety or depressive symptoms. This is further corroborated by the lack of relations between FI and functional outcomes. Surprisingly, there are no available RCTs of AD in HR. Future studies are urgently needed.

Poster #M146**THE RELATIONSHIP BETWEEN POSITIVE PSYCHOTIC AND DEPRESSIVE SYMPTOMS AND FUNCTIONING IN YOUNG PEOPLE WITH MENTAL HEALTH ISSUES**

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Background: Attenuated psychotic symptoms constitute a common feature of emerging mental disorders in young people. These psychotic symptoms will subside either spontaneously or via early intervention for the majority of clients with decrease of depressive symptoms. For a subset of clients, however, these attenuated psychotic symptoms will put them at risk for developing frank disorders, such as psychosis or other full-blown mood disorders, exerting a major impact on individuals social and role functioning.

Methods: We conducted clinical interviews at baseline with 73 clients with mental health issues ($M_{age} \pm SD = 20.7 \pm 2.6$, range 16-26 years, 51 females) consisting of the positive symptoms subscale of the Comprehensive Assessment of At Risk Mental States (CAARMS), the Quick Inventory of Depressive Symptoms (QIDS), and the Global Functioning: Social and Role scale. After 6 months, these individuals were followed up with the same assessment battery (n=27). Linear regression and correlation analyses with positive psychotic and depressive symptoms and social and role functioning at baseline and after 6 months were performed.

Results: At baseline, depressive symptoms, but not positive psychotic symptoms, showed a significant association with functioning. Individuals scoring high on depression and experiencing (sub)clinical psychotic symptoms showed lower social ($p=0.088$) and role functioning ($p=0.002$), compared to those having low levels of depressive symptoms but experiencing similar levels of (sub)clinical psychotic symptoms. Similarly, depressive symptoms but not psychotic symptoms predicted functioning at 6 months, but only for social function ($p=0.008$). Depressive symptoms at baseline predicted intensity ($F(1,26) = 5.811$, $p=0.02$, $R^2=0.183$) but not frequency of positive psychotic symptoms at 6 months. Intensity of psychotic symptoms at baseline correlated negatively with social functioning at baseline ($r=-0.291$, $p=0.012$), but did not predict functioning after 6 months. Frequency of psychotic symptoms at baseline also correlated negatively with social functioning at baseline ($r=-0.298$, $p=0.01$), and was predictive of role functioning after 6 months ($F(1,26) = 6.848$, $p=0.016$, $R^2=0.208$).

Discussion: Social and role functioning in individuals with emerging mental health issues appear to be more strongly influenced by the presence of depressive than subclinical or clinical psychotic symptoms. However, both intensity and frequency of psychotic symptoms seem to be associated with a decline in functioning in these individuals. Neurodevelopmental trajectories of these associations with illness progression and transition to psychosis, however, require further longitudinal exploration.

Poster #M147**GENDER DIFFERENCES IN COGNITIVE FUNCTIONING IN AT-RISK MENTAL STATE FOR PSYCHOSIS, FIRST-EPIISODE PSYCHOSIS AND HEALTHY CONTROL SUBJECTS**

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Background: Several gender differences in schizophrenia have been reported including differences in cognitive functioning. In healthy controls, it has been established that men perform better in visuo-spatial and working memory tasks, whereas women outperform men in verbal learning and memory. Studies with schizophrenia patients indicate that men fail to exhibit the normal sex advantage on spatial and working memory domains, while the sex advantage for women in verbal domains is preserved. However, findings have been inconsistent, with some studies reporting either no gender differences or even contradictory results. Furthermore, no study has yet analysed gender related cognitive performance differences in at-risk mental state for psychosis (ARMS) individuals. Thus, the aim of the present study was to investigate gender differences in ARMS, first-episode psychosis (FEP) and healthy control (HC) subjects. We expected a better

verbal learning and memory performance of women in all groups and a better working memory performance of men in the HC group but not in ARMS and FEP subjects.

Methods: As part of the Früherkennung von Psychosen (FePsy) study, 117 ARMS, 87 FEP individuals and 86 HC's completed a cognitive test battery. We used the Mehrfachwahl-Wortschatz Test for measuring verbal IQ, the Leistungsprüfssystem for nonverbal IQ, the Tower of Hanoi, Wisconsin Card Sorting Test and Go/No-Go subtest of the Test of Attentional Performance (TAP) for executive functions, the 2-back task of the TAP for working memory, the Continuous Performance Test (CPT-OX) for vigilance, and the California Verbal Learning Test (CVLT) for verbal learning and memory. Analyses of covariance models were applied to evaluate the main effects of gender and group (ARMS, FEP, HC) as well as their interactions on cognitive functioning. Differences were adjusted for the influence of age, years of education and use of antipsychotics.

Results: In the whole study sample, women showed less retroactive interference (i.e., influence of newly learned words on the recall of previously learned words) in the CVLT ($p=0.038$; $d=0.275$), whereas men demonstrated a shorter working memory reaction time ($p=0.044$, $d=-0.239$). Moreover, there was a trend for better performance in women in the CVLT long delay free recall ($p=0.094$; $d=0.215$) and number of remembered words in the CVLT trials 1–5 ($p=0.056$; $d=0.250$) independent of group. Furthermore, there was a significant interaction effect ($p=0.031$) between gender and diagnostic group (ARMS, FEP and HC) on verbal IQ, which was due to a non-significantly worse performance of women in the ARMS ($d=-0.279$) and FEP group ($d=-0.135$) and a non-significantly better performance in the HC group ($d=0.178$). Considering each group separately there were no gender differences in ARMS, FEP as well as HC's.

Discussion: In line with our hypothesis and consistent with the literature, our results suggest that women perform better in the domain of verbal learning and memory independent of the diagnostic group. However, we could not confirm a sex \times group interaction effect on working memory (i.e., that male FEP patients fail to exhibit a sex advantage in terms of working memory normally seen in HC's). Instead, we found a significant sex \times group interaction effect on verbal IQ suggesting that sex differences regarding verbal IQ differ between HC, ARMS and FEP individuals.

Poster #M148

SOCIAL COGNITIVE FUNCTIONING IN PRODRMAL PSYCHOSIS: A META-ANALYSIS

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Background: Social cognition is impaired in patients with schizophrenia, and it may be a vulnerability marker for this disorder. However, a domain-by-domain analysis of social cognitive deficits in individuals with clinical high risk (CHR) for psychosis has not been performed.

Methods: Electronic databases were searched for studies on social cognitive performance in individuals with CHR. The included social cognitive domains, classified based on the recent NIMH consensus statement, were the following: theory of mind, social perception, social knowledge, attributional bias, and emotion processing.

Results: Twenty studies including 809 individuals with CHR and 585 healthy controls met the inclusion criteria. The overall effect size for social cognition was medium ($g = -0.558$, 95% CI = -0.654 to -0.462). The largest effect sizes were seen in attributional bias ($g = -0.767$, 95% CI = -1.186 to -0.348). A medium effect size was observed in emotion processing ($g = -0.665$, 95% CI = -0.823 to -0.507), and small effects were observed in ToM ($g = -0.408$, 95% CI = -0.579 to -0.237) and SP ($g = -0.383$, 95% CI = -0.63 to -0.136). No studies targeting social knowledge in individuals with CHR were identified.

Discussion: The present study indicated that individuals with CHR showed significant impairments in all domains of social cognition compared with healthy controls, with the largest effect size found in attributional bias.

Poster #M149

ARE UHR PATIENTS WHO PRESENT WITH HALLUCINATIONS ALONE AT LOWER RISK OF TRANSITION TO PSYCHOSIS?

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Background: In recent years hallucinations have been reported to occur much more commonly in the general population than clinically diagnosed psychiatric disorders. As such, it has been suggested that hallucinations may be less specific to psychosis than other types of psychotic experience. In light of our evolving understanding of the clinicopathological significance of hallucinations it would now seem timely to reassess the role hallucinations may play in the emergence of psychosis. The "Ultra High Risk" (UHR) or putatively prodromal population, who are associated with a several hundred fold increase in risk of transition to psychosis, offer a unique group to investigate this research question. Aims: 1. Investigate whether UHR patients who present with hallucinations alone i.e. with no other attenuated psychotic symptoms, are at lower risk of transition to psychosis than patients meeting UHR criteria due to presence of other attenuated symptoms or trait criteria. 2. Secondary aims are to assess if:

- Hallucinations when found in the presence or absence of other clinical symptoms at baseline makes transition to psychosis less likely.
- Different hallucination forms are associated with different risks of transition to psychosis e.g. visual hallucinations are associated with a lower risk of transition than auditory hallucinations.

Methods: A retrospective "case-control" study of patients meeting the UHR criteria treated at a specialised UHR clinic was developed. There were 59 cases and 59 controls. We performed a survival analysis using Log-rank test and Cox regression to investigate the relationship between symptom variables and transition to a psychotic disorder.

Results: Hallucinations alone at baseline were not associated with a reduced risk of transition to psychosis (adjusted hazard ratio 0.83, $p=0.67$). Any hallucination with no thought disorder was associated with a reduced risk of transition to psychosis (adjusted hazard ratio 0.58, $p=0.05$). Visual hallucinations and no substance use (adjusted hazard ratio 0.44, $p=0.05$) was also associated with a reduced risk of transition.

Discussion: Hallucinations on their own do have a clinical significance in this population and shouldn't be dismissed. However, our data suggests that there are certain combinations in the UHR population that make transition a little less likely. Investigation of the significance of hallucinations in other populations is warranted.

Poster #M150

CANNABIS USE IN A SAMPLE OF SUBJECTS AT RISK FOR DEVELOPING PSYCHOSIS

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Background: Numerous studies support the association between cannabis and psychosis, with consistent evidence suggesting the use of cannabis in the adolescence as a risk factor for developing psychosis. However, less is known about the relationship between cannabis use and high-risk symptoms in subjects considered at high risk for psychosis also denominated At Risk Mental State or Psychosis Risk Syndrome (PRS). We determine the prevalence of cannabis use in a group of PRS subjects and we study the differences in clinical characteristics and general functioning at baseline in PRS patients with and without history of cannabis use. We also study the correlation between age at onset of symptoms and age at onset of cannabis use.

Methods: A prospective longitudinal study with PRS patients of child and adolescent population (age 10–17). Help-seeking subjects who met PRS criteria were recruited from the Child and Adolescent Psychiatry and

Psychology departments of Hospital Clinic and Hospital Sant Joan de Déu (Barcelona, Spain). Two groups were compared: CNN users PRS patients (PRS+) and non CNN users PRS patients (PRS-). Any time of CNN use was considered as lifetime CNN use. Inclusion criteria were: 1) Attenuated positive or negative symptoms in the previous 12 months; 2) Brief intermittent psychotic symptoms; 3) First or second degree relative with schizophrenia or schizotypal disorder plus impairment of functioning. Exclusion criteria: IQ<70 and a diagnosis of neurodevelopmental disorder. The Semistructured Interview for Prodromal Syndromes and Scale of Prodromal Symptoms (SIPS/SOPS) were administered to assess prodromal symptoms. So it also has been assessed the global functioning, social and role functioning, and other clinical symptomatology. SPSS 19.0 were used to analyze data performance.

Results: 46 PRS subjects (mean age 15.15, range 11–17; 39% male) were included. We divided the sample into two groups depending on the presence of lifetime cannabis use. 10 PRS+ patients (age 16.3 range 14–17, 30% male) and 36 PRS- patients (age 14.83 range 11–17; 41.7% male). Only 1 patient met DSM-IV-TR criteria of substance abuse. We found significant differences between groups in gender and age with more female ($p<0.001$) and an older age ($p=0.013$) in the PRS+ group. Mean age at onset of cannabis use was 14.8 ± 1.48 and mean age at onset of high risk symptoms was 16.3 ± 1.03 . We found significant differences in three items of the SIPS/SOPS scale between both groups. Specifically, in positive attenuated symptoms of grandiosity (P3) ($p=0.049$) and disorganized communication (P5) ($p=0.016$). All of them were more sever in the PRS- group. No more differences were founded in other prodromal symptoms and clinical characteristics. We also found a positive correlation between a younger age at onset of cannabis use and a younger age at onset of symptoms ($p<0.001$, coefficient=0.919). These results should be considered preliminary pending to increase the sample size to draw further conclusions.

Discussion: With the data available at this moment, we have found differences in the severity of symptoms only in a few prodromal symptoms. We can't determine a different profile of clinical characteristics of the sample in relation to the cannabis use. This is consistent with previous research in high-risk population.

Poster #M151

A MULTIMODAL BIOMARKER TO PREDICT THE ONSET OF SCHIZOPHRENIA

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Background: The onset of psychosis is typically preceded by a prodromal phase which is characterized by the emergence of isolated psychotic symptoms and is known as At Risk Mental State (ARMS) but only one third of these individuals go on to develop full blown psychosis within 2 years. At present is not possible to distinguish between ARMS subjects who will and will not later develop psychosis on purely clinical grounds. Knowledge is currently being gathered on the impact on genetic and environmental risk factors in the brain of individuals with an ARMS. This project makes use of this knowledge to build a multimodal biomarker tool, useful in a clinical setting, to predict which ARMS individuals will make a transition to psychosis, so that treatment can be targeted to those who need it.

Methods: This project involved the examination of ARMS individuals at baseline involving 1) genotyping selected genetic variants previously genome-wide-associated with psychosis to assess genetic susceptibility, 2) structural Magnetic Resonance Imaging (sMRI) to assess brain phenotypic differences, 3) psychosocial, neuropsychological and clinical interview to assess frequency and severity of prodromal symptoms, previous and current exposure to environmental stressors (such as cannabis use, childhood trauma and serious life events) and IQ. A 2-year (minimum) follow-up of subjects was performed to assess whether subject had converted to a psychotic illness.

Results: Using machine learning classification we built an algorithm that can predict conversion based on baseline data. The predictive value of the genetic, neuroimaging, neuropsychological and environmental information, in combination and in isolation, for distinguishing between "converters" and "nonconverters" to psychosis was calculated.

Discussion: While most studies to date have applied machine learning

methods to a single data type to make prognostic or diagnostic predictions, this study confirms that this analytical technique can also be applied to a combination of different data types, resulting in more sensitive and more specific prognostic accuracy. By using this tool to target treatment in the clinic, side-effects, stigma and economic costs of preventative treatment for psychosis may be avoided.

Poster #M152

CLINICAL DEPRESSION PREDICTS PARANOIA IN HIGH-RISK PATIENTS.

RESULTS OF THE EPOS PROJECT

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Background: Since the nineteenth century, the causal connection of affective mood and paranoid thinking has been one of the most interesting questions in psychiatric psychopathology. Patients with affective disorders or symptoms may have non-psychotic or psychotic paranoid symptoms. On the other hand, paranoid patients often reveal depressive or anxiety symptoms. Causal direction between affective disorders and paranoia is difficult to evaluate in patients with full-blown paranoia. In a prospective follow-up study, we aimed to study whether clinical depressive or anxiety disorders predict occurrence of paranoid-like symptoms in clinical high-risk (CHR) patients.

Methods: In the EPOS project, 245 young help-seeking CHR patients were examined and followed for 18 months. At baseline, patients' current clinical diagnoses (the Structured Clinical Interview for DSM-IV), as well as depressive and anxiety symptoms (the PANSS) were assessed. Persecutory/paranoid symptoms were assessed by the Structured Interview for Prodromal Syndromes (SIPS) at baseline and at the 9 and 18 months follow-up. Baseline paranoid symptoms were subtracted from follow-up paranoid symptoms (FoPa). The difference was digitomised (yes/no) and analysed in logistic regression analysis.

Results: From clinical diagnoses, depressive and anxiety disorders associated significantly with FoPa. Likewise, depressive and anxiety symptoms had a significant association with FoPa. In logistic stepwise regression analysis, clinical depressive disorder and anxiety symptoms predicted significantly FoPa.

Discussion: It seems that from affective disorders, depression is a major predictor of paranoid symptoms. However, also anxiety symptoms, especially excessive social anxiety, play a role in occurrence of paranoid symptoms.

Poster #M153

ENVIRONMENTAL RISK FACTORS, PRODROMAL PSYCHOTIC SYMPTOMS AND PSYCHOPATHOLOGY OF CHILD AND ADOLESCENT OFFSPRING OF PARENTS WITH BIPOLAR DISORDER, SCHIZOPHRENIA AND COMMUNITY CONTROLS. THE BIPOLAR AND SCHIZOPHRENIA YOUNG OFFSPRING STUDY (BASYS)

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Background: Objective: To compare environmental risk factors, prodromal psychotic symptoms and prevalence of DSM-IV Axis I disorders in child and adolescent offspring of Bipolar disorder (BD), Schizophrenia (SZ), and community controls (CC).

Methods: The Bipolar and Schizophrenia Young Offspring Study (BASYS) is a follow-up study designed to evaluate clinical, neuropsychological, neu-

roimaging and genetic variables in child and adolescent offspring of parents with BD and SZ. BD and SZ parents with children aged between 7 and 17 years were recruited through the adult mental health services of the Hospital Clinic of Barcelona and Hospital Gregorio Marañón of Madrid. Offspring of CC were recruited from the same geographical area. Offspring sample: 90 BP-offspring (BpO), 40 SZ-offspring (SzO) and 107 community control offspring (CcO) were assessed by a qualified psychiatrist or psychologist blinded to parental status. DSM-IV psychiatric diagnoses and prodromal symptoms were evaluated by K-SADS-PL and Structured Interview for Prodromal Symptoms (SIPS), respectively. Environmental risk factors and premorbid adjustment were assessed by Murray-Lewis Obstetric Complications scale (OCS), Stressful Life Events Schedule (SLES) and Premorbid Adjustment Scale (PAS). General functioning was estimated by Children Global Assessment Scale (cGAS).

Results: Environmental risk factors: SzO presented higher rates of obstetric complications than CcO. Stressful life events were more frequently reported by both SzO and BpO parents than by parents of CcO. Premorbid adjustment and functioning: Both SzO and BpO presented poorer premorbid adjustment and lower functioning than CcO. In addition, SzO also presented poorer premorbid adjustment and lower functioning than BpO. Prodromal psychotic symptoms: SzO scored higher than both BpO and CcO in all subscales of the SOPS. BpO only scored higher than CcO in disorganization subscale. Psychopathological features: 60% of SzO, 36.7% of BpO and 17.8% of CcO had experienced a DSM-IV psychiatric disorder. Attention Deficit Hyperactivity Disorder (ADHD) was the most prevalent disorder in the three groups followed by disruptive behaviour disorders in SzO, mood disorders in BpO and anxiety disorders in CcO. After controlling for confounders, compared to CcO, SzO showed increased rates of ADHD and anxiety disorders and BpO showed increased rates of mood disorders and ADHD. When SzO and BpO were directly compared, ADHD was more frequent in SzO.

Discussion: In line with previous investigations which studied SzO1,2 or BpO3,4,5, we found that both groups presented higher rates of psychopathology than CcO. Our findings suggest a gradient of clinical severity between SzO, BpO and CcO. SzO, also presented the highest rates of obstetric complications, the poorest premorbid functioning and the highest rate of ADHD, which also suggest a gradient of neurodevelopmental impairment between SzO, BpO and CcO. Finally, SzO presented more positive and negative prodromal symptoms than both BpO and CcO. Therefore, follow-up of at risk population has the potential to inform on the clinical trajectory leading to disease.

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Poster #M154

PREVALENCE OF PSYCHOSIS-RISK CRITERIA AND SYMPTOMS IN AN INPATIENT AND GENERAL POPULATION SAMPLE OF CHILDREN AND ADOLESCENTS

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Background: For adolescents from the community in defined age-ranges (11-13 and 13-15 years of age), increased prevalence rates of attenuated psychotic symptoms (APS) and positive symptoms were recently reported. The two Irish studies indicated an age effect: 22.6% of the younger sample reported APS or positive symptoms, especially (attenuated) hallucinations, as compared to 7% of the older age group. In the younger sample, APS-related risk criteria were met by 7.7%. Furthermore, APS were related to a higher psychiatric morbidity. Thus, APS and possibly other risk criteria and symptoms might be even more frequent in clinical child and adolescent samples, even if the clinical picture does not suggest the possible development of psychosis.

Methods: We studied the prevalence and possible clinical impact of risk criteria and symptoms according to the ultra-high risk (UHR) and basic symptom (BS) approaches in an inpatient (ClinS) and a general population sample (GPS) of 8-17-year-olds (at the time of writing: ClinS: N=41; GPS: N=55). The inpatient sample comprised 5 diagnostic groups for that increased rates of subsequent psychosis had been reported: Eating (n=19),

ADH (n=6), Anxiety (n=5), Obsessive Compulsive (n=5) and Asperger's (n=6) Disorders. UHR and BS criteria and the included 19 symptoms were assessed with the "Structured Interview for Psychosis-Risk Syndromes" (SIPS) and the "Schizophrenia Proneness Instrument, Child and Youth version" (SPI-CY), and psychosocial functioning with the "Social and Occupational Functioning Assessment Scale".

Results: Only 1 patient of the ClinS (2%), but 5 persons of the GPS (9%) acknowledged the presence of any one at-risk criterion. Additional 15 inpatients (37%) and 25 subjects of the GPS (46%) acknowledged at least any 1 past or present risk symptom. Thereby, "perceptual abnormalities/hallucinations" of the SIPS and SPI-CY, were by far the most frequent phenomenon in both samples.

Discussion: Currently used risk symptoms – particularly when related to perception – are frequent in children and adolescents with severe mental disorders requiring inpatient treatment and in youths from the community. Since risk criteria have predominately been developed in adult samples in that perceptual phenomena are much less frequent, the findings call for further studies on the psychopathological significance of risk symptoms in children and adolescents.

Poster #M155

MEDIATION MODELS OF THE RELATIONSHIP BETWEEN CHILDHOOD TRAUMA AND DEPRESSIVENESS IN PATIENTS AT-RISK FOR PSYCHOSIS AND IN HELP-SEEKING CONTROLS

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Background: Childhood trauma is related to a variety of mental health problems including psychotic symptoms. A higher prevalence rate of trauma has been found in patients with psychosis and those symptomatically at risk for psychosis compared to healthy controls. Therefore, the experience of trauma is assumed to act as a risk factor for transition to psychosis. However, the processes underlying the link between trauma and the development of psychosis are poorly understood. Trauma has found to be associated with an excessive use of external attributions, dysfunctional coping patterns, and elevated levels of depressiveness in healthy subjects but such studies are missing in patients at-risk for psychosis. Moreover, it remains unclear if this mechanisms is specific for psychosis or if it represents an unspecific mechanisms for the development of mental health problems in general.

Methods: We applied structural equation modeling to evaluate theoretically based models of pathways from trauma to depressiveness in a large sample of 137 patients at-risk for psychosis according to UHR and/or basic symptom criteria and in 228 help-seeking controls. Intervening variables between childhood trauma (Trauma And Distress Scale; TADS) and depressiveness (Beck Depression Inventory II; BDI-II) were attribution styles (Competence and Control Beliefs Questionnaire; FKK) and coping strategies (Stress-Coping-Questionnaires, SVF-120/SVF-K).

Results: A measurement model demonstrated that all latent variables (trauma, attribution styles, coping, and depressiveness) were well represented by their respective indicators. The final model with a path running from trauma to external attribution styles to maladaptive coping strategies to depressiveness demonstrated a good fit to the data. The indirect effect between trauma and depressiveness mediated by attribution and coping patterns was significant. This model hold true for both the at-risk for psychosis and the help-seeking sample.

Discussion: Our findings suggest that childhood trauma increases the risk for maladaptive outcomes by the development of dysfunctional attribution styles that lead to an excessive use of negative coping strategies and heightened levels of depressiveness. Against this background, integrated interventions designed to target these factors may enhance resilience, and may prevent the persistence of distressing symptoms or transition not only to psychosis but also to psychiatric disorders in general.

Poster #M156**UNDERSTANDING SOCIAL FUNCTIONING IN "AT RISK MENTAL STATE" FINDINGS FROM THE ZURICH EARLY RECOGNITION PROGRAM**

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Background: Poor social functioning is one of the diagnostic criteria of schizophrenia in DSM-5. Part of the disability produced by psychotic illnesses especially schizophrenia and bipolar disorder develops already during the prepsychotic period. Internationally employed definitions of the "at risk mental state" are existing. Previous studies found that low functioning in an "at-risk mental state" is associated with higher conversion rates. Disability plays also a role in a putative "attenuated psychosis risk syndrome". This study aims to explore possible predictors and mediators of functioning.

Methods: In this prospective longitudinal multi-level-approach (psychopathology, neuropsychology, genetic, electrophysiology, sociophysiology/social cognition, MRI and NIRS) subjects, at risk for schizophrenia or bipolar disorder, from the Canton Zurich were recruited. In our symptomatic high-risk group we target these individuals for intensive monitoring. Data about the socio-demographic background, physical health, obstetric and family history, premorbid adjustment, functioning and disability by psychiatric symptoms, daily hassles stress and quality of life, perceived stigma, general self-esteem, social distance were collected. To model simultaneously the relations of clinical and socio-demographic variables with the dependent variables, path analysis models will be used.

Results: Participant baseline characteristics and descriptive data: 221 persons entered the study group. 133 (60.2%) subjects were male. The mean age of the sample was 20.99 (± 6.0) years (range 13-35 years, median 20 years) with no significant difference between males (21.25 \pm 6.1 years) and females (20.60 \pm 5.7 years). Among the 221 participants, 81 (36.7%) fulfilled high risk and 107 (48.4%) ultra-high risk criteria for psychosis, 155 (70%) fulfilled risk criteria for bipolar disorder.

Discussion: We found a huge overlap between the different at-risk groups. In this study we examined the underlying processes of social functioning deficits and their associations in a population of individuals with a high risk for psychosis. Understanding etiologically factors, underlying psychosocial functioning, could have an impact on refined intervention strategies.

Poster #M157**THE DANISH HIGH RISK AND RESILIENCE STUDY - VIA 7-ATTACHMENT STYLE, HOME ENVIRONMENT AND EMOTIONAL CLIMATE AMONG 7-YEAR- OLD CHILDREN WITH FAMILIAR HIGH RISK OF DEVELOPING SCHIZOPHRENIA SPECTRUM DISORDER OR BIPOLAR DISORDER**

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Background: Background The dominating hypothesis is that schizophrenia

is a neurodevelopmental disorder, and that both genes, environment and gene-environment-interactions contribute to the risk of developing the disease. Children of parents with schizophrenia have a higher risk of developing a serious mental illness during life and, as a group, they have a higher rate of developmental abnormalities, emotional and social difficulties, and cognitive problems compared to children without genetic disposition. Focus on the child's attachment style and upbringing conditions Recent evidence has highlighted the importance of attachment style and the child's subjective experiences of the quality of care and support from the parents for the development of future mental health. Insecure and disorganized attachment styles are viewed as risk factors for being more vulnerable to developing emotional difficulties, poorer emotional control, lower self-esteem, and poorer mentalization etc. which may lead to a higher risk of developing mental disorders. In this context, the home environment and the circumstances under which the child is raised with varying degrees of stimulation and support, represents an important prognostic factor. Aim We aim to analyse the influences of genetic risk and environmental factors, including childhood rearing conditions, in a population of 7-year-old children with either 0, 1 or 2 parents diagnosed with schizophrenia spectrum psychosis or bipolar disorder on their cognitive, neuromotor, and psychosocial development and on the presence of psychopathology. We hypothesize that a larger percentage of the children growing up with a parent suffering from a severe mental disorder like schizophrenia or bipolar disorder, will display insecure or disorganized attachment patterns, compared with the children of parents without these disorders.

Methods: Design and method We are establishing a cohort of 500 children and their parents, who will be assessed with a comprehensive test battery, where cognition, behaviour, psychopathology and neuromotor development of the child are the main outcome measures. Both parents and the child will be examined with a wide range of validated instruments, interviews, tests, observations and questionnaires to map these domains. The participants are recruited via Danish Registers to ensure representativity. Data from registers concerning social status, birth complications, somatic illnesses and hospitalization will be included in the database. In addition, we also map psychological and relational factors, such as the emotional climate around the child, the degree of stimulation and support in the home environment, and the perceived support from the social network of the parents, the parents attachment style and finally the child's attachment patterns.

Results: Status/results Data collection started 15 December 2012 and is very successful in terms of making the families positive for participation. About 80% of the invited families accept to participate, equal for all groups, and drop-out rates are very low. 150 families are included in the study by Dec 3. Results will be available from 2015.

Discussion: Method and background will be discussed

Poster #M158**NEURAL CORRELATES OF REWARD PROCESSING IN UNMEDICATED PERSONS AT-RISK FOR PSYCHOSIS**

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Background: Alterations of the brain reward system have been related to both positive and negative symptoms in schizophrenia. Only recently, positron emission tomography studies have suggested that dopaminergic dysregulation begins before the first psychotic episode. However, the relationship between functional activation in response to rewards has not yet been investigated in an unmedicated at-risk sample. Thus, the aim of this study was to examine the neural response to reward expectation and reward outcomes in unmedicated participants at-risk for psychosis compared to healthy adults. We were particularly interested whether neural activity in reward and salience associated areas (i.e. ventral Striatum (VS),

medioorbitofrontal Cortex (mOFC) and right anterior Insula (alns) were related to symptoms seen in the at-risk state.

Methods: A modified version of the monetary incentive delay task was presented to 21 unmedicated individuals at-risk for psychosis and 24 healthy controls during fMRI scanning (matched for age, gender and handedness). Participants fulfilled basic symptom or ultra-high risk criteria. Psychopathology was rated with the Structured Interview for Psychosis-Risk Syndromes, the Schizophrenia Proneness Instrument and the Calgary Depression Scale for Schizophrenia. Data analysis focused on neural responses to expectation (contrasting anticipation of reward with anticipation of neutral outcome) and receipt of reward (contrasting the receipt with omission of reward). The individual parameter estimates were then extracted in each region-of-interest (ROI; i.e. left and right VS, alns and mOFC) and were used to determine how these were correlated with clinical symptom scores.

Results: Behaviorally, there was no significant group-difference in either, reaction time ($p > 0.5$), or error rate ($p > 0.2$). Whole-brain analysis revealed no difference between the groups during the feedback phase. However, during anticipation of possible rewards increased activation in the risk-group compared to controls was shown in the mediofrontal gyrus, superior frontal gyrus and precuneus. ROI-based analysis revealed positive correlation between positive symptom scores and activation in the left and right VS ($\rho > 0.54$, $p < 0.012$) and alns ($\rho = 0.52$, $p = 0.015$) during anticipation. Furthermore, during receipt of reward, we found a negative correlation of depressive symptoms with activity in mOFC ($\rho = -0.46$, $p = 0.037$), and negative symptoms with activity in left VS ($\rho = -0.44$, $p = 0.045$).

Discussion: To our knowledge this is the first study exploring the reward system in unmedicated participants at-risk for psychosis. During anticipation of rewards an increased activation in the high-risk sample was found only in areas not primarily associated with reward processing, but rather higher order cognitive processes. This could possibly reflect a compensatory mechanism for maintaining task performance. Furthermore, specific disturbances in the reward system were associated with symptom dimensions. We found a positive relationship between positive symptoms and activity in VS and alns. Dysfunctional activation of both brain regions has been associated with the aberrant attribution of salience to external and internal stimuli. Moreover, activation in mOFC during receipt of reward was negatively correlated with depressive symptoms, which could reflect impaired hedonic reward processing. These findings suggest that altered reward processing may already be present in the pre-psychotic period and might contribute to the clinical features of the high-risk state.

Poster #M159

SYMPTOMATIC OUTCOME OF NON-CONVERTERS WITH AT-RISK MENTAL STATE PATIENTS IN SUPPORT FOR WELLNESS PROGRAMME, INSTITUTE OF MENTAL HEALTH, SINGAPORE

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Background: At-Risk-Mental-State (ARMS) is the period of subtle changes in a person's thinking, behaviour and emotional states before one's first psychotic episode. Research has shown that during this period, intervention could delay, reduce, or even prevent the conversion to psychosis. Extensive researches have looked into conversion to psychosis. However, not many studies look at the 79% who did not convert (Simon AE et al., 2011). This descriptive study looks at the non-converters under the 2-year Support for Wellness Achievement Programme (SWAP) in the Institute of Mental Health, Singapore. SWAP is a clinical programme for the assessment and intervention of ARMS patients. It takes in help-seeking patients between the ages of 16–30years fulfilling the criteria on the Comprehensive Assessment of At-Risk Mental State (CAARMS) – an assessment tool for ARMS. Entry into SWAP is clinically decided aided by CAARMS. Patient is usually distressed, has had a consistently low or 30% decline in functioning in the past year and fulfills one of the 3 main criteria below: a) Vulnerability (Vul) Group – family history of Psychosis in first-degree relative, OR with Schizotypal Personality Disorder; b) Attenuated Psychosis (APS) Group – attenuated symptoms that are not severe and/or do not occur frequent enough; c) Brief Limited Intermittent Psychotic Symptoms (BLIPS) Group –

recent frank psychotic episode that resolved spontaneously within a week. The aims of this study are to find out which of the group above the ARMS patients fall into at baseline; how did they fare at 1-year and how many are still having ARMS after 2 years.

Methods: 109 non-converted patients who were admitted into the SWAP from March 2008 to October 2011 fulfilling the 2-year period with SWAP at November 2013 would have had CAARMS administered at baseline, and at either 1-year or 2-year. CAARMS are administered mainly in-person by trained Case Managers who followed their patients throughout the 2 years. The results were collated into the research database and categorized into 7 groups: 1) Vul Group; 2) APS Group; 3) BLIPS Group; 4) Vul + APS Group; 5) Vul + BLIPS Group; 6) Not ARMS; 7) Others.

Results: Number of patients who did not meet the CAARMS criteria at the end of the 2-year reduced significantly. At baselines more than half (55 out of 109; 50.45%) of the patients fulfilled the APS criteria. 18 (16.51%) belonged to the Vul Group and the rest fell into either the BLIPS (1; 0.92%); Vul + APS (13; 11.93%) or Vul + BLIPS (1; 0.92%). And 21 (19.27%) entered SWAP directly due to clinical decision. At 1-year, the APS group reduced from 55 to 23 (21.10%); only 2 (1.83%) from the Vul Group; and 5 (4.59%) under the Vul and APS group. No patient had BLIPS or Vul + BLIPS. For those who did not have ARMS, the number rose to 61 (55.97%). After 2 years with SWAP, only 10 patients fulfilled the CAARMS criteria, with 8 (7.34%) belonging to APS; and 1 (0.92%) each for Vul Group and Vul + APS. Almost three quarters, 81 (74.31%) did not have ARMS reflecting almost a 4-fold increase from 21. There were also 18 patients not accounted for at 1-year and 2-year who could be either not contactable, only contactable through family, text messages via handphone, or had an early discharge from SWAP.

Discussion: Only 10 out of the 88 ARMS patients fulfilled the CAARMS criteria after 2 years. This significant drop could be due to timely therapeutic intervention; supportive case management; better understanding of their illness; better coping skills; more supportive families; and for a few patients, low dose of antipsychotics, could be the difference for the improvement of the symptoms and functioning. More in-depth and longitudinal studies could be carried out to explore the protective factors of these non-converters.

Poster #M160

IMPROVED INDIVIDUALISED PREDICTION OF SCHIZOPHRENIA IN SUBJECTS AT GENETIC HIGH RISK, BASED ON NEUROANATOMICAL AND CLINICAL DATA

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Background: Early diagnosis of schizophrenia requires the identification of those subjects who will later develop psychosis. Currently no validated biomarkers for determining disease transition exist. Schizophrenia research studies have, however, reported a host of behavioural, neuropsychological and neuroanatomical deficits in individuals at high risk (HR) for the disorder that might be predictive of future disease transition. Recent neuroanatomical-based pattern classification studies were able to predict at a single-subject level those HR subjects who will make a transition to schizophrenia (from those who will not) with over 80% accuracy. One would expect that combining clinical and magnetic resonance imaging (MRI) data would provide a clearer view of disease development and enhance predictive performance. However, no pattern recognition-based study has yet examined the diagnostic performance of combining information from multiple data sources into a single automated learning framework in order to predict transition to schizophrenia.

Methods: In this work, we examined the diagnostic performance of Support Vector Machine (SVM) in predicting future transition to schizophrenia in a cohort of genetic HR subjects who were chosen on the basis of having two or more first or second degree relatives affected with schizophrenia. We included baseline structural MRI and behavioural data of 17 HR subjects who developed schizophrenia after nearly 2.5 years of follow-up (HR[ill]) and 17 age and sex-matched HR subjects who had psychotic symptoms without making a transition (HR[symp]). Recursive feature elimination

(RFE) was employed to detect the most significant and relevant features to the classification task.

Results: Classification performance improved when clinical and neuroanatomical data were combined than when either quantitative measure was employed alone (79% accuracy for the only-clinical and 97% accuracy for the only-structural MRI analyses). Our SVM-RFE method achieved an accuracy of 100%, via leave-one-out cross-validation, in distinguishing at baseline those genetic HR subjects who developed schizophrenia from those who did not. Among the clinical data, measures of schizotypy were the most reliable predictors of transition, whereas the discriminative neuroanatomical pattern involved gray matter volume differences in prefrontal, superior and medial temporal lobe structures and cerebellar regions.

Discussion: Our findings suggest that the SVM-based early prediction of schizophrenia is feasible and can be improved by combining clinical and neuroanatomical variables. We acknowledge, however, that our predictive model should be validated by classifying a new, independent HR cohort. Combining data of various types into a single learning algorithm is of high clinical relevance because a more detailed view of the patient's status and more insight into disease development and progression could be achieved.

Poster #M161

THE BRIEF NEGATIVE SYMPTOM SCALE: PSYCHOMETRIC PROPERTIES AND FACTOR ANALYSIS OF THE GERMAN TRANSLATION

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Background: The reliable and valid assessment of negative symptoms is critical for the development of effective treatments. Based on the results of a consensus conference under the auspices of the National Institute of Mental Health, Kirkpatrick, Strauss and colleagues developed the Brief Negative Symptom Scale (BNSS). The BNSS is a 13-item instrument, which allows rapid assessment of negative symptoms based on a semi-structured interview. The scale has been shown to have excellent psychometric properties and to predict functional outcome. Here, we present the psychometric properties and factor analysis of the German translation of the BNSS.

Methods: We plan to include 80 patients with a diagnosis of schizophrenia or schizoaffective disorder to analyze the factor structure and psychometric properties of the BNSS, including inter-rater reliability, and discriminant and convergent validity. In addition to the BNSS, participants complete a psychopathological assessment that includes the following instruments: MINI Neuropsychiatric Interview, Scale for the Assessment of Negative Symptoms, Positive and Negative Syndrome Scale, Calgary Depression Rating Scale, and the Simpson-Angus Scale for extrapyramidal side effects. Functioning is assessed with the Personal and Social Performance Scale. Preliminary data from 35 participants are available. At the conference results from the full sample will be presented.

Results: The BNSS factor structure was best represented by a 2-factor solution (motivation/pleasure and expressivity), replicating the findings from the original studies. Good convergent validity was established by correlating the BNSS total score with the SANS total score ($r=0.856$, $p<0.01$). Discriminant validity was shown by a lack of correlation with the PANSS positive factor ($r=0.073$, $p>0.1$) and the Calgary Depression Scale ($r=0.082$, $p>0.1$). The BNSS total score was significantly correlated with the Personal and Social Performance Scale as a measure of functioning ($r=-0.800$, $p<0.01$).

Discussion: In the preliminary analysis the German translation of the BNSS shows excellent psychometric properties and largely replicates the factor structure of the original version. These results suggest that the BNSS can be employed to assess negative symptoms across languages and health care systems. This is of particular importance for potential use in future international multicenter trials that target negative symptoms.

Poster #M162

WHICH NEGATIVE SYMPTOMS DO SITE RATERS HAVE THE MOST TROUBLE RATING?

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Background: Assessment of negative symptoms using the Positive and Negative Syndrome Scale (PANSS) requires a complex evaluation of behavior observed during the interview, assessment of the patient's internal experience, and information provided by informants. In order to inform future training, we ranked the seven PANSS Marder negative subscale items with respect to the degree of dissonance in scoring between site raters and same-language local experts utilizing data from eleven global schizophrenia trials.

Methods: Prior to study initiation, raters were trained at investigators meetings by highly interactive procedures, including slide presentations, rating of videotaped patient interviews, and, in some cases, interview and rating of live actors trained to portray schizophrenia symptoms. 2,520 site PANSS interviews were recorded and uploaded for evaluation by an independent same-language local expert. The external reviewers provided feedback on an ongoing basis to the site and sponsor on diagnostic and scoring accuracy and interview quality.

Results: In rating the Marder negative scale, the proportion of major discrepancies (>2 anchor points) between the site and external rater was greater ($t=2.59$, $p <0.05$) than for the remainder of PANSS items. There were fewer exact matches (47.6% vs. 61.0%) ($t=11.70$, $p <0.001$) and more major discrepancies (>2 anchor points) (10.3% vs. 6.0%) ($t=4.43$, $p <0.01$) for items N1 (Blunted affect), N3 (Poor rapport) and N6 (Lack of spontaneity of conversation) compared to items N2 (Emotional withdrawal), N4 (Passive apathetic social withdrawal), G7 (Motor retardation) and G 16 (Active social avoidance). In addition, the proportion of items in exact agreement vs. major discordance (<2 anchor points) was statistically significantly higher for US vs. Rest of World sites for items N1, N3, N4, N6, G7 and G16.

Discussion: Major discrepancies between the site and external rater occurred more frequently in rating negative symptoms than other PANSS items. Negative symptoms rated purely based on behavioral observation (N1, N3, N6) were harder to obtain agreement on than negative symptoms that included verbal report from the patient or informant. Symptoms rated on the basis of behavioral observation alone may require more intensive training. Division of observational phenomena into quantifiable components (eg, blunted affect into the components of prosody, facial expression, gestures) may facilitate reliability of measurement. The current results are based on data from ongoing and recently completed studies. Additional data and analyses addressing regional variation will be reported.

Poster #M163

NEGATIVE SYMPTOM SUBGROUPS HAVE DIFFERENT EFFECTS ON CLINICAL COURSE AFTER FIRST EPISODE OF SCHIZOPHRENIA: A 24 MONTHS FOLLOW-UP STUDY

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Background: Recent factor analytic studies show that negative symptoms in schizophrenia have two subgroups as expression and motivation-pleasure deficits. The aim of this study is to assess the factor analytic structure of negative symptoms at the admission of first episode schizophrenia (FES) patients, and their relationship with course and functionality during two years of follow-up.

Methods: We assessed 176 patients with first-episode schizophrenia at admission when they were drug-naïve, by using the Brief Psychiatric Rating Scale, the Scale for Assessment of Negative Symptoms, the Scale for Assessment of Positive Symptoms, Global Assessment of Functioning Scale, Premorbid Adjustment Scale and an 8 item cognitive test battery. Clinical measures were recorded during monthly outpatient visits for 24 months; we also recorded their functionality, remission and work status at 12th and 24th months.

Results: A two-factor structure appeared at baseline: one consisted of alogia-restricted affect (expression factor) and the other of avolition-anhedonia (motivation and pleasure factor). However only one factor was

found in the 12th and the 24th months. There was a negative correlation between the expression factor and the patients' education levels and composite global cognition scores. The expression factor was significantly higher in the early-onset group and significantly lower in the patients who meet and sustain the remission criteria. Motivation and pleasure factor was related with family history of schizophrenia, work status before admission and at the second year of follow-up.

Discussion: Our findings suggest that these two factors have different etiologies and impacts on the course and functionality after FES.

Poster #M164

IMPROVEMENT IN NEGATIVE SYMPTOMS IN PATIENTS TREATED WITH ANTIPSYCHOTICS

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Background: In line with previous research, a recent review by Darba et al (2011) found that antipsychotics are effective against negative symptoms. Whether this effect is actually a consequence of improvement in positive or depressive symptoms, a consequence of a smaller risk of atypical antipsychotics to cause extrapyramidal symptoms or an action on primary negative symptoms is a matter of debate. The NIMH-MATRICS consensus statement on negative symptoms proposed that although persistent and clinically significant negative symptoms are an unmet therapeutic need in a large proportion of cases, the distinction between primary and secondary negative symptoms is not essential for the purpose of testing therapeutics for negative symptoms, if a study enrolls subjects with persistent negative symptoms and simultaneously controls for the principal sources of secondary negative symptoms. We present a post-hoc analysis of the World-Schizophrenia Health Outcomes Study (W-SOHO) which explores effect of antipsychotics on negative symptoms.

Methods: The W-SOHO study is a three year follow-up study on the outpatient care of schizophrenia that included 17,876 patients from 37 countries. Patients were recruited in W-SOHO by their treating psychiatrists when starting or changing antipsychotic medication. Evaluation was conducted during the normal course of care and was scheduled every six months after the baseline visit. Positive, negative, depressive, cognitive symptoms and overall severity were assessed with the CGI-SCH scale. The current analysis include patients with low level of positive symptoms (CGI-positive<4), high level of negative symptoms (CGI-negative>3) and starting treatment with one antipsychotic at baseline. Following these criteria, a total of 3,712 patients were included. Patients were classified into three treatment cohort: olanzapine, other atypical antipsychotics and typical antipsychotics. Antipsychotic discontinuation rates were calculated using the Kaplan Meier product limit estimation method. Cox regression, MMRM and GEE models were applied to adjust for sociodemographic and clinical differences of the three cohorts and to account for the correlation between the visits of the same patient.

Results: At baseline, patients in the olanzapine cohort (4.68 SD 0.74) had slightly more severe negative symptoms at baseline than patients being treated with other atypical antipsychotics (4.63 SD 0.73) or typical antipsychotics (4.59 SD 0.71). Antipsychotic medication discontinuation rates were lower for olanzapine (38%) than for other atypicals (54%) or typical (64%) antipsychotics. The Cox regression model confirmed that this difference was statistically significant when adjusting for confounders. Olanzapine had a lower discontinuation rate than other atypical and typical antipsychotics. Patients treated with olanzapine also had a greater improvement in negative symptoms during follow-up (adjusted mean difference of 0.23 with other atypicals and 0.46 difference with typical antipsychotics, p<0.001).

Discussion: Our results suggest that olanzapine maybe associated with higher improvement in negative symptoms than patients taking other atypical antipsychotics or typicals. These results should be interpreted conservatively due to the observational design of the study

Poster #M165

NEGATIVE SYMPTOMS OF SCHIZOPHRENIA CORRELATE SPECIFICALLY WITH DEFICITS IN SOCIAL FUNCTIONING

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Background: Despite existing treatments for schizophrenia, negative symptoms persist and are predominant in many patients. Although it is believed that negative symptoms are associated with everyday disability, the specific aspects of everyday functioning associated with negative symptoms are not entirely clear. Further, the relative contribution of negative symptoms, compared to cognitive deficits, functional capacity, and psychosis, to disability has not been examined in a truly systematic manner. In this study we performed a systematic examination of the differential correlation of negative symptoms with three different aspects of functional outcomes in three independent samples of people with schizophrenia.

Methods: We examined the correlation of negative symptoms of schizophrenia, as measured by the factor analysis derived negative symptoms factor from the PANSS, with functioning, via high contact clinician ratings on the Specific Levels of Function (SLOF). Three dimensions of everyday functioning were rated: social functioning, residential functioning, and vocational functioning. Three samples of schizophrenia patients (N=195; 235; 85), all assessed similarly with symptom ratings, functional outcomes, and performance-based measures collected by different individuals, were used as the data source. We also examined the patients in all three samples with a performance-based measure of functional capacity, the UPSA-B, as well as neuropsychological performance, and self-reports of depression with the BDI-II.

Results: In all three samples, the factor analytically derived PANSS negative symptom factor was the only significant correlate of social functioning (*r*'s ranged from *r*=0.33 to *r*=0.48) while cognition, psychosis, functional capacity, and depression were not correlated with social functioning in any sample. In contrast, in all three samples, negative symptoms did not predict either vocational or residential outcomes, which correlated with the severity of deficits in functional capacity, cognition, and the severity of depression. Finally, across the three samples, the individual negative symptoms most strongly correlated with social deficits were emotional withdrawal, blunted affect, and active and passive social withdrawal.

Discussion: These results demonstrate the robust nature of the correlation between negative symptoms and social deficits in schizophrenia. Negative symptoms were the only factors we measured that correlated with social deficits and their correlation was consistent. While these analyses appear to suggest that the treatment of negative symptoms may help in the reduction of social disability, further work would be necessary to clarify this relationship. It is unclear what the implications would be for other aspects of functioning. Additionally the factors strongly correlated with negative symptoms such as emotional withdrawal, blunted affect, and social withdrawal may have important prognostic significance when it comes to treatment. As the current data are cross-sectional, it is possible that quite different relationships would be detected over time, and this is an important topic for future research.

Poster #M166

EVOLUTION OF RISK FACTORS FOR LATE AND PERSISTENT NEGATIVE SYMPTOMS OVER TIME: RESULTS FROM A 12-YEAR FOLLOW-UP OF FIRST EPISODE PSYCHOSIS PATIENTS

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Background: Late and persistent negative symptoms are associated with poor outcomes. However, we currently lack evidence regarding predictors of these at long-term follow-up. We aimed to clarify clinically important baseline risk factors and important clinical information that emerges over follow-up that predict negative symptoms at year 12 and persistence of negative symptoms from year 8-12.

Methods: We recruited 154 consecutive referrals with first episode non-

affective psychotic disorders and reviewed their status prospectively (years 4, 8 and 12). Negative symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). Firstly, proportions with persistence of negative symptoms were assessed between each time point. Secondly, we used univariate methods to measure the associations between baseline and follow-up demographic and clinical information and negative symptoms at year 12 and persistence from year 8-12. Finally, we used multivariate methods to examine these risk factors in the context of other information that was available at the same time points (baseline, year 4 and year 8) in order to determine the most important risk factors for clinicians at each time point.

Results: Prevalence of negative symptoms declined from 56% at baseline to 30% at 8 years but increased to 40% at 12 years. Demographic and clinical information at baseline, as well as emerging clinical information over follow-up are associated with negative symptoms at year 12 and persistence of negative symptoms from year 8-12. However, over the course of follow-up emerging clinical information (including function at year 4 and negative symptoms at year 4 and 8) better predicts negative symptoms at year 12 and persistence from year 8-12 than baseline factors (such as duration of untreated illness and education level).

Discussion: While baseline demographic and clinical factors are associated with later negative symptoms and persistence of negative symptoms, much of this information becomes less important in predicting outcomes as later clinical information emerges. For clinicians, this highlights the importance assessing prognosis in the light of the full range of information available at an individual's point of illness.

Poster #M167

ASSESSING EFFORT-BASED DECISION-MAKING IN SCHIZOPHRENIA WITH TWO NOVEL BEHAVIORAL PARADIGMS

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Background: Negative symptoms significantly interfere with daily functioning for individuals with schizophrenia and are a considerable unmet treatment need. Among the different types of negative symptoms, experiential negative symptoms are the primary determinants of impaired functioning. The evaluation of the negative symptoms of schizophrenia currently relies on clinical interviews. Performance-based measures of motivation and effort could yield clinical trial endpoints that may be more sensitive to treatment effects. These measures are being developed for experimental studies with healthy subjects, but have rarely been adapted and used in people with schizophrenia. This current study assesses motivation in participants with schizophrenia using two new effort-based decision-making tasks. We hypothesized a difference between participants with schizophrenia and controls such that participants with schizophrenia would show less willingness to exert effort for rewards. Furthermore, we hypothesized that within the schizophrenia group, those with high negative symptoms would show less motivation than participants with low levels of negative symptoms.

Methods: The data collection is ongoing and more data will be available at the time of the meeting. We present here preliminary data on 30 participants with schizophrenia and 15 healthy controls. Participants with schizophrenia were split into two groups, classified as "high" or "low" negative symptoms, based on a median split on the PANSS negative symptom subscale. 1) Deck Choice Task. A computerized task in which participants choose from one of two decks of cards, labeled as "easy" or "hard." The hard deck consists of cards that alternate between yellow and blue (each color requires a different mental activity). The easy deck consists of cards that are all the same color (requiring no shifting of mental activity). The hard option is paired with increasingly larger financial incentives (i.e., \$10, \$20, \$40). The primary dependent variable is the ratio of low to high-demand choices.

2) Perceptual Effort Task. This task involves identifying a stimulus that varies in perceptual salience from the visual background. Task difficulty is manipulated by adjusting the degree of contrast between the stimulus and background. Participants select the preferred demand-level (easy, hard) while considering reward level (i.e., \$10, \$20, \$40). The primary dependent variable is the ratio of low to high-demand choices.

Results: For both tasks there were significant main effects of reward level such that all participants increased willingness to employ effort for reward as reward value increases. On the Deck Choice Task, there was a significant effect of group such that significantly fewer participants with schizophrenia chose the hard option than controls, across all reward values ($F(1,40)=8.05$, $p<0.01$). Within the schizophrenia group, on average the participants with high negative symptoms chose the easy option more often than those with low levels of negative symptoms. For the Perceptual Effort Task, the participants with schizophrenia selected the difficult option less often than controls at a trend level. Within the schizophrenia group, those with high negative symptoms tended to choose the easier option more frequently than those with low levels; however, the group differences are not statistically significant with the current sample size.

Discussion: The two tasks presented in this talk performed as hypothesized: participants with schizophrenia were less willing to expend effort for rewards than controls, and the tasks were sensitive to negative symptom severity. The results support the further development of objective measures of experiential negative symptoms for clinical trials. When the samples are larger, we will also examine the associations of these effort-based tasks with neurocognitive ability and daily functioning.

Poster #M168

DNA METHYLATION OF THE 5-HT1A RECEPTOR GENE PROMOTER IS ASSOCIATED WITH NEGATIVE SYMPTOM RESPONSE TO ANTIPSYCHOTIC DRUG TREATMENT

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Background: Individual variability and inadequate response of negative symptoms are major limitations of antipsychotic treatment in schizophrenia. A functional polymorphism, rs6295, in the 5-HT1A receptor gene (HTR1A) contributes to this variability in negative symptom response to antipsychotic treatment in first episode psychosis. The DNA sequence containing rs6295 is rich in cytosine methylation (CpG) sites; CpG methylation is an epigenetic factor that, like the rs6295 polymorphism, can modify transcriptional control. We investigated whether DNA methylation of HTR1A influences response to antipsychotic treatment.

Methods: We determined cytosine methylation in the sequence around the rs6295 polymorphism in a sample of 82 previously-untreated Chinese subjects with a first psychotic episode. After extraction, genomic DNA from blood collected at treatment initiation was bisulfite-modified and the percentage methylation at each of four sites plus the polymorphism site was determined by pyrosequencing. The rs6295 polymorphism was also genotyped. Treatment response after 10 weeks was measured by PANSS items divided into five symptom factors according to Wallwork et al (2010). **Results:** Methylation of one CpG site (CpG13) within a recognition sequence for HES transcriptional repressors was found to correlate with changes in total PANSS score ($p=0.006$) and negative factor subscore ($p<0.001$) following 10 weeks' initial antipsychotic treatment, as well as with baseline negative factor score ($p=0.019$) but no other symptom score. The effect on symptom change remained after correction for the association with baseline score. A trend towards a significant effect was observed for CpG13 in the change in depression score ($p=0.065$). This relationship of CpG13 methylation with negative symptom response remained significant in each of the rs6295 genotype subgroups with or without a G allele. In each case greater methylation related to better treatment response.

Discussion: These results indicate how the extent of methylation at a specific site in the promoter sequence of the HTR1A gene can influence antipsychotic treatment response in a first-episode Chinese sample. We failed to replicate in this sample the specific effect of genotype on negative and depressive symptom response, but observed a strong effect of methylation at a binding site for the HES transcription factors on the response of negative symptoms to antipsychotic treatment. These preliminary findings suggest promoter methylation may contribute to determining treatment

outcome, and further emphasise the role of the 5-HT1A receptor in response to antipsychotic treatment.

Poster #M169

PERSISTANT NEGATIVE SYMPTOMS AFTER FIRST-EPIISODE SCHIZOPHRENIA; RESULTS OF 2 YEARS FOLLOW-UP

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Background: Negative symptoms have a limited response to treatment and tend to be persistent during the course of schizophrenia. Rate of persistent negative symptoms (PNS) at first year after first episode schizophrenia reported as 6.5–6.7%. PNS group were reported as having longer DUP, less adherent to treatment and lower rate of employment (1,2)

Methods: We studied the course of negative symptoms after FES during the 2 years follow-up in 86 patients with schizophrenia. When they were drug-naïve, we completed a cognitive test battery and Premorbid Adjustment Scale. Symptoms were recorded by using BPRS,SANS and SAPS at first admission, and then in monthly outpatient visits. Those who had at least one mild negative symptom in global score of restricted affect, alogia, avolition-apathy and anhedonia-amotivation subscales of SANS were regarded as having any negative symptom. Those who had negative symptoms both at 3rd month after first admission and at 1st year of follow-up. We repeated the same assessment at 24th month

Results: Frequency of any negative symptoms were 85% at first admission, 47% at 3rd month, 38% at 12th month, and 31% at 24th month. Frequency of PNS was 35.8% at 12th month and 15% at 24th month. Those who had PNS at 12th month had worse premorbid adjustment, have lower rates of work/study both before admission and follow-up, lower rates of remission and higher rates of relapse.

Discussion: PNS rates in our study are higher than previous FES samples. As our definition of negative symptoms include both primary and possible secondary negative symptoms, this may explain our higher rates. We will also analyse our results by excluding negative symptoms due to depression and positive symptoms. Our findings imply that rather than existence of negative symptoms, their persistence has an negative impact on the course of the illness. Relationship between PNS and poor premorbid adjustment suggest that they have affected by neurodevelopmental factors.

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Poster #M170

NEGATIVE SYMPTOMS IN THE EARLY COURSE OF SCHIZOPHRENIA: THEIR LONGITUDINAL STABILITY AND RELATIONSHIP TO EARLY COGNITIVE PROCESSES

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Background: Understanding the longitudinal course of negative symptoms in first-episode schizophrenia patients is relevant to developing intervention approaches. The longitudinal relationship between negative symptoms and cognitive deficits may also impact intervention strategies. We examined the longitudinal course of negative symptoms following a first psychotic episode and the longitudinal association between negative symptom severity and cognitive deficits.

Methods: The study included 149 first-episode schizophrenia patients, from three National Institute of Mental Health-funded protocols at the Aftercare Research Program at the University of California, Los Angeles, who had a mean age of 23.7 (standard deviation [SD]=4.4) years and mean education level of 12.9 (SD=2.2) years. Treatment programs included a range of psychosocial interventions, including a novel vocational rehabilitation program for some patients, as well as either oral or injectable atypical antipsychotic medications. Negative symptom assessments (Brief Psychiatric Rating Scale [BPRS] and Schedule for Assessment of Negative

Symptoms [SANS]) were conducted frequently by trained raters from the point of medication stability throughout the first outpatient year. Cognitive assessments (Degraded Stimulus Continuous Performance Test [CPT], Span of Apprehension Test [SPAN, 3–7 CPT]) were administered at baseline and at 1-year follow-up. Cross-lagged panel analyses examined relationships between negative symptoms and cognitive functioning at baseline and 12 months.

Results: After antipsychotic medication stabilization, negative symptoms during the first outpatient year were moderately stable (intraclass correlation coefficient [ICC]=0.64). In addition, specific negative symptom domains were moderately stable: blunted affect (ICC=0.61), emotional withdrawal (ICC=0.53), and motor retardation (ICC=0.63). Beyond this overall moderate stability, 24% of patients experienced at least one period of negative symptom exacerbation, defined using operational criteria as remission followed by relapse or significant exacerbation, or persisting symptoms followed by significant exacerbation. Notably, 5% of patients had at least two periods of negative symptom exacerbation. Furthermore, negative symptom severity at baseline significantly predicted poorer sustained attention (Degraded Stimulus CPT) at 1 year ($p<0.01$) and showed a similar tendency for early perceptual processing (SPAN) ($p<0.08$).

Discussion: Discussion: This study is among the first to systematically examine longitudinal patterns of negative stability and fluctuations of negative symptoms in a sample of first-episode schizophrenia patients. We found that negative symptoms during the first outpatient year are generally stable over time but do exacerbate in a subset of patients. In addition, negative symptom severity at baseline appears to contribute to deficits in early cognitive processing at 1 year. We conclude that negative symptoms under current treatment conditions often continue during the first outpatient year, may contribute to later cognitive functioning, and are an important target for intervention to promote recovery.

Poster #M171

BOTH PSYCHOSIS PATIENTS AND THEIR UNAFFECTED SIBLINGS SHOW INCREASED CONCENTRATIONS OF RED BLOOD CELL MEMBRANE POLYUNSATURATED FATTY ACIDS AS COMPARED TO CONTROLS - FOR GROUP (GENETIC RISK AND OUTCOME OF PSYCHOSIS)

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Background: Two recent meta-analyses showed decreased levels of red blood cell (RBC) polyunsaturated fatty acids (PUFA) in schizophrenia and related disorders (Van der Kemp et al, 2012; Hoen et al, 2013). The most distinctive findings concerned decreased concentrations in patients of docosahexaenoic acid (DHA), docosapentaenoic acid (DPA) and arachidonic acid (AA). However, both these meta-analyses report considerable heterogeneity, which may be related to differences in patient samples between the studies. Moreover, it remains unclear whether the association between altered concentrations of RBC PUFA and schizophrenia reflects the consequence of acute or chronic disease processes, compensatory mechanisms, (shared) environmental effects (i.e. diet), or genetic risk for psychotic disorders. In this study we investigated whether altered RBC PUFA concentrations are associated with (familial risk of) psychotic disorder, and thus may be an intermediate phenotype of the disorder.

Methods: For the present study, we investigated a total of 528 subjects (230 patients, 200 siblings and 98 controls) whose blood samples were taken for multiple fatty acid analysis. The study sample was a subset of the Genetic Risk and Outcome of Psychosis (GROUP) study. Based on two recent meta-analyses we a priori selected the following fatty acids to compare: docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), arachidonic acid (AA), and linoleic acid (LA). Additionally, we tested nervonic acid (NA, a myelin constituent) and eicosapentaenoic (EPA, a precursor of anti-inflammatory cytokines). The association between the concentration of each of the selected RBC PUFA and group (controls, siblings and patients) was tested using multilevel mixed models, which were used because the patients and siblings were related.

Results: Compared to controls, both patients and siblings showed signifi-

cantly increased concentrations of DPA ($p<0.001$; $p<0.02$), AA ($p<0.001$; $p<0.001$), LA ($p=0.05$; $p=0.05$), and NA ($p=0.001$; $p<0.001$) (p values reflect the Bonferroni corrected post-hoc comparisons of patients vs controls and siblings vs controls, respectively). DHA was significantly increased in siblings only (NS; $p=0.03$). The concentrations of EPA were not significantly different between the three groups.

Discussion: We find increased concentrations of the RBC PUFA DPA, AA, LA, and NA in both patients and their siblings as compared to controls. Importantly, the direction of change is similar in both patients and siblings for these four PUFA. To our best knowledge, this is the first study, in the largest sample to date, to investigate RBC PUFA in siblings of patients. Our findings largely contrast previous studies, which generally showed decreased levels of RBC PUFA in patients. However, differences between patient samples reflecting state of disorder, dietary patterns, medication use and drug abuse were identified as possible modifiers of PUFA concentrations, contributing to the heterogeneity present in the meta-analyses (Van der Kemp et al, 2012; Hoen et al, 2013). Interestingly, previous studies by Assies et al (2001) and Kemperman et al (2006), also investigating Dutch samples, showed trends towards increased concentrations for some PUFA. Possibly, regional differences in behavioural patterns (i.e. diet or drug abuse) may modify PUFA concentrations. Planned analyses will be used to further investigate these factors. In summary, our findings suggest that increased levels of RBC PUFA may be an intermediate phenotype for psychotic illness. Alternatively, increased levels of RBC PUFA may be the result of (shared) environmental factors, i.e. diet, social economic status, or cannabis use.

Poster #M172

MOLECULAR MECHANISMS UNDERLYING SYNAPTIC PATHOLOGY IN SCHIZOPHRENIA

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Background: Significant progress has been made over the recent years in understanding the genetic architecture, cellular substrates, brain circuits, and phenotypic profiles of schizophrenia. However, we are still far from understanding this disorder. While antipsychotic medications are effective in controlling the positive symptoms in most patients, cognitive symptoms are currently untreatable. Hence understanding the neurobiological bases of cognitive deficits in schizophrenia is essential for the development of novel therapeutic strategies for their treatment. Multiple lines of evidence from genetic, neuropathological, pharmacological, and imaging studies support a key role for abnormal synaptic connectivity in schizophrenia. Structural and functional imaging studies have consistently shown reductions in cortical gray matter and reduced functional connectivity. Amongst the ultrastructural changes thought to directly contribute to these abnormalities are reductions in synapse and dendritic spine density. Because cognitive function and dysfunction in humans and animal models have been intimately linked to synapse structure and function, cognitive deficits are thought to be most closely associated with alterations in synapses. Mounting evidence indicates that many schizophrenia risk genes encode proteins that affect synapse structure and function. Conversely, many known regulators of synapses have been associated with schizophrenia. This strongly supports the model that perturbations in the molecular network underlying synapse development and plasticity are critically involved in the pathogenesis of schizophrenia.

Methods: We have used a multidisciplinary and multi-level combination of molecular and cellular approaches, cellular confocal and two-photon imaging, neuronal culture models, knockout mice, as well as genetic approaches and brain imaging in humans.

Results: In this talk I will discuss recent findings from our laboratory that implicate molecules previously associated with schizophrenia by human genetic and postmortem neuropathological studies in the regulation of neuronal dendrites and synapses. One of these molecules is the protein product of the KALRN gene, which interacts with proteins encoded by the schizophrenia susceptibility genes DISC1, NRG1 and ERBB4, to regulate spine and dendrite plasticity. Inactivation of the KALRN gene in mice leads to a post-adolescent emergence of frontal cortical spine loss, cortical thinning, cognitive deficits, and other schizophrenia-related behavioral phenotypes. We also identified a novel mutation in the spine plasticity gene KALRN in a subject with schizophrenia and his sibling, but not in

control subjects, which impairs protein function and spine morphology. The subjects carrying this mutation had unusually low IQ and reductions in cortical gray matter thickness as compared to their peers.

Discussion: In the mammalian brain most excitatory synapses are located on dendritic spines, tiny protrusions of dendrites. Changes in synapse numbers and shape have been intimately associated with cognitive function. Alterations in synapses and dendrites have also been extensively reported in schizophrenia. Many schizophrenia-associated molecules, such as NRG1, ERBB4, DTNBP1, and DISC1 have functions in dendrites and synapses, and many known regulators of neuronal synapses have recently been associated with schizophrenia. Studying these pathways could lead to a better understanding of disease neurobiology and could yield novel targets for treatments. By integrating multiple levels of analysis and diverse methodologies with translational and basic research, such studies will enhance the understanding of cellular and synaptic substrates of pathology in schizophrenia and will facilitate the development of novel treatments for cognitive deficits.

Poster #M173

STUDYING HEART ARRHYTHMIAS IN RELATION TO PSYCHOSIS (SHARP). INCREASED PREVALENCE OF CARDIAC ARRHYTHMIAS IN RECENT ONSET SCHIZOPHRENIA

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Background: In schizophrenia an increased risk of sudden cardiac death has been shown (Heart 2010), which has traditionally been associated with increased prevalence of prolonged corrected QT (QTc) interval and cardiovascular risk factors (Glassman 2005, Fan 2013). However defective ion channels have been implicated as well in the pathophysiology of schizophrenia (Imbrici 2013). Specifically, genetic defects in the potassium and calcium gene (Somers 2012 & Ripke 2013) and autoimmune antibodies against the potassium channel have been associated with an increased risk of schizophrenia (Martinez 2013). Malfunctioning of several ion channels (potassium, sodium and calcium) has been implicated in cardiac arrhythmias (Wilde 2013). Importantly, various drugs (including some psychotropic drugs) could increase the risk of cardiac arrhythmias.

Methods: We included 295 subjects with recent onset schizophrenia, who underwent ECG during admission between 2006 and 2012 to screen all for signs of Cardiac Arrhythmias and prolonged QTc interval. All patients who had an ECG suspect for Cardiac Arrhythmias were asked to be seen by a cardiologist to perform a provocation test to diagnose/exclude Cardiac Arrhythmias. Of patients diagnosed with a cardiac arrhythmia, we ask informed consent to screen for genetic defects and autoimmune antibodies against the potassium and sodium channel, which could underlie this disorder. Also we included a healthy control group of approximately the same age without psychiatric disorder.

Results: Analysis of the ECG's of 295 patients revealed a remarkably high proportion of suspected Cardiac Arrhythmias, namely 6%. Apart from that, 3% of patients had a prolonged QTc interval. Correlations with clinical measures will be presented. All patients with an ECG were asked for additional analysis described above. These analyses and the comparison with the healthy control group are currently analyzed and will be presented.

Discussion: This study shows that in a considerable subset of patients with recent onset schizophrenia have an ECG suggestive of a cardiac arrhythmia or have a prolonged QTc interval. If a cardiac arrhythmia is confirmed in these patients, this may imply that there is a common pathophysiologic mechanism between cardiac arrhythmias and schizophrenia. Specifically, malfunctioning ion channels could be a pathophysiological factor in both clinical entities. This is relevant to prevent sudden cardiac death. Several antipsychotic medications used by these patients pose an increased threat of provoking ventricular arrhythmias. Accordingly, these drugs must be avoided in these patients, and alternative drugs must be sought. In a subset of these patients, preventive implantation of an implantable cardioverter defibrillator (ICD) may be necessary. Furthermore, unveiling the pathophysiological mechanism can prompt development of a treatment targeting the underlying problem in this subset of patients with schizophrenia and the cardiac arrhythmia.

Poster #M174**TRAUMA MAY INDUCE EARLY COGNITIVE DEFICITS ANTEDATING SCHIZOPHRENIA IN CHILDREN AND ADOLESCENTS AT HIGH GENETIC RISK**

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Background: Schizophrenia may start from a cognitive decline emerging in childhood. We previously reported in densely affected multigenerational families that the children having a parent affected by schizophrenia or bipolar disorder carry severe cognitive deficits [1–4], particularly under the form of impaired visual and verbal episodic memory, working memory and executive functions, as seen in adult patients. In parallel, recent research supports the causal relationship between childhood trauma and psychosis [5–8]. However, developmental mechanisms underlying this association remain unknown. The present study aimed at testing whether childhood trauma may have its effect on schizophrenia by impacting on early cognitive precursors.

Methods: The sample consisted in 66 offspring of an affected parent descending from densely affected multigenerational families. Cognitive measures encompassed global IQ, visual and verbal episodic memory, working memory and executive functions of initiation. Information about the lifetime presence of childhood trauma (neglect, physical aggression, sexual abuse, emotional abuse or exposure to family violence) came from direct interviews with the offspring, their parents and relatives and from the review of all lifetime medical records of the parents and children, blind to the neuropsychological variables.

Results: Children at genetic risk exposed to childhood trauma had poorer cognitive performances than those non-exposed in IQ ($F_{1,62} = 6.96$, $p=0.01$, $d=0.65$) and particularly in visual episodic memory ($F_{1,62} = 10.82$, $p=0.002$, $d=0.81$) and executive functions ($F_{1,62} = 23.23$, $p<0.001$, $d=1.19$). HR exposed to more severe trauma showed a trend toward an amalgamation of such deficits. Trauma exposure and cognitive deficits both significantly enhanced the risk that offspring develop attenuated psychotic symptoms.

Discussion: Childhood trauma may induce on one hand specific cognitive deficits in visual episodic memory and executive functions and on the other hand a clustering of such deficits which may additionally hamper social adaptation and prognosis. Since such cognitive impairments in children at risk may be strongly predictive of later disease occurrence, our findings propose a longitudinal mediating mechanism for explaining the predictive effect of childhood abuse and neglect on schizophrenia. These findings have significant implications for preventive interventions.

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Poster #M175**GENE SET ENRICHMENT OF DIFFERENTIAL EXPRESSION AND SPLICING ANALYSIS BY RNA-SEQ IN POSTMORTEM DLPFC AND PBMCS IN SCHIZOPHRENIA**

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Background: The analysis of gene expression and splicing in schizophrenia is confounded by its complex genetic heterogeneity. By stepping back from molecular level association, we have the opportunity to understand changes in the redundant network architecture that defines the biology

of the disorder. This systems based approach to complex disease analysis has the potential to identify common multifactorial genetic and epigenetic relationships that reflect aspects of the symptomatology in individuals, and provides new avenues for treatment and early intervention. We have been exploring the application of high-resolution RNA sequencing (RNA-Seq) to characterise the transcriptional diversity in schizophrenia. This approach, with its unprecedented coverage of combinatorial differences in exon and promoter utilisation down to nucleotide resolution, is statistically challenged by its capacity to perform millions of tests. By using a gene-set enrichment analysis (GSEA) strategy we are seeking to understand what is common at the biological network and pathway level rather than putting too much weight on individual variants that are possibly redundant in a complex system. In this study we investigated differentially expressed transcriptional networks in schizophrenia using a new implementation of GSEA known as Seq-GSEA, a tool for cut-off free analysis of differential expression and splicing in RNA-Seq data.

Methods: The RNA from postmortem dorsolateral prefrontal cortex BA46 (DLPFC) from the New South Wales Tissue Resource Centre (TRC) and PBMCs from the Australian Schizophrenia Research Bank (ASRB) was subjected to RNA-Seq analysis using the SOLID and HiSeq2000 platforms respectively. Short reads were then aligned to the reference genome with Tophat, to yield BAM/SAM-formatted outputs. SeqGSEA was then used to derive differentially expressed gene sets of differentially expressed reference genes and splice variants (<http://bioconductor.org/packages/release/bioc/html/SeqGSEA.html>).

Results: SeqGSEA models read count data in RNA-Seq by negative binomial distributions, allowing biological integration of differential expression and splicing associated with a phenotype category. Seq-GSEA analysis of the DLPFC RNA-Seq data yielded several overrepresented gene sets compared with controls. The leading set included the GABA receptor signalling and included GABRE, GABBR1, GABBR2 and GABRP. Seq-GSEA analysis of the PBMC RNA-Seq data also revealed a number of differentially expressed gene sets including Intercellular Junction Assembly pathway. These gene sets are significant at a genome-wide level whereas analysis at the individual gene level failed to satisfy this criterion.

Discussion: The molecular pathology of schizophrenia is complicated by underlying genetic and environmental heterogeneity. To make further progress we may need to move away from individual genes and consider their collective influence in networks and systems that support different biological functions. While our understanding of molecular networks is still in its infancy, GSEA can utilise this information to ascertain biological insight useful to complex disorders. In this study we used SeqGSEA to identify networks involved in SZ-associated change in the DLPFC where we observed changes in GABA receptors consistent with an overall deficit in GABAergic function in schizophrenia. We also identified significant changes in gene sets in PBMCs from patients including the Intercellular Junction Assembly pathway which is also significant to schizophrenia.

Poster #M176**MESSENGER RNA AND MICRORNA EXPRESSION PROFILING OF PYRAMIDAL NEURONS, PARVALBUMIN-IMMUNOREACTIVE NEURONS, DOPAMINE NEURONS AND OLIGODENDROCYTES IN SCHIZOPHRENIA AND PARKINSON'S DISEASE**

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Background: The human brain is an extraordinarily complex structure consisting of heterogeneous subsets of neurons that mediate distinct aspects of information processing. Disturbances of these neurons compromise the functional integrity of the connectional architecture of the brain, resulting in various psychiatric and neurologic disorders.

Methods: In order to explore how the molecular integrity of various neuronal subtypes might be compromised in schizophrenia (SZ) or Parkinson's disease (PD), we combined laser capture microdissection, microarray and TaqMan-based miRNA profiling technologies to determine the convergence and specificity of the gene networks and signaling cascades that are altered in these disorders.

Results: In pyramidal neurons from the prefrontal cortex in SZ, we found

differentially expressed mRNAs that belong to the transforming growth factor beta and the bone morphogenetic proteins signaling pathways, and in the parvalbumin (PV)-immunolabeled neurons from the same region differentially expressed transcripts were associated with WNT, NOTCH and PGE2 signaling and transcription factors such as LHX6, in addition to genes that regulate cell cycle and apoptosis. In the dopamine neurons from the substantia nigra in PD, there was a predominant down-regulation of genes that are involved in PD pathogenesis, such as members of the PARK gene family and genes associated with programmed cell death, mitochondrial dysfunction, neurotransmitter and ion channel receptors, as well as neuronal survival mechanisms. In addition to the gene expression profiles, we identified a set of differentially expressed miRNAs in both SZ and PD. Enrichment analysis of their predicted targets revealed signaling pathways and gene networks that were also found by the microarrays to be dysregulated raising an interesting possibility that dysfunction of these neurons in SZ or PD may in part be mediated by a concerted dysregulation of gene network functions as a result of the altered expression of miRNAs. Oligodendrocytes from SZ subjects, however, exhibit distinct expression pattern that is consistent with dysregulation of cell cycle events.

Discussion: Our data show mostly distinct, but also some overlapping dysfunctional gene and miRNA networks between SZ and late stage PD, and provide a platform for future downstream analyses aiming to understand the molecular processes of individual neuronal dysfunction in psychiatric and neurological disorders.

Poster #M177

LACK OF HABITUATION OF MIRROR NEURON ACTIVITY: STUDY USING TRANSCRANIAL MAGNETIC STIMULATION PARADIGMS

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Background: Mirror neurons are specialized aggregation of nerve cells that fire during performance of an action as well as during observation of the same action. They are hypothesized to underlie social cognition abilities in both healthy and diseased states. Neuronal habituation refers to decreased firing of neurons due to repeated stimuli. There is little evidence on habituation of mirror neurons in humans. In this study we assessed if mirror neurons demonstrated habituation in healthy individuals and patients with schizophrenia.

Methods: Fifty-four right handed schizophrenia patients and 45 healthy controls underwent a TMS experiment to assess putative premotor mirror neuron activity (MNA). We used 10 stimuli each of resting motor threshold (RMT), motor threshold to elicit 1 millivolt amplitudes of potentials (MT1), short and long interval intracortical inhibition (SICI/LICI) paradigms in random sequence in right first dorsal interosseous (FDI) muscle. These were applied while the subjects observed a goal-directed action involving the FDI (actual action and its video) and a static image. The difference in the amplitude of the motor evoked potential (MEP) while they observed the static image and the action provided a measure of MNA. Habituation pattern was assessed by analyzing the MEP across each of the 10 trials of individual stimulus paradigms.

Results: RMANOVA did not show statistically significant differences in measures of MNA across trials in RMT, SICI, MT1 and LICI parameters. There was no difference in habituation pattern of MNA across the patient group and healthy individuals.

Discussion: This experiment shows lack of habituation pattern in MNA in schizophrenia patients and healthy controls, which is consistent with similar findings in primate experiments. These results also have implication in designing TMS experiment as increased trials might give more accurate information without being confounded by adaptation phenomenon.

Poster #M178

VISUAL HABITUATION IS IMPAIRED IN SCHIZOPHRENIA: A STUDY WITH PATTERN REVERSAL VISUAL EVOKED POTENTIALS

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Background: Schizophrenia is characterized by impairment in a wide range of cognitive domains and perceptual modalities including early stages of visual processing. Visual habituation, a reduction of the visual evoked response to sequential presentation of spatially structured stimuli, is a direct measure of visual cortex excitability. As a measure of sensory gating, this phenomenon has been considered as a protective mechanism against over-stimulation. Impaired habituation mechanisms have been suggested to play a key role in the pathophysiology of schizophrenia. We investigated visual habituation with a Pattern-Reversal Visual Evoked Potential (PR-VEP) paradigm to verify whether patients with Schizophrenia (SCZ) showed abnormalities in the evoked response amplitude compared to healthy volunteers (HV).

Methods: Thirty-three SCZ (21 men and 12 women; age, mean ±SD: 35.67±10.21), with a clinical and pharmacological stable condition, were selected from an outpatient program. Thirty-three HV (21 men and 12 women; age: 34.91±9.77) was recruited as control group. EEG signal was continuously recorded from a midline occipital electrode. Monocularly full-field black-and-white checkerboard pattern subtending 15° of arc was presented, reversing in contrast at 3.1 reversal/s with 100% contrast for 800 consecutive trials. The EEG recording was divided in eight blocks of 100 consecutive trials. The peak latencies of N75, P100 and N145 components as well as the N75-P100 and P100-N145 peak-to-peak amplitudes for each block were measured. As a measure of habituation we used the slope of the linear regression line of the N75-P100 and P100-N145 peak-to-peak amplitudes.

Results: Schizophrenia patients had significantly lower N75-P100 and P100-N145 amplitudes than healthy volunteers in the eight-block PR-VEP grand-average. Repeated measure ANOVA models showed that the N75-P100 and P100-N145 amplitudes for the whole sample decreased between first and eighth block. There was a significant difference between healthy volunteers and schizophrenia patients who did not present a reduction in VEP amplitude over the eight blocks. The slope measure confirmed the impaired visual habituation in the schizophrenia patients respect to healthy volunteers. We didn't find significant differences between the two groups in the N75, P100 and N145 latencies in the average response to the 800 stimuli and between the 8 blocks.

Discussion: The findings of this study contribute to the existing evidence of impaired early sensory processing in schizophrenia. One of the possible pathophysiological mechanisms of the visual habituation deficit could involve occipital lobe structures regulating neuronal inhibitory/excitatory balance, and in particular of deficit in GABA-ergic transmission in the visual cortex. Our data suggests that gating deficits in schizophrenia involve multiple sensory domains and visual habituation should be investigated more systematically.

Poster #M179

REDUCED THETA BAND RESPONSE TO RELEVANCE IN SCHIZOPHRENIA

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Background: Alterations in differential processing of relevant versus irrelevant stimuli may contribute to abnormal salience in schizophrenia.

Methods: EEG was recorded and analyzed in both chronic and minimally

treated patients with schizophrenia and healthy controls during an odd-ball paradigm task. Relative power (RP) spectra response to target (relevant) and non-target (irrelevant) conditions of the task in gamma (35–45 Hz) and theta (4–8 Hz) bands were compared between these groups for two time windows (25–200 and 250–550 ms post-stimulus onset).

Results: Healthy controls showed a markedly larger RP in the theta band during the 250–550 ms window following the relevant as compared to the irrelevant stimuli. Patients obtained statistically significant lower differences in RP between the relevant and irrelevant conditions ((R-I) RP) than controls. Furthermore, theta (R-I) RP values for patients were inversely associated to negative symptoms, and directly to verbal and working memory performance. Patients and controls did not differ significantly in the magnitude of (R-I) RP for any of the time windows in the gamma band or for the 25–200 ms window in the theta band.

Discussion: The patients' response to the relevant stimuli of the theta band in a P300 task was similar to their response to the irrelevant stimuli, which might contribute to abnormal salience in schizophrenia.

Poster #M180

BEHAVIORAL MONITORING DEFICITS IN SCHIZOTYPAL PERSONALITY DISORDER: DECREASED ERN AS A TRAIT MARKER OF SCHIZOPHRENIA-SPECTRUM DISORDERS

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Background: Certain new diagnostic categories in DSM-5, such as the "Attenuated psychotic syndrome", are based on the existence of a continuum between health and disease. This approach warrants research on biological markers of a transition to psychosis. Deficits in behavioral monitoring, which may underlie symptoms such as delusions and thought disorders, could also be present to varying degrees in the general population. Schizophrenia has been associated with a lower amplitude of the Error Related Negativity (ERN), a robust neurophysiological correlate of behavioral monitoring. However, virtually no research has addressed behavioral monitoring in Schizotypal Personality Disorder (SPD), a syndrome characterized by attenuated psychotic symptoms, which may develop into a full-blown psychotic disorder. SPD is a convenient model in the search for biomarkers of psychosis-proneness as it is free from confounding factors such as medication and hospitalization. The present study aimed to investigate potential deficits in behavioral monitoring in SPD patients and the validity of the ERN as a trait marker of schizophrenia-spectrum disorders.

Methods: Nine individuals who were not currently receiving any medication or psychiatric treatment were identified as meeting DSM-IV-TR criteria of SPD. Following recruitment for the study they were compared to 20 healthy controls scoring 1 SD below the mean on several instruments measuring schizotypal traits (O-LIFE, SPQ). All participants performed the Eriksen flanker task while the electroencephalogram was recorded at 29 standard scalp locations. Behavioral data and ERN amplitudes following commission errors were compared between patients and controls.

Results: SPD patients performed significantly worse than controls in the task, showing longer reaction times to correctly responded stimuli and longer correction times following erroneous responses. At the neurophysiological level, the amplitude of the ERN was significantly smaller in the SPD patients than in the control group.

Discussion: The current findings highlight impaired self-monitoring in SPD patients as compared to healthy controls. Our results are remarkably similar to reports from patients in the early and chronic phases of schizophrenia. The fact that the data were obtained from individuals free of any medication and who were not showing the deterioration associated with chronic illness further support the validity of the ERN as a neurophysiological trait marker of the schizophrenia-spectrum disorders.

Poster #M181

SEX-RELATED DIFFERENCES OF EEG COHERENCE BETWEEN PATIENTS WITH SCHIZOPHRENIA AND HEALTHY CONTROLS

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Background: Alteration of epigenetic effects of testosterone during early development was suggested as an ancillary mechanism for the genesis of schizophrenia. EEG coherence was thought to be a marker for cerebral laterality of which important determinant was testosterone during early development. We studied sex-related differences of EEG coherence between patients with schizophrenia and healthy controls to examine the sex effects in the genesis of schizophrenia.

Methods: EEG was recorded in 35 patients with schizophrenia and 46 healthy controls in the eyes closed resting state. Pair-wise EEG coherence were calculated over delta, theta, alpha, beta and gamma frequency bands. To examine the differences of EEG coherence according to sex in each group, ANCOVA was performed using SAS (Statistical Analysis system, Ver 9.3) and R (Ver 2.15.2). Bonferroni correction was used as a preventative post-hoc control of the Type I Error.

Results: Healthy control males showed increased right intrahemispheric coherence compared with healthy control females at delta, theta, alpha and beta frequency bands. In patients with schizophrenia, this male dominant pattern in right intrahemispheric coherence was attenuated especially at alpha and beta frequency bands. Healthy control females showed increased interhemispheric coherence compared with healthy control males at delta, theta, beta and gamma frequency bands. In patients with schizophrenia, this female dominant pattern in interhemispheric coherence was attenuated especially at delta, theta, and beta bands, which were commonly observed in frontal to central areas.

Discussion: Sex differences in resting EEG coherence were attenuated in patients with schizophrenia. These results imply that sex-related aberrant cerebral lateralization might exist in patients with schizophrenia, which are partly due to sex hormones via epigenetic mechanisms.

Poster #M182

EEG COHERENCE IN SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

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Background: EEG coherence is an important parameter that is shown to be altered in schizophrenia. Current theories of schizophrenia have emphasized that the core feature of pathophysiology arises from a disconnection syndrome between and within cortical areas of the brain (Uhlhaas et al., 2010). Thus, to date no evidence on altered connectivity exists in schizoaffective disorder.

Methods: We analysed the EEG coherence in resting state and while performance of the arithmetical task (subsequent subtraction of 7 from 200) in 32 patients with first episode of schizophrenia (SCH, n=32), 32 patients with first episode of schizoaffective disorder (SAD, n=32) and healthy controls (HC, n=40). Coherence between the groups in the rest condition (high and low coherence) and coherence alteration relative to the baseline (increasing and decreasing of coherence) were computed between each pair of electrodes for each group. The rank sums obtained were converted to error probabilities.

Results: In the rest condition coherence was lower in SCH then in controls in *alpha*, *beta-1* and *beta-2* bands registered in the anterior regions. Same difference was obtained in HC vs. SAD comparison. The coherence in prefrontal areas in *theta* band was higher in SAD then in HC and SCH. Direct comparison of SCH vs. SAD revealed an increased coherence in SAD in contrast to SCH primarily in the high frequency bands in the posterior regions. During task performance the analysis of coherence in HC showed significant increase of connectivity between prefrontal brain regions in *delta* band predominantly in the left hemisphere during task performance compared to baseline. In *theta* band the coherence between prefrontal brain regions, specifically left prefrontal and right parietal areas was higher than in the rest condition. At the same time, coherence was decreased in the left

prefrontal, central and occipital areas. In *alphaband* there was a decrease between anterior and posterior areas. In *beta1* connectivity was reduced in prefrontal and frontal areas, whereas in *beta2* and *gamma1*- increased connectivity in the same cortical areas. In *gamma2* band connectivity was enhanced between neighboring areas such as occipital and right parietal and left prefrontal and central brain regions. In SCH group we found a significant increase of connectivity in *delta* band in anterior regions, specifically frontal, temporal and decrease in the posterior regions, namely parietal and occipital regions. The decreased connectivity was detected in *theta*, *alpha* and *gamma1* during task performance compared to the rest condition. In *beta1*, *beta2* and *gamma2* there was a decrease of connectivity in left frontal areas bands while the increased connectivity was found between right prefrontal and occipital, central and frontal areas, respectively. In SAD there was increased connectivity in high frequency bands (*beta1-gamma2*). In *delta* band we observed increased connectivity in central, parietal and occipital areas along with the decreased connectivity between temporal areas of the brain. In *theta* band connectivity was inclined between long distant areas such as central and occipital of the left hemisphere while connectivity of the right hemisphere was also compromised between long distant areas: prefrontal and occipital, central and parietal areas etc. In *alpha* band there was general increase of connectivity where while there was a simultaneous decrease in the left hemisphere.

Discussion: Disconnectivity in frontal cortical areas in SAD, similar to SCH at rest indicates neurobiological similarities of these disorders. However, the increased connectivity in SAD patients during cognitive task performance discordant to SCH may underline distinct neurophysiological mechanism of cognitive task processing in SAD.

Poster #M183

THOUGHT DISORDERS AND FAMILY LIABILITY IN FIRST EPISODE PSYCHOSIS

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Background: Thought and language disorders are among the most crucial aspects of Schizophrenia, however there are still many unexamined questions about these aspects. There is not enough study looking at thought abnormalities at the beginning of schizophrenia. The main objective of the current study was to examine familial liability to schizophrenia and thought disorder in a sample of first episode psychosis.

Methods: The sample of the study consisted of 56 First Episode Psychosis and 33 healthy individuals. Patient and control groups were matched regarding demographic variables including gender, age, education level. "Familial liability" was assessed according to the interview with patients and their relatives and asking them about diagnosis of schizophrenia in their relatives. Both clinical and healthy samples were administered Thought and Language Index. This index consists 8 subscales; assessing poverty and disorganization of thought. Poverty of thought was assessed with items for poverty of speech, weakening of goal and perseveration of ideas, whereas disorganization of thought was assessed with items for looseness, peculiar word use, peculiar sentence construction, peculiar logic and distractibility. Associations between Thought and Language Index scores and familial liability to schizophrenia were examined.

Results: In this study familial liability for schizophrenia was found to be significantly related to poverty of thought ($p=0.022$), poverty of speech ($p=0.004$), and weakening of goal ($p=0.043$).

Discussion: Thought and language disorders in first episode psychosis are related to familial liability and may be genetically transmitted. Characteristics of thought disorder in first episode of schizophrenia need to be examined in larger clinical samples.

Poster #M184

SELF-ESTEEM AND PSYCHOPATHOLOGY AMONG CHINESE TEENAGERS AND UNIVERSITY STUDENTS

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Background: Self-esteem has been reported to be an important predictor of psychopathology including depression, suicidal ideation, and aggression. However, these findings are mainly from Western populations and their impact on Chinese adolescent's mental health is unknown. The objective of present study was to evaluate the role of self-esteem on psychopathology in a Chinese young population.

Methods: A sample of 90 school and university students aged between 15-23 years old was registered in the present study, including 44 female and 46 male. Self-esteem was measured by the Rosenberg Self-Esteem scale (RSES). This yielded 3 measures: overall score, self-competence and selfliking. The Symptom Checklist 90-R (SCL-90-R) was applied to assess specific psychopathology including somatization, obsessive compulsive behavior, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychotism. In addition, the total score of those nine dimensions provided a Global Severity Index (GSI). We used multiple linear regression analysis to explore whether self-esteem could predict psychopathology after controlling the potential confounding effects of age and gender.

Results: In our data setting, after adjustment for age and gender, there were significant negative correlations between the overall RSES score and score of phobic anxiety ($\beta=-0.27$, $P=0.01$). Furthermore, significant correlations were found between RSES self-liking scores and obsessive compulsive behavior ($\beta=-0.33$, $P=0.002$), interpersonal sensitivity ($\beta=-0.33$, $P=0.002$), depression ($\beta=-0.37$, $P=0.0003$), anxiety ($\beta=-0.35$, $P=0.001$), hostility ($\beta=-0.21$, $P=0.048$), phobic anxiety ($\beta=-0.33$, $P=0.002$), psychotism ($\beta=-0.29$, $P=0.007$), and GSI ($\beta=-0.34$, $P=0.001$). Higher self-liking in Chinese teenagers and university students was related with less psychopathological risk of obsessive compulsive behavior, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety as well as psychotism. Interestingly, no significant correlation was detected for self-competence scores.

Discussion: In this Chinese cohort of adolescents and young adults, consistently with the western population, self-esteem significantly correlated with psychopathology. Specifically, higher self-liking predicted less psychopathology. The results promote better understanding of the relationship between self-esteem and the risk of mental illness, which may inform potential clinical intervention programs in the future.

Poster #M185

COGNITION, SELF-ESTEEM AND QUALITY OF LIFE IN SCHIZOPHRENIA; A 12 MONTH FOLLOW-UP COGNITIVE REMEDIATION CLINICAL TRIAL

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Background: Schizophrenia can be considered a chronic illness that affects all aspects of daily life, ranging from social functioning to subjective well-being. Quality of life (QoL) is an important outcome in the treatment of people with schizophrenia. Computerized procedures that were originally developed in the field of neurological disorders are currently being used for remediation of cognitive impairment in psychiatric disorders. In fact, A recent meta-analytic study (Grynszpan, 2011) highlighted the effectiveness of computer-assisted cognitive remediation (CACR) in patients with schizophrenia. In our previous study (Garrido et al., 2013) we examined neurocognitive outcomes of CACR in a sample of schizophrenia patients and quality of life and self-esteem were measured as a secondary outcomes. Our results indicated that patients who received CACR showed a significant cognitive improvement compared to an active control group. However, despite the empirical evidence and results of meta-analyses that cognitive remediation is effective in cognition there is still debate about the usefulness of a cognitive remediation post-therapy. Thus, the current study addresses this issue by comparing several cognitive outcomes, QoL and self-esteem in

these two groups of patients (CACR vs active control group) after 12 month post therapy.

Methods: This study investigates the durability effectiveness of CACR in a single blind randomized controlled trial with two groups. One group received 48 CACR sessions and the other participated as an active control group. The trial registration number is NCT01598220. The main outcomes were performance on cognitive tests assessed at 12 months follow-up. Secondary outcomes were quality of life and self-esteem, also assessed at 12 months follow-up. Participants were recruited from schizophrenia outpatients of the Department of Mental Health of Consorci Sanitari de Terrassa. Sixty-seven participants were recruited to the trial, of whom 38 were randomized to cognitive remediation therapy and 29 to active control condition. For the follow up study a total of 33 participants were enrolled in the study, 20 of CACR condition and 13 active control condition. Sixteen subjects dropped out. Measures of psychomotor speed, working memory, verbal learning and executive function were considered as primary outcomes and QoL and self-esteem as secondary outcomes.

Results: The results showed a significant group x time interaction, indicating that the CACR therapy group presented improvements in processing speed, reasoning and problem-solving cognitive domains compared to control active group. In addition, the therapy group showed a clear durability of improvements in quality of life and self-esteem measurements. Significant interaction effects were observed between group x time in several neurocognitive measures and in QoL and self-esteem measurements.

Discussion: Our data showed that the effects of cognitive remediation are durable after 12 months post therapy. These effects also contributed to improvements in QoL and self-esteem measurements. These findings support those of previous studies (Wykes et al. 2011; Poletti et al., 2010)

Poster #M186

NEUROCOGNITIVE ARCHITECTURE OF SCHIZOPHRENIA

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Background: Elucidating the cognitive architecture of schizophrenia is necessary to advance understanding of the clinical and biological substrates of the illness. Traditional cross sectional neuropsychological approaches differentiate impaired from normal cognitive abilities but are limited in their ability to determine latent substructure. The current study examined the latent architecture of abnormal cognition in schizophrenia via a systematic approach.

Methods: Exploratory and Confirmatory Factor Analysis (EFA and CFA) were carried out on a large neuropsychological dataset including the Brief Assessment of Cognition Schizophrenia, Continuous Performance Test, Wisconsin Card Sorting Test, Judgment of Line Orientation Test, and Matrix Reasoning derived from 1012 English speaking ethnic Chinese healthy controls and 707 schizophrenia cases recruited from in and outpatient clinics.

Results: A six factor "Correlated Factor Model" consisting of fit cognitive data in healthy and schizophrenia subjects (RMSEA-Cases = 0.039, 90% CI = 0.030–0.049; RMSEA-Controls = 0.036, 90% CI = 0.028–0.044). Latent factors include F1 (CPT-IP Hits); F2 (Executive Function/Spatial Reasoning); F3 (WCST-64); F4 (Semantic Fluency); F5 (CPT-IP Commission Errors) & F6 (CPT-IP False Alarms). Additional attempts were made to reduct the six factor model further to minimize methodological variance and refine cognitive domains. Further modelling accounted for methodological variance between tests, and indicated that a three factor model of executive functioning, vigilance/speed of processing, and memory appeared to best discriminate schizophrenia cases from healthy controls.

Discussion: Latent factors elucidated within the cognitive architecture of patients with schizophrenia could represent subtle variations from "g" that prove useful for interrogating biological substrates underlying cognitive deficits in schizophrenia and enriching effect sizes for these associations. However, "g" is an essential factor to be estimated in context of the increased need for cross centre replication studies.

Poster #M187

NEUROCOGNITIVE IMPAIRMENTS IN ADOLESCENTS WITH AND WITHOUT AT-RISK STATES OF PSYCHOSIS

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Background: In the early detection of psychosis, additional neuropsychological predictors such as verbal fluency, processing speed, verbal and spatial working memory have been suggested and already evaluated predominately on adult samples. The aim of this pilot was to assess distributions of potential neuropsychological predictors by comparing persons fulfilling current at-risk criteria, a clinical non-psychotic inpatient sample as well as a general population sample. Thus, we examined if the same neuropsychological deficits can also be found in a purely adolescent at-risk sample and might be specific to it.

Methods: The pilot was conducted on 27 subjects identified as at-risk for psychosis (AtRisk; mean age=14.69, 33.3% male), 54 inpatient controls with other psychiatric diagnosis (ClinS; mean age=14.61, 31.5% male) and 82 subjects of a general population sample (GPS; mean age=13.77, 47.6% male). The four neuropsychological domains were assessed by a verbal fluency test, the Digit-Symbol Test (DST) and the Trail Making Test (TMT) A and B, the German version of Auditory Verbal Learning Test (AVLT) and the Subject Ordered Pointing Task (SOPT). To control for general effects of IQ, a measure of verbal IQ, the "Peabody Picture Vocabulary Test" (PPVT), was assessed. For the small sample sizes and lack of power, effect size (r , ϕ) rather than level of significance was the guiding criterion.

Results: Compared to ClinS and GPS, AtRisk performed worse in all tests (Rosenthal's r =0.11–0.37). Furthermore, AtRisk exhibited more frequently deficits according to the norms provided for the tests. In all, deficits in verbal memory (AVLT learning capacity) and processing speed measured with the TMT B discriminated best by showing a moderate group effect on the test score.

Discussion: Deficits in processing speed, verbal memory, verbal fluency and spatial working memory that have repeatedly been demonstrated in (predominately) adult at-risk samples were replicated in this purely adolescents at-risk for psychosis. Thereby, verbal memory and processing speed deficits were most specific – even when compared to a more severely ill inpatient group. This gives first support that the same neurocognitive predictors as in adult samples might be useful in adolescent samples.

Poster #M188

IMPLICIT AND EXPLICIT SELF-EVALUATION AS UNDERLYING MECHANISMS OF IMPAIRED INSIGHT IN PATIENTS WITH SCHIZOPHRENIA

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Background: People with psychotic disorders and poor insight typically insist their psychotic beliefs are correct, often despite evidence showing otherwise. It has been suggested that poor insight arises from abnormalities in self-evaluation (S-E). S-E can be divided in explicit S-E and implicit S-E. Implicit S-E is automatic, rapid and effortless, and therefore prone to mistakes. Explicit S-E is a conscious, effortful and cognitive process and may be used to correct these mistakes. However, patients often lack explicit S-E due to cognitive deficits. We investigated the relationship between insight and implicit & explicit S-E with an implicit Self-esteem Task (implicit S-E) and a metacognitive version of Wisconsin Card Sorting Task expanded with a Feedback hint (explicit S-E). We hypothesized that in patients with impaired insight, implicit S-E is biased towards maintaining an incorrect self-image. Subsequently, we expected that if explicit self-evaluation is distorted the implicit self-image will not be actively changed.

Methods: Thirty-five schizophrenia patients and twenty healthy control subjects participated in the study. Patients were assessed with the Scale Assessment of Insight Expanded (SAI-E) and the Beck Cognitive Insight Scale (BCIS). Implicit S-E was measured with the Implicit Self-Esteem Task, using a working memory 2-Back task, while primed with a "Stupid" or "Clever" verbal stimulus. Explicit S-E was measured with an adjusted version of the WCST used by Koren et al. (2004). Patients were allowed to use the additional feedback to their advantage. They had the opportunity to in- or exclude a response in their total score and even correct their answer.

Results: Cognitive insight (BCIS composite score) was positively related to both implicit S-E ($r=0.393$, $p < 0.05$; Implicit Self-Esteem Task) and explicit S-E ($\rho = 0.346$, $p < 0.05$, WCST with feedback hint). No significant relationship was found between clinical insight and implicit/explicit S-E. Patients and controls did not significantly differ on both tasks.

Discussion: Caregivers and mental health workers often try to convince patients that their psychotic beliefs may be incorrect, but these attempts are typically in vain and do not lead to better insight. This poor insight may be the result of a general underlying problem in the implicit and explicit use of feedback of others to modify one's self-image. Indeed, our present findings suggest that patients with impaired cognitive insight are less sensitive for implicit and explicit S-E. They seem to fail in integrating the information, including a mental illness, into their self-image. This gives us a better understanding of how impaired insight is related to implicit and explicit S-E.

Poster #M189

THE EFFICACY OF OCCUPATIONAL THERAPY IN THE REHABILITATION OF EXECUTIVE FUNCTIONS IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA: A PILOT RANDOMIZED CONTROLLED TRIAL

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Background: To test the efficacy of Occupational Therapy based on the Occupational Goal Intervention (OT-OGI) for the improvement of executive functions (EF) in patients with Treatment-Resistant Schizophrenia (TRS) as compared with a Control Group (CG) (craft activities).

Methods: This is a single blinded pilot randomized controlled trial (RCT), with 25 participants ages 18-55, who were randomly assigned to the OGI group or the CG. The patients were evaluated before (T0) and after treatment (T1) with scales for assessment of EF using the BADS (Behavioral Assessment of Dysexecutive Syndrome), basic and instrumental activities of daily living using measured by the Direct Assessment of Functional Status (DAFS) and activities of daily living measured by the Independent Living Skills Survey (ILSS) as well as a standard neuropsychological battery. Both groups undertook 30 sessions over a period 14-15 weeks.

Results: Patients and controls showed no difference at baseline in almost all measures. As compared with controls, patients who received the OGI method showed significant improvement in some EF. Subtasks of BADS showed medium to high effect sizes on: Action program ($d=0.75$; $p=0.07$), Key search ($d=0.90$; $p=0.03$), Zoo map ($d=1.17$; $p=0.03$). In the ILSS the patients showed clinical improvement in the following tasks of activities of daily living: Food ($d=0.75$; $p=0.07$), Personal care ($d=1.32$; $p=0.00$), Household ($d=1.31$; $p=0.00$), Food storage and preparation ($d=1.82$; $p=0.00$), Health ($d=0.95$; $p=0.02$), Money management ($d=1.79$; $p=0.00$), Transport ($d=0.77$; $p=0.06$), Leisure ($d=1.10$, $p=0.01$). In the functional aspect measured by DAFS the effect sizes were on subtasks Communication ($d=0.87$; $p=0.03$) and DAFS total ($d=0.70$; $p=0.08$). No differences were found in terms of neuropsychological tests.

Discussion: The intervention of OT-OGI showed clinical efficacy expressed in terms of effect sizes medium to high and significant subtasks battery BADS (EF). Significant improvement in the functionality of the patients who submitted to intervention group assessed by the DAFS and ILSS-BR. The improvement in executive functioning of intervention patients based on the method of OT-OGI had an impact on the performance of basic life activities of daily living and instrumental and, consequently, in its functional global.

Considering the improvement in EF in functional results of this study, the TO is appropriate and can corroborate for the rehabilitation of occupational performance of patients with TRS. Limitations of the study: there were not significant effect sizes on neuropsychological outcomes; sample size is already small due to the fact that the second phase of the project (follow up) is still in progress.

Poster #M190

DISORGANIZATION AND TIMING OF MOTOR BEHAVIOR: INSIGHT FROM GESTURE IMPAIRMENTS AND MOVEMENT PATTERNS IN SCHIZOPHRENIA

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Background: Motor symptoms are frequent phenomena across the entire course of schizophrenia [1]. Some have argued that disorganized behavior was associated with aberrant motor behavior. We have studied the association of motor disturbances and disorganization in two projects focusing on the timing of movements.

Methods: In two studies, we assessed motor behavior and psychopathology. The first study applied a validated test of upper limb apraxia in 30 schizophrenia patients [2,3]. We used standardized video assessments of hand gestures by a blinded rater. The second study tested the stability of movement patterns using time series analysis in actigraphy data of 100 schizophrenia patients [4]. Both stability of movement patterns and the overall amount of movement were calculated from data of two hours with high degrees of social interaction comparable across the 100 subjects.

Results: In total, 67% of the patients had gesture performance deficits [3]. Most frequently, they made spatial, temporal and body-part-as-object errors. Gesture performance relied on frontal lobe function [2]. Poor gesture performance was associated with increased disorganization scores. In the second study, we found disorganization to be predicted only by more irregular movement patterns irrespective of the overall amount of movement [4].

Discussion: Both studies provide evidence for a link between aberrant timing of motor behavior and disorganization. Disturbed movement control seems critical for disorganized behavior in schizophrenia.

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Poster #M191

KEEPING THE BODY IN MIND FOR YOUNG PEOPLE WITH FIRST EPISODE PSYCHOSIS

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Background: Young people experiencing a first episode psychosis (FEP) are susceptible to the cluster of physical health issues that comprise the metabolic syndrome, including insulin resistance, central adiposity, hypertension and dyslipidaemia. Despite established benefits of regular physical activity and optimal dietary intake, young people experiencing FEP are less likely to be physically active or meet key food group requirements compared to the general population. It has been previously demonstrated that initiation of atypical antipsychotic medications may be followed by

a rapid deterioration of metabolic health within the initial 12 weeks of commencement of treatment (Correll 2009). The Keeping the Body in Mind (KBIM) project aims to determine if a multi-disciplinary, 12-week intervention comprising exercise physiology and dietetic interventions for young people experiencing a first episode psychosis can attenuate the expected decline in metabolic health.

Methods: Young people aged 15-25 years admitted to the Bondi Early Psychosis Program (EPP) from January 2013 onwards were eligible for referral to KBIM. Exercise physiology services including structured assessment and exercise prescriptions were provided as well as optional use of a supervised gym embedded within the EPP. Clients also received 12-weeks of intensive one-on-one dietetic monitoring and education. Outcome measures assessed at baseline and 12-weeks post include the individual risk factors for metabolic syndrome as defined by the International Diabetes Federation criteria including waist circumference, lipid profile, blood glucose, and blood pressure. Paired t-tests were used to determine if significant deterioration in metabolic health occurred.

Results: As of December 2013, 25 patients (13 males; 12 females) had completed baseline assessments, with a mean age of 20.4 (SD=2.2) years. At baseline, two males met IDF criteria for metabolic syndrome, 39% of males (n=5) had no risk factors and 61% (n=8) had one or more risk factor for metabolic syndrome. For females, 58% (n=7) had no risk factors whilst 42% (n=5) had one or more risk factor at baseline. For the 14 participants with available follow-up data, mean increase in waist circumference was 0.5cm (95% CI -1.8cm to 2.7cm; p=0.66). For weight, mean increase was 1.6kg (95% CI 0kg to 3.2kg; p=0.051).

Discussion: Preliminary analyses suggest that young people with FEP have less than ideal physical health at baseline, and individualised exercise physiology and dietetic interventions attenuate antipsychotic-induced weight gain in this vulnerable group. Such interventions have the potential to improve the typical physical health trajectory of young people experiencing psychotic illness.

Poster #M192 THE DJ'S CHOICES APPROACH ADAPTED FOR FAMILIES

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Background: Non adherence is recognized as a major issue in schizophrenia. Family support is known to improve adherence. However, there are very few clinical tools specifically adapted for families to support their relatives in treatment adherence.

Methods: We have previously developed an original program to facilitate patient's groups on adherence support that integrates psycho educational, cognitive-behavioural techniques and motivational approach. This program, entitled The DJ's choices, was originally created to facilitate discussions among patients in presence of health care providers. It was conceived in a youth-friendly design, where the DJ is recognized as the patient himself, the owner of his treatment plan, the one who can choose the nuance and the music of his recovery. After many requests from family associations to make it available for their members, we now have developed an adapted version of The DJ's choices for families. A DVD was developed around patient's and parent's testimonies and supported by professional inputs as well. This DVD is accompanied by a booklet containing comprehensive adapted information for families that can be consulted in addition to the DVD.

Results: Six chapters were produced and can be played independently on at-home DVD and discussed progressively in families. The information is made accessible, while comprehensive on several important subjects: Chapter 1: Amplify your basis revises basic notions on illness presentation; Chapter 2: Make up your mix shares psychoeducational notions on relapse prevention and treatment efficacy; Chapter 3: Get your beat allows exchanges on side effects and impression on medication; Chapter 4: Explore leads facilitates discussion on families' perception and influence of environment on adherence; Chapter 5: Keep the tempo states an individual action plan on daily integration of adherence; Chapter 6: Share with your band presents how family can promote and sustain adherence in daily living. It will be distributed from Institut Universitaire en santé mentale de Québec

among Quebec province (Canada) through family associations and other family resources to promote the importance of family support in treatment adherence. It will be translated in English in 2014.

Discussion: Families are looking for innovative ways to discuss adherence with their relatives. Use of videotapes of patients or family members to witness their own experience with treatment, side-effects, their struggle with non-adherence and relapse may contribute to facilitate discussions in families. This initiative gathered together social workers, psychologists, doctors and pharmacists to share approaches to acknowledge patients' and families' perception and support tips around medication adherence, promoting importance of family support in treatment adherence.

Poster #M193

THE IMPACTS OF AEROBIC EXERCISE AND MIND-BODY EXERCISE (YOGA) ON NEURO-COGNITION AND CLINICAL SYMPTOMS IN EARLY PSYCHOSIS - A SINGLE-BLIND RANDOMIZED CONTROLLED CLINICAL TRIAL

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Background: Impairments of attention and memory are detectable in early psychosis, and often result in severe, longstanding functional impairments. Pharmacological interventions for cognitive impairments have been largely unsuccessful. The current study aims to explore the effects of aerobic exercise and mind-body exercise (yoga) on cognitive functioning and clinical symptoms in female patients with early psychosis. The potential neuromechanism underlying the clinical consequences was also investigated.

Methods: Female patients (n=120) diagnosed with schizophrenia spectrum disorders, brief psychosis, psychosis NOS, or delusional disorder (according to SCID) were recruited from three hospital/clinic sites. They were randomized into integrated yoga therapy group, aerobic exercise programme group, and waiting list as the control group. Both interventions were held three times weekly. At baseline and at 12 weeks, clinical symptoms, cognitive functions, quality of life and fitness levels were assessed in all participants, and completed structural MRI data were collected in 58 patients. Repeated measures ANOVA and ANCOVA analyses of the clinical, cognitive, quality of life and fitness data were compared between baseline and at 12 weeks among the three groups. Post-hoc Bonferroni test was used for comparing between two groups. Structural MRI data was analyzed by FreeSurfer V5.1 and Qdec V1.4 to calculate the brain volume and cortical thickness.

Results: Completed clinical and cognitive data were collected in 85 patients, and completed MRI imaging data of good quality were collected in 39 patients. No significant differences in age, education years, and duration of the illness at baseline were observed among the three groups. Both yoga and aerobic exercise groups demonstrated significant improvements in verbal encoding ($p<0.01$), short-term memory ($p<0.05$), long-term memory ($p<0.01$), and working memory ($p<0.01$) with moderate to large effect sizes compared to control groups. The yoga group showed significantly enhanced attention and concentration ($p<0.05$). Both yoga and aerobic exercise significantly improved overall clinical symptoms ($p<0.05$) and depressive symptoms ($p<0.05$) after 12 weeks. Significant increases were observed in the thickness of the left superior frontal gyrus and the right inferior frontal gyrus (pars triangularis) in the aerobic exercise group. Significant increases were observed in the volume of the postcentral gyrus and the posterior corpus callosum in the yoga group. There was a statistically significant correlation between improvements in working memory and changes in the postcentral gyrus ($r=0.54$, $p<0.01$) after controlling for the multiple comparisons with a Bonferroni adjusted alpha level.

Discussion: Both types of exercise improved memory in early psychosis patients, with yoga having a superior effect on attention than aerobic exercise. Observed increments in the cortical thicknesses and volume may indicate improved neurogenesis.

Poster #M194**THE EFFECT OF MOTIVATIONAL INTERVIEWING ON MEDICATION ADHERENCE AND HOSPITALIZATION RATES IN NONADHERENT PATIENTS WITH MULTI-EPSISODE SCHIZOPHRENIA**

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Background: Medication nonadherence in patients with schizophrenia presents a serious clinical problem. Research on interventions incorporating motivational interviewing (MI) to improve adherence have shown mixed results. Primary aim is to determine the effectiveness of a MI intervention on adherence and hospitalization rates in patients, with multi-episode schizophrenia or schizoaffective disorder, who have experienced a psychotic relapse following medication nonadherence. Secondary aim is to evaluate whether MI is more effective in specific subgroups.

Methods: We performed a randomized controlled study including 114 patients who experienced a psychotic relapse due to medication nonadherence in the past year. Participants received an adapted form of MI or an active control intervention, health education (HE). Both interventions consisted of 5-8 sessions, which patients received in adjunction to the care as usual. Patients were assessed at baseline and at 6 and 12 months follow-up.

Results: Our results show that MI did not improve medication adherence in previously nonadherent patients who experienced a psychotic relapse. Neither were there significant differences in hospitalization rates at follow-up between MI and HE (27% vs 40%, P=0.187). However, MI resulted in reduced hospitalization rates for female patients (9% vs 63%, P=0.041), non-cannabis users (20% vs 53%, P=0.041), younger patients (14% vs 50%, P=0.012), and patients with shorter illness duration (14% vs 42%, P=0.040).

Discussion: Targeted use of MI may be of benefit for improving medication adherence in certain groups of patients, although this needs further examination.

References:

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Poster #M195**THE INTERACTION BETWEEN CNR1 GENETIC VARIATION AND CANNABIS EXPOSURE PREDICTS PREFRONTAL FUNCTIONAL CONNECTIVITY AND BEHAVIOR DURING WORKING MEMORY**

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Background: Background: Previous evidence suggests an association between cognition and cannabis use in healthy subjects and in patients with schizophrenia. However, results on this association are not always consistent and they do not always indicate a deleterious effects of cannabis on cognition. Several different factors may be invoked to explain these differences, including the possibility that deleterious effects of cannabis use are best elicited on particular genetic backgrounds. A crucial determinant of cannabinoid signaling in the brain is the cannabinoid receptor 1 (CNR1), which has also been associated with schizophrenia in previous reports and is coded by the CNR1 gene. Here, our aim was to investigate in healthy subjects the association between CNR1 variation and prefrontal expression of CNR1. Once this association was established, we also studied if functional variation in CNR1 and cannabis exposure interact in modulating prefrontal functional connectivity during working memory processing, as well as related behavior.

Methods: Methods: CNR1 mRNA expression as a function of genetic variation was investigated in post-mortem prefrontal human tissue using

Braincloud (<http://braincloud.jhmi.edu/>). Based on this investigation, a single nucleotide polymorphism, rs1406977, was selected. Thus, 232 healthy subjects (125 males) were genotyped for this SNP by DNA direct sequencing. Assessment of cannabis use was performed with the Cannabis Experience Questionnaire. Furthermore, all individuals performed the 2-back working memory task during functional Magnetic Resonance Imaging (fMRI). A General Linear Model and the Independent Component Analysis approach were used within SPM8 to study functional connectivity as a function of CNR1 genotype, of cannabis use and of their interaction.

Results: Results: A single nucleotide polymorphism (SNP) within CNR1 (rs1406977) was associated with CNR1 prefrontal mRNA expression in prefrontal cortex. In particular, G carrier individuals had significantly lower mRNA levels than AA subjects. Moreover, rs1406977 G carrier cannabis users had greater functional connectivity in the left ventrolateral prefrontal cortex (VLPFC) compared with G carrier cannabis naïve and AA cannabis users. Furthermore, G carrier cannabis users also had lower behavioral accuracy and slower reaction time than the other groups.

Discussion: Discussion: genetically mediated low levels of prefrontal CNR1 levels may modulate the association between cannabis use and working memory processing in healthy subjects. Relevance of these findings for the pathophysiology of schizophrenia should be further investigated.

Poster #M196**EMOTIONAL INTELLIGENCE IN SERIOUS MENTAL ILLNESS – GENDER DIFFERENCES IN PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR I DISORDER**

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Background: Emotional Intelligence (EI) as a part of social cognition is a rather new area of interest which focuses on personality traits and abilities enabling people to cope with both their own feelings as well as those of others. The MSCEIT (Mayer-Salovey-Caruso-Emotional-Intelligence Test) is a valid and reliable instrument which exclusively covers the emotional components of social cognition. It consists of four categories (perceiving emotions, using emotions, understanding emotions, and managing emotions), which cover all aspects of EI and can be divided into "experiential" (perceiving + using) and "strategic" (understanding + managing) EI. Several studies have shown that patients with serious mental illness (SMI) have deficits in emotion recognition via facial expression and affective prosody. Female schizophrenia patients tend to have a higher overall emotional intelligence (assessed with the MSCEIT) but gender differences in general seem to be small. Importantly, deficits in experiencing as well as recognizing emotions reduce the potential for effective vocational and interpersonal functioning in patients with schizophrenia. To date, studies on EI using the MSCEIT in BD patients haven't been conducted yet.

Methods: We present preliminary data of an ongoing study on potential gender differences in EI in clinically stable outpatients suffering from SMI (schizophrenia and bipolar I disorder according to DSM-IV) by using the MSCEIT.

Results: So far, 21 female and 29 male patients have been included into the study. Women reached significantly higher scores in the "managing emotions" branch of the MSCEIT (p=0.04) and showed a higher level of "strategic emotional intelligence" (p=0.07, trend level). No further gender differences could be detected.

Discussion: Our results suggest that male patients with SMI may have a lower EI compared to female patients – especially in the "management" and "strategic" use of emotions. This corresponds in part to previous findings in healthy subjects and suggests that male patients might have a particular need for specialized social cognitive training programs. Further studies are needed in order to investigate whether such programs could increase EI in patients suffering from SMI and whether this might have a positive effect on patients' outcomes.

Poster #M197**NON-LINEAR DYNAMICS OF SPEECH IN SCHIZOPHRENIA:
A MACHINE-LEARNING APPROACH**

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Background: The speech of patients with schizophrenia is often described as monotonous, flat and without emotion. Distinctive speech patterns are qualitatively assessed in the diagnostic process and deeply impact the quality of everyday social interactions. In this project, we investigate and model speech patterns of people with schizophrenia contrasting them with matched controls and in relation to positive and negative symptoms. We employ both traditional measures (pitch mean and range, pause number and duration, speech rate, etc.) and 2) non-linear techniques measuring the temporal structure (regularity and complexity) of speech. Our aims are (1) to achieve a more fine-grained understanding of the speech patterns in schizophrenia than has previously been achieved using traditional, linear measures of prosody and fluency, and (2) to employ the results in a supervised machine-learning process (discriminant function) to classify speech production as either belonging to the control or the schizophrenia group, based solely on acoustic features.

Methods: We analyze the speech production of 57 Danish adults with first-episode of schizophrenia (23F 34M, Mean Age=22.93 SD=3.46) and 57 matched controls. All participants underwent extensive diagnostic interviews and symptoms-related questionnaires: Schedules for Clinical Assessment in Neuropsychiatry and Scale for Assessment of Negative/Positive Symptoms for schizophrenia (SANS and SAPS). Our analysis is based on previously acquired narratives of the Frith-Happé triangles with 8 narratives per subject. We extracted basic measures of pause behavior (Number of Pauses, Average Length), fundamental frequency (Mean, Range) and speech rate as well as measures of regularity and complexity of the temporal dynamics (Detrended Fluctuation Analysis and Recurrence Quantification Analysis) of these three aspects of speech. The most relevant features were selected via ElasticNet (10-fold cross-validation, Alpha=0.5). Diagnosis was predicted using a 10-fold cross-validated discriminant function (Mahalanobis rule). Accuracy was balanced using Variational Bayesian mixed-effects inference. SANS and SAPS scores were predicted using a 10-fold cross-validated multiple linear regression. Both analyses were iterated 1000 to test for stability of results.

Results: Voice dynamics allowed discrimination of patients with schizophrenia from healthy controls with a balanced accuracy of 85.68% ($p<0.000001$, Confidence Intervals: 82.50–86.97%), a sensitivity of 81.27% and a specificity of 86.97%. Voice dynamics explained 26.76% (measured as Adjusted R Square, $p<0.000001$, CI=26.07–27.45%) of the variance of SANS scores and 20.33% ($p<0.00000001$, CI=19.76–20.90%) of SAPS scores. In comparison to healthy controls, the model developed characterizes schizophrenics' speech as: i) Slower and with longer pauses; ii) Less structured, that is, with fewer repetitions of fundamental frequency sequences; iii) More "stable", that is, the same low level of regularity is kept constant over time, while the controls tend to vary the amount of repetitions over time.

Discussion: The study points toward the usefulness of non-linear time series analyses techniques in picking out the subtle differences that characterize the unusual voice characteristics of people with schizophrenia and in relating them to the symptoms. Automated analysis of voice dynamics reveals potential for the assessment and monitoring of the disorder. Future work includes further validation of the approach, as well as more detailed investigation of the relation between speech patterns and other symptoms.

Poster #M198**IS THE DINE ADEQUATE FOR CAPTURING DIETARY PATTERNS AMONG PATIENTS WITH SEVERE MENTAL ILLNESS?**

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Background: The Dietary Instrument for Nutrition Education (DINE) has previously been used to assess the dietary patterns of patients with severe mental illness (SMI). Respondents are classified according to their saturated

fat, unsaturated fat, and fibre intake, based on self-reported consumption of various foods (e.g. cheese, beefburgers or sausages; butter, margarine, cooking fat; cereals, vegetables). Yet, the adequacy of the DINE as an indicator of dietary habits within SMI patients has received little research attention. This study explored, within a large cohort study, the sensitivity of the (saturated fat component of the) DINE to foods consumed by SMI patients.

Methods: Four hundred and thirty-five SMI patients were recruited from the community setting within the UK, as part of a wider health promotion intervention study (the IMPACT study). Dietary intake over the previous seven days was assessed using the DINE, supplemented with items measuring consumption of takeaway meals (one summary item), (seven types of) ready meals, and (two types of) soft drinks (two items). Measures were administered in face-to-face interviews. For the purposes of the present study, patients were classified into three groups (high, medium, or low saturated fat intake), in line with standard DINE coding protocol. Descriptive statistics were used to detail frequency of consumption of takeaway meals, ready meals, and soft drinks within the high saturated fat group.

Results: 102 patients were classified as having high saturated fat intake, 129 patients had medium, and 204 low saturated fat intake. Within the high saturated fat group, the supplementary items captured dietary elements not reflected by the DINE. Within the high saturated fat group, there was an even distribution in takeaway meal frequency, with patients most commonly consuming these 1-2 times per week (N=42; 41.2%), 14 patients (13.7%) "seldom or never" consuming them, and 7 patients consuming 5 or more takeaway meals per week (6.9%). Most patients did not consume ready meals (~70%), but those who did tended to regularly consume 1-2 ready meals per week (~20%). Soft (fizzy) drink consumption was normally distributed: one-third of patients did not drink fizzy drinks (N=32; 31.4%), while 27 patients (26.5%) consumed one or two 500ml bottles per day, and 20 (19.6%) consumed three or more bottles per day.

Discussion: These data highlight the potential for variation in consumption of specific foods high in saturated fat among patients with SMI, and so demonstrate that the saturated fat component of the DINE fails to distinguish between commonly consumed sources of saturated fat. Understanding the sources of saturated fat intake may be an important precursor to the development of interventions to reduce fat intake in patients with SMI. Researchers must therefore acknowledge the limitations of the DINE for capturing the dietary consumption patterns of patients with SMI.

Poster #M199**BETWEEN SELF-CLARITY AND RECOVERY IN SCHIZOPHRENIA: REDUCING THE SELF-STIGMA AND FINDING MEANING**

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Background: Although there are extensive theoretical reviews regarding the self-experience among persons with schizophrenia, there is limited research that addresses the implications of self-clarity on the recovery of persons with schizophrenia while exploring the role of possible mediators within this process. Accordingly, the current study explored the relationship between self-clarity and recovery while examining the possible mediating role of self-stigma and sense of meaning in life.

Methods: 80 persons with schizophrenia or schizoaffective disorder were administered four scales: self-concept clarity, self-stigma, meaning in life, and recovery. To explore the relationships between all variables, we performed Pearson correlations. In addition, to examine the mediation hypotheses, we performed linear regression analysis and the Sobel test. Significance was set at the 0.05 level, and all tests of significance were two-tailed.

Results: The hypothesized mediation model in which self-clarity affects self-stigma, self-stigma affects meaning in life, and meaning in life affects recovery, was confirmed. Results of the regression revealed a significant negative correlation between self-stigma and meaning in life when controlling for self-clarity ($\beta=-0.58$, $p<0.001$) and a significant positive correlation

between self-clarity and meaning in life when controlling for self-stigma ($\beta=0.21$, $p<0.05$). The Sobel test revealed that this difference was significant ($Z=3.09$, $p<0.01$). In addition, analysis revealed a significant positive correlation between meaning in life and recovery when controlling for self-stigma (and self-clarity) ($\beta=0.62$, $p<0.001$) but did not reveal a significant negative correlation between self-stigma and recovery when controlling for meaning in life (and self-clarity) ($\beta=-0.11$, $p>0.05$). The correlation between self-stigma and recovery decreased from $\beta=-0.47$ to $\beta=-0.11$ when controlling for meaning in life (and self-clarity). The Sobel test revealed that this difference was significant ($Z=-3.96$, $p<0.001$). No direct relationship was uncovered between self-clarity and recovery.

Discussion: The growing empirical and theoretical attention to both the experience of self in schizophrenia and the concept of recovery calls for the need to better understand the relation between the two and identify possible mediators. The results of the current study are consistent with previous literature on the experience of the self, self-stigma and meaning among persons with schizophrenia. It adds to this literature by suggesting a process model regarding the construction of self-experience and meaning are in the recovery process. Implications of the current study for future research and clinical practice are discussed with the emphasis on the importance of the self-experience with regard to the process of recovery.

Poster #M200

ASSESSING THREAT RESPONSES TOWARDS THE SYMPTOMS AND DIAGNOSIS OF SCHIZOPHRENIA BY MEASURING VISUAL PERCEPTUAL BIASES

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Background: Stigma towards individuals diagnosed with schizophrenia continues despite increasing public knowledge about the disorder. Questionnaires are used almost exclusively to assess stigma despite self-report biases affecting their validity. Perceived threat is known to be a key element in stigma, and recently researchers have argued that perceptual biases for point-light walkers (PLFs) may be moderated by perceived threat. Specifically, researchers have found that greater facing the viewer (FTV) biases for depth-ambiguous PLFs (i.e., a bias to see these figures as facing towards you more often) is associated with greater perceived threat (e.g., more anxious people tend to have greater FTV biases). Observing perceptual biases elicited by such figures may therefore provide an implicit method of analyzing stigma because it allows researchers to assess perceived threat without asking participants about this directly. The purpose of this experiment was to implicitly assess stigma towards individuals with schizophrenia by measuring participants' FTV biases immediately before and after participants conversed with a confederate.

Methods: Participants entered the laboratory and immediately completed the perceptual bias task. The perceptual bias task consisted of short (0.5 s) presentations of rotating PLFs, which participants then responded to regarding which way they perceived the figure rotating (i.e., clockwise or counter-clockwise). Unbeknownst to participants, all PLFs were rendered rotating counter-clockwise, but could be perceived rotating in either direction because of their depth-ambiguous nature. We could thus calculate each participant's FTV bias by comparing their responses with the veridical walker positions. Once participants completed the initial perceptual bias task, they then conversed with a confederate for 10 minutes. We manipulated both the diagnostic label attributed to the confederate (peer vs. schizophrenia) and the presence of behavioural symptoms (present vs. absent). Immediately after conversing with the confederate, we again measured participants' FTV biases using the perceptual bias task. Following the completing of the PLF task, we administered an explicit measure of stigma as well (i.e., the Community Attitudes toward the Mentally Ill questionnaire, or CAMI).

Results: As researchers have found that stronger FTV biases are elicited by more threatening stimuli, we hypothesized that FTV biases would be greater after participants conversed with someone they believed had schizophrenia, and also after they conversed with someone who presented symptoms of schizophrenia. We found partial support for these hypotheses. Participants had significantly greater FTV biases in the Peer Label/Symptoms Present condition. Interestingly, while FTV biases were lowest in the Schizophre-

nia Label/Symptoms Present condition, participants in this condition were most likely to believe that people with schizophrenia should face social restrictions.

Discussion: Our findings support that both implicit and explicit beliefs help develop and sustain stigma. Our study was the first to assess the feasibility of using the FTV bias for PLFs as an implicit measure of perceived threat. Implicit assessments of stigma may be able to provide more information than explicit measures alone. This has implications for future stigma research, as the PLF task that we used in the present study can provide a fast and easy-to-administer implicit assessment of stigma. Future research on stigma using implicit measures is necessary in order to identify the contributions that implicitly and explicitly held beliefs have towards the development and maintenance of stigma towards individuals with schizophrenia.

Poster #M201

EXPERIENCE SAMPLING METHOD THROUGH A SMARTPHONE APP: THE CASE OF CITY LIVING & PSYCHOSIS

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Background: The Experience Sampling Method [ESM] is a structured diary technique that captures moment-to-moment information within the flow of daily life. This approach has many advantages (eg. combating recall bias). ESM is commonly administered using palmtops or similar equipment which can present methodological challenges (eg. malfunction and forgetting to carry equipment). The development of new technologies, such as Smartphone applications (apps), grants an opportunity for improvement in ESM research. Apps can be used to gather data at multiple times a day over a prolonged period of time removing some of the methodological challenges discussed, making this type of research more practical and cost-effective. Examining the relationship between city living and psychosis is an ideal topic to test the feasibility of this approach given the unique benefits of an app (eg. use of GPS co-ordinates rather than reliance on self-reported location).

Methods: A group of staff and students from a several UK universities are followed over a period of 7 days and asked to respond to 3 beeps/alerts a day reporting their psychopathological symptoms (mood and psychotic like experiences). At the time of responding the GPS co-ordinates of the participants' location is recorded. At the end of the study participants are asked to provide feedback on the experience of using the app.

Results: Data pertaining to the feasibility of the app and preliminary findings of this pilot study will be presented.

Discussion: The costs and benefits of using apps within the research arena will be addressed.

Poster #M202

COMPARING ILLNESS PRESENTATION, TREATMENT AND FUNCTIONING BETWEEN PATIENTS WITH EARLY- AND ADULT-ONSET PSYCHOSIS

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Background: Early studies have shown that patients with early- and adult-onset schizophrenia differ in their illness presentation, psychopathology, pre-morbid traits and prognosis. Whether adult-onset schizophrenia represents a separate entity distinct from early-onset schizophrenia is yet uncertain. Therefore, the current study aimed at characterizing and contrasting adult-onset patients with an early-onset cohort in their basic demographics, illness presentation, treatment and functional level.

Methods: Participants were recruited from two territory-wide early intervention services for early-onset (n=671; from the Early Assessment Service for Young People with Psychosis Program, EASY) and late-onset psychosis patients (n=360; from the Jockey Club Early Psychosis Project, JCEP) in Hong Kong. Patients from the early-onset cohort had their initial psychotic episode during 2001 and 2003; data were then collected retrospectively by systematic case note review. The adult-onset cohort was prospectively

recruited as part of a larger interventional study during 2009 and 2011; information was collected prospectively via face-to-face interviews with patients.

Results: At baseline, adult-onset psychosis (mean of 36.6 years old) was significantly associated with more females, more non-local birth, more full-time employment, better functioning level, fewer smokers, fewer with schizophrenia than early-onset psychosis (mean of 20.4 years old), better medication adherence and more psychiatric hospitalization. No significant group differences in duration of untreated psychosis were found.

Discussion: Managing psychotic illnesses optimally is an important challenge in health care delivery. The finding that adult-onset patients had better functioning challenges the view that early-onset psychosis and adult-onset psychosis share a similar prognostic trajectory. There is a need to adapt intervention processes, specifically for patients recovering from a first episode illness, in particular for early- and adult-onset, as they may face different unique sets of challenges.

Poster #M203

SCHIZOPHRENIA "FOR LIFE" – A REGISTRY AND INTERVIEW STUDY AMONG ELDERLY WITH LIFELONG SCHIZOPHRENIA

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Background: The elderly demographic is on the rise – and this includes elderly living with schizophrenia. Yet very little is known about their lives, how they cope with their condition and how it develops over time. There appear to be no Danish studies of this patient group, and internationally too, research is sparse. While the few studies available provide a somewhat mixed picture of how schizophrenia evolves over the life course, they indicate a tendency for elderly patients to manifest fewer psychotic symptoms and less pronounced psychopathologies with age. Opinions are divided on the degree and extent to which this tendency reflects remission and/or recovery in older patients. In this study we investigate the course of the illness over the lifespan, quality of life, mental and physical health as well as functional competence of elderly (55+) with schizophrenia in Denmark in order to identify factors associated with a positive outcome. Also we compare the trajectory and prognosis of schizophrenia (a chronic mental illness) with type 1 diabetes (a chronic somatic illness).

Methods: Registry study: A nationwide register cohort study (1970-79) will identify psychiatric admissions (aged 18-40) who received their first schizophrenia diagnosis. By drawing on sources that include the Psychiatric Central Register, the Danish National Patient Register, Statistics Denmark and more, we are able to examine in detail the prognoses and long-term outcomes of patients with schizophrenia in terms of the extent of contacts to the healthcare system, socio-economic situation as well as co-morbidity, causes of death and use of medicine. Data on type 1 diabetes are matched on the same criteria bar the diagnosis (1977-79). Interview study: A cross-sectional survey where 150 randomly drawn members of the register cohort resident in the former County of Fynen will be interviewed on the basis of semi-structured interviews based on internationally validated assessment tools. Hereby assessing the current status of psychopathology, somatic illness, quality of life, psycho-social functioning, cognition, addiction, use of medicine, social and economic status.

Results: The project has just been initiated and as yet no results are available.

Discussion: This study will yield vital insights into how schizophrenia develops over time, isolating factors that determine how well patients fare – including focus on such measures as completion of education/vocational training, employment, family relationships and longevity. The perspective is to advance knowledge of elderly with schizophrenia with a view to optimizing and increasing the effectiveness of the interventions offered to this group.

Poster #M204

OUTCOMES OF PATIENTS WITH FIRST-EPIISODE SCHIZOPHRENIA AT ONE-YEAR FOLLOW-UP: FINDINGS FROM THE NATIONAL MENTAL HEALTH REGISTRY IN MALAYSIA

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Background: This first outcome study for people with first-episode schizophrenia (FES) in Malaysia was based on data collected from the National Mental Health Registry (NMHR). The aim of the study was to assess the outcome of patients diagnosed with schizophrenia, one year after contact with mental health services; and to evaluate treatments as well as the utilization of medical and other services in the country.

Methods: All patients with FES registered in NMHR between 1 March 2004 and 28 February 2005 were included and 79 centers carried out outcome assessments. Socio-demographic and clinical data were collected and compared with the data in NMHR that was gathered one year ago. Descriptive statistic was used to analyze the data.

Results: Of 2604 registered patients with FES, only 37.7% had their outcomes successfully assessed. Among those assessed, 25.5% were lost to follow-up and 45.8% were followed-up in different centers. Only two patients committed suicide. Increases in weight gain and body mass index were major concerns. On a positive note, employability improved. Forty percent of the patients had their antipsychotics changed over the one-year period but about 20% of patients were on polytherapy at baseline and after one year. The use of anticholinergic medication dropped remarkably after the one-year treatment period.

Discussion: This study has shown that one of the great barriers in conducting a nationwide outcome assessment of FES patients was the high attrition rate. Nevertheless, these findings provided an important glimpse into the socio-demographic and clinical outcomes of the patients.

Poster #M205

DURATION OF UNTREATED PSYCHOSIS – RELATION TO FUNCTIONAL OUTCOME OF PATIENTS WITH SCHIZOPHRENIA

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Background: Duration of untreated psychosis (DUP) can influence the prognosis of schizophrenia. The aim of this study was to demonstrate that the characteristics of the DUP are correlated with the long-term social functional outcome of patients with schizophrenia by means of a retrospective design.

Methods: Retrospective data obtained from clinical records were collected regarding DUP and outcome variables (number of hospitalizations, duration of hospitalization, marital status, socio-economic status) for a cohort of 66 patients (24 males and 42 females) affected by schizophrenia according to DSM IV TR admitted in a university psychiatric clinic.

Results: Mean duration of follow up was 17.3 years and mean duration of untreated psychosis was 14 months. Patients with a shorter DUP (≤ 1 year) displayed more frequent cases with smaller number (≤ 3) of hospital admissions (80%) versus patients with longer DUP (> 1 year) (44.4%), with a mean duration of hospitalization of 23 days versus 30 days for the group with longer DUP; were married in 16.6% of cases versus 19.4% and showed a difference in employment status, 23.3% were employed versus 16.6% of patients with longer DUP.

Discussion: In our study DUP seems to be associated with differences in the long term functional outcome of patients with schizophrenia, thus the importance of early intervention for the future of these patients.

Poster #M206**PERFORMANCE ON THE UCSD PERFORMANCE-BASED SKILLS ASSESSMENT (UPSA) AND REAL-WORLD OUTCOMES IN SEVERE MENTAL ILLNESS: A SYSTEMATIC REVIEW OF THE LITERATURE**

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Background: There is a regulatory agency expectation that pharmacotherapies developed to treat cognition in schizophrenia must demonstrate improvement on cognitive and functional co-primary endpoints. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative conducted the Validation of Intermediate Measures study (VIM) to assess the psychometric characteristics and practicality of alternative functional measures. Results of this study identified the UCSD Performance-based Skills Assessment (UPSA) as the superior co-primary measure due to its psychometric properties and reasonable acceptability and practicality. The objective of this study was to systematically evaluate literature regarding the UPSA's relationship to real-world functional outcomes that are relevant to treatment and coverage decisions in today's cost-constrained medical environment.

Methods: Systematic searches of articles published between January 2001 and April 2013 were conducted in multiple databases. Results were reviewed using predetermined inclusion and exclusion criteria. Included articles utilized any version of the UPSA and either milestone (direct) or rating scale measures of real-world outcomes. After relevant studies were selected, data were extracted (e.g., study design, patient characteristics, country of study, study size, duration, UPSA version, measures of real-world outcomes, rater, summary of results relating to the relationships between the UPSA and real-world outcomes). Results of studies were compared and contrasted.

Results: Forty studies met the inclusion criteria, with most being conducted in the U.S. (n=31). Seven studies utilized milestone measures, 27 used rating scale measures, and six evaluated both milestone and rating scale measures of real-world outcomes. Overall, the studies reviewed suggest the UPSA and the UPSA-B are associated with real-world outcomes, whether milestone or rating scale measures were utilized. Studies evaluating residential and employment milestones reported significant correlations with UPSA and UPSA-B scores. Studies of the correlations between the UPSA and various components of the rating scales generally showed modest associations. The Specific Level of Function (SLOF) rating scale, a measure of real world function (personal care, interpersonal relationships, social acceptability, activities of community living, work skills), was used in 16 of the 40 studies. SLOF scores rated by clinicians and informants have been found to be significantly correlated to both UPSA and UPSA-B scores ($r=0.18-0.63$). Less consistent results and weaker associations were reported for self-reports and in countries outside the US.

Discussion: This review identified substantial evidence indicating the UPSA is associated with the real-world status/capabilities of patients with schizophrenia. However, further research is needed to better understand how social support and healthcare systems in countries other than the US impact the UPSA and real-world outcomes associations. Taken together, the evidence reviewed supports the use of the UPSA as a proxy for functional improvements that are relevant not only to patients, families, physicians and treatment teams, but also to reimbursement authorities.

Poster #M207**USE OF RELIABLE CHANGE INDEX TO EVALUATE CLINICAL SIGNIFICANCE IN THE POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS): A CATIE ANALYSIS**

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Background: The PANSS is the most widely used measures of psychopathology in schizophrenia. It is commonly used in both randomized controlled trials (RCT) and non-controlled evaluations. RCTs assess clinical efficacy of an intervention relative to a placebo or control condition by making group comparisons and evaluating for statistically significant differences. However, statistical significance does not in itself provide concise information

about a given intervention's clinically meaningful effects. The process of defining clinical significance remains a challenge. As an attempt to develop a standard method of estimating clinically significant change, we propose adoption of a two-part strategy: The first part of the strategy involves using the Reliable Change Index (RCI). The second part involves use of examination of clinical significance (CS). RCI is whether patients changed sufficiently that the change is unlikely to be due to measurement unreliability. CS change takes the patient from a score typical of schizophrenia to a score typical of the "normal" population. Studying RCI and CS has moved the outcomes paradigm from studying treatment groups to studying individual change within those groups. Assessments must move beyond symptom focus and evaluate individuals with respect to the complex broader domains of their functional, real-world, lives in which clinically significant change is operationalized.

Methods: Data on symptomatology, PANSS, from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) were analyzed. Three methods of RCI (Jacobson-Truax, Edwards-Nunnally, and Hageman-Arindell methods) were compared to CS change (pre to post change of at least 2 SDs from the original mean, 20% improvement, and change in PANSS remission criteria).

Results: For the three RCI methods, 29.73%, 31.08% and 52.70% showed reliable improvements in PANSS scores. For CS, 22.97% showed greater than 20% improvement, 29.73% improved on the PANSS remission criteria, and only 8.11% showed CS improvement of 2 SDs from the mean. When comparing RCIs with CS, only 18.92% of CS improvement also resulted in RCI significant improvement. Regarding clinically meaningful improvement, the Hageman-Arindell method was most concordant with all three RCI measures and with the 20% improvement as this method differentially analyzes clinically meaningful change at the individual level and at the group level (i.e., obtaining proportions of patients who have reliably changed and passed the cutoff point).

Discussion: Reliable and clinically significant change should be reported in articles to complement the more familiar group summary methods. Assessment of clinically meaningful change is useful for evaluating treatment response. Outcome studies often assess statistically significant change, which may not be clinically meaningful. Comparisons of the proposed methods of determining clinically significant PANSS outcomes to biomedical standards of clinical significance will help determine the validation of this procedure, and improve the precision and effectiveness of the PANSS in clinical trials.

Poster #M208**AGEING IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW**

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Background: Schizophrenia is generally a lifelong condition. Despite high mortality, most survive into old age. Few prospective longitudinal studies have analysed trajectories from early-mid adulthood into old age. Systematically review longitudinal studies of the progression of schizophrenia into old age, focusing on cognition, functioning, co-morbidity, mortality and quality of life. Advance understanding of the course of schizophrenia and highlight interventions that improve outcomes and even achieve a state of wellbeing in later life.

Methods: Electronic search of PubMed, PsychINFO and Scopus. Search terms: (ageing OR "older adult" OR elderly OR geriatric OR "late life") AND (schizophrenia OR schizoaffective OR schizophreniform"). Articles and books searched manually.

Results: The course in later life is variable. Many remain symptomatic and mortality and somatic comorbidity increase. Higher rates of decline in cognitive functioning affect ability to function independently. However, many individuals have a favourable clinical course and may stop receiving treatment altogether. 18-27% achieve recovery in old age. Growing evidence base for interventions that alleviate symptoms, improve social and cognitive functioning and quality of life. Inequalities remain in the quality and range of treatment interventions available to older people with schizophrenia.

Discussion: Early introduction of regular psychiatric and somatic assessments and prompt and adequate treatment of symptoms and comorbidities throughout the life course are essential. Cases of remission/recovery are often excluded in clinical research. This risks presenting a biased, somewhat

pessimistic description of the illness course into later life. Evidence base for interventions needs improvement and future trials must include older participants.

Poster #M209

THE LONGITUDINAL COURSE OF SCHIZOPHRENIA: A SYSTEMATIC REVIEW

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Background: Naturalistic studies of schizophrenia have been completed prior to the emergence of neuroleptics in the last part of the last century. Since the advent of neuroleptics longitudinal studies of schizophrenia have mostly followed medicated patients. In addition to changes in the medication background of schizophrenia, a number of changes in the diagnostic criteria over time brings an additional layer of complexity to any attempt to systematically organize data about the longitudinal course of schizophrenia. In this context a systematic review of the literature is essential to properly understand the longitudinal course of schizophrenia, with important implications for early diagnosis and intervention, prophylaxis, diagnostic validity, and prognosis. Further, properly charting the longitudinal course of schizophrenia is essential to improve our definition of concepts such as partial response, remission and recovery.

Methods: We completed a systematic literature search for longitudinal, both retrospective and prospective studies of schizophrenia. To decrease the heterogeneity of studies span using different diagnostic criteria and important confounders in the study population (e.g. non-medicated vs. medicated patients, institutionalization status) we organized our review based on historical periods which were deemed "homogeneous" in rapport to important variables of interest (e.g. institutionalization and deinstitutionalization, pre and post neuroleptic periods).

Results: The majority of the longitudinal studies of schizophrenia report that up to 30-50% of patients present with a stable or favorable course. Gender, age of onset, duration of illness, core symptoms (positive, negative, cognitive) can putatively affect prognosis and course.

Discussion: The literature indicated that the course of schizophrenia is one of stability of symptoms over time for the majority of patients. Stability is maintained at a lower level of functioning than pre-diagnosis - and as such is not the optimal outcome - at the same time stability also implies that gradually deterioration is unlikely for the majority of patients. Of note, the literature tends to emphasize the less favorable outcome of the minority of the patients (less than 50%) who show a gradual and progressive deterioration during the course of illness. A "bleaker" interpretation of course and prognosis dat while justified from a public health perspective might not be as informative to the clinician aiming to have an objective and, if not unjustified, appropriately hopeful discussion of course and prognosis with individual patients.

Poster #M210

THE UCSD PERFORMANCE-BASED SKILLS ASSESSMENT-BRIEF JAPANESE VERSION (UPSA-B_J): DISCRIMINATIVE VALIDITY FOR SCHIZOPHRENIA

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Background: The UCSD Performance-based Skills Assessment (UPSA) has been developed to assess daily living skills related to neurocognition in people with psychiatric disorders (Patterson et al, 2001). Specifically, its brief version (UPSA-B; Mausbach et al, 2007) has been widely used for evaluating functional capacity in patients with schizophrenia (Harvey, 2009). To enhance the clinical utility of this battery, its sensitivity, i.e. an optimal cut-off point discriminating between normal subjects and patients, needs to be clarified. The current study investigated the issue using the Japanese version of UPSA-B (UPSA-B_J; Sumiyoshi et al., 2011).

Methods: Sixty-four Japanese patients meeting DSM-IV-TR criteria for schizophrenia (M/F=34/30; mean age=35.2) and 113 normal controls (university students=9/21, mean age=20.6; office workers=71/12, mean age=34.6) entered the study. The UPSA-B_J and MATRICS Cognitive Consensus Battery Japanese version (MCCB_J) was administered to all participants. The group differences (students vs. workers vs. patients) were analyzed by one-way ANOVA for the UPSA-B_J Total score, and by ANCOVA (controlling for education) for the MCCB T-score. The profiles UPSA-B_J were created to show task-specific performance in each group. Receiver Operating Characteristic (ROC) curve analysis was conducted for the UPSA Total score. The optimal cut-off was determined in a manner to maximize the sum of sensitivity (% of hit) and specificity (% of correct rejection) (Youden, 1950; Mausbach, 2011).

Results: Overall results: Normal students and workers performed better than patients both in the MCCB_J (Students > Workers > Patients; F=56.65, df=2 170, p<0.5) and UPSA-B_J (Students=Workers > Patients: F=38.19 df=2 174, p<0.01). The profiles for UPSA-B_J revealed that scores of the memory-oriented tasks in the Communication part for normal workers and patients tended to be worse compared to those for normal students. ROC analysis: The area under the ROC curve (0.80, CI: 0.73-0.87, p <0.001) and d' (1.46) indicated good discriminative power of the UPSA-B_J. The optimal cut-off was estimated as 81.5 (MAX=100), at which sensitivity and specificity were 81.3% and 65.5%, respectively.

Discussion: The UPSA-B_J Total score around 80 was found to distinguish adequately between patients and control subjects. This cut-off seems to be consistent with a previous study reporting "functional milestones (i.e. residential of employment status)" in patients were to be around this point (Mausbach, 2011). Result from MCCB_J and UPSA-B_J indicated that daily-living skills (especially Communication), as measured by the UPSA-B, depend on neuropsychological abilities.

References:

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Poster #M211

THE THREE FACES OF SCHIZOPHRENIA: SUB-TYPING SCHIZOPHRENIA BASED ON RESPONSE AND IMPLICATIONS FOR TREATMENT

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Background: Treatment and classification of schizophrenia continues to present an enormous challenge, in part due to the disease's heterogeneous nature. Of note, response to a particular treatment, or lack thereof, is used for diagnostic purposes in other areas of medicine (e.g., Insulin/Non-Insulin Dependent Diabetes Mellitus, certain cancers). The present work set out to establish if, in fact, antipsychotic treatment response can be used to subtype distinguishable groups of schizophrenia that may, in turn, be used to better elucidate differences in underlying pathophysiologic mechanisms.

Methods: Relevant literature was reviewed with specific reference to antipsychotic treatment response. Where available, we focused on the early stages of the illness and evidence that sequentially followed antipsychotic trials, including use of clozapine in individuals identified as treatment resistant. This approach aligns with evidence that early and effective treatment favourably alters clinical and functional outcome measures.

Results: While the first-episode schizophrenia population has very high symptom response rates, approximately 25-30% do not respond favourably. For patients experiencing partial or non-response to first-line treatment, current guidelines indicate a switch to another non-clozapine antipsychotic before resorting to clozapine as a third (or later) line of treatment. Clinicians also often employ dose increase and/or polypharmacy in these cases, although the benefit of these strategies has been called into question. These early non-responders, or treatment-resistant patients (TRs), generally respond exclusively to clozapine. While D2 blockade is identified as central to the antipsychotic effect observed with standard antipsychotics, clozapine's mechanism(s) of action are currently unclear. In those demonstrating suboptimal response to clozapine (i.e. URS) we currently have no effective treatments, making it even more difficult to speculate regarding underlying pathophysiological differences.

Discussion: Antipsychotic response patterns identify three subtypes of

schizophrenia: (i) responder (to first or second generation antipsychotic), (ii) treatment-resistant (TRS; suboptimal response to two antipsychotic trials, first or second generation, and candidate for clozapine), and (iii) ultra-resistant (URS; suboptimal response to first or second-generation antipsychotics and clozapine). Approximately 70% of patients are classified as responders. Of the remaining 30%, 30–60% will respond to clozapine (i.e., TRS), meaning that 40–70% will not (i.e., URS). These three subtypes can be identified very early in the course of illness and diagnostic criteria for these three subtypes are available. Unfortunately, to date there has been virtually no systematic effort to delineate how URS differs from TRS in terms of specific mechanisms. Subtyping individuals with schizophrenia acknowledges the illness' heterogeneity and can facilitate early identification and appropriate treatment to maximize longer term outcomes.

Poster #M212

ECOLOGICAL VALIDITY OF THE SCHIZOTYPY DIMENSIONS AND STRESS-REACTIVITY MODEL OF PSYCHOTIC-LIKE EXPERIENCES

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Background: Positive (PS) and negative (NS) schizotypy exhibit differential patterns of impairment in daily life. However, studies have not examined the association of schizotypy with real-world expression of psychotic-like, paranoid, and negative symptoms. This study employed Experience Sampling Methodology (ESM) to assess: a) the expression of PS and NS in daily life, and b) the validity of the stress-sensitivity model, which suggests that daily life stressors may play a critical role in the expression of psychotic-like experiences (PLEs). In order to test the validity of the stress-sensitivity hypothesis across the psychosis continuum, the association of stress and positive symptoms was examined in both nonclinical schizotypic participants and early psychosis patients.

Methods: ESM is a structured diary method in which participants are prompted at random intervals to report their thoughts, feelings, symptoms, stress, and contextual factors. Participants were prompted randomly eight-times daily for one week. ESM was employed in a large sample of nonclinical young adults ($n=206$; mean age=19.8 years) and a sample of early psychosis patients ($n=29$; mean age=22.5). The clinical sample comprised individuals with At Risk Mental States for Psychosis ($n=17$) and first episode patients ($n=12$). Both samples received the same ESM questionnaire that included a comprehensive assessment of PLEs. Nonclinical participants completed the self-reported Wisconsin Schizotypy Scales and were assigned SCID-II interview dimensional ratings of spectrum personality disorders.

Results: PS was associated with momentary PLEs and paranoid symptoms, whereas NS was associated with a subset of these symptoms and negative symptoms. PS was related to emotional dysregulation and subjective stress, whereas NS was related to experiencing diminished positive affect and social interest and pleasure. The momentary expression of interview ratings of schizotypal, paranoid and schizoid personality disorders closely resembled the differential pattern described for self-reported PS and NS, with paranoid showing a greater resemblance to the schizotypal profile. Regarding stress-sensitivity, appraisals of stressful situations and social stress (feeling rejected and feeling distant), but not merely being alone, were associated with PLEs and paranoid symptoms in the moment, but not with negative symptoms. The association of stress with PLEs and paranoid symptoms was moderated mostly by PS, such that only high PS scorers showed the association between stress and symptoms. The association between situational and social stress with PLEs and paranoia also occurred for early psychosis patients. Finally, in order to disentangle the temporal sequence of stress and symptoms, time-lagged analyses examined whether stress at the preceding signal predicted PLEs at the current assessment (controlling for levels of PLEs at the preceding signal). In nonclinical participants, stress at the preceding signal predicted PLEs at the current assessment, but only for individuals high in PS. In clinical participants, stress also predicted PLEs.

Discussion: Positive and negative schizotypy dimensions were differentially expressed in daily life in terms of spectrum symptoms, affect, social

functioning and stress reactivity. The results are consistent with models linking stress-sensitivity with the experience of psychotic symptoms at both nonclinical and clinical levels of the psychosis continuum. Furthermore, the findings demonstrate that ESM is an effective method for predicting the experience of PLEs symptoms, as well as their precursors, in daily life.

Poster #M213

PREVALENCE AND PREDICTORS OF DEPRESSIVE SYMPTOMS IN NON-AFFECTIVE PSYCHOSIS PATIENTS IN JOCKEY CLUB EARLY PSYCHOSIS (JCEP) PROJECT IN HONG KONG

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Background: Depressive symptoms are frequently found in the early stage of psychotic disorders and are associated with heightened risk of suicide. In this study, we aimed to examine the prevalence and factors predictive of the occurrence of depressive symptoms in adult patients presenting with first-episode non-affective psychosis to JCEP project in Hong Kong.

Methods: A total of 343 patients aged 26 to 55 years presenting with first-episode non-affective psychosis (DSM-IV schizophrenia, schizophreniform disorder, delusional disorder, brief psychotic disorder or psychosis NOS) to Jockey Club Early Psychosis (JCEP) project were recruited. Patients who scored 6 or above in Calgary Depression Scale (CDS) were classified as having clinically significant depressive symptoms. Premorbid functioning was examined by Premorbid Adjustment Scale (PAS). Psychopathology was assessed with Positive and Negative Syndrome Scale (PANSS). Global functioning was measured using Social and Occupational Functioning Assessment Scale (SOFAS). Medication Compliance Questionnaire (MCQ) was used to assess patients' attitude to treatment. Drug-induced Parkinsonism side-effects were evaluated using Simpson Angus Scale (SAS). A series of univariate analyses were conducted to determine relationship of "depressed clinical status" with potential predictive variables, followed by multivariate binary logistic regression to identify predictors of depressive symptoms.

Results: Fifty-two patients (14.8%) had clinically significant depressive symptoms at study entry. No significant difference between depressed and non-depressed patients in age at entry and onset, sex, premorbid adjustment and duration of untreated psychosis. Univariate analyses revealed significant associations of "depressive clinical status" with educational attainment ($p<0.05$), log-transformed duration of untreated illness (LogDUI) ($p<0.05$), SOFAS rating ($p<0.05$), PANSS positive ($p<0.05$) and negative symptom ($p<0.05$) subscale scores, SAS score ($p<0.05$) and MCQ attitude subscale score ($p<0.05$). Multivariate logistic regression indicated that more severe positive and negative symptoms, worse drug-induced Parkinsonism side-effects, and poorer attitude to medication treatment independently predicted occurrence of clinically significant depressive symptoms (Nagelkerke R²=0.215, $p<0.001$). Depressed patients had significantly poorer global functioning than non-depressed counterparts ($t=3.6$, $p<0.01$).

Discussion: In a large representative cohort of Chinese adult patients with first-episode non-affective psychotic disorders, approximately 15% experienced clinically significant depressive symptoms which were predicted by more severe positive and negative symptoms, higher level of antipsychotic-induced motor side-effects and poorer attitude to medication treatment.

Poster #M214

BODY-ORIENTED PSYCHOTHERAPY FOR PERSONS WITH SCHIZOPHRENIA: INTERPRETATIVE PHENOMENOLOGICAL ANALYSIS OF PARTICIPANTS' EXPERIENCE

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Background: Phenomenological psychiatry has thoroughly described schizophrenia exploring patients' first person experience. According to this tradition, schizophrenia shall be conceptualized as a disorder of the self: more specifically, anomalous self-experience has been described as

disturbed basic self consciousness, loss of natural self evidence and dis-embodiment. The minimal self, the implicit, basic and bodily level of experience, has been shown to be at the core of the disorder. Consistently with this theoretical background, specific body-oriented psychotherapy interventions for schizophrenia have been developed, addressing first and foremost the implicit and bodily level of experience. Current studies on outcome of body-oriented psychotherapy have already shown a significant reduction of negative symptoms in the case of schizophrenia, although results are still controversial in relation to improvement of life quality and other aspects of psychopathology (Roericht & Priebe, 2006). Notwithstanding the clinical relevance of these results, the assessment of symptoms may not be enough if we are to understand the process of therapeutic change and its impact on patients' quality of life. Indeed, these studies shifted from a first-personal stance for understanding schizophrenic disorder to a third person observation of symptoms as a measurement of therapy outcome. The aim of this study is thus to take a first-person phenomenological perspective on the study of therapy process and outcome by qualitatively analyzing participants' experience of body-oriented psychotherapy.

Methods: A body-oriented manualized intervention for persons with schizophrenia has been implemented at the Psychiatric University Clinic of Heidelberg, Germany. According to the manual (Roericht, 2000), the intervention was implemented in a group format (five participants) and took place over a period of ten weeks, with two weekly sessions of ninety minutes. Qualitative semi-structured interviews, exploring participants' experience of therapy (Change interviews; Elliott et al., 2001), were implemented after the ten weeks by a researcher trained in clinical psychology. The interviews were transcribed and analyzed with Interpretative Phenomenological Analysis (Smith et al., 2009) in order to identify core relevant themes within those narratives. The reliability of the analysis process was checked through independent audit.

Results: Recurrent relevant themes related to the experience of therapeutic change were identified and grouped. These are the preliminary emerging themes, all sharing an underlying idea of recovery of a sense of self: 1) Being a whole: connecting body and mind. 2) Being unique: feeling accepted for who one is. 3) Being part of a group: feeling of social belonging. 4) Being the center of one's own agency: active stance. 5) Being worth, being able: hoping and investing in the future. These themes will be qualitatively discussed in relation the specific aspects of body-oriented psychotherapy that fostered them.

Discussion: The implications of taking a phenomenological stance in the study of psychotherapy process and outcome will be discussed. Indeed, the qualitative analysis of first person experience showed that the efficacy of body-oriented psychotherapy goes beyond the mere reduction of negative symptoms: it fosters a process of change towards the recovery of a sense of self at different levels of patients' experience. Besides, through an in depth analysis of the above mentioned aspects of therapeutic change related to this particular intervention, more general implications will be drawn for an effective treatment approach to schizophrenia.

Poster #M215

THE COURSE OF OBSESSIVE-COMPULSIVE SYMPTOMS IN PATIENTS WITH NON-AFFECTIVE PSYCHOTIC DISORDERS AND IN UN-AFFECTED SIBLING: A 3 YEARS FOLLOW-UP STUDY

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Background: The course of obsessive-compulsive symptoms (OCS) and its association with alterations in other clinical characteristics in patients with non-affective psychotic disorders and non-psychotic siblings is insufficiently known.

Methods: Patients (n=674) and siblings (n=662) from the Dutch Genetic Risk and Outcome in Psychosis (GROUP) study were investigated at baseline and after 3 years followed-up. Severity of psychotic symptoms was measured with the Positive and Negative Syndrome Scale (PANSS) in patients while the Community Assessment of Psychic Experiences (CAPE) was used to assess prevalence of subclinical positive, negative and depressive symptoms in siblings. Severity of OCS was measured with the Yale Brown

Obsessive Compulsive Scale (YBOCS). Participants were assigned to different groups based on the course of clinically relevant OCS over time: no-OCS, persistent OCS, OCS remission and de novo OCS.

Results: Patients suffering from co-morbid OCS reported significantly higher severity of psychotic and depressive symptoms as well as lower overall social functioning compared to patients without co-morbid OCS. These differences were highly stable over time for patients reporting persistent OCS. Subsequent repeated measure analysis revealed significant interaction effects for groups reporting changes in their OCS. While the OCS remission group showed significant improvement in PANSS scales, the de novo group reported stable high psychopathology. Similar results were found in siblings without a psychotic disorder.

Discussion: The presence of clinically relevant co-morbid OCS was associated with greater severity of psychotic and affective symptoms and indicated lower levels of overall social functioning and additional burden for the affected patients. Findings strengthen the need for a better understanding of the co-occurrence and clinical research aiming at multimodal therapeutic interventions.

Poster #M216

LONG-TERM IMPROVEMENTS IN AVHS: CLINICIAN VS. PATIENT PERSPECTIVES

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Background: The present study is a longitudinal examination of patients with persistent AVHs to uncover which dimensions improve over the course of 1 year treatment and how physical symptom domains are related with subjective stress separately from the clinician and patient perspectives.

Methods: A total of 87 patients with schizophrenia presenting persistent AVHs were assessed at 6-month and 1-year from the baseline using both the clinician-rated Psychotic Symptom Rating Scales - Auditory Hallucination Subscale (PSYRATS-AH) and self-reported Hamilton Program for Schizophrenia Voices Questionnaire (HPSVQ).

Results: The prevalence of AVHs was significantly decrease among 68 patients followed at the 6-month (T1) with 8 no longer showing the symptoms of AVHs (McNemar χ^2 , p=0.008). At 1-year assessment (T2), significant decrease in the prevalence of AVHs from 6-month was not observed among 49 patients. The decrease in the prevalence of AVHs over 1-year period (T3) for 51 patients was significant with 8 no longer showing the symptoms of AVHs (McNemar χ^2 , p=0.008). From the clinician perspective, PSYRAT-AH showed significant improvements in frequency, duration, degree of negative content, amount of distress, and disruption to life at T1. At T2, no significant changes were observed. Over the course of year (T3), duration of illness, belief re origin of voices, degree of negative content, amount of distress, and intensity of distress improved. In contrast, from the patient perspective as based on the HPSVQ, significant decrease in only frequency and distress occurred at T1, no significant changes followed at T2, and duration, distress, how bad they make you feel, and clarity improved in T3. In terms of cross-sectional correlations between items pertaining to distress and disruption to life and other aspects of the AVHs, from the clinician viewpoint, frequency, amount of negative content, and degree of negative content were significantly associated with amount of distress, intensity of distress, and disruption to life across all assessments. The duration of auditory hallucination was significantly associated with the intensity of distress and disruption to life across all assessments, but was significantly associated with amount of distress only at the baseline. Similarly, beliefs re origin was associated with disruption to life across all assessments, but was significantly associated with intensity of distress only at the baseline. From the patient perspective, frequency, how bad is content, and obey commands items were significantly associated with distress, how bad they make you feel, and interference life items across all assessments, with one exception of marginal significance between how bad is content and interferences with life at 1 year assessment: for duration and loudness items, they were significantly correlated with the three items of distress only for baseline and 6-month assessments: lastly, the clarity items was significantly correlated with the three items of distress at only 6-month assessment.

Discussion: Our results demonstrated that significant disagreement exists between clinician and patient evaluations of improvement in symptoms and their relationships with distress and interference with life. To understand the long-term course of AVH, we need to consider perspectives of patients as well as clinician.

Poster #M217

A NETWORK APPROACH TO THE PSYCHOPATHOLOGY OF PSYCHOSIS

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Background: Manuals of psychiatric disorders distinguish separate classes of mental illness. Although clinically useful, these labels are not very helpful in understanding the true nature and development of psychopathology and mental disorders. Recently, it has been proposed that mental disorders should not be seen as latent constructs giving rise to different sets of symptoms. Rather, mental disorders are better represented as networks of symptoms. In this theory, symptoms do not flow from an underlying construct, but exist *per se*, as causal, independent actors. Following from this idea, it can be hypothesized that the network connectivity of mental states is increased in individuals with mental disorder compared to network connectivity in individuals without mental disorder. A second hypothesis is that networks of mental states are expected to differ between individuals with different types of mental disorder. In three separate studies, I investigated the application of this network approach to the field of psychopathology.

Methods: In several large samples of healthy controls, individuals with depression, individuals with psychosis and their siblings, longitudinal networks of moment-to-moment effects between momentary affective states were visualized and different aspects of network connectivity were explored.

Results: Network connectivity between mental states was shown to increase with increasing levels of psychopathological severity. In addition, networks of mental states showed both overlap and (quantitative as well as qualitative) differences in network characteristics between different groups (eg healthy controls vs individuals with mental disorder, or individuals with psychotic disorder vs individuals with depressive disorder). Furthermore, mental state connectivity was shown to be dependent on affective and environmental factors.

Discussion: A network approach to mental disorder may prove valuable to complement current diagnostic practice and may help us to better understand both phenomenology and development of psychopathology. It may also offer explanations for clinical aspects such as comorbidity. These studies represent first explorations of the network approach to mental state connectivity in the field of psychopathology.

Poster #M218

PATHWAYS TO CARE FOR YOUNG INDIVIDUALS WITH A FIRST-EPIISODE PSYCHOSIS IN SOUTH LONDON: USE OF PRODROMAL SERVICES

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Background: The onset of schizophrenia (SZ) may be preceded by a prodromal phase, also termed as At Risk Mental State (ARMS), which is characterised by presence of either "attenuated" psychotic symptoms, brief and self-limiting psychotic symptoms, or a significant decrease in functioning in the context of a genetic risk. Estimates of transition rates to schizophrenia spectrum disorders of people presenting with the ARMS range from approximately 20-40% in the following 12 months after onset.

The Outreach and Support in South London (OASIS) service is a large and well-established prodromal psychosis service and currently covers four boroughs in South East London, UK, a region with high prevalence rates of psychosis. This study sought to a) establish what proportion of the total number of individuals with a first episode of psychosis (FEP) who present to catchment area mental health services provided by the South London Maudsley NHS Foundation Trust come via OASIS (which covers the same catchment) and b) examine differences in socio-demographic characteristics and pathways to care between those who entered mental health services via OASIS and those who did not.

Methods: Data on demographic characteristic, first presentation to mental health services and pathways to care for all individuals with FEP over a one-year period (aged 18-35 years) were extracted from electronic records obtained from the Maudsley Biomedical Research Centre (BRC) Case Register Interactive Search (CRIS) system for which secondary data analysis has been ethically approved. All analyses were performed in STATA (11).

Results: During the study period, 150 patients with FEP presenting to services for the first time were identified. Of these, 25 (16.7%) had had a prior contact with OASIS. The mean age in the OASIS groups was 24 years ($sd=4.12$) compared with 26 years ($sd=4.75$) in the non-OASIS group ($p=0.05$). There groups did not differ in gender ($\chi^2=14$, $df=1$, $p=0.71$), living arrangements ($\chi^2=2.80$, $df=2$, $p=0.25$), level of educational achievement ($\chi^2=0.21$, $df=1$, $p=0.90$), occupational ($\chi^2=1.24$, $df=2$, $p=0.54$), relationship status ($\chi^2=5.1$, $df=2$, $p=0.25$), and cannabis use ($\chi^2=0.96$, $df=1$, $p=0.33$) at the time of presentation. The entire FEP sample included a higher proportion of individuals of black ethnicity ($n=59$; 39.6%) compared with white British ($n=38$, 25.5%) ($p<0.001$). A higher number of individuals of back ethnicity had prior contact with family practitioners (GPs) ($n=49$; 44.1%) compared to white British ($n=23$; 20.7%) ($\chi^2=10.79$, $df=2$, $p=0.005$). However, this group was less likely to have had a prior contact with OASIS (black: 16.7%; white British 54.2%; $\chi^2=13.28$, $df=2$, $p<0.001$). Individuals from black ethnic minority groups had somewhat higher rates of an acute onset of psychotic symptoms ($n=23$, 39%) compared to white British ($n=10$, 26.3%), though this difference was not significant ($p=0.34$). Those who accessed OASIS were primarily referred by GPs, nurses and other health professionals ($\chi^2=12.87$, $df=1$, $p<0.001$).

Discussion: In the area of SE London studied, only a small proportion of individuals who present with a first episode of psychosis to the main secondary mental health provider have previously been in contact with prodromal services. Those who do are more likely to be white British. Individuals of black ethnicity appear to actively seek help, but gain access to services by other routes. Further work is needed to establish whether prodromal services fail to reach prodromal patients and/or the proportion of FEP which presents acutely without a prodrome.

Poster #M219

THE ASSOCIATION OF AUTISTIC TRAITS AND PSYCHOSIS PRONENESS IN CHINESE EARLY ADULTS: THE TWINS SCAN CHINA STUDY

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Background: Autism and Psychotic Disorder are both spectrum disorders that include a range of symptom severity from mild to severe. Studying the sub-clinical or prodromal symptoms can help the conceptualization and distinction of the two disorders. The current study aims to replicate Hurst et al. (2007) in studying the relationship between psychotic experiences or symptoms and autistic traits in a non-clinical Chinese adolescent sample. It was hypothesized that 1) when the domains of autistic traits and psychotic traits are compared, positive correlation will be observed. Specifically, we predicted a stronger association between communication and social skills, two of the main features of autism, and psychosis proneness, and 2) autistic traits would predict psychosis proneness.

Methods: The study included 148 Chinese healthy participants aged 15-21. Self-report questionnaires of autistic traits and psychotic experiences and symptoms, including Autism Spectrum Quotients (AQ), Community Assessment of Psychic Experiences (CAPE) and Symptom Checklist 90-Revised (SCL-90-R), were administered.

Results: Consistent with expectations, the autistic traits and psychosis proneness were positively correlated. When the domains were examined one by one, social functioning impairment of AQ and negative symptoms measured by CAPE were found to be most strongly correlated. Results were consistent with the literature that autistic traits and psychotic traits overlap mainly on the impaired social-interpersonal areas and communication problems aspects. Further, autistics traits were found to have a predictive effect to psychotic experiences, although further longitudinal research should be done on this specific relationship.

Discussion: Symptoms on interpersonal sensitivity may mediate an increased risk of having psychosis proneness in early adults with large number of autistic traits. Future research should continue to investigate the overlap and distinction between autistic traits and psychosis proneness, to provide better conceptualization and distinction between the two disorders. Overall, the findings contribute to the emerging research on relationship between autism and psychosis in a Chinese non-clinical population. This supports further research into this area.

Poster #M220

FREQUENCY AND DURATION OF AN AT-RISK MENTAL STATE (DUI-ARMS) IN FIRST-EPSISODE PSYCHOSIS INPATIENTS: RESULTS FROM A RETROSPECTIVE ASSESSMENT

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Background: In first-episode psychosis, a long duration of both untreated psychosis (DUP) and untreated psychosis (DUI) has frequently reported and was associated with poorer outcome. Thereby, DUI is generally defined by the time between the first sign of the disorder and onset of adequate antipsychotic treatment. Yet, this definition ignores the fact that two types of non-psychotic symptoms occur in this phase: (1) truly unspecific symptoms by whose presence alone an increased risk of psychosis could not be detected (US), and (2) symptoms that are currently regarded as sufficiently specific indicators of the beginning disorder, e.g. according to the ultra-high risk or the basic symptom approach (ARMS).

Methods: We therefore studied the frequency and duration of (1) unspecific prodromal symptoms not included in current at-risk criteria (DUI-US), (2) prodromal symptoms included in current at-risk criteria, i.e., attenuated psychotic symptoms and/or cognitive and perceptive basic symptoms (DUI-ARMS), and (3) positive psychotic symptoms (DUP) prior to onset of treatment defined by hospital admission in 126 in-patients with schizophrenia-spectrum psychosis. Patients had been recruited as part of the awareness study of the German Research Network Schizophrenia and given informed written consent. They were examined for the presence and onset of symptoms with the "Early Recognition Instrument based on the Instrument for the Retrospective Assessment of the Onset of Schizophrenia" (ERIraos) in remission.

Results: Of the 126 patients, 86 (68.3%) reported an onset of the disorder with US and, consequently, presence of a DUI-US, 23 (18.3%) reported ARMS, either an attenuated psychotic symptom (APS) or a cognitive or perceptive basic symptom (BS), as the first sign of the emerging illness, and 17 (13.5%) recalled an acute onset with their illness starting already with a psychotic symptom (PS). Altogether 58 (46.0%) recalled ARMS before the onset of PS and thus a DUI-ARMS. In 35 (27.8%) of cases, the DUI-ARMS followed a DUI-US.

Discussion: The duration of untreated illness irrespective of the type of the first sign (DUI) was 8.4 (± 7.2 ; range 0–33.2) years on average in the whole sample. While it was shortest in those who reported an acute onset with PS (4.5 ± 5.0 yrs.), it was similar in those with an onset with ARMS (8.6 ± 7.5 yrs.) or US (9.1 ± 7.2). Thereby, in the latter two groups, the DUP was only about half the time than in the acute onset group (ARMS: 2.3 ± 3.7 ; US: 1.9 ± 3.5 yrs.). Furthermore, the DUI-ARMS was shorter in those starting with an US (3.2 ± 5.1 yrs.) than in those having an ARMS as first sign of the illness (6.3 ± 6.7 yrs.).

Poster #M221

STRUCTURAL BRAIN IMAGING CORRELATES OF AT-RISK MENTAL STATE

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Background: At-Risk Mental State (ARMS) is characterised by a significant drop of global functioning over a period of 12 months and having a close biological relative with a psychotic disorder and/or experiencing attenuated or very brief episodes of psychotic symptoms. Young people meeting this profile have a profound risk of developing a severe mental illness such as schizophrenia. Since regional cortical grey matter reductions have been reported for prodromal, first-episode and chronic schizophrenia, we tested the hypothesis whether the defining clinical characteristics of ARMS are associated with reduced regional grey matter thickness.

Methods: Cortical grey matter thickness was measured in high-resolution MRI scans of 42 individuals meeting ARMS criteria of the Comprehensive Assessment of At-risk Mental State (CAARMS). Correlation maps of cortical grey matter thickness and summative scores of positive and negative CAARMS symptom ratings and function levels rated on the Global Assessment of Functioning (GAF), Socio-occupational Function Assessment (SOFA) and social/role functioning (GF), respectively, were generated with Freesurfer.

Results: High total CAARMS symptom rating scores correlated ($P < 0.05$ corrected) with reduced grey matter thickness in left and right superior frontal gyri, right anterior cingulate, and right lingual gyrus while negative symptom expression correlated with reduced grey matter in left and right superior occipital gyri. Low global, socio-occupational, and social/role function ratings correlated with reduced grey matter in frontal, prefrontal and occipital cortex in both hemispheres. Age, gender, handedness, history of substance abuse, and exposure to psychotropic medication were ruled out as potentially confounding factors.

Discussion: Our findings provide evidence that reduced regional grey matter is associated with key ARMS criteria (i.e. low-grade psychotic symptom expression and functional impairment). Since grey matter reduction in these brain areas has also been found in schizophrenia, the corresponding regional grey matter reductions in ARMS may indicate increased risk of developing a psychotic illness.

Poster #M222

PSYCHOSIS EARLY DETECTION: HELPFUL OR STIGMATIZING EXPERIENCE? A QUALITATIVE PILOT STUDY

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Background: One major criticism concerning psychosis early detection services is related to the potential stigma and discrimination associated with the at-risk mental state (ARMS). There is a large scientific debate about this topic, but studies examining this matter from the subjective perspective of patients are rare. This pilot study aims to address how affected individuals perceive their symptoms, their first contact with the early detection centre and their treatment. Most importantly, we investigate whether there is evidence for expected or self-experienced stigma in the ARMS individuals or if the knowledge about the ARMS state is rather experienced as helpful.

Methods: Eight qualitative semi-structured interviews were conducted with ARMS individuals currently in the follow-up of the prospective Basel Früherkennung von Psychosen (FePsy; English: Early Detection of Psychosis) study. The interview covered the subjective perspective of ARMS individuals regarding self-perceived symptoms, first contact with the psychosis early detection centre, being confronted with having a risk status and received treatment. The qualitative data was analysed using the Interpretative Phenomenological Analysis.

Results: Analysis of the interviews showed that the majority of ARMS individuals knew when they first experienced symptoms that there was "something wrong or weird with them" and felt in need of help. They

stated that they wanted to be informed about their risk status and that it was helpful to assign a name to their symptoms. Nevertheless, the risk status also raised questions, insecurities and fear. Several of the individuals interviewed had previously been afraid to seek help because they did not want to have contact to a psychiatric clinic. The positive aspects of the treatment in the early detection clinic they saw were manifold and differed largely from individual to individual. Overall, the ARMS individuals felt supported by the staff at the early detection clinic. Most of the individuals interviewed only told their inner social circle of family and close friends about their visits to the psychosis early detection centre and their risk status because they were afraid of discrimination and stigma. If they talked about their therapy and their risk status they mostly experienced support and sympathy.

Discussion: Our results are in accordance with another qualitative study that also found that ARMS individuals wanted to know about their risk status and were glad there was a name for it. They also found that ARMS individuals mostly kept their risk status a secret because they were afraid of discrimination and stigma, but that they experienced understanding, help and support, once they told someone. Moreover, in our study we detected some new aspects concerning affected individuals' understanding of the risk status and their view of helpful aspects of treatment.

Poster #M223 A FOLLOW-UP OF FUNCTIONING IN AT-RISK MENTAL STATE

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Background: Most research with the at-risk mental state (ARMS) population has focused on transition to psychosis, with a few studies on symptomatic remission. As the change in functioning over time is more strongly related to transition than baseline functioning regardless of the level of baseline functioning, functioning as an outcome and its associated factors should be investigated, especially of those who do not transit to psychosis. It has been shown that some individuals who no longer fulfill criteria for ARMS after 2 years still reported difficulties in social and role functioning. This study aims to examine i) the functional outcome at 1 year of individuals with ARMS under the Support for Wellness Achievement Programme (SWAP), a service for this population in Singapore ii) the baseline socio-demographic and clinical factors associated with functional outcome. This would help the service to identify areas that intervention should target for better functional outcome.

Methods: SWAP accepts individuals who have met criteria, according to the Comprehensive Assessment of At-Risk Mental State, for i) family history of psychosis in first degree relative or the individual has schizotypal personality disorder, ii) psychotic symptoms of subthreshold frequency or intensity, iii) frank psychotic episode that resolved spontaneously within a week. They also must have experienced a 30% decline in functioning or score of ≤ 50 in the past year as measured on the Socio-Occupational Functional Assessment scale (SOFAS) or expressed distress despite no significant decline in functioning. Data is routinely collected at baseline and 1 year using a semi-structured questionnaire on socio-demographic information, Structured Clinical Interviews for DSM-IV, Positive and Negative Syndrome Scale and SOFAS. Data for individuals who have presented to SWAP from 2008 to 2012 and did not transit to psychosis while on follow-up were included for the study. The criterion for good functional outcome at 1 year was defined as scoring above the median of the SOFAS. Descriptive statistics for baseline variables and binary logistic regression were computed to explore predictors of good functional outcome.

Results: Of the 175 individuals, 2 were lost to follow-up and 7 were transferred out of the programme due to reasons such as seeking treatment at other services. There were a further 58 individuals with missing data on the SOFAS at 1 year. The sample (N=108) consisted of 71 males (65.7%) and 37 females (34.3%) of ethnic composition comparable to the Singapore population with mean age of 21 years (SD=3.6, Range=15–31), mostly single (N=103, 95.4%), with secondary school level education or higher (N=98, 90.7%) and in age-appropriate employment (N=103, 95.4%). Seventy-nine (73.1%) had a comorbid Axis-I disorder and the mean total PANSS score was 48.3 (N=101, SD=11.8, Range=30–91) and baseline SOFAS

was 52.9 (N=96, SD=9.8, Range=30–80). Median SOFAS score of the sample at 1 year was 60. Fifty-eight (53.7%) scored above 60, meeting criteria for good functional outcome. Logistic regression showed that Malay (OR 0.005, p=0.004; as compared to Chinese) and smokers (OR 0.093, p=0.039) were less likely to have good functional outcome. Better functioning at baseline was associated with good functional outcome (OR 1.135, p=0.018).

Discussion: Our study provides preliminary results of the functional outcome after 1 year follow-up of individuals with ARMS and the associated baseline factors. However, the study was limited by the small sample size due to missing data, not accounting for the duration of untreated illness, and the effects of intervention these individuals received. Future research should involve a larger sample and additional measures of functioning across time.

Poster #M224 DURATION OF ANTIPSYCHOTIC MEDICATION TREATMENT IS A MODIFIER FOR WEIGHT GAIN

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Background: Previously, it has been shown that antipsychotics (AP) induce weight gain and longer duration of use (around 52 weeks) has been associated with a higher proportion of clinically relevant (>7%) weight gain [1] and more increase in BMI in AP naïve patients [2]. However, previous meta-analyses did not include duration of AP use.

Methods: Outcomes in our meta-analysis included changes in body weight, BMI and 7% body weight gain or loss. Duration of AP-use was stratified as follows: ≤ 6 weeks, 6–16 weeks, 16–38 weeks and >38 weeks. Forest plots stratified by AP as well as by duration of use were generated and meta-regression analysis was performed.

Results: 305 articles met inclusion criteria. Almost all AP showed weight gain after prolonged use, except for amisulpiride, aripiprazole and ziprasidone, for which prolonged exposure resulted in negligible weight change. AP-naïves had more weight gain for all AP on all outcomes. Meta-regression showed that duration of AP use is an important factor in weight change.

Discussion: Given prolonged exposure, virtually all AP are associated with weight gain. The rationale of switching AP to achieve weight reduction may be overrated. In AP-naïve patients, weight gain is more pronounced.

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Poster #M225 AMISULPIRIDE FOR ELDERLY PATIENTS WITH CHRONIC SCHIZOPHRENIA

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Background: A large and growing number of older people across the world suffer from schizophrenia. Recommendations for their treatment are largely based on data extrapolated from studies of the use of antipsychotic medications in younger populations. The present study was designed to evaluate the efficacy and safety of Amisulpiride monotherapy in a diagnostically homogeneous group of elderly patients without cognitive impairment suffering from schizophrenia (DSM-IV-TR criteria for schizophrenia). Mortality and re-hospitalization over a 5 years period were the pre-defined outcome measures.

Methods: A retrospective analysis of computerized medical charts of elderly (60 years and older) inpatients suffering from schizophrenia treated at our center during the period January 2007–December 2012 was undertaken. The Abarbanel Mental Health Center is a university-affiliated tertiary care center servicing the urban catchment area of the greater Tel-Aviv with approximately 900,000 persons. Elderly inpatients suffering from schizophrenia (DSM-IV criteria) that were treated at our center during the study period were included in the study according to the following

criteria: (1) 60 years and older, (2) patients who had been unsuccessfully treated with at least two different antipsychotic compounds during the last 5 years prior to the study period. This study was approved by the local internal review board (IRB).

Results: Of 527 elderly patients suffering from schizophrenia over a 5 years period (2007–2012) 30 patients, mean age 65.2±5.8 years, were treated with Amisulpiride monotherapy. There were 19 women and 11 men in the analysed group. Mean duration of disease was 34.4 years. All had been exposed to at least 3 first and second generation antipsychotics prior to Amisulpiride treatment. Amisulpiride was very well tolerated by the patients and mortality rate (10% vs 19%) was significantly lower than that of other first and second generation antipsychotics ($p<0.02$). Re-hospitalization rates with Amisulpiride were numerically lower than those with other second generation antipsychotics – not reaching statistical significance.

Discussion: Our preliminary results demonstrate that Amisulpiride is efficacious and safe atypical antipsychotic for the treatment of elderly schizophrenia patients. However, the sample size was too low to reveal potential confounders. Amisulpiride thus appears to be suitable for the treatment of schizophrenia in the elderly

Poster #M226 COMPLIANCE TO MEDICAMENT ALGORITHM FOR FIRST-EPIISODE PSYCHOSES; EXPERIENCES FROM TIPS-2 PROJECT

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Background: This is a prospective study which examines the medicament treatment given to patients with first-episode psychosis (FEP) in TIPS-2 project. Was the algorithm followed for patients who didn't remit during the first year?

Methods: Our study included all the patients (N=249) with FEP in the period January 1, 2002, through September 30, 2010. At one-year follow-up (N=198), we selected the patients who had then been continuously psychotic and examined whether the medicament algorithm was followed or not. The algorithm described 3 drug alternatives where clozapine was the third one. One of the authors (PD) read through the patient files and test reports (SCID and PANSS) to quality test that the patients had not gone in remission or relapse during the first year after inclusion, document the medicament treatment in detail and check whether use of clozapine was indicated. In addition it was performed a digital search in all the patients' medical journals in the hospital's data system, with index "clozapine" and "Leponex". Unclear cases were discussed with the co-authors. The diagnoses which were considered to qualify for use of clozapine were paranoid schizophrenia, schizoaffective disorder and paranoid psychosis. Affective disorders, psychoses NOS and substance induced psychoses were excluded.

Results: At one-year follow-up, there were 198 patients (79, 5% of those included) who were reassessed. 51 patients didn't show up at one-year control, one of them had died meanwhile. Out of the 198 patients who met at one-year control, there were 78 who didn't remit during the first year. 45 of them had a diagnosis that qualified for treatment with clozapine. Of these patients, only one was offered and given Leponex (2, 22%).

Discussion: The therapists of FEP patients who didn't remit during the first year, didn't follow the evidence-based algorithm for the medicament treatment. We will discuss the consequences of this and the possible reasons for the recommended guidelines not to be followed.

Poster #M227 SAFETY AND TOLERABILITY OF CARIPRAZINE IN THE LONG-TERM TREATMENT OF SCHIZOPHRENIA

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Background: Schizophrenia is a chronic and disabling disorder that results in high levels of morbidity, mortality, and functional impairment. Atypical antipsychotics are considered first-line medications for schizophrenia and

most patients require long-term treatment. However, discontinuation of therapy due to tolerability issues is common and rates of long-term adherence are low. Cariprazine is an orally active, potent dopamine D3-preferring D2 and D3 receptor partial agonist that is in late-stage clinical development for the treatment of schizophrenia and bipolar mania. The efficacy and safety of cariprazine was established in 3 phase II/III trials in patients with acute exacerbation of schizophrenia. The current study (NCT01104792) assesses the long-term safety and tolerability profile of cariprazine in patients with schizophrenia.

Methods: A multicenter, open-label, flexible-dose, 53-week study of cariprazine 3–9 mg/day in adult patients with schizophrenia. Eligible patients comprised both new patients and patients who completed double-blind treatment in 1 of 2 lead-in studies (NCT01104766 or NCT01104779). An up to 1-week no-drug screening period was followed by 48 weeks of open-label cariprazine treatment and a 4-week follow-up period. Safety evaluations included adverse events (AEs), vital signs, laboratory measures, ECG, ophthalmologic examinations, the Columbia-Suicide Severity Rating Scale (C-SSRS), and assessments on the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), and the Simpson-Angus (SAS). Schizophrenia symptom severity and global illness was assessed using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impressions-Severity (CGI-S) scale, respectively.

Results: Of 586 patients in the safety population, 226 (38.6%) completed the study. Treatment-emergent adverse events (TEAEs) were reported by 81.2% of patients; most were considered mild or moderate in intensity. The most frequently reported TEAEs were akathisia, headache, insomnia, and weight increased. Serious adverse events (SAEs) were reported in 59 patients (10.1%) during open-label treatment; 73 patients (12.5%) discontinued due to AEs. Worsening of schizophrenia or psychotic disorder were the most common SAE/AEs leading to discontinuation. Mean changes in clinical laboratory values, and ECG parameters were generally small and not clinically meaningful. No patient met Hy's Law criteria. Prolactin levels decreased from baseline to end of study. Mean change in body weight from baseline to end of study was small (+1.53 kg); 26% of patients had ≥7% increase in body weight and 11% of patients had ≥7% decrease in body weight. Mean changes from baseline for glucose, triglycerides, HDL, LDL, and total cholesterol were generally small and not clinically relevant. For blood pressure and pulse rate, mean changes from baseline to the end of study were small; 20.5% of patients met criteria for orthostatic hypotension with no report of syncope. One patient had a postbaseline QTcF value >500 msec. Incidences of treatment-emergent parkinsonism (SAS>3) and akathisia (BARS > 2) were 11.1% and 17.8% respectively. Suicidal ideation was recorded for 2.8% of patients and there were no patients who recorded suicidal behavior on the C-SSRS during the treatment period. Ophthalmologic testing revealed no significant changes. Mean PANSS total and CGI-S scores decreased during the study.

Discussion: Cariprazine 3–9 mg/day administered for up to 48 weeks was generally safe and well tolerated, with relatively few new AEs associated with long-term administration compared with acute treatment.

Poster #M228 FLEXIBLY DOSED PALIPERIDONE PALMITATE IN NON-ACUTE PATIENTS WITH SCHIZOPHRENIA SWITCHED FROM PREVIOUSLY UNSUCCESSFUL MONOTHERAPY WITH ORAL ATYPICAL ANTIPSYCHOTICS

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Background: To explore tolerability, safety and treatment response of flexibly dosed paliperidone palmitate (PP) in adult non-acute schizophrenia patients previously unsuccessfully treated with oral antipsychotic monotherapy with either risperidone (RIS), paliperidone ER (Pali ER), olanzapine (OLA), quetiapine (QUE) or aripiprazole (ARI).

Methods: International, prospective 6-month open-label study. Outcomes were response (≥20% improvement in Positive and Negative Syndrome

Scale (PANSS) total score), Personal and Social Performance scale (PSP), treatment-emergent adverse events (TEAEs) and Extrapyramidal Symptom Rating Scale (ESRS), weight change at endpoint.

Results: Intent-to-treat population: n=191 (RIS), n=104 (Pali ER), n=87 (OLA), n=44 (QUE), n=46 (ARI). Patients presented some differences in baseline demographics, e.g. in age, years since diagnosis and BMI. Patient's wish was most frequent reason for switching to PP from oral RIS, Pali ER and ARI, patient's wish and lack of efficacy for OLA, lack of compliance and lack of efficacy for QUE. Baseline mean PANSS total scores ranged from 74.7±14.9 (ARI) to 70.8±13.1 (QUE) and 70.8±15.1 (RIS). Between 67.4% (ARI) and 83.2% (RIS) of patients completed the study. At endpoint, 74% (RIS), 58% (Pali ER), 61% (OLA), 66% (QUE) and 52% (ARI) of patients improved ≥20% in PANSS total score. Mean PSP improvement at endpoint was: 10.4±13.8 (RIS), 7.0±13.8 (Pali ER), 4.5±15.9 (OLA), 7.9±12.4 (QUE) and 3.9±13.2 (ARI); all p<0.05. TEAEs reported at least once in all subgroups were injection site pain, insomnia and psychotic disorder. Mean change in ESRS from baseline to endpoint was -1.1±3.4 (RIS), -0.8±(Pali ER), -1.2±4.2 (OLA), -0.3±3.0 (QUE) and -0.6±3.4 (ARI; p<0.05 for all except QUE). Mean weight change from baseline to endpoint was ranged between -0.3±4.6 (OLA) and 3.5±6.3 kg (ARI).

Discussion: PP was well tolerated and associated with clinically relevant treatment response in patients previously unsuccessfully treated with oral atypical antipsychotic monotherapy, regardless of the medication that was switched.

Poster #M229

EFFICACY AND RELEVANCE OF THE MODULATION OF KV3 CHANNELS TO ALLEVIATE COGNITIVE DYSFUNCTION IN AN ANIMAL MODEL OF SCHIZOPHRENIA SYMPTOMATOLOGY

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Background: Cognitive dysfunction remains a major clinical unmet need for patients with schizophrenia, leading to the disorder being dubbed the "forgotten illness" [1]. Development of improved medications that treat cognitive symptoms is therefore of great importance. Cognitive dysfunction had been linked to specific deficits in corticolimbic circuits that have been observed in post-mortem brains of patients with schizophrenia, with attention focused on the role parvalbumin (PV)-positive GABAergic interneurons in these circuits [2]. The potassium voltage gated ion channel (Kv3) is a key component of PV interneurons, allowing them to fire at high frequency in order to synchronise local neural activity. Evidence linking Kv3 channels with schizophrenia suggests that positive modulation of the channels may help to normalise the function of PV interneurons and thus may have the potential to treat cognitive symptoms of schizophrenia [3]. Our aim was therefore to explore the efficacy of two novel and selective Kv3.1 channel modulators, AUT6 and AUT9, in our carefully validated animal model of cognitive impairment in schizophrenia, sub-chronic PCP treatment in rats [4]. To better understand the neurobiological mechanisms underlying the PCP effects, we also examined the influence of PCP treatment on the expression of Kv3.1 channels in the prefrontal cortex (PFC) and hippocampus.

Methods: 70 adult female hooded-Lister rats were used for these studies. The first cohort (n=60) were trained to criterion in our reversal learning (RL) task and then received vehicle (n=10) or sub-chronic PCP (n=50, 2 mg/kg) i.p. twice daily for 7 days, followed by 7 days washout. PCP-treated rats received risperidone at 0.1 mg/kg, i.p.; AUT6 at 30-60 mg/kg, i.p. or AUT9 at 10-60 mg/kg, i.p. and were tested 30 min later in the RL task. Brains of a second cohort of vehicle and PCP-treated rats (n=5 per group) were removed to determine i) the co-localisation of PV and KV3.1 channels in the PFC and hippocampus and ii) the effects of PCP on Kv3.1 channel expression in the PFC and hippocampus using immunofluorescent and immunohistochemical techniques. Data were analysed using a one-way ANOVA followed by post-hoc LSD t-test and paired or unpaired t-tests.

Results: Sub-chronic PCP produced a significant and selective deficit in the reversal phase of the RL task (P<0.001 vs. vehicle). This deficit was significantly attenuated by AUT6 (P<0.001 vs. PCP) and AUT9 (P<0.05-0.001 vs. PCP) at all doses tested as well as by risperidone (P<0.001 vs.

PCP). Immunofluorescent studies demonstrated that KV3.1 channels are located on parvalbumin-containing interneurons (co-localisation of ~80%) in both the PFC and hippocampus of the rat brain. Furthermore we found a significant reduction in the number of Kv3.1-positive cells in the PFC (~60%, P<0.05), but no significant changes were found in the hippocampus (~20%, P>0.05) of PCP treated rats.

Discussion: These data demonstrate the efficacy of two novel Kv3.1 channel modulators in the PCP model of cognitive deficits of schizophrenia. Efficacy of AUT6 and AUT9 was also consistent with the observed reduction in Kv3.1 expression in the cortex of PCP-treated rats. These data suggest that modulation of Kv3 channels could be an important novel approach to the treatment of schizophrenia.

Poster #M230

QTC PROLONGATION IN CHILDREN AND ADOLESCENTS IN SECOND-GENERATION ANTIPSYCHOTICS TREATMENT: A REVIEW

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Background: Prolongation of the QTc interval is a known side effect of antipsychotics. QTc prolongation is associated with an increased risk of Torsade de Pointes, a condition which can be fatal and requires immediate treatment. The incidence of QTc prolongation varies between different drug classes and has been extensively examined in adult populations, but in safety studies of children and adolescents, ECG assessments are often omitted. The purpose of this study is to review the published data relating to QTc change and prolongation during antipsychotic treatment in children and adolescents.

Methods: A Pubmed search was conducted on September 23rd, 2013, using the following search terms: (child OR children OR childhood OR adolescent OR adolescence) AND (antipsychotic* OR neuroleptic* OR risperidone OR olanzapine OR aripiprazole OR quetiapine OR perospirone OR ziprasidone OR clozapine OR amisulpride OR asenapine OR blonanserin OR clothiapine OR iloperidone OR lurasidone OR mosapramine OR paliperidone OR remoxipride OR sertindole OR sulpiride OR tiapride OR chlorpromazine OR thioridazine OR mesoridazine OR loxapine OR molindone OR perphenazine OR thiothixene OR trifluoperazine OR haloperidol OR fluphenazine OR droperidol OR zuclopentixol OR pimozide OR flupenthixol OR prochlorperazine). Eligible studies had to be prospective studies, written in English, with available abstract and ECG assessment reporting on QTc values or change in youth aged <18 years old exposed to antipsychotic treatment.

Results: The preliminary electronic search yielded 11667 articles. After filtering for English language and available abstract, 7484 articles were reviewed on title and abstract level, resulting in N=977 potentially eligible studies. Preliminary analyses suggest that across a total of 61 studies reporting on QTc changes or prolongation in patients aged <18, during treatment with second-generation antipsychotics, only 22 studies (36.1%) reported quantitative results, as opposed to noting "no significant ECG or QTc changes". The available data show that treatment with ziprasidone (studies=7) increases the risk of QTc prolongation, while aripiprazole, olanzapine and risperidone seem to be safe. QTc prolongation was not seen with quetiapine in children, but has been demonstrated in adult studies. Data for clozapine and other SGAs were missing. Full data from studies with published QTc data or data retrieved from the authors will be presented at the SIRS meeting.

Discussion: Preliminary analyses suggest that only few studies examined the QTc prolongation effects of antipsychotics in psychiatric patients below 18 years of age. While randomized trial data in adults suggest that, with the exception of thioridazine and, possibly, sertindole, orally ingested antipsychotics are safe regarding QTc changes in most adult populations, extension of these results to high-risk individuals and youth populations is less clear. Based on the analyses of the full data set, we will discuss whether children and adolescents can be treated safely with antipsychotics from a cardiac/QTc prolongation point of view.

Poster #M231**TWO NOVEL KV3 ION CHANNEL MODULATORS ALLEVIATE COGNITIVE DYSFUNCTION AND SOCIAL BEHAVIOUR DEFICITS OF RELEVANCE TO SCHIZOPHRENIA IN AN ANIMAL MODEL**

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Background: Cognitive dysfunction and negative symptoms remain a major clinical unmet need in schizophrenia [1]. Development of improved medication is therefore of great importance. Cognitive dysfunction has been linked to dysfunction in corticolimbic circuitry with attention focused on parvalbumin (PV)-positive GABAergic interneurons. The voltage gated ion channel Kv3.1 is a key component of PV interneurons, allowing them to fire at high frequency in order to synchronise local neuronal activity. Evidence linking Kv3 channels with schizophrenia [2] suggests that positive modulation of the channels may help to normalise the function of PV interneurons and thus may have the potential to improve symptoms of schizophrenia. Our aim was to explore the efficacy of two novel and selective Kv3 channel modulators, AUT6 and AUT9, in our carefully validated animal model of cognitive and social behaviour deficits in schizophrenia, sub-chronic PCP treatment in rats [3]. The working hypothesis is that acute treatment with Kv3 channel modulators will attenuate the selective deficits induced by sub-chronic PCP, in a manner comparable to risperidone, as measured in the novel object recognition (NOR) and social interaction (SI) tests.

Methods: 240 adult female hooded-Lister rats received sub-chronic phenylcyclidine, n=160 (PCP) (2 mg/kg) or vehicle, n=80 i.p. twice daily for 7 days, followed by 7 days washout. PCP-treated rats then received risperidone at 0.1 mg/kg, i.p.; AUT6 at 10-60 mg/kg, i.p. or AUT9 at 10-60 mg/kg, i.p. and were tested 30 min later, either in NOR or in SI. Data were analysed using a one-way ANOVA followed by post-hoc LSD t-test and paired or unpaired t-tests.

Results: In the NOR task, vehicle treated rats showed a significant preference for the novel over the familiar object during the retention trial ($P<0.001$), an effect that was abolished in PCP-treated rats ($P>0.05$). AUT6 ($P<0.05-0.001$) and AUT9 ($P<0.05-0.001$) at all doses significantly restored recognition memory in the task, as did risperidone ($P<0.05-0.01$). In SI, sub-chronic treatment with PCP induced a significant reduction in sniffing behaviour ($P<0.01$) and a significant increase in avoidance behaviour ($P<0.001$) compared to the vehicle group. In this test, the positive control risperidone significantly attenuated both PCP-induced deficits ($P<0.05$ and $P<0.001$, respectively). AUT6 significantly attenuated the reduction in sniffing behaviour ($P<0.01$ at 10 mg/kg; $P<0.05$ at 30 mg/kg and 60 mg/kg) as well as the increase in avoidance behaviour ($P<0.001$ at all doses tested) induced by PCP. Similarly, AUT9 significantly restored the PCP-induced reduction in sniffing behaviour ($P<0.01$ at 10 mg/kg; $P<0.05$ at 30 mg/kg and 60 mg/kg) and in avoidance behaviour ($P<0.001$ at all three doses).

Discussion: These data demonstrate the efficacy of two novel Kv3 channel modulators in two symptom domains (visual recognition memory for cognition and social behaviour for an aspect of negative symptoms) in the PCP model. Efficacy was comparable to low dose risperidone. These data suggest that modulation of Kv3 channels could be an important novel approach to the treatment of schizophrenia and that Kv3 channel modulation could improve several symptom domains in schizophrenia.

References:

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Poster #M232**NEUROPLASTIC ALTERATIONS IN RATS EXPOSED TO PRENATAL STRESS: PREVENTIVE EFFECT OF LURASIDONE TREATMENT DURING ADOLESCENCE**

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Background: Environmental factors, which might occur as early as during in utero life, exert profound influences on the structural and functional development of individuals, giving rise to changes that can persist throughout life. Indeed, a growing body of evidence suggests that early life adversities are implicated in early programming of adult psychiatric diseases, which are characterized by a deterioration of neuronal plasticity, an array of mechanisms that may contribute to structural modifications and to powerlessness to adapt or respond to environmental changes. With this respect, animal models are very useful to characterize the molecular and functional mechanisms that may be persistently affected after exposure to early-life stressors (ELS).

Methods: We used a model of prenatal stress in rats consisting in repetitive immobilization stress three times a day for 45 minutes from E14 until delivery. We carried out all the subsequent analysis in the offspring, both in males and females, at different time points: immediately after birth (PND1), during infant life (PND7), at weaning (PND21), during adolescence (PND40) and in the early adulthood (PND62), in order to create a time-profile of the changes under investigation. Since we found that the majority of alterations became fully manifest at early adulthood, we tried to prevent these abnormalities with an early pharmacological intervention. To address this point, we treated rats during adolescence with the multi-receptor antipsychotic lurasidone, which was proven to be effective in animal models of schizophrenia.

Results: We found that exposure to ELS results in adult impairment of neuroplasticity and reduced expression of Bdnf that develops post-puberty, with major changes occurring on long 3'-UTR Bdnf mRNA levels, the pool of neurotrophin transcripts that undergoes dendritic targeting. Moreover, ELS rats displayed an altered responsiveness of Bdnf when exposed to an acute stress at adulthood, which is suggestive of impaired coping ability under challenging conditions. Moreover, we found that sub-chronic lurasidone administration during adolescence increased the expression of the long 3'-UTR Bdnf at 24 h and, more importantly, it was able to prevent the reduction of long 3'-UTR Bdnf mRNA levels occurring at adulthood in rats that were exposed to ELS.

Discussion: Collectively, our results provide further support to the notion that exposure to early life stress has a negative impact on neuronal plasticity and that preventive pharmacological intervention during critical time windows may prove effective in preventing neuroplastic dysfunctions. The ability of lurasidone to normalize defects associated with environmental animal models of stress-related disorders may ameliorate functional capacities closely associated with alteration in neuronal plasticity, a core feature common to several psychiatric conditions.

Poster #M233**A RATER-BLINDED, RANDOMIZED, COMPARATIVE STUDY OF ARIPIPRAZOLE VERSUS BLOANSERIN IN JAPANESE PATIENTS WITH SCHIZOPHRENIA**

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Background: Several meta-analyses showed that blonanserin and aripiprazole were an efficacious treatment for the positive and negative symptoms of schizophrenia and had also been well tolerated. However, there is no study that compares the efficacy and the safety of blonanserin with aripiprazole.

Methods: A rater-blinded, randomized, comparative study has carried out to compare the efficacy and safety of blonanserin and aripiprazole in the antipsychotic-free DSM-IV-TR schizophrenic patients including the first episode patients for the 8-week study. Subjects were randomized in a 1:1

ratio to flexible-dose oral blonanserin (4-24 mg/day) or aripiprazole (6-30 mg/day). Primary end-point was change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score. Safety assessments included adverse events, vital signs, laboratory measures, electrocardiograms, weight and body mass index, and movement disorder ratings. All patients who received at least 1 dose of study medication and had at least 1 efficacy assessment were included in the intent to treat analysis. The PANSS total scores were assessed using a last observation carried forward analysis to account for missing values.

Results: In the RCT, 22 subjects were treated with blonanserin or aripiprazole. Although the two study antipsychotics produced significant improvements from baseline in PANSS total scores, there was also no significant difference between the two treatment groups. The two study drugs also demonstrated good safety profiles.

Discussion: The evidence suggests that blonanserin and aripiprazole has a beneficial effect on the psychopathology of schizophrenia.

Poster #M234

KETAMINE AS A MODEL FOR SCHIZOPHRENIA DEFICITS

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Background: The purpose of this investigation was to determine whether specific schizophrenia deficits could be mimicked in healthy participants under the influence of ketamine. We sought to replicate three significant findings in schizophrenia. The first was the indirect semantic hyper-priming finding. This is an unusual result which has been verified by both meta-analysis (Pomarol-Clotet, Oh, Laws, & McKenna, 2008) and review (Rossell & Stefanovic, 2007). The second was to replicate the impairment in configural face processing reported in schizophrenia (Butler et al., 2008; Shin et al., 2008). Finally, the finding that schizophrenia is associated with deficient global, but intact local processing (dissociation effect), (Chen, Nakayama, Levy, Matthesse, & Holzman, 2003; Johnson, Lowery, Kohler, & Turetsky, 2005) was investigated under the influence of ketamine.

Methods: This was a placebo-controlled double-blind cross over study. Nineteen healthy individuals aged between 18-35 with no personal or family history of psychosis and no drug use or neurological issues were included. In the placebo condition, participants were given saline and in the ketamine condition, a bolus of 0.12mg/kg was administered to rapidly raise the level of ketamine in the blood followed by a steady infusion of 0.8mg/kg/hour of ketamine over an 80-minute period.

Results: Significant Indirect reaction time (RT) priming (unrelated RT-related RT) was exhibited after ketamine administration (23.32 ± 42.42 ; $t(19)=2.40$, $p=0.02$) but not in the placebo condition (20.36 ± 62.04 ; $t(19)=2.46$, $p=0.16$) supporting the schizophrenia hyper-priming literature. In terms of configural face processing, results showed that there was no difference in RT to the same (1819.52 ± 277.36) versus different faces (1680.34 ± 248.58) under the influence of ketamine ($t(15)=1.87$, $p=0.08$) but there was for the placebo condition ($t(18)=-3.39$, $p<0.01$) with a faster RT to different (1647.34 ± 244.01) versus the same face (1647.34 ± 244.01). Further, under ketamine, there was no difference in RT to upright (1716.96 ± 213.07) versus inverted faces (1782.91 ± 255.61 ; $t(13)=-1.68$, $p=0.12$) whilst placebo was associated with a significant inversion effect with participants demonstrating a faster RT to upright (1789.92 ± 331.07) versus inverted faces (1939.43 ± 349.58 ; $t(15)=-3.15$, $p=0.01$). The global/local data showed that whilst in both conditions, participants demonstrated intact local processing, there was no difference in accuracy to globally congruent ($97.01 \pm 2.63\%$) versus incongruent stimuli ($95.70 \pm 3.69\%$; $t(15)=-1.43$, $p=0.17$) under ketamine. In the placebo condition however, participants were more accurate to congruent ($98.57 \pm 2.11\%$) than incongruent global stimuli ($93.62 \pm 6.70\%$; $t(15)=-2.73$, $p=0.02$).

Discussion: The pattern of responses matches the findings in the schizophrenia literature across all three tasks. One interesting finding on the faces task was that in the placebo condition, participants responded faster to "different" versus "same" face pairs. While studies often find a faster RT to "same" versus "different" faces (Butler, et al. 2008; Shin, et al. 2008) there are differences in methodology between the current and previous research. Specifically, previous studies spaced facial features by some

4 to 5 pixels, whilst spacing was 2 pixels in the current study. This more subtle task may have shifted the pattern of responding so that participants needed to spend more time trying to determine if there were differences in "same" pairs rather than quickly responding to obviously "same" pairs and focusing on those that appeared different. Overall, the results support the use of ketamine as a model for schizophrenia.

Poster #M235

THE EFFECT OF BLOOD PLASMA CLOZAPINE LEVELS ON SPECIFIC MEASURES OF BEHAVIOR IN CHILDHOOD ONSET SCHIZOPHRENIA

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Background: Schizophrenia affects approximately 1% of the world's population. Childhood onset schizophrenia (COS) affects roughly 1 in 2,500 children younger than age 15 and is associated with a worse prognosis, more severe symptoms, and less pharmacological efficacy than seen in the treatment of adult onset schizophrenia. Clozapine has superior efficacy in treatment-resistant and non treatment-resistant schizophrenia, and has been shown to reduce the risk of recurrent suicidal behavior in patients with schizophrenia. Previous studies demonstrate that among adult patients, clozapine blood levels greater than 300 ± 50 ng/mL improve specific outcome measures when compared to blood levels less than 300 ± 50 ng/mL.

Methods: Since 1991, patients meeting DSM-IV criteria for schizophrenia with an onset of psychosis before age 13 have been recruited nationally for participation in a longitudinal study of individuals with Childhood-Onset Schizophrenia conducted at the National Institute of Mental Health. We conducted a chart review of patients admitted to this protocol from September 2004 to September 2013. Clozapine blood level data was compared to demographic data, research rating data and clinical data obtained from the study. Specific rating scales evaluated include Childhood Global Assessment Scale (CGAS), Brief Psychiatric Rating Scale for Children (BPRS-C), and Scale for the Assessment of Negative Symptoms (SANS).

Results: 42 total subjects (20 males, 22 females) were included in the study. 15 subjects had the full compliment of data available (i.e. all of the measures were obtained at baseline and several were taken while on clozapine). 27 subjects did not have a full compliment of baseline data. Patients either improved or did not worsen on all behavioral measures when on clozapine compared to their baseline scores. Clozapine had a significant effect on improving scores on the CGAS, SANS, BPRS-C, SANS item 8 (Global Rating of Affective Flattening), and SANS item 25 (Global Rating of Attention) ($p<0.001$). There was no clinically significant correlation between blood plasma clozapine level and improved score on any measure used. No difference was found between groups with respect to age, weight, and gender at baseline. There was a positive correlation between clozapine blood levels/dose and weight among females ($r=0.155$, $p=0.491$). There was a negative correlation between blood plasma clozapine level/dose and weight among males ($r=-0.163$, $p=0.505$). There was no correlation between blood plasma clozapine level/dose and age among females ($r<0.1$). There was a negative correlation between blood plasma clozapine level/dose and age among males ($r=-0.190$, $p=0.422$).

Discussion: Clozapine significantly improves the symptoms of schizophrenia among children with COS. We found no correlation between blood plasma clozapine level and improved scores on specific rating scales, which is consistent with previous findings of other studies. There was a trend toward significance when evaluating the difference in weight between males and females with respect to clozapine blood level at a given dose. This difference may have reached significance with a larger sample size. Limitations of this study include a small sample size, retrospective design leading to lack of controlled dosing, steady state blood draws that differed from 1-7 days pre/post max dose, dose targeting of clinical symptoms rather than an a priori dosing regimen, only a selected number of available behavioral measures used, and the potential effect of concomitant medications that could have had an effect on clozapine metabolism was not addressed.

Poster #M236**THE POTENTIAL BENEFICIAL EFFECTS OF CELECOXIB OR OMEGA-3 AS ADJUVANT THERAPY IN SCHIZOPHRENIA INDUCED IN EXPERIMENTAL ANIMALS**

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Background: schizophrenia is one of the most complex psychotic illnesses. Inflammation or immune imbalance between type I and type II immune responses takes place in schizophrenia. Nuclear factor-kappa B (NF-κB), a prototypic transcription factor and cyclo-oxygenase -2 (COX-2), which is an enzyme involved in the immune responses were found to be activated by various cytokines such as interlukin-1 beta (IL-1β), TNF-α, IL-6 and IL-10. The high levels of these cytokines in the CNS compartment is accompanied by increased NF-κB and COX-2 expressions which in turn triggers more inflammatory responses.

Methods: In this study, we aimed to investigate the possible mechanisms that may be involved in schizophrenia. We also studied the possible protective effect of the antioxidant alpha omega-3 fatty acid or the anti-inflammatory celecoxib in schizophrenia induced in rats. This was achieved by measuring brain tissue contents of dopamine, serotonin, IL-6, TNF-α, malodialdehyde and nitric oxide. Also, Expression of NF-κB and COX-2 in brain tissues were performed. White albino male rats of 150-200 gm were categorized into 8 groups. Group I received control vehicle, Group II were injected with amphetamine (2.5 mg/kg, s.c.), Group III were injected with vehicle (1ml/kg) 20 min before amphetamine, Group IV were injected with risperidone (0.1mg/kg, i.p.) 20 min before amphetamine, Group V were injected with celecoxib (5 mg/kg,i.p.) 20 minutes before amphetamine, Group VI received omega-3 FA (0.1 gm, p.o.) 20 minutes before amphetamine, Group VII were injected with a combination of risperidone and celecoxib 20 minutes before amphetamine and Group VIII were injected with a combination of risperidone and omega -3 FA. All drugs were given every other day for a total of five doses

Results: Amphetamine caused significant increase in all assessed parameters while pre-treatment with omega 3 -FA or celecoxib caused significant reduction in all assessed parameters.

Discussion: Schizophrenia is characterised by stimulation of immune system. This is accompanied by stimulation of the release of inflammatory cytokines such as IL-6 and TNF alpha. Also, increased expression of COX-2 and NF-κB. The use of standard treatment risperidol was not able to significantly reduce these parameters. The use of an antiinflammatory drug such as celecoxib or an antioxidant omega -3 fatty acid as addjuvant therapy with standard treatment was able to significantly reduced such parameters.

Poster #M237**HISTAMINE H2 BLOCKERS FOR SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS**

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Background: A meta-analysis of the add-on histamine H2 blockers treatment for schizophrenia has not previously been reported.

Methods: We carried out a systematic review of the literature available in PubMed, the Cochrane Library database and PsycINFO up to 3 December 2013. We conducted a systematic review and meta-analysis of individual patient data from randomized controlled trials (RCTs) comparing H2 blockers augmentation therapy with placebo. The outcome measure for efficacy was the psychopathology of schizophrenia and the measures for safety were discontinuation rate and several side effects.

Results: Seven RCTs H2 blockers augmentation studies (two studies with famotidine, four with nizatidine and one with ranitidine) were identified. There were no statistically significant effects of H2 blockers augmentation therapies on overall symptoms ($p=0.96$). All-cause discontinuation ($p=0.70$), weight change ($p=0.11$) and extrapyramidal symptoms ($p=0.46$) were similar in both groups.

Discussion: Our results suggest that 5-HT1A agonist has a more beneficial effect on MDD than placebo, but has several side-effects.

Poster #M238**EFFECT OF LURASIDONE ON COGNITIVE IMPAIRMENT: FROM THE LAB TO THE CLINIC**

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Background: Lurasidone is an atypical antipsychotic that has been approved by the FDA and other regulatory authorities for the treatment of schizophrenia and bipolar depression.

Methods: Based on the results of a Medline search, we briefly review here the published literature on the pre-clinical behavioral evidence that lurasidone may have an effect on cognitive function, and the results of the first randomized trial that evaluated the efficacy of lurasidone in a clinical population with an acute exacerbation of schizophrenia.

Results: The effects of lurasidone on aspects of cognitive function has been evaluated in a series of pre-clinical behavioral tests (Horisawa et al, 2011), including the passive-avoidance and Morris water maze tests (assessing learning and memory), radial-arm maze test (working memory), the novel object recognition test (NOR), and the object retrieval with detour task (ORD; executive function and attention). In this pre-clinical battery, lurasidone restored MK-801-induced memory impairment in the passive avoidance and Morris water maze tests, and improved working memory in the radial-arm maze test. Treatment with lurasidone also improved sub-chronic PCP- induced deficits in novel object recognition in rats, and increased the success rate of monkeys in performing an object retrieval with detour task. The potential effectiveness of lurasidone in treating cognitive deficits associated with schizophrenia has been evaluated in a recent trial (Harvey et al, 2013) in which patients with an acute exacerbation of schizophrenia were randomized to 6 weeks of double-blind, placebo-controlled treatment with lurasidone or quetiapine-XR. Upon completion of the initial 6-week study, eligible patients were enrolled in a 1-year, double-blind extension study, where patients continued treatment with either flexible-dose lurasidone 40–160 mg/d or quetiapine-XR 200–600 mg/d. A computerized cognitive battery was administered at intervals during the study. For the evaluable sample with valid CogState scores (N=267), lurasidone 160 mg was found to be significantly superior to both placebo and quetiapine XR on the neurocognitive composite score at month 6, while lurasidone 80 mg, quetiapine XR, and placebo did not differ.

Discussion: These findings provide preliminary clinical evidence that supports pre-clinical data indicating the potential of lurasidone for improving cognitive deficits in patients with psychotic illness. Assessment of the longer term effects of lurasidone on cognition needs additional clinical confirmation. Furthermore, development of improved preclinical models of cognitive impairment might be useful in prediction of relevant drug effects in humans.

Sponsored by Takeda Pharmaceuticals International, Inc., and Sunovion Pharmaceuticals Inc. (a US subsidiary of Dainippon Sumitomo Pharma, Ltd.).

References:

- [1] Horisawa T et al. The effects of selective antagonists of serotonin 5-HT7 and 5-HT1A receptors on MK-801-induced impairment of learning and memory in rats. Behav Brain Res 2011;220:83–90.
- [2] Harvey PD et al. Effect of lurasidone on neurocognitive performance in patients with schizophrenia. Eur Neuropsychopharmacol 2013;23:1373–82.

Poster #M239**EXPLORATION OF THE THERAPEUTIC POTENTIAL OF SELECTIVE TAAR1 AGONISTS IN PRECLINICAL PARADIGMS**

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Background: Dysregulation of monoaminergic neurotransmission is a hall-

mark of major neuropsychiatric disorders. The trace amine-associated receptor 1 (TAAR1) is a Galpha-s protein-coupled receptor activated by trace amines like p-tyramine and beta-phenylethylamine, endogenous compounds with structural similarity to biogenic amines.

Methods: Through a medicinal chemistry program taking advantage of the considerable overlap between the pharmacophore space occupied by TAAR1 ligands and ligands of other biogenic amine receptors, potent and selective TAAR1 ligands were identified and further optimized with respect to physicochemical and pharmacokinetic properties. In addition, Taar1 knock-out as well as Taar1 overexpressing animals were characterized.

Results: We showed that TAAR1 modulates dopaminergic, serotonergic and glutamatergic neurotransmission and thus revealed that TAAR1 activation represents a novel therapeutic option for neuropsychiatric disorders. In rodents, activation of TAAR1 by these compounds blocked psychostimulant-induced hyperactivity and reversed cocaine-induced facilitation of intra-cranial self-stimulation of the ventral tegmental area. Importantly, TAAR1 agonists did not induce the typical side-effects produced by current antipsychotic drugs such as catalepsy or weight gain in rats. TAAR1 agonism even reduced haloperidol-induced catalepsy and, remarkably, prevented olanzapine from increasing body weight and fat accumulation. Finally, TAAR1 agonists produced pro-cognitive effects as well as antidepressant-like properties in rodents and non-human primates.

Discussion: These data suggest that TAAR1 agonists may provide broad therapeutic benefits as treatments for schizophrenia.

Poster #M240

BEHAVIORAL EFFECTS OF THE NOVEL BENZODIAZEPINE POSITIVE ALLOSTERIC MODULATOR SH-053-2'F-S-CH3 IN AN IMMUNE-MEDIATED NEURODEVELOPMENTAL DISRUPTION MODEL

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Background: The central γ-aminobutyric acid (GABA) system is strongly implicated in cognitive processes. Accumulating evidence suggests that GABAergic interneurons critically regulate neuronal oscillatory activity, which in turn is believed to serve various complex functions, including perception, cognition, and memory. Moreover, GABA-mediated inhibitory networks are involved in the regulation of subcortical dopaminergic functions. Impaired GABAergic signaling may thus contribute to the emergence of cognitive deficits and subcortical dopaminergic hyperactivity in patients with schizophrenia and related psychotic disorders. It has been therefore proposed that pharmacological interventions targeting GABAergic dysfunctions may prove useful in correcting such cognitive impairments and dopaminergic imbalances. Thus, we explored possible beneficial effects of the novel benzodiazepine positive allosteric modulator SH-053-2'F-S-CH3 with selective activity at the α2, α3, and α5 subunits of the GABA_A receptor in an immune-mediated neurodevelopmental disruption model.

Methods: Pregnant C57BL6 mice received, on gestation day 17 (GD 17), a single injection of poly(I:C) (5 mg/kg, i.v.) or vehicle (saline, i.v.). A cohort of adult behaviorally naïve offspring was allocated to gene expression analysis, while another was assigned to behavioral and cognitive testing. The animals that underwent behavioral testing were treated with either SH-053-2'F-S-CH3 (15 or 30 mg/kg i.p.) or vehicle (i.p.) 20 minutes before each test.

Results: Prenatal Poly(I:C) exposure produced significant behavioral and cognitive deficits associated with changes in the mRNA levels for α subunits of the GABA_A receptor in the medial prefrontal cortex and in the ventral hippocampus of adult offspring, relative to control offspring. Systemic administration of SH-053-2'F-S-CH3 failed to normalize the poly(I:C)-induced deficits in working memory and social interaction, but instead impaired performance in these cognitive and behavioral domains both in control and poly(I:C) offspring. In contrast, SH-053-2'F-S-CH3 was highly effective in mitigating the poly(I:C)-induced amphetamine hypersensitivity phenotype without causing side effects in control offspring.

Discussion: Our preclinical data suggest that benzodiazepine-like positive allosteric modulators with activity at the α2, α3, and α5 subunits of

the GABA_A receptor may be particularly useful in correcting pathological overactivity of the dopaminergic system, but they may be ineffective in targeting multiple pathological domains that involve the co-existence of psychotic, social, and cognitive dysfunctions.

Poster #M241

DESCRIPTION OF THE IMPACTS OF CLOZAPINE USE IN AN EARLY STAGE PSYCHOSIS POPULATION

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Background: Although clozapine's superior efficacy in chronic treatment-resistant schizophrenia is well established, significant risks have constituted barriers to its earlier use in the course of treatment. However, the link observed between longer duration of untreated psychosis and poorer outcome may also suggest a harmful impact of treatment resistance. Hence, clozapine may have an especially positive impact when used earlier during illness. The aim of the present study is to describe demographic, clinical and tolerability characteristics associated with clozapine use in an early stage population.

Methods: Data for the study were obtained from the clinical database of Clinique Notre-Dame des Victoires, in Quebec City, an early intervention psychosis program. Thirty-three patients with schizophrenia spectrum psychotic disorders who were treated with clozapine and for whom this medication was initiated between the ages 18 to 35 were included. Clinical (CGI, PANSS), functional (SOFAS) and tolerability (UKU) scales were collected before and after clozapine introduction.

Results: We observed significant reductions on all of the five factors of the PANSS ($p<0.01$) and on the three subscales of the CGI ($p<0.01$). A significant increase in SOFAS score confirmed functional improvement ($p<0.01$). Furthermore, a significant improvement was observed for the UKU's psychic ($p=0.01$) and neurologic ($p<0.01$) subscales. The mean weight gain (5.2 ± 9.3 kg) was mostly observed during the first six months and a worsening of metabolic profile was observed in the first year of treatment; these tended to stabilize afterwards.

Discussion: These results suggest clinical and functional benefits in favour of early use of clozapine. Finally, side effects improved on clozapine compared to previous medication, while weight gain and metabolic perturbations, although worsened, remained relatively modest

Poster #M242

OBSESSIVE-COMPULSIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA COMPARING TREATMENT WITH CLOZAPINE, OLANZAPINE, RISPERIDONE AND NO ANTIPSYCHOTICS: A LONGITUDINAL STUDY OF 550 PATIENTS AFTER 3 YEARS OF TREATMENT

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Background: We aim to compare the prevalence of obsessive-compulsive symptoms (OCS) in a population of patients with schizophrenia using clozapine, olanzapine or risperidone or using no antipsychotic medication between baseline and at 3-year follow-up.

Methods: Baseline data of the Genetic Risk and Outcome of Psychosis study were collected between April 2005 and October 2008. 3-year follow-up data were collected between January 2008 and March 2011. We conducted a naturalistic longitudinal study of 550 patients with schizophrenia and related disorders, meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association 1994) criteria, using no antipsychotic medication, using clozapine, olanzapine or risperidone. OCS severity was measured with the Yale-Brown Obsessive Compulsive Scale. We compared data collected at baseline to data collected at 3-year follow-up.

Results: Patients using clozapine reported OCS during the last week sig-

nificantly more often (38.9%), when compared to patients using olanzapine (21.6%, $\chi^2=8.28$, $p=0.004$), risperidone (25.2%, $\chi^2=4.45$, $p=0.035$) and patients not using antipsychotics (21.4%, $\chi^2=6.59$, $p=0.010$). When patients used clozapine for more than 6 months they reported OCS significantly more often than patients using clozapine for less than 6 months, 47.3% versus 11.8% ($\chi^2=6.89$, $p=0.009$). When patients switched from any other antipsychotic to clozapine they reported OCS during the last week more often, when compared to switches to other antipsychotics.

Discussion: Treatment with clozapine in patients with schizophrenia is associated with a higher prevalence of OCS, especially when patients have been using clozapine for more than 6 months. We can not rule out the possibility that this association is related to illness characteristics. Patients treated with risperidone, olanzapine or without treatment with antipsychotic medication had comparable prevalence of OCS.

Poster #M243

PALIPERIDONE PALMITATE – IMPACT ON NEGATIVE, DISORGANIZED AND DEPRESSIVE SYMPTOMS, SUBJECTIVE WELL-BEING AND PATIENT SATISFACTION IN PATIENTS WITH SCHIZOPHRENIA PREVIOUSLY UNSUCCESSFULLY TREATED WITH ORAL ANTIPSYCHOTICS

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Background: Negative, disorganized and depressive symptoms are among the major unmet needs in the treatment of patients with schizophrenia. The objective of this analysis was to specifically explore the impact of flexibly dosed paliperidone palmitate (PP) on negative and depressive symptoms, disorganized thoughts, subjective well-being and patient satisfaction in adult non-acute but symptomatic patients with schizophrenia previously unsuccessfully treated with oral antipsychotics.

Methods: International, prospective 6-month open-label multicenter study. Outcomes analyzed here were changes from baseline to endpoint in the negative symptoms, the disorganized thoughts and anxiety/depression Marder factors of the Positive and Negative Syndrome Scale (PANSS), patient well-being (Subjective Well-Being with Neuroleptics, short version), and patient treatment satisfaction.

Results: 593 patients (intent-to-treat population), 63.1% male, mean age 38.4 ± 11.8 years, 78.6% paranoid schizophrenia, were analyzed. 74.5% of patients completed the 6-month study. Most frequent reasons for early discontinuation were subject choice (9.3%) and side effects (6.1%). The median mode maintenance dose of PP was 100 mg eq once monthly. Relatively high mean baseline PANSS negative subscale scores (20.2 ± 5.4) improved significantly by -3.5 ± 5.4 points from baseline to endpoint (95% confidence interval [CI] -3.9 ; -3.0), the PANSS negative symptoms Marder factor score improved from 19.6 ± 5.6 to 16.1 ± 5.7 (95%CI of change -3.9 ; -3.1), and the disorganized thoughts Marder factor score improved from 16.2 ± 4.4 to 13.9 ± 4.6 (95%CI -2.6 ; -1.9). Similarly, the anxiety/depression Marder factor score improved from 9.3 ± 3.1 to 7.6 ± 3.1 (95%CI -2.0 ; -1.5 , all mentioned above $p < 0.0001$). Subjective well-being increased from 80.1 ± 17.2 at baseline to 85.5 ± 17.3 at endpoint (95%CI 4.0 ; 6.7), and patient treatment satisfaction improved significantly from 55.3 ± 19.6 to 63.9 ± 22.8 (95%CI 6.4 ; 11.0 , both $p < 0.0001$).

Discussion: Flexibly dosed paliperidone palmitate treatment of non-acute but symptomatic patients with schizophrenia over 6 months showed significant and clinically relevant improvements in negative and depressive symptoms, disorganized thoughts and patient-relevant outcomes such as subjective well-being and treatment satisfaction.

Poster #M244

THE USE OF MIRTAZAPINE AS ADD-ON THERAPY IN THE TREATMENT OF SCHIZOPHRENIA

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Background: 75% of patients with schizophrenia do not achieve pharmacological remission despite the use of second-generation antipsychotic medications. This has driven the attempt to improve clinical outcomes with add-on medications. To date, no add-on agent has been approved by the FDA for such an indication. A recent meta-analysis supports the use of anti-depressant medications as add-on therapy to D2 antagonists in schizophrenia by improving negative symptoms. Mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSA) used primarily in the treatment of depression, has been shown in numerous small trials over the last 10 years to be an effective add-on therapy agent in schizophrenia predominately through the improvement in negative symptoms. The purpose of this report is to determine whether practicing physicians are increasing their use of mirtazapine as add-on therapy in schizophrenia.

Methods: Clinical diagnosis values for US mirtazapine prescriptions were obtained from a random sample of 1,380 physician reports per month; sampling methodology employed a two-stage stratified cluster, randomly drawn. Two workdays per month were subsampled from each physician, and 8,280 physician-workdays were collected each quarter. Total mirtazapine prescription data were based on a total of 5,770 hospitals and 472 wholesalers to retail pharmacies. Prescription data were categorized by indication (clinical diagnosis) including major depressive disorder and schizophrenia. Data were collected by the IMS Institute for Health Informatics.

Results: Mirtazapine prescriptions in the United States increased in both the hospital and retail settings from 2002 to 2012. Hospital prescriptions increased by 106% and retail prescriptions increased by 39% over the ten year period. Schizophrenia-specific mirtazapine prescriptions increased 18% over the same time period.

Discussion: Mirtazapine became a generic medication in 2004, and its utilization has increased substantially since that time primarily for the treatment of depression. Only minor increases in its utilization can be attributed to its use in schizophrenia. Despite recent evidence that mirtazapine is an effective add on agent to D2 blockers for the treatment of schizophrenia, prescription trends suggest it's utilization for this indication has changed minimally over the last 10 years.

Poster #M245

POSITIVE RESULTS WITH ITI-007 FOR THE TREATMENT OF SCHIZOPHRENIA: A RANDOMIZED, DOUBLE-BLIND, PLACEBO- AND ACTIVE-CONTROLLED PHASE 2 STUDY

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Background: ITI-007 modulates serotonergic, dopaminergic and glutamatergic neurotransmission and represents a novel approach to the treatment of schizophrenia and other neuropsychiatric disorders. ITI-007 is a potent 5-HT2A receptor antagonist, a dopamine phosphoprotein modulator (DPPM) with activity as a pre-synaptic partial agonist and post-synaptic antagonist at dopamine D2 receptors, a glutamate GluN2B receptor phosphoprotein modulator and a serotonin reuptake inhibitor. ITI-007's broad pharmacological profile and mesolimbic/mesocortical selectivity is predicted to translate clinically to broad antipsychotic efficacy against positive and negative symptoms and to improve mood and social integration. ITI-007 was evaluated in a randomized, double-blind, placebo- and active-controlled Phase 2 clinical trial designed to evaluate the efficacy and safety of ITI-007 in patients with acute schizophrenia.

Methods: Patients with an acutely exacerbated episode of schizophrenia were randomized to receive one of four treatments in a 1:1:1:1 ratio: 60 mg ITI-007, 120 mg ITI-007, 4 mg risperidone (positive control) or placebo. Patients received study treatment orally once daily in the morning for 28 days. The primary endpoint was change from baseline on the total Positive and Negative Syndrome Scale (PANSS) on study Day 28. Secondary endpoints included weekly assessments of the total PANSS as well as its subscales. Safety and tolerability were assessed.

Results: ITI-007 at a dose of 60 mg improved schizophrenia as measured by statistical significance ($p = 0.017$) on the trial's pre-specified primary endpoint, change from baseline on the total PANSS score, compared to placebo. The higher dose, 120 mg ITI-007, did not significantly separate from placebo on the total PANSS at Day 28; the positive control did separate from placebo on the primary endpoint demonstrating assay sensitivity. Sedation/somnolence was the most frequent adverse event, particularly frequent with 120 mg ITI-007. The lower dose, 60 mg ITI-007, was safe and well tolerated and significantly improved a wide range of symptoms associated with schizophrenia, including improvement of the Positive Symptom Subscale of the PANSS and the General Psychopathology Subscale. ITI-007 (60 mg) also improved the Negative Symptom Subscale, particularly in subjects with prominent Negative Symptoms at baseline. Overall, 60 mg ITI-007 improved a broad range of positive and negative symptoms and general psychopathology with a differentiating response profile consistent with improved social function.

Discussion: The present study is the first to demonstrate antipsychotic efficacy with ITI-007. Moreover, robust efficacy was observed at a moderate dose of ITI-007, 60 mg, which was safe and well tolerated, with a response profile consistent with improved social integration and enhanced social function. The higher dose of ITI-007 produced frequent sedation when administered in the morning and might be more appropriately administered in the evening. ITI-007 represents a new approach to the treatment of schizophrenia and other neuropsychiatric and neurological disorders.

Poster #M246

SOCIAL ANXIETY AS A TREATMENT TARGET TO IMPROVE SOCIAL ADJUSTMENT AND QUALITY OF LIFE IN SCHIZOPHRENIA

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Background: Previous studies have reported a possibility that social anxiety symptoms which are revealed in about 30 percent of the patients with schizophrenia disturb their social adjustment. Social anxiety in schizophrenia seems to appear from prior term of illness and related to social cognitive function which needs comprehension to others' intention. It is suggested that schizophrenia patients perceive dangers and damages more severely than healthy people and form the basis of delusion because of their distortion of recognition for others' intention and motivation. Therefore, social anxiety is thought to be one of the useful indicators of progress of psychopathology in the prodromal and early phases and relapse in the chronic phase of schizophrenia. We revealed that deterioration of social anxiety in remitted patients with schizophrenia is associated with change in psychotic symptoms and decline in quality of life. In the present study, we aimed at demonstrating co-morbidity and clinical factors associated with social anxiety in outpatients with schizophrenia.

Methods: Twenty-five Japanese outpatients with schizophrenia aged 40 years or younger (13 men, 12 women) were recruited at the Toho University Omori Medical Center, Tokyo. They were diagnosed as schizophrenia using the Mini-International Neuropsychiatric Interview (M.I.N.I.) and the DSM-IV-TR. The mean age of the patients was 32.0 years and mean illness chronicity was 101.2 months. All the patients were taking antipsychotics. The primary outcome measure was the Liebowitz Social Anxiety Scale Japanese version (LSAS-J) which measures the severity of social anxiety symptoms. Other measures included the Positive and Negative Syndrome Scale (PANSS), the Calgary Depression Scale for Schizophrenia (CDSS), the Japanese And Caucasian Facial Expressions of Emotion (JACFEE), the Theory of Mind (ToM) task, the Clinical Global Impression-Severity of Illness (CGI-S), the Global Assessment of Functioning (GAF), the Social Functioning Scale Japanese version (SFS-J), the Sheehan Disability Scale (SDIIS), the World Health Organization Quality of Life 26 (WHOQOL26), the Subjective Well-being under Neuroleptic drug treatment Short form Japanese version (SWNS-J), and the Scales to Assess Unawareness of Mental Disorder Japanese version (SUMD-J). We excluded patients under IQ 70 using the Japanese Adult Reading Test (JART). This study was approved by the Ethics Committee of Toho University School of Medicine. Written informed consent was obtained from every participant.

Results: The mean fear and avoidance score on the LSAS-J was 23.4 and

40.1, respectively. Two of the participants were identified as social anxiety disorder by the M.I.N.I. The mean positive symptoms, negative symptoms, and general psychopathology score on the PANSS were 14.2, 15.9, and 31.9, respectively. The mean scores for other measures were: CDSS score, 4.0; JACFEE score, 31.9; ToM score, 2.3; CGI-S score, 2.9; GAF score, 57.5; SFS-J score, 126.4; WHOQOL 26 score, 3.4; and SWNS-J score, 78.8. The mean work/school, social life, and family life score on the SDIIS were 3.1, 2.2, and 1.7, respectively. The mean present and past awareness score on the SUMD-J were 1.2 and 2.0, respectively. We examined the correlations between the fear score in the LSAS-J and other measures. The negative symptoms on the PANSS, WHOQOL 26, CDSS, the work/school score on the SDIIS and the SWNS-J were significantly correlated with the fear score.

Discussion: The significant associations of social anxiety with social functioning and quality of life were demonstrated in patients with schizophrenia. Social anxiety was thought to be an important target to improve patients' social adjustment.

Poster #M247

CAN WORK HISTORY AT BASELINE PREDICT WORK BEHAVIOR WITHIN THE FIRST FOUR WEEKS OF VOCATIONAL REHABILITATION?

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Background: Employment is an important aspect of daily living, and providing individualized and effective vocational services for people with schizophrenia is an ongoing concern. Accurate assessment of vocational functioning is essential for precise evaluation of vocational rehabilitation programs. The Work behavior inventory (WBI) has been developed for this purpose, and studies show that it is sensitive to change in vocational functioning in people with schizophrenia. The WBI has been translated and tried out in a Norwegian vocational rehabilitation study, the Job Management Program (JUMP). Work history has been shown to predict later employment. We explored the association between work history and work behavior measured with the Work Behavior Inventory around the fourth week of work. We expected work history to be positively associated with the global score of the Work Behavior Inventory (WBI) at four weeks. Gender, age and education were included as control variables.

Methods: Adults with psychotic disorders in the JUMP study ($n=149$) received vocational rehabilitation, enhanced by close collaboration between health and vocational services, employers and employment specialists. After baseline assessments participants entered sheltered, stipended or competitive employment. Work behavior was assessed within the first four weeks of work, using the global score of the Work Behavior Inventory (WBI). WBI global score was included as the dependent variable in a hierarchical linear regression analysis. Gender, age, education and work history were included as potential predictors.

Results: At the bivariate level the WBI global score correlated significantly with all independent variables: age ($r=0.21$), gender ($r=0.18$), education ($r=0.20$) and work history ($r=0.36$). To further examine the relationship between the WBI global score and work history and education, a one-way between-group analysis of variance (ANOVA) was performed. Levels of education were significantly associated with the WBI global score $F(2,138) = 6.321$, $p < 0.001$. Post-hoc analyses showed significant differences between having a college or university degree and having an elementary ($p=0.002$) or high school education ($p=0.019$), with higher education being associated with a higher WBI global score. Work history was significantly correlated with the WBI global score $F(2,61) = 16.908$, $p < 0.001$, with post-hoc analysis showing significant differences between having more than three years work experience versus having less than three years ($p < 0.001$). In a multiple hierarchical regression analysis work history ($\beta=0.33$, $t=3.49$, $p > 0.001$) was the only significant predictor of the WBI global score, explaining 15% of the variance. Gender reached marginal significance ($\beta=0.16$, $t=1.97$, $p=0.05$).

Discussion: Work history is significantly correlated with work behavior as measured with the WBI global score at four weeks. Having three years' of work experience or more is significantly associated with better outcome understood as better vocational functioning on the WBI global score. Implications may be that those with little work experience require additional support while acquiring adequate work experience to improve their vo-

cational performance. The predictive value of work history needs to be further examined with longitudinal studies.

Poster #M248

IMPROVING SOCIAL FUNCTIONING IN SCHIZOPHRENIA THROUGH SOCIAL COGNITIVE REMEDIATION

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Background: Social functioning deficits in schizophrenia represent a core domain of performance that has not been effectively addressed. Social cognition refers to how we think about and process information that is social in nature, and has been identified as a most unique contributor to our ability to function as social beings. There is a growing evidence-base endorsing social cognitive training at being effective in improving the social cognitive abilities of schizophrenia populations, however continued research is needed to establish: whether improved social cognition actually transpires into effective changes to daily social behaviour; whether the effects of this training are sustainable over time; and whether the targeted population regard and value the training.

Methods: This pilot study applied a social cognitive training program over 13 weeks to a sample of community mental health consumers with schizophrenia. Participants were assessed at baseline, post-training and at a six-month follow up period and compared to a treatment as usual group. The domains of interest were social cognition, social functioning and quality of life. Further, narrative data was obtained from participant interviews over time.

Results: Results revealed preliminary evidence that the treatment group improved significantly in all domains of social cognition and social performance. Longitudinal data revealed that these gains were maintained and furthermore, significant improvements to social functioning and quality of life emerged over time. Finally, the narrative data obtained from participants strongly suggested that the training had a positive impact on various aspects of their functioning.

Discussion: The overall findings provide endorsement for the utility and efficacy of social cognitive intervention in ultimately improving functional outcomes for people with schizophrenia that are durable over time. The narrative feedback represents an exciting addition to the treatment literature and provides impetus for how receptive and important this type of training can be to the people who need it.

Poster #M249

HELPING PEOPLE WITH PSYCHOTIC DISORDERS BACK TO WORK – THE sJUMP STUDY

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Background: Although the majority (50-90%) of people with schizophrenia wishes to work, unemployment rates remain high (75 to 95%). Employment holds several economic, social and psychological benefits for people with schizophrenia. Possible barriers to employment are related to both internal factors such as cognitive impairment and psychotic symptoms, and external factors such as stigma, service availability and benefits. The purpose of the JUMP (Job Management Program) study is to explore the feasibility of vocational rehabilitation for people with psychotic disorders in a Scandinavian welfare society, and to examine the association between employment and psychotic symptoms.

Methods: Participants (n=150) were enrolled in a 10 months vocational rehabilitation program offering close collaboration between health- and vocational services, competitive or sheltered work and either cognitive remediation (CR) or cognitive behavioral therapy (CBT) techniques focusing on work related issues. Participants were assessed with MINI PLUS, WASI and SCI-PANSS as well as on employment- and income status.

Results: At baseline, 13% of the participants were employed but none had paid work as their main income. At 10 months, employment rates had increased to 77% and 5% had paid work as their main income. To examine whether gaining employment was associated with change in psychotic

symptom levels, a paired t-test was carried out. The results show a small, but significant improvement on all SCI-PANSS scales.

Discussion: Preliminary analyses suggest that people with psychotic disorders in a Scandinavian welfare society are willing and able to work, both in competitive and sheltered settings, when given access to vocational rehabilitation and adequate support. Further analyses may potentially identify characteristics of those who might benefit more from either CR or CBT in this vocational rehabilitation program.

Poster #M250

THE ROLE OF GENDER AND SYMPTOMS IN PREDICTING FUNCTIONING IN EARLY EPISODE PSYCHOSIS

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Background: The early phases of psychosis are characterized by significant heterogeneity in clinical symptoms, functioning, and course of illness. Few studies have recognized gender as an important feature in the early stages of psychosis; however gender differences may account for some of the variability in symptoms and functioning. The aim of the current study was to examine gender differences in clinical symptoms and the relationship between symptoms and functioning. Specifically, we were interested in whether gender moderated the relationship between symptoms and functioning and whether symptoms predicted functioning at a 6-month follow-up.

Methods: Patients with early episode psychosis (150 males, 46 females), who were enrolled in an early intervention program, completed baseline assessments consisting of the Brief Psychiatric Rating Scale (BPRS) and the Social and Occupational Functioning Assessment Scale (SOFAS). A subset of patients completed a 6-month follow up assessment.

Results: An examination of gender differences in baseline clinical symptoms and level of functioning revealed a significant difference in levels of BPRS Withdrawal/Retardation between males ($M=7.04$, $SD=3.52$) and females ($M=5.48$, $SD=3.14$) with early psychosis, $t(194)=2.70$, $p=0.008$. There were no significant gender differences in BPRS Thought Disturbance, Hostility/Suspiciousness, Anxiety/Depression, or functioning as measured by the SOFAS. More severe clinical symptoms, as measured by the BPRS Total Psychopathology score, were significantly correlated with lower functional status, $r=-0.602$, $p\leq0.001$. Interestingly, a moderated regression analysis revealed that gender had a significant moderating effect on the relationship between symptoms and functioning. To follow-up, a simple slopes analysis found that higher levels of symptom severity were significantly associated with lower levels of functioning for males ($B=-0.452$, $t=-3.801$, $p<0.001$), but that this relationship was more robust for females ($B=-0.771$, $t=-8.768$, $p<0.00001$). Furthermore, a 6-month follow-up assessment was conducted for a subset of patients. Baseline clinical symptoms (Thought Disturbance, Withdrawal/Retardation, Hostility/Suspiciousness, or Anxiety/Depression) were entered into a stepwise regression to predict functional status on the SOFAS six months later. BPRS Withdrawal/Retardation emerged as a significant predictor of functioning at follow-up, $F(19)=11.79$, $p=0.003$.

Discussion: Negative symptoms, such as emotional withdrawal and motor retardation, were more prevalent in males with early episode psychosis and this symptom was associated with worse functioning at a 6-month follow up. Clinical symptoms were differentially related to functioning, where higher levels of symptom severity were more robustly associated with lower functioning in female, compared to male, patients. Typically, early intervention programs do not differentially tailor services to male and female patients in the early stages of psychosis. However, the present study suggests that differential management of symptoms based on gender may be particularly important in mitigating poor long-term functional outcomes.

Poster #M251**METHODOLOGICAL CONSIDERATIONS IN THE IMPLEMENTATION OF THE US MOSAIC REGISTRY: A LARGE-SCALE, LONG TERM STUDY OF PEOPLE WITH SCHIZOPHRENIA**Philip D. Harvey¹, Cedric O'Gorman²¹*Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine; ²Genentech USA, Inc. - Member of the Roche Group*

Background: Registry studies of various medical and neuropsychiatric diseases have provided substantial information about the natural history of these conditions. The Management of Schizophrenia in Clinical Practice (MOSAIC) study is a registry study examining the 5-year course of schizophrenia in a large sample of people with schizophrenia in geographically diverse locations in the US. The goal of the study is to examine the course of schizophrenia and its relationship to treatments offered, from the perspective of patients, treating clinicians, and caregivers, using self-report, performance-based, and interview assessments. Challenges exist in the execution of any large-scale patient registry and there are some unique challenges specific to a schizophrenia registry of this size. Conflicting information between self-report, medical records and observation is one example while differences in types of care provided, including urban – rural differences further cause divergent results. Multiple issues related to registry recruitment can also result in an over- or under-representation of patient type within an observational study which may not truly reflect the real world population.

Methods: Clinical treatment sites recruit and refer patients along with medical record information to centralized Patient Assessment Centers (PACs). Treatment sites provide recent treatment information to PACs, who then perform structured diagnostic assessments, clinical evaluations, and performance-based assessments on patients, while contacting key informants who report on both patient characteristics and their own experiences. Domains of assessment include medical history, clinical symptoms and cognitive performance and everyday functioning, examined by patient interviews, informant reports, and clinician information. Patients are seen quarterly for the first year and semiannually each subsequent year, with information collected from clinicians and informants in similar time frames

Results: Of the first 161 patients examined, several interesting findings have emerged. Nine out of the first 12 (75%) clinical assessment sites are from urban areas and 7 out of 12 (58.3%) are at academic centers. About 42% of the sample of patients collected had 10 or fewer years of illness. Approximately 60% of patients reported annual income below \$20,000 with 43% having some college degree or vocational schooling, 42% reporting current employment and 71% living in a private house or apartment. Nine percent reported being a current student. As might be expected, the convergence between medical records, patient reports, and informant reports was only modest. Rates of problems like obesity and diabetes appear to be under-reported by both clinicians and patients. Further, the characteristics of the current sample are notably affected by the recruitment sites, with several of the sites recruiting with much more efficiency than the others. The self-report data on concomitant medication did not consistently match with the prevalence of comorbidities either reflecting under-treatment or failures in self-reports.

Discussion: These results highlight both the importance and challenges of registry studies. Convergence between information sources is a critical issue for outcomes assessment in schizophrenia in both naturalistic and treatment trials and the MOSAIC study is well poised to expand on previous smaller studies (e.g., VALERO) aimed at this topic. While schizophrenia patients are known to show considerable evidence of disability, very low functioning patients are under-represented in this sample, despite their role in the high treatment cost of the illness; their inclusion may be challenging but nevertheless important to implement in this longitudinal study. This study, with its focus on caregiver roles and burden will also provide critical information about caregiver characteristics and burdens that are better understood in neuropsychiatric conditions such as Alzheimer's Disease. Despite inherent challenges and limitations, MOSAIC has the potential to fill several critical knowledge gaps in the area of the course and correlates of schizophrenia in community dwelling patients.

Poster #M252**PATIENTS' OPINIONS ON KEY ISSUES OF PSYCHOSOCIAL FUNCTIONING AMONG NON-PSYCHOTICS, PSYCHOTIC RESPONDERS AND NON-RESPONDERS: CORRELATION WITH CLINICAL VARIABLES AND SYMPTOM DOMAINS RELEVANT TO REMISSION FROM PSYCHOSIS**Felice Iasevoli^{1,2}, Sara Giordano³, Raffaele Balletta³, Elisabetta^{F. Buonaguro³, Carmine Tomasetti³, Rodolfo Rossi³, Valentina Gilardi³, Claudia Cucciniello³, Cristiana Elce³, Roberto Acampora³, Andrea de Bartolomeis³}¹*University; ²Department of Neuroscience, Reproductive Sciences and Odontostomatology; ³University "Federico II" of Naples, Italy*

Background: Remission of psychotic symptoms is a difficult target to reach in both responder and non-responder patients. Psychosocial functioning is one of the parameters that can be affected by the inefficacy of treatments, and is a predictor of the patient's global outcome. The aims of this study were to investigate patients' opinions on key aspects of psychosocial functions and to determine a correlation between patients' opinions and psychopathological parameters predictive of remission in psychotic patients

Methods: We included 82 patients referring to our Outpatient Unit from May to September 2013. Patients were subdivided in non-psychotic (NP), psychotic responders (PR) and psychotic non-responders (PNR) according to the following criteria: i) having a diagnosis or currently showing symptoms of diseases belonging to the psychotic spectrum; ii) having or not responded to antipsychotic treatments, as defined by APA guidelines. Opinions on key psychosocial functions were obtained through a self-reported questionnaire. Demographics and clinical variables were recorded for all patients. All patients were administered the Positive and Negative Syndrome Scale (PANSS) and the Personal and Social Performance (PSP) scale

Results: PNRs responded "true" significantly less frequently than PRs and NPs at the question whether they may take care of children ($p<0.0001$). The clinical factors more significantly associated with responses to this question were: i) non-spontaneous conversation, and mannerisms in PNRs; ii) score on PANSS negative subscale in PRs. NPs responded "not true" significantly more frequently than both PRs and PNRs at the question whether love stories are difficult to occur for those having their diseases ($p=0.0117$). The clinical factors more significantly associated with responses to this question were: i) passive social withdrawal, score on PANSS positive subscale, and score on the PSP in PNRs; ii) previous compulsory hospitalizations in PRs. NPs responded "not true" significantly more frequently than PRs and PNRs ($p=0.0003$) at the question whether it is difficult marrying or having a stable partner for people with their diseases. The clinical factors more significantly associated with responses to this question were: i) mannerisms and score on the PSP in PNRs; ii) passive social withdrawal, antipsychotic doses, and previous compulsory hospitalizations in PRs. NPs responded "not true" significantly more frequently than PNRs ($p=0.044$) at the question whether people with their disease are a burden for the family. The clinical factors more significantly associated with responses to this question were: i) delusions, conceptual disorganization, non-spontaneous conversation, and mannerisms in PNRs; ii) scores on the PANSS total scale, negative subscale, and general psychopathology subscale in PRs. Both NPs and PRs responded "often" and "sometimes" significantly more frequently than PNRs ($p=0.04$ and $p=0.0018$, respectively) at the question whether some friend or relative had actively searched for the patient in the last period. The clinical factors more significantly associated with responses to this question were: i) non-spontaneous conversation, and mannerisms in PNRs; ii) performances on the verbal fluency task in PRs.

Discussion: The results reflect the worse psychosocial adaptations in PNRs compared with both PRs and NPs. PNRs appear to be sufficiently aware of their difficulty in psychosocial functioning. Clinical factors associated with patients' opinions are: flattened conversation, mannerisms, social withdrawal, and global psychosocial functioning for PNRs. Negative symptoms and previous compulsory hospitalizations are associated with self-judgment on psychosocial functioning in PRs

Poster #M253**VOCATIONAL RECOVERY IN FIRST EPISODE PSYCHOSIS: PRELIMINARY RESULTS FROM A LARGE RANDOMISED CONTROLLED TRIAL OF INDIVIDUAL PLACEMENT AND SUPPORT**

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Background: Vocational recovery has been consistently shown to be a number-one priority of people with mental illness generally, and schizophrenia and first episode psychosis (FEP) specifically. Two previous randomised controlled trials (RCT) demonstrated the benefit of an employment intervention called Individual Placement and Support (IPS) for young people with FEP. The current study was conducted in order to examine not only the vocational benefits of such an approach, but to study a wide range of predictors and consequences of vocational recovery in FEP.

Methods: 146 young people with FEP were recruited to a RCT of IPS versus treatment as usual at the Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne. Those randomised to IPS received 6 months of vocational intervention with a specialist employment consultant. Follow up assessments occurred at 6, 12 and 18 months post baseline. The aims of this presentation will be to present the data pertaining to the vocational recovery at the 6 month time point of this study.

Results: In terms of studying at the six month time point there was no difference between the two groups ($\chi^2(1)=2.08$, $p=0.149$), nor of the number currently in paid work on the day of assessment at 6 months. ($\chi^2(1)=3.42$, $p=0.065$). However, when employment over 6 months was compared there was a difference ($\chi^2(1)=5.74$, $p=0.017$).

Discussion: The preliminary results of this study indicate that IPS is effective at getting people into employment.

Poster #M254**DIFFERENTIAL EFFECTS OF ANTIPSYCHOTICS ON QUALITY OF LIFE AND FUNCTIONING IN CHINESE PATIENTS WITH FIRST-EPISEDE PSYCHOSIS**

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Background: Meta-analysis of RCTs suggested that patients with second generation antipsychotic treatment have higher functioning and quality of life than those with first generation antipsychotic treatment. However, findings from CATIE and CUTLASS raised doubt about their difference in real clinical settings, especially in patients with first-episode psychosis. We compared the effects of antipsychotics on quality of life and functioning in Chinese patients with first-episode psychosis.

Methods: A total of 285 patients were assessed with the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS), the Udvælg for Kliniske Undersøgelser (UKU), the Social and Occupational Functioning Assessment Scale (SOFAS), the Role Functioning Scale (RFS) and the Medical Outcomes Study Short Form 12-Item Health Survey (SF-12) after stabilization of mental condition. Difference between individual antipsychotic medications was investigated using ANOVA and post-hoc analysis.

Results: Significant differences were found between different antipsychotic medications in the mean of UKU neurological subscore, BARS total score, SOFAS score and SF-12 mental component summary score (MCS) score. Patients with haloperidol had higher mean UKU neurological subscore than patients with olanzapine or amisulpiride. Patients with risperidone had higher mean BARS total score than patients with olanzapine, amisulpiride or sulpiride. Patients with amisulpiride had higher mean MCS than patients with risperidone.

Discussion: Antipsychotics have differential effects on quality of life and functioning in patients with first episode psychosis. Future prospective study is warranted to investigate if patients with first episode psychosis will benefit from specific type of antipsychotics more than the others.

Poster #M255**INTERPERSONAL TRAUMA AND THE SOCIAL FUNCTIONING OF ADULTS WITH FIRST EPISODE PSYCHOSIS**

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Background: Social functioning is an important treatment outcome for psychosis, and yet, we know little about its relationship to trauma despite high rates of trauma in people with psychosis. Trauma or maltreatment in childhood coincides with the period for a child's development of relational understanding such as attachment to others and the reflective awareness of self and others. Childhood trauma is likely to disrupt the acquisition of interpersonal relatedness skills including the desire for affiliation and thus lead to impaired social functioning in adulthood. We hypothesized that childhood trauma would be a predictor of poor social functioning for adults with psychosis and that further trauma in adulthood would moderate this relationship.

Methods: A first-episode psychosis sample from the TIPS2 study and aged 15–65 years (N=233) completed measures of social functioning (Lehman's Quality of Life Interview and Strauss Carpenter Functioning Scale) and trauma (Brief Betrayal Trauma Survey), as well as clinical assessments.

Results: Childhood trauma (any type) was associated with poorer premorbid functioning and was experienced by 61% of our sample. There were no associations with clinical symptoms. Interpersonal trauma was more common than non-interpersonal trauma in both childhood (36% vs 15.8%) and adulthood (36.8% vs 12.1%). Trauma in both childhood and adulthood was experienced by 14% of the sample. Interpersonal trauma in childhood was a significant predictor of social functioning satisfaction in adulthood, but this was not the case for interpersonal trauma in adulthood. However, 45% of adults who reported childhood interpersonal trauma also experienced adulthood interpersonal trauma.

Discussion: As predicted, childhood trauma was associated with disruptions to social functioning, and this was evident in the premorbid phases of childhood, early adolescence and late adolescence as well as adulthood. By early adolescence, there was also evidence of poorer academic functioning for adults who had experienced childhood trauma. Our results emphasize the importance of early relationship experience such as interpersonal trauma, on the social functioning of adults with psychosis. We recommend extending our research by examining the impact of interpersonal childhood trauma on occupational functioning in psychosis.

Poster #M256**THE EFFECTS OF SELF-STIGMA CONTENT AND PROCESS ON SUBJECTIVE QUALITY OF LIFE IN PEOPLE WITH SCHIZOPHRENIA**

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Background: People with schizophrenia may endorse and internalize public stigma directed against them and at times experience self-stigma. Having self-stigmatizing thoughts per se does not necessarily lead to chronic psychological distress. Only when such thinking occurs frequently and automatically as a mental habit does this generate constant mental chaos, which may have deleterious effects on the subjective quality of life of individuals. The mental process of self-stigma should be distinguished from the mental content, assessed independently, and not be assumed to be homogeneous across all people with schizophrenia. The present study aims empirically to test whether habitual self-stigma contributes to decreased subjective quality of life after controlling self-stigmatizing cognitive content.

Methods: A community sample of 144 people with schizophrenia was recruited in Hong Kong. Subjective quality of life was measured with the Satisfaction With Life Scale (SWLS). Self-stigmatizing cognitive content was assessed with the Self-Stigma Scale-Short Form (SSS-S). We developed a self-reported measure of habitual self-stigma, that is, the Self-stigmatizing Thinking's Automaticity and Repetition (STAR) scale. The STAR contains 15 items rated on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree) measuring the extent to which individuals experience frequent, automatic, and self-descriptive self-stigmatizing thinking.

Results: 47% of participants reported repetitive self-stigma, while 68% reported automatic self-stigma. Taken together, the prevalence of habitual self-stigma was 40%. More negative cognitive content of self-stigmatizing thinking ($r=-0.246$, $p=0.003$) and stronger self-stigmatizing thinking habit ($r=-0.314$, $p<0.001$) were correlated with decreased subjective quality of life. SWLS was regressed on SSS-S (Step 1) and STAR (Step 2) in a hierarchical multiple regression. Self-stigmatizing cognitive content yielded a significant relationship with subjective quality of life at Step 1 ($p=0.003$) which disappeared at Step 2 ($p = 0.243$) when STAR was added and found to be significant ($p=0.008$).

Discussion: The construct of self-stigmatizing thinking habit offers new perspectives on self-stigma's theory, assessment, and intervention. Given that the deleterious effects of self-stigma on subjective quality of life are due to both the negative content and the habitual manifestation of self-stigmatizing thinking, the impact of self-stigma on people with schizophrenia may be underestimated if it is based solely on traditional content-oriented measures. Existing self-stigma interventions, which are cognitive content-oriented, should be improved by additionally targeting the automatic processes involved in the mental habit. In mitigating self-stigmatizing thinking habit, practitioners may apply mindfulness-based psychotherapies to enhance individuals' awareness of automatic self-stigma process at the present moment. Interventions should also seek to help individuals with schizophrenia extend their self-definition beyond their minority status, thereby thinking about their stigmatized condition less.

Poster #M257

VARIABLES INFLUENCING SUBJECTIVE WELL-BEING IN PATIENTS WITH SCHIZOPHRENIA

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Background: Subjective well-being in patients with schizophrenia is recognized as important clinical outcome measures. The purpose of this study is to analyze the relationship between subjective well-being and other clinical parameters, such as sociodemographic and clinical variables, which include positive and negative symptoms, depressive symptoms, insight, drug adverse effects.

Methods: Fifty-one outpatients who were diagnosed with schizophrenia were monitored. All patients took only one kind of oral antipsychotic. Subjective Wellbeing on Neuroleptics-Short form (SWN-K) was used to measure subjective well-being. In addition, sociodemographic variables, Positive and Negative Syndromes of Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS), Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS), Korean Version of the Revised Insight Scale of Psychosis (KISP), Multidimensional Scale of Perceived Social Support (MSPSS) were also evaluated. The relationships between subjective well-being and these clinical variables were assessed.

Results: Education years and social support score were positively correlated with the total score of SWN-K. However, severity of illness, severity of depression, severity of side effect and score on the insight were negatively correlated with the total score of SWN-K. Stepwise multiple regression analyses indicated that the total score of SWN-K in patients with schizophrenia was associated with negative symptoms and insight.

Discussion: Better insight and severer negative symptoms in patients with schizophrenia may be associated with worse subjective well-being. The careful evaluation of subjective well-being in patients with schizophrenia should be required for their proper treatment.

Poster #M258

QUALITY OF LIFE AND DEPRESSION AMONG CAREGIVERS OF SCHIZOPHRENICS

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Background: Caring for a patient with schizophrenia is a challenge in itself. Schizophrenia not only impacts the patient's life but also for the caregivers. Researchers have studied the impact of caregiving for a schizophrenic on quality of life of caregivers. Depression in such caregivers is another aspect which cannot be ignored. The present study was designed to assess the quality of life and level of depression among caregivers of schizophrenics based on socio-economic status, education, gender, employment, marital status and age. For the purpose of this study 144 caregivers of patients with schizophrenia were selected using purposive sampling from a government hospital.

Caregivers who did not have any pre-existing psychiatric disorder and physical defect were included. General Health Questionnaire (GHQ 12) and Beck Depression Inventory (BDI) were administered. Results indicated that caregivers from lower socio-economic status and with less education played an important role in reducing quality of life whereas sex, marital status, age and employment did not significantly affect caregivers' quality of life. The level of depression was significantly found to be mild to moderate in caregivers from lower socio-economic status and who were illiterate, unemployed, married and female and between the age group of 31–45 years.

Methods: Based on the review of literature, the present research aims to assess the Quality of life and Depression in caregivers of patients with Schizophrenia. This section elaborates on the objective of the study, rationale, hypothesis, research design, sample, and inclusion and exclusion criteria, the tools used for procedure and statistical analysis which will be done for the thesis.

4.1 Objective: The objective of the research is to study the Quality of life and Depression in caregivers of Schizophrenics.

The study focuses: 1. The quality of life and depression in caregivers of Schizophrenics. 2. To assess the quality of life of caregivers in relation to socio-economic status. 3. To assess quality of life of caregivers in relation to employment status. 4. To assess quality of life of caregivers in relation to age. 6. To assess depression in caregivers in relation to socio-economic status. 7. To assess depression in caregivers in relation to employment status. 8. To assess depression in caregiver in relation to age.

4.2 Rationale: The researcher chose this topic for dissertation as she felt the need to investigate the quality of life and depression in caregivers of Schizophrenics. There have been researches documented which have already been done on caregivers. The need to investigate quality of life and depression, in caregivers of Schizophrenics is to revive the interest, focus and attention of mental health professionals towards the unaddressed psychological needs of caregivers of Schizophrenics. It is important to provide mental health services to caregivers as well so as that their psychological well-being is restored and their efficiency in providing care to the patient remain consistent.

4.3 Hypothesis: 1. There will be significant difference in quality of life and level of depression among caregivers of lower, middle and upper socio-economic status. 2. There will be significant difference in the quality of life of educated and uneducated caregivers of schizophrenics. 3. Caregivers with lower education will have significant level of depression. 4. There will be significant difference in the level of depression and quality of life among male and female caregivers. 5. Unemployed caregivers will have significant level of depression. 6. There will be significant difference in quality of life and level of depression among married and unmarried caregivers. 7. There will be significant difference in quality of life and level of depression in younger and older caregivers of schizophrenics.

4.4 Research design: Single group design

4.5 Statistical analysis: One way ANOVA

4.6 Samples: Experimental group – 144 Caregivers of Schizophrenics

4.7 Sampling technique: Purposive sampling technique will be used for this research.

4.8 Study population: 144 caregivers of Schizophrenics

4.9 Variables: Independent variables: Age, Employment, Socio-economic status (low, middle, upper), marital status (married, unmarried). Dependent variables: quality of life, depression.

4.10 Inclusion criteria: Age of participants: 18 to 60 years Caregivers who are employed or unemployed Caregivers who are studying Caregivers who are not studying Caregivers who are married Caregivers who are unmarried. Caregiver who are employed Caregiver who are unemployed

4.11 Exclusion criteria: Caregivers with any physical defects. Caregivers with any pre-existing psychiatric disorder. Caregivers below 18 years and above 60 years.

Tools Used: GHQ, BDI.

Results: Table 4.1 shows level of depression and general health of caregivers according to socio-economic status. Socio-economic status.

From the above table we can look that there is significant difference in the level of depression in all the three socio-economic groups. Lower socio-economic group (mean 11.75), middle socio-economic group (mean 4.50) and upper socio-economic group (mean 3.87) ($F=13.603$). Depression is found to be higher in lower socio-economic group which is significant at 0.01 level. In terms of general health, lower socio-economic group (mean 19.26), middle socio-economic group (mean 21.33) and upper socio-economic group (mean 20.68) ($F=4.86$) there was no significant difference at 0.01 level although middle socio-economic group have showed higher in terms of general health. Table 4.2 shows level of depression and general health of caregivers according to education.

From the above table it is inferred that there is significant difference in the level of depression in all four education group. Illiterate (mean 15.666), below graduation (9.608), graduate (mean 6.708) and above graduation (mean 3.666) ($F=15.271$) which is significant at 0.01 level although depression was found to be higher in the illiterate group. In terms of general health, illiterate (mean 18.25), below graduation (mean 19.89), graduate (20.33) and above graduation (mean 20.75) ($F=5.20$) there was significant difference in terms of general health. The graduate and above graduate group have shown higher in terms of general health which is significant at 0.01 level. Table 4.3 shows level of depression and general health of caregivers according to gender. From the above table it is inferred that there is no significant difference in the level of depression among males and females. Males (mean 8.35) and females (12.39) ($F=0.16$) which is significant at 0.01 level although depression was found to be higher in females. In terms of general health, males (mean 20.02) and females (mean 19.09) ($F=2.477$) there was no significant difference among males and females. The male group has shown slightly higher in terms of general health significant at 0.05 level.

Table 4.4 shows level of depression and general health of caregivers according to employment status. From the above table we can look at the significant level of depression in the employed and unemployed. Employed (mean 7.63) and unemployed group (13.05) ($F=1.242$) which is significant at 0.01 level. Depression was found to be higher in unemployed group. In terms of general health, employed (mean 19.97) and unemployed (mean 19.20) ($F=1.554$) there was no significant difference in general health at 0.05 level. Table 4.5 shows level of depression and general health of caregivers according to marital status. From the above table it is inferred that there is significant difference in the level of depression in the two groups. Married (mean 10.91) and unmarried (6.96) ($F=2.04$) which is significant at 0.01 level. Depression was found to be higher in the married group. In terms of general health, there is no significant difference in general health of both the married and unmarried groups. Married group (mean 19.51) and unmarried group (mean 20.00) ($F=1.95$).

Table 4.6 shows level of depression and general health according of caregivers according to age. From the above table it is inferred that there is no significant difference in the level of depression in all the three age groups. 18–30 yrs (mean 8.35), 31–45 yrs (mean 11.13) and 46–60 yrs (mean 10.97) ($F=1.95$) which is not significant at 0.05 level although depression was found to be slightly higher in the age group of 31–45 yrs. In terms of general health, 18–30 yrs (mean 19.59), 31–45 yrs (mean 19.22) and 46–60 yrs (mean 20.00) ($F=1.037$). There was no significant difference in terms of general health which is not significant at 0.05 level.

Discussion: The present study aimed at assessing quality of life and level of depression among caregivers of schizophrenics. – Socio-economic status – Education – Gender – Employment – Marital status – Age.

Problem 1: There will be significant difference in quality of life and level of depression among caregivers of lower, middle and upper socio-economic status. From the analysis table 4.1 and graph 4.1 (chapter 4), it is seen that there is no significant difference in quality of life of all the three socio-economic status caregivers. Although, results indicate that middle socio-economic status caregivers have a little more severe problems and psychological distress than lower and upper socio-economic status caregivers. This could be due to: • Caregivers' inability to cope up with the patient's illness. • Financial constraints which arise due to treatment cost of the patient. • Anticipation about their patient's recovery and functioning. • Caregivers viewing the patient's illness as a stigma. In terms of level of depression among caregivers from lower, middle and upper socio-economic status caregivers from lower socio-economic status were found to have mild to moderate level of depression. This is supported by a study done

by Osman, Alipah, Tutiiryani, Ainash (2010) in which they found that depression had a significant association with socio-demographic characteristics and family functioning of caregivers of schizophrenics. Another study conducted by Tantawi, Rayya and Yaser (2010) evaluated depression among caregivers of schizophrenia patients and its relations with burden of care and perceived stigma. 60 care givers of patients with schizophrenia were recruited as experimental group whereas 30 healthy non caregivers were selected as control group. Both groups were screened for depressive symptoms by center of epidemiological studies for depression scale. The tools used were the caregiver strain index and the discrimination devaluation scale. Results showed that depression was higher among caregivers than control group. Depression was correlated with burden of care and perceived stigma among caregivers.

Problem 2: There will be significant difference in the quality of life of educated and uneducated caregivers of schizophrenics. From the analysis table 4.2 and graph 4.2 (chapter 4), it is seen that there is significant difference in quality of life of educated and uneducated caregivers. Results show that graduate and above graduate caregivers have better quality of life than illiterate and below graduate caregivers of schizophrenics. This finding is supported by a research conducted by Zamzam, Midin, Hooi, Yi, Ahmad, Azman, Borhanudin and Radzi (2011) on patient, caregivers and illness factors associated with quality of life of individuals involved in providing care to schizophrenics. 117 individuals who were caregivers of schizophrenics were selected for the study. WHOQOL-BREF was used to assess caregivers' quality of life and BPRS was used to assess the severity of patient's symptoms. Social readjustment rating scale (SRRS) was also used to assess stress level in caregivers due to various life events. The result showed that mean scores of WHOQOL-BREF in physical, psychological, social and environmental domains were 66.62 (14.36), 61.32 (15.52), 62.77 (17.33), 64.02 (14.86) consecutively. Using multiple regression analysis, factors which were significantly associated with higher quality of life among caregivers were higher educational level, absence of any medical/physical problems, later onset and longer illness, patients not attending day care program. BPRS scores of patients were mainly on physical and environment domain. SRRS scores of caregivers had a significant negative correlation with quality of life in environmental and physical domain. Researchers concluded that caregivers who had more social advantages such as higher educational level, good physical health and less severe illness of patients had higher quality of life in various aspects. Another study conducted by Lua and Bakar (2011) reported that significantly better health-related quality of life profiles were demonstrated by caregivers who were adequately educated, male, younger than 50 years, employed, and without health problems and were receiving monthly income.

Problem 3: Caregivers with lower education will have significant level of depression. From the analysis table 4.2 and graph 4.2 (chapter 4), it is seen that there is significant level of depression in caregivers lower education. Results indicate that caregivers with lower education have mild to moderate depression and this is supported by a research conducted by Magana, Garcia, Hernandez and Cortez (2007) on mental health of Latino caregivers having a schizophrenic relative in the family. Interviews were conducted in English and Spanish in three regions – Wisconsin, California and Texas. 85 Latin Americans caregivers were chosen for the research and tools used were epidemiological studies-depression scale, the Zarit burden scale and Greenley stigma scale. Researchers found that depressive symptoms were more prominent in caregivers who were young, had lower level of education and higher level of the patient's schizophrenic symptoms. Moreover, a clear link was established between caregivers' perceived stigma and depression. Hence, it was concluded that younger Latino caregivers with lower educational level were at risk of depression. Researchers emphasized on availability of mental health services for caregivers of schizophrenics caregivers also.

Problem 4: There will be significant difference in the level of depression and quality of life among male and female caregivers. From the analysis table 4.3 and graph 4.3 (chapter 4), it is seen that there is significant difference in level of depression in female caregivers. Results show that female caregivers have higher depression than male caregivers of schizophrenics. This result is supported by a study done on gender differences in psychiatric morbidity among family caregivers by Jennifer L. Yee and Richrad Schulz (2000) in Pittsburgh. The major goal was to review and synthesize the empirical research on caregiver gender and psychiatric morbidity, with the aim of answering three questions: (1) Is there greater psychiatric morbidity among female than male caregivers, (2) is the excess

psychiatric morbidity among female caregivers attributable to caregiving, and (3) what factors in the caregiving situation contribute to the excess psychiatric morbidity among female caregivers? In almost all studies reviewed, women caregivers reported more psychiatric symptoms than men caregivers. Comparisons with non-caregiving community samples suggest that female caregivers experience excess psychiatric morbidity attributable to caregiving. Using a stress process model as an organizing framework, the study demonstrates that at all stages of the stress process; women are at greater risk for psychiatric morbidity than men. As far as general health is concerned it is found that there is no significant difference among male and female caregivers although male caregivers have shown slightly higher in terms of general health. This could be explained as: • Male caregivers have additional responsibilities and social roles. • They might have poor life skills. • Such caregivers have to keep themselves economically stable so that the patient's treatment cost and the household needs are fulfilled.

Problem 5: Unemployed caregivers will have significant level of depression. From the analysis table 4.4 and graph 4.4 (chapter 4), it is seen that unemployed caregivers will have significant level of depression. Results indicate that unemployed caregivers have mild to moderate depression than employed caregivers. This could be due to: • Caregiver's feeling of being incapable of fulfilling the treatment needs of the patient. • Inadequate skills to deal with patient. • Absence of support system. • Poor self-esteem. • Lack of knowledge about patient's illness.

Absence of financial funds to provide treatment to patient. • Self-blame in terms of considering oneself incapable of taking care of the patient. • Inability to fulfill financial responsibility of the family.

Problem 6: There will be significant difference in quality of life and level of depression among married and unmarried caregivers. From the analysis table 4.5 and graph 4.5 (chapter 4), it is seen that there is no significant difference in quality of life of married and unmarried caregivers of schizophrenics. This might be due to: • Similar experiences of dealing with patient's symptoms. • Chronicity of patient's illness. • Duration of living with the patient. • Similar skills to deal with the patient.

As far as level of depression is concerned married caregivers have higher depression than unmarried caregivers. The explanation for this might be: • Guilt, loss, helplessness, fear, vulnerability, and cumulative feelings of defeat, anxiety, resentment, and anger in married caregivers. • They might feel isolated, restricted from pursuing their own activities, and may be overwhelmed by a lack of support from friends, family and treatment providers. • Frustration in ensuring medication adherence, coping with disturbed or awkward interpersonal behavior and fatigue from continuous supervision of a family member with schizophrenia.

Problem 7: There will be significant difference in quality of life and level of depression in younger and older caregivers of schizophrenics. From the analysis table 4.6 and graph 4.6 (chapter 4), it is seen that there was no significant difference in terms of quality of life among younger and older caregivers of patients with schizophrenia. However, the level of depression was found to be mild to moderate in caregivers falling in age group 31–45 years.

Poster #M259

SOCIAL SUPPORT, QUALITY OF LIFE, PSYCHOTIC SYMPTOMS, AND DEPRESSION IN SCHIZOPHRENIA

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Background: Depression is common in the course of schizophrenia. This study aimed to assess the association between social support, quality of life, psychotic symptoms, and depression in participants with schizophrenia in Thailand.

Methods: This is a cross-sectional study conducted in 80 participants with schizophrenia. Depression was evaluated using The Thai version of Calgary Depression Scale for Schizophrenia (CDSS-Thai). The six social support deficits (SSDs) scale, the World Health Organization Quality of Life, Thai version (WHOQOL-BREF-THAI), and the Positive and Negative Syndrome Scale (PANSS) were used to assess social support deficits, quality of life, and psychotic symptoms, respectively. Logistic regression and linear regression was used to determine the associations between these factors and depression.

Results: Three out of six social support deficits were significantly associated with depression in participants with schizophrenia, including lack of re-

ciprocity between family members, difficulty in relationship with relatives, and dissatisfaction with support from family, with the odds ratios of 6.3, 12.7, and 19.1, respectively. Those with at least one social support deficit were 10.0 times more likely to be depressed than those without a social support deficit. Participants with schizophrenia and depression had significantly reduced quality of life in the aspect of psychological (mean difference -4.5 ± 1.1), social ($MD -1.5 \pm 0.5$), and environment ($MD -4.5 \pm 1.2$), compared with those without depression. We also found that depression was significantly associated with increased positive symptoms ($MD 5.9 \pm 1.1$), negative symptoms ($MD 4.4 \pm 1.2$), and general psychopathology ($MD 4.5 \pm 1.2$).

Discussion: Our study suggested that social support deficits and lower quality of life were significantly associated with depression in patients with schizophrenia. Moreover, depression was significantly associated with the increase in psychotic symptoms. Early detection of depression as well as enhancing social support should be emphasized in intervention to improve depression in participants with schizophrenia.

Poster #M260

THE ROLE OF CONSUMER FEEDBACK IN SHAPING RECOVERY SERVICES FOR AGITATED PSYCHOTIC PEOPLE

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Background: The recovery model emphasizes the central importance of the consumer perspective. Consumers stress the importance of staff treating them with respect, communicating with them in a meaningful way and involving them in treatment decisions. Much of the early work focused on the rehabilitation of people with sub-acute and chronic mental illness. In recent years there has been a greater emphasis on the incorporation of recovery based practice into all areas of mental health service delivery. There are challenges in the implementation of recovery principles in the acute setting.

Methods: This study took place in a ten bed psychiatric intensive care unit that provides services for urban and rural areas of South Australia. Recovery principles were progressively incorporated into clinical practice and included "meet and greet" services (based on hospitality principles), safety care plans, de-escalation strategies, collaborative care with negotiation of treatment options where possible, sensory modulation strategies, comfort room, exercise facilities, group activities, debriefing after restraint and seclusion, and exit interviews. A consumer consultant was employed to work on the ward. The results of the debriefing and exit interviews were reviewed by unit staff at a regular multidisciplinary meeting and by a restraint and seclusion minimization committee chaired by a senior peer specialist. The exit interview, consisting of thirteen questions, was offered to all consumers as they left the unit. Data for 3 months is presented. The exit interview was designed to sample consumers' views about their admission to the unit, their interaction with staff, their involvement in discussion about treatment options, their experience of coercive interventions, debriefing after restraint and seclusion, the safety care plan, perceived strengths and weakness of the unit, and suggestions for improvement of the unit.

Results: 63 of 84 patients completed an exit interview (75%). Their average age was 38 years (range 20–62), gender male to female 2:1. The most common diagnoses were schizophrenia (32%), drug induced psychosis (18%), bipolar disorder - manic episode (18%). The average length of stay was 11.5 days. 14% of consumers were Aboriginal or Torres Strait Islanders and 11% were forensic consumers. Nearly half (48%) of respondents did not believe that they should have been admitted to an intensive care unit. Recurring themes that emerged from the analysis of the responses included the importance of the ward environment, reciprocal relationships with staff and adequate discussion about treatment options. 70% of respondents perceived staff to be approachable and helpful; however 50% of respondents were unhappy with the manner in which their treatment and in particular medication was discussed with them. 38% identified the environment as the most helpful aspect of their stay in the unit although 20% of respondents suggested that the physical environment could be improved. Five respondents (8%) reported that they had been physically restrained or secluded. They reported negative views about this. Only 13% were opposed to the non-smoking policy.

Discussion: This study aims to give consumers a greater voice in shaping

services in a psychiatric intensive care unit. The results highlight a number of important issues related to the environment, interaction with staff, and negotiation of treatment options, that can be used to guide the further development of services in the acute setting. A more positive experience in the acute setting is likely to lead to better engagement with mental health clinicians in all areas of the service.

Poster #M261

HEALTH SERVICE AND RESOURCE USE AT 12 YEARS IN FIRST EPISODE PSYCHOSIS

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Background: Planning services is increasingly important in times of constrained resources. By identifying those more likely to require contact with mental health services in the longer term, we can target need specific interventions earlier in the course of illness. This study examines health service use at 12 years in a first episode cohort attending the adult community mental health services. The aim of the study was to identify potential predictors and characteristics of long term contact with mental health service in a cohort of people with first episode psychosis (FEP).

Methods: The cohort consisted of an epidemiological sample of individuals with FEP who first presented to the adult mental health services from 1995-1999 (n=171) and were followed up at 12 years. The follow-up rate by face to face interview was 68.4%. Information on health service use (HSU) was collected using Client Socio-Demographic and Service Receipt Inventory (CSSRI). Data was analysed using PSAW SPSS version 20. Chi squared tests, Mann-Whitney tests and independent t-tests were used to examine relationships between variables.

Results: There was no difference in baseline socio-demographic or clinical characteristics between those followed-up and not followed-up. At 12 years, 41% were in contact with adult mental health services alone and 27% were in contact with both their general practitioner and adult mental health services. 19% were in contact with their GP alone and 15% were not in contact with any service. At the 5% significance level there was no relationship between duration of untreated psychosis (DUP) ($p=0.3$), duration of untreated illness (DUI) ($p=0.4$) or baseline global assessment of functioning (GAF) (NS) and being in contact with health services in the longer term. Having mania like symptoms as described by the excitement factor subscale of the PANSS predicted HSU at 12 years ($p<0.04$). Those in contact with health services at 12 years had lower GAF scores indicating a lower level of functioning ($p\leq0.002$), a diagnosis of schizophrenia spectrum disorder ($p<0.04$) and made significantly more suicide attempts during the 12 years than those who were not ($p=0.01$).

Discussion: There is a subgroup at baseline that have hostility, uncooperativeness, excitement and poor impulse control as demonstrated by the excitement subscale of the PANSS. This group had heavier service and resource use at 12 years. No other predictors of long term service use were identified at baseline. It was clear from the socio-demographic characteristics at 12 years that those in contact with services were more vulnerable – they were less likely to be married, to be employed, to have good levels of functioning and were more likely to have medical cards and be on social welfare. Implications from this study are that need specific services such as identification and management of suicide risk, interventions to improve functioning and early identification and treatment of illness are important.

Poster #M262

ACUTE MEDICAL CARE UTILISATION IN PSYCHIATRIC INPATIENTS

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Background: Standardised mortality ratios are about double the population average in the year after a mental health admission, yet there is a relative paucity of research on general medical care for psychiatric in-patients. Psychiatrists in inpatient units are not merely providing treatment for patients' mental health. Rates of medical co-morbidity are high and people may have neglected their physical health needs prior to admission. In recent years, as the threshold for psychiatric admission has risen with the increasing sophistication of home treatment services, people requiring psychiatric admission are especially ill, thus increasing the practical challenges of providing physical health care.

Methods: A retrospective database analysis was performed to ascertain the frequency and pattern of acute medical care use of psychiatric inpatients, including rates of attendance at A&E and admission to general hospitals. Data was gathered through a static linkage between anonymised clinical records in the Clinical Record Interactive Search (CRIS) database in the South London and Maudsley NHS Foundation Trust (SLaM), and the Hospital Episode Statistics (HES) database over a one year period from 14th December 2010 to 13th December 2011. Data is presented by (a) psychiatric admission episodes and by (b) numbers of psychiatric inpatients in relation to (c) general hospital admission episodes and general hospital A&E visits.

Results: During the study period 4674 patients in total (2483 male patients) were admitted to SLaM psychiatric inpatient beds, and there were 8023 SLaM psychiatric inpatient admission episodes, giving a total of 358666 bed days (201317 days used by males). Over the one year study period, sixteen percent (n=740) of psychiatric inpatients were admitted to a general hospital, during the course of 831 psychiatric admission episodes. The mean duration of general hospital admission was 7 days per person admitted to a general hospital from a psychiatric inpatient bed. Eighteen percent (n=855) of psychiatric inpatients were referred to A&E over the study period. Patients were simultaneously registered as occupying beds in both general and psychiatric hospitals for a total of 5163 bed days at a cost of £2.4 million. Fifty percent of these hospital admission episodes were associated with diagnoses of psychotic or affective illnesses, with 26% (n=218) having a diagnosis of schizophrenia, schizotypal disorder or delusional disorder and 24% (n=196) a diagnosis of an affective disorder (including bipolar affective disorder and depressive disorder).

Discussion: Our study provides the largest retrospective analysis of general hospital and A&E usage by psychiatric inpatients. This large and inclusive population based linkage indicates a high rate of general hospital utilisation by psychiatric inpatients, much unplanned. The need for integrated, flexible practical approach to the medical care of psychiatric inpatients is highlighted, with the aim of reducing unplanned care. The psychiatric inpatient setting remains overwhelmingly the central point of inpatient care for individuals with SMI and thus could provide the optimal setting for such an integrated package of medical and psychiatric care. However, this is a question which remains unresolved, without there being any randomised trials assessing the benefits or otherwise of such an integrated approach. These study findings would indicate that such an intervention should be assessed under randomised trial conditions, to assess the impact on the rates of general hospital and A&E admissions, the duration of psychiatric hospitalisation and medical and psychiatric functional outcomes.

Poster #M263

CLOZAPINE PRESCRIPTION TO TREATMENT-RESISTANT SCHIZOPHRENIA PATIENTS IN COMMUNITY MENTAL HEALTH SERVICES IN SÃO PAULO, BRAZIL

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Background: Despite guidelines recommendations of clozapine use in

treatment-resistant (TR) schizophrenia, this drug remains under-used for this group of patients. To evaluate the patterns of clozapine and other antipsychotic drugs prescription to the TR schizophrenia patients in community mental health services of São Paulo, Brazil.

Methods: In order to identify the TR schizophrenia patients, a multiple-choice questionnaire was applied to fifteen psychiatrists at five services inquiring about patients' clinical condition, adherence to oral treatment and current antipsychotic treatment. History of previous and current antipsychotic treatment was collected through medical chart review. Obstacles to prescribing clozapine were investigated through an open questionnaire.

Results: Out of 442 schizophrenia patients, 103 (23.3%) fulfilled the criteria for TR schizophrenia. Fifty-eight patients (56.3%) were receiving polypharmacy; 30 (29.1%) were on atypical antipsychotic monotherapy, 14 (13.6%) were on typical antipsychotic monotherapy, and 25 (24.3%) were taking depot antipsychotic medication. Only 22 (21.4%) patients were receiving clozapine and there was no evidence that the drug was ever suggested to the patients. Psychiatrists pointed "blood counts" and "laboratory delays" as the main obstacles to prescribe clozapine.

Discussion: Although the Government subsidizes clozapine distribution, the large majority of the TR patients (78.6%) do not receive proper treatment. Instead of providing clozapine, the best evidence-based medication for TR schizophrenia, psychiatrists prescribe antipsychotic polypharmacy. Government authorities should make every effort to provide these services with medical training and the necessary equipment and logistic support to adequately serve those patients who could benefit from clozapine treatment.

Poster #M264

DIFFERENCES IN CANNABIS-RELATED EXPERIENCES BETWEEN PATIENTS WITH A FIRST EPISODE OF PSYCHOSIS AND HEALTHY CONTROLS

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Background: Many studies have suggested that cannabis use can increase the risk of a first-episode of psychosis (FEP). Until now only a few studies have investigated the nature of cannabis-related experiences in FEP patients, and none has examined whether these experiences are similar in the psychotic and normal populations. The aim of this study, therefore, was to explore the differences between general and FEP populations.

Methods: 252 subjects, who met ICD10 criteria for FEP and 217 healthy controls, were selected from the Genetic and Psychosis (GAP) samples, on the basis of their having previously used cannabis. The Medical Research Council Social Schedule and the Cannabis Experience Questionnaire were used to collect socio-demographic data and information about of cannabis use respectively.

Results: The following experiences were more commonly reported by the FEP patients than controls: feeling like going mad ($\chi^2=13,729$; $p=0,001$), feeling nervous ($\chi^2=12,287$; $p=0,002$), feeling suspicious without a reason during ($\chi^2=9,556$; $p=0,002$); and after the effect of cannabis worn off ($\chi^2=6,737$; $p=0,034$), feeling happy ($\chi^2=10,439$; $p=0,005$), feeling full of plans ($\chi^2=8,544$; $p=0,014$), hearing voices ($\chi^2=10,644$; $p=0,005$), difficulty to concentrate ($\chi^2=13,496$; $p=0,001$) and not being able to think clearly after the effect of cannabis had worn off ($\chi^2=9,887$; $p=0,007$). Through factor analysis, four components were found (Cognitive Experiences, Pre-Psychotic Experiences, Enjoyable Experiences, Psychotic Experiences) which explained 61,82% of the variance. Linear regression analysis showed that a positive psychotic family history, gender, age of first cannabis use, type and frequency of cannabis use, and genetic susceptibility all contributed to determining both intensity and frequency of these experiences with the exception of Enjoyable Experiences.

Discussion: These results suggest a higher sensitivity to cannabis use for people who have First Psychotic Episode; this hypersensitivity is not only for "bad experiences" but also for "enjoyable experiences".

Poster #M265

THE IMPORTANCE OF PHARMACOLOGICAL AND NON-PHARMACOLOGICAL FACTORS FOR THE DEVELOPMENT OF ORGAN LESIONS AND OCCURRENCE OF "SUDDEN CARDIAC DEATH" IN PATIENTS WITH SCHIZOPHRENIA. A PhD PROJECT AS PART OF SURVIVE

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Background: The mortality of persons diagnosed with schizophrenia is more than doubled and life expectancy reduced by up to 25 years, when compared to the general population. Pharmaceuticals used in the treatment of schizophrenics, such as antipsychotics, have numerous side effects such as weight increase, hyperglycaemia, hypercholesterolemia, and hypertension. Each of these conditions predispose for developing cardiovascular disease. Furthermore, obesity, hyperglycaemia, hypercholesterolemia and hypertension are among the criteria used to diagnose the Metabolic Syndrome (MetS). The occurrence of MetS is related to increased risk of developing cardiovascular diseases and Type 2-Diabetes; the more of the components of MetS are present, the higher the cardiovascular mortality rate. Numerous studies have documented, that the prevalence of MetS is increased among schizophrenics compared to the general population. The purpose of this PhD project is to identify causes of death among schizophrenics and identify new prognostic markers for MetS and cardiovascular disease, respectively, among schizophrenics.

Methods: "SURVIVE: Let the dead help the living" is a prospective, autopsy-based study. The study is a nation-wide and cross-disciplinary project between the three departments of forensic medicine in Denmark. The overall study includes thorough analysis in each case, such as computed tomography scanning, forensic toxicological analysis, and genetic testing. A detailed algorithm has been developed to ensure autopsies are performed in a strictly standardized way. The project includes all cases of known or suspected mental illness and all cases of known or suspected treatment with antipsychotic pharmaceuticals that are subject to medico-legal autopsy during the two-year study period. Based on retrospective studies it is estimated, that approximately 500 persons are included. This PhD-project will focus on the detection of organ lesions and their possible association with consumption of antipsychotic pharmaceuticals and lifestyle factors. As some antipsychotics are associated with myocardial fibrosis, thorough examination of the myocardium by stereology will be performed. This includes special histological staining and development and validation of stereological analysis of fibrosis are performed.

Results: Inclusion of cases started May 1, 2013 resulting in 140 cases during the first 6 months. If the inclusion rate continues unchanged, approximately 560 cases are included; all cases that will be included in this PhD-study, as it runs for a period of three years, starting November 1, 2013.

Discussion: We will contribute towards giving the mentally ill a better and longer life. SURVIVE is a unique research cooperation, we want to identify risk factors for deaths among schizophrenic patients in Denmark using autopsy-based studies. Autopsies of the schizophrenics can clarify a number of conditions including diseases of the heart and liver, obesity and excessive use of medicine by studies that would otherwise be impossible. SURVIVE wants to link autopsy results directly to clinical medicine and disease prevention. Addressing new technologies in a combined genetic, metabolic and toxicologic approach to death on an autopsy material in a "bottom up" method (going from the dead to the living), a new and groundbreaking concept.

Poster #M266

CLINICAL CHARACTERISTICS IN EARLY ONSET FIRST-EPISTODE PSYCHOSIS WITH CANNABIS USE

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Background: Previous studies have demonstrated an association between

cannabis use and an earlier onset of psychosis. Exploration of the sociodemographic and clinical characteristics in association with cannabis use in adult-onset first-episode psychosis (FEP) has resulted in inconsistent findings. Moreover, whilst cannabis exposure in early adolescence further increases the risk of developing psychosis, characteristics in adolescents with FEP remain widely understudied. We aimed to compare the frequency of cannabis use between adolescent- and adult-onset FEP, and explore the sociodemographic and clinical characteristics associated with cannabis use in a) the overall population with FEP, and b) in those with adolescent-onset FEP.

Methods: In this naturalistic cross-sectional study, sociodemographic and clinical data were collected using the MiData [1] audit tool for all new FEP referrals to Early Intervention Services (EIS) for psychosis, between 2003–2009, fulfilling the following criteria: i) age 14–35; ii) first presentation to mental health services within the last year; iii) <6 months antipsychotic treatment for psychosis; iv) ≥1 week of unremitting positive psychotic symptoms at presentation to EIS. Data was obtained from nine EIS teams covering a population of 2.7 million in London, UK. Clinical assessment scales utilised were: Drake Substance Misuse Scale to measure substance use in the preceding six months, Positive and Negative Syndrome Scale and Young Mania Rating Scale to assess the severity of psychopathology, Global Assessment of Functioning Scale, Brief Psychiatric Rating Scale to measure violence, and the Nottingham Onset Schedule to record age of onset of psychosis and duration of untreated psychosis (DUP).

Results: Over a quarter of individuals reported cannabis abuse/dependence in the total sample. These individuals were more likely to be male ($\chi^2(1)=20.20$, $p<0.001$), White ($\chi^2(4)=16.70$, $p=0.002$) and unemployed ($\chi^2(4)=18.55$, $p=0.01$). In the total sample, cannabis abuse/dependence was associated with an earlier onset of psychosis by 2.0 years ($U=31587.0$, $p<0.001$), greater manic and positive (but not negative) psychotic symptoms ($U=36963.0$, $p<0.001$, and $U=36282.5$, $p<0.001$ respectively), poorer functioning ($U=40819.5$, $p=0.013$), less insight ($U=34043.0$, $p=0.003$) and increased violence ($U=42939.5$, $p=0.011$). There was no significant difference in the frequency of cannabis use between adolescents and adults ($\chi^2(1)=0.545$, $p=0.460$). In adolescents, cannabis abuse/dependence was associated with greater positive psychotic symptoms ($t(73)=-2.65$, $p=0.010$), poorer functioning ($t(75)=2.20$, $p=0.031$) and a longer DUP by 9.7 months ($U=377.5$, $p=0.032$).

Discussion: Similar frequencies of cannabis use amongst adolescents and adults suggest that substance misuse services should be provided to both age-groups with FEP, with a view to reducing consumption and further decline. Cannabis users had an earlier onset of psychosis, more severe symptomatology and reduced functioning in the overall population with

FEP, as well as a prolonged DUP in the adolescent age-group. Greater vigilance amongst clinicians is required to enable earlier detection of FEP in substance misusing adolescents, to reduce DUP and minimise associated poor outcomes. Further work into the association between functioning and positive/manic symptoms in cannabis users is needed to determine whether functioning can be improved through the treatment of symptoms.

References:

- [1] Fisher H, Theodore K, Power P, Chisholm B, Fuller J, Marlowe K. et al. Routine evaluation in first episode psychosis services: feasibility and results from the Mi-Data project, *Social psychiatry and psychiatric epidemiology* 2008; 43:960–7.

Poster #M267

DOES SUBSTANCE ABUSE INCREASE THE RISK OF SCHIZOPHRENIA?

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Background: This study will aim to examine whether people with a diagnosis of substance use disorder or people having received treatment for substance use disorder will develop schizophrenia or a psychotic disorder more frequently than the background population. The Danish National Health Board estimates, that 60–70% of people with substance use disorders in Denmark have psychiatric comorbidity. A few studies have already postulated a causal link between cannabis and psychosis, suggesting that adolescence exposure to cannabis increases the risk of later psychotic illness. Cannabis has also been found to impact negatively on dimensions related to psychosis e.g. symptom levels, psychiatric hospitalization rates and antipsychotic medication adherence. The existing research on risk factors for schizophrenia and psychosis is however still insufficient; hence we are interested in investigating whether the substance use is preceding the psychotic symptoms to evaluate a possible causal link.

Methods: The study population will be all people born in Denmark from 1955 to 1999. Data on abuse will come from the national "Substance Abuse Database" and the "Psychiatric Central Registry", and this register will also contain information regarding all psychiatric admissions. Substances will be alcohol, cannabis, ecstasy, opioids and other related substances. Psychiatric illness will primarily be schizophrenia and related psychotic disorders. Data sources will be: Psychiatric Central Registry, Substance Abuse Database, National Alcohol Treatment Registry, National Patient Registry, CPR-Registry, National Prescription Registry and Statistics Denmark.

Results: The data analyses are not run yet, so no results are present at the moment.

Discussion: The discussion is not considered yet.

Poster Session**TUESDAY POSTER SESSION****Poster #T1****PREVALENCE AND CORRELATES OF HIV RISK BEHAVIOUR AMONG PERSONS WITH SCHIZOPHRENIA IN SOUTHWESTERN NIGERIA**Olukayode Abayomi

Ladoke Akintola University of Technology Teaching Hospital

Background: Despite being recognized as a significant health and social problem, little is known about HIV risk behavior in persons with schizophrenia in Nigeria. This study aimed to determine the prevalence of HIV risk behaviour and associated clinical variables among persons with schizophrenia.

Methods: This was a cross-sectional study of persons with ICD-10 diagnosis of schizophrenia presenting consecutively at two major hospitals in southwestern, Nigeria. Participants completed structured and standardized measures including HIV risk screening instrument (HIS) and Alcohol use disorder Identification Test (AUDIT-C).

Results: Out of 98 patients invited, 95 (96.9%) participated in the study. The mean age of respondents was 32.3 years (SD = 8.71). Majority of the subjects were male (71.4%), never married (64.3%) and had attained secondary level of education (62.2%). Lifetime and past year alcohol use were 59.2% and 43.5% respectively. Tobacco and cannabis use were reported by 26.5% and 20.4% respectively. Significant proportions of sexually active respondents were aged 26–35 years ($\chi^2=7.83$; $p=0.02$), married ($\chi^2=11.54$; $p=0.001$) and female ($\chi^2=5.54$; $p=0.019$). Up to 79.6% of the respondents had a lifetime history of sexual activity. The prevalence of HIV risk behaviour was 47.4%. About 36.8% of the participants reported two or having more sexual partners, 11.6% reported a sexually transmitted disease (STD), 14.7% reported sex trading and no reports of intravenous drug use were made. Up to 16.8% reported a single risk factor, 13.7% had two risk factors and 16.8% had three or more risk factors. HIV risk behaviour was significantly likely to be related to alcohol use ($p=0.004$; OR=3.55; 95% CI = 1.50–8.36), tobacco use ($p=0.004$; OR=4.26; 95% CI = 1.59–11.45), cannabis use ($p=0.032$; OR=3.18; 95% CI = 1.10–9.15).

Discussion: Screening for risky behaviour in mental health settings may facilitate identification of vulnerable persons with schizophrenia. Future research needs to focus on developing culturally appropriate strategies for HIV prevention in this population.

Poster #T2**PERSPECTIVE-TAKING ABILITIES IN THE BALANCE BETWEEN AUTISM TENDENCIES AND PSYCHOSIS PRONENESS**Ahmad Abu-Akel, Stephen Wood, Peter Hansen, Ian Apperly

University of Birmingham, UK

Background: The relationship between schizophrenia and autism has been an issue of debate since autism was first described, and current clinical reality suggests that absolute forms of the disorders are in fact not the norm. Several recent lines of evidence suggest that these disorders co-occur at a higher than expected rate and can themselves be mutual risk factors. Both disorders are also thought to exist on extended phenotypic continua, with overlapping diagnostic and non-diagnostic traits. Despite evidence for such overlaps, no studies to date have examined the impact that diagnostic or trait-level co-occurrence could have on cognition and behavior. Socio-cognitive difficulties are a core feature of both disorders, and are variably affected by the degree of their severity. On the assumption that both autistic and psychotic tendencies exist on a continuum, ranging from normality to disorder, one approach to evaluating the impact of co-occurring traits on social cognition is by examining the association of psychosis proneness and autistic tendencies among non-clinical populations. It is predicted that socio-cognitive difficulties will uniquely be associated with increased autism tendencies and psychosis proneness. In addition, autism tendencies and psychosis proneness are predicted to have an interactive effect on socio-cognitive difficulties.

Methods: The socio-cognitive abilities of 201 healthy adults (43 males, 158 females; ranging from 17–51 years old) were examined using Apperly

et al.'s (2010) variant of the Keysar et al. (2000) referential communication task in which participants are required to follow the instructions of a co-participant (a director). Specifically, in this task the participant is required to accommodate the director's requests/instructions based on inferences one should make of the director's state of knowledge. Psychosis proneness was assessed using the Community Assessment of Psychic Experiences (CAPE) Questionnaire, and autism tendencies were assessed using the Autism Spectrum Quotient (AQ) Questionnaire. Participants were excluded from the study if they had a history of psychiatric illness, epilepsy, neurological disorders, suffered brain injury or may have current alcohol or substance abuse problems.

Results: A Poisson regression mixture model indicates that participants made more perspective-taking errors as a function of increased psychosis proneness and autism tendencies. But surprisingly, their interaction was associated with a decrease in perspective-taking errors. In a further analysis, the occurrence of perspective-taking errors was associated with the relative dominance of autism proneness or psychosis proneness, following a U-shape pattern.

Discussion: The current study supports the continuity/dimensional models of autism and schizophrenia spectrum disorders and suggests that sub-clinical manifestations of core disease features are detectable in a healthy population and can influence socio-cognitive abilities. The association of the interaction between autistic tendencies and psychosis proneness with a decrease in perspective-taking errors can be seen as support for the diametrical model (Crespi and Badcock, 2008) which posits that autism and schizophrenia have opposing effects on behavior and cognition. While the mechanisms underlying such diametric influences are not apparent, it is intriguing to entertain the possibility that autism-schizophrenia comorbidity can have an attenuating effect on socio-cognitive difficulties similar to the "normality effect" that is observed in certain co-occurring pathologies such as Parkinson disease and hemiballismus.

Poster #T3**PREDICTORS OF THEORY OF MIND AND SOCIAL FUNCTIONING IMPAIRMENTS IN PATIENTS WITH RECENT-ONSET OF PSYCHOSIS**Amelie M. Achim^{1,2}, Marc-André Roy^{1,3}, Marie-Audrey Lavoie¹, Philip Jackson¹¹Université Laval; ²Centre de Recherche de l'Institut Universitaire en Santé Mental de Québec, Canada; ³Institut Universitaire en Santé Mentale de Québec, Canada

Background: Theory of Mind (ToM) is more affected than other cognitive and social cognitive abilities in patients with first-episode psychosis (FEP) and these deficits appear linked to these patients' social functioning similarly to what is observed in chronic schizophrenia. Getting a better understanding of ToM deficits and how they impact functioning is thus of particular interest in the early stages of psychosis given the importance of this period for promoting recovery.

Aims: Our work aims to further understand the mechanisms leading to ToM deficits and their functional consequences in people with FEP.

Methods: Using a complete social cognition test battery, we examined whether the scores of several social cognition measures were predictive of social and occupational functioning (measured with the SOFAS) in 59 patients from our first-episode clinic in Quebec City, Canada (70% with schizophrenia, 17% schizoaffective disorder, 13% other). The social cognition test battery included measures of ToM, social knowledge, and emotion recognition, as well as a control condition consisting of short stories with non-social (physical) reasoning questions. Given that social anxiety is also increasingly recognized as having a strong influence on functioning in schizophrenia, we assessed the direct effect of social anxiety on functioning and its moderating effect on the relationship between social cognition and functioning.

Results: Path analyses revealed that only ToM was a significant direct predictor of functioning in our FEP patients (unstandardized path coefficient (UPC)= 6.43, SE=2.15, $p=0.004$), whereas social knowledge and general non-social reasoning had a significant indirect effect on functioning through their respective effects on ToM (CI = 0.3–2.4 and CI = 0.4–6.1, respectively). Interestingly, moderated mediation analyses revealed a significant mediation effect (UPC=−0.80, SE=0.33, $p=0.02$) indicating that non-social reasoning was significantly affecting ToM performance and hence function-

ing in patients without social anxiety ($CI = 1.2\text{--}13.1$) but not in patients with social anxiety ($CI = -0.08$ to 4.0).

Discussion: ToM was the best direct predictor of functioning in this sample of FEP patients. Social knowledge and general non-social reasoning also impacted functioning, but the effects were indirect because they went through ToM ability and/or were specific to patients without social anxiety. Patients with and without social anxiety might have different underpinnings to their ToM deficits and hence different treatment needs.

Poster #T4

VALUE RECALIBRATION IN FIRST-EPIISODE SCHIZOPHRENIA

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Background: In addition to positive, negative, and cognitive symptoms, schizophrenia is characterized by mild to severe functional deficits that reflect poor vocational and psychosocial engagement. The various factors contributing to these deficits remain to be elucidated, although the impact is profound. In general, these deficits respond poorly to treatment but account for the majority of economic burden produced by schizophrenia. It is important to better understand these functional deficits if we are to improve the prognosis of schizophrenia in this regard. Schizophrenia and its treatment are extremely disruptive to the established lifestyle of the patient, routinely resulting in decreased participation in valued activities (Bettazzoni, 2008). Cognitive deficits may also preclude typical goal-related behaviors, possibly contributing to changes in value structures that better align with the substantial changes in lifestyle. This notion of some form of value recalibration fits with more recent evidence that patients with first-episode schizophrenia are just as happy as healthy controls (Agid, 2012). Values are affectively infused criteria or motivational goals used to select and justify or evaluate actions, people, and the self (Schwartz, 1992). There are 10 basic, independent human values, each with their own motivational content that range in importance to the individual (Schwartz, 1992). These values are organized along a quasi-circumplex of motivational conflicts and compatibilities, meaning that, along the circle, those values close to each other share similar motivations whereas those across from each other represent conflicting motivations. The importance of any one value as well as the hierarchical organization of values can differ between individuals. Within individuals, value systems change while maintaining the basic quasi-circumplex model (Maio, 2009), particularly following the occurrence of major life-changing events, such as the onset of schizophrenia (Bardi, 2011). Thus, the objective of this study was to assess the value structure of patients with first-episode schizophrenia in comparison to healthy controls.

Methods: Fifty-six first-episode patients in remission (age = 26 [4.7] years) were randomly recruited from the outpatient division of a First-Episode Schizophrenia Program in Toronto, Canada. Fifty-six age and sex matched healthy controls were recruited and screened for possible DSM-IV diagnoses. Participants completed the Schwartz Values Survey along with demographic and clinical questionnaires. Using Structural Equation Modeling and Multidimensional Scaling Smallest Space Analysis, results confirmed that both samples' value structures conformed to the theoretical model.

Results: Patients with schizophrenia reported functioning at low levels (SOFAS=56.2) and placed significantly more priority on the value dimensions of Tradition ($p=0.019$) and Power ($p=0.029$), and significantly less priority on Self-Direction ($p=0.007$) and Stimulation, ($p=0.008$). Significant correlations between value dimensions and functional measures were found within the patient group.

Discussion: The present findings support a recalibration of values in schizophrenia soon after or even before the illness' onset. When compared to healthy controls, this recalibration in first-episode schizophrenia may help explain the differences exhibited in terms of goals and behavior, as well as the difficulty in engaging this population in functional rehabilitation programs. Of note, personal value systems may be amendable to change outside of life-altering events (Bardi, 2011), and it is possible that these techniques could be applied to functional rehabilitation programs to increase their efficacy.

Poster #T5

ESCALATED SOCIAL AGGRESSION AND EXTRACELLULAR SYNAPTIC ACTIVITY AFTER BLOCKAGE OF NMDA AND mGluR1 RECEPTORS IN CENTRAL NUCLEUS OF AMYGDALA IN DEVELOPMENTAL SCHIZOPHRENIC MODEL

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Background: Impaired social interactions are a hallmark of schizophrenia and improvement of social skills is an important element in treatment and outcomes for individuals with the disease. A significant minority of individuals engages in escalated levels of aggression after rearing social Isolation. Interactions between cells and the extracellular matrix (ECM) have long been accepted to have pivotal roles in neural development. Isolation rearing in rats from weaning produces a range of persistent behavioral and ECM changes in the young adult, including hyperactivity in response to novelty and altered responses to conditioning. These are associated with alterations in neurotransmitter functions such as glutamate in the mesolimbic areas and other brain regions.

Methods: Present study investigated whether isolation rearing alters effect of the MK801 and LY367385 selective antagonist of ionotropic and metabotropic of glutamate receptors, N-methyl D aspartate (NMDA) and metabotropic glutamate receptor 1 (mGlur1), was examined behavioral and electrophysiological tests into central nucleus of amygdala (CeA) to further characterize cognitive disorders in post weaning social isolation model and explore possible neurobiological mechanisms associated with them. Isolation rearing was performed in male Wistar rats from weaning for 6-8 weeks. There was no distinction between behavior or corticosterone levels in drug-free isolates or socially housed rats.

Results: Social isolation of rats for 8 weeks prior to the experiments caused a significant increase of scale of aggressive behaviors ($p<0.05$), as well as increase significantly the amplitude with low duration on synaptic activity waves in single unite recording compared with socially rats ($p<0.004$). After the administration of MK801 (1 μ g/kg) and LY367385 (1 μ g/kg) into CeA indicated the increase percentage of aggressive behaviors ($p<0.02$, $p<0.04$), furthermore the amplitude of synaptic activity in MK801 was increased but on LY367385 was taken not any changes in electrophysiologically activity.

Discussion: These results indicate that increased Antagonist of NMDA receptor responsiveness accompanies isolation-rearing and may contribute to the enhanced response to stress and the increased aggressive behaviors in this animal model. In isolation reared rats, rapid up-regulation of sensitive NMDA and mGluR1 receptors may occur in the CeA following glutamate receptors antagonist challenge.

Poster #T6

CHILDHOOD TRAUMA, FKBP5 GENE AND PSYCHOTIC EXPERIENCES IN GENERAL POPULATION

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Background: Childhood adversity is a recognized environmental risk factor for psychosis (Varese et al 2012). A neurobiological mechanism proposed to underlie the link between childhood trauma and psychosis involves dysregulation in the hypothalamic-pituitary-adrenal (HPA) axis, a key system in stress response (Van Winkel et al 2008). Thus, genes involved in the HPA axis regulation can be plausible candidates to be considered when examining genetic vulnerability for the negative effects of childhood adversity (Van Winkel et al 2008). In this regard, the FKBP5 is a co-chaperone of heatshock protein 90 (hsp90) which regulates glucocorticoid receptor (GR) sensitivity (Binder, 2009). Single nucleotide polymorphisms (SNPs) in the gene encoding FKBP5 (FKBP5 gene) have been shown to associate

with differential upregulation of FKBP5 following GR activation and differences in GR sensitivity and stress hormone system regulation. Interestingly, variability at the FKBP5 gene has been found to interact with childhood trauma to present subclinical psychosis (Collip et al 2013). The current study was aimed to extend research on this gene-environment interaction (GxE) effect by examining the putative moderating role of the FKBP5 gene in the association between childhood adversity and psychotic experiences (PEs).

Methods: PEs, childhood abuse, and the rs1360780 SNP of the FKBP5 gene were assessed in 533 individuals from the general population (Mean age: 23 years; SD=5; 45% males). The Community Assessment of Psychic Experiences (CAPE; Stefanis et al 2002) was used to assess positive and negative PEs. Childhood abuse was assessed by the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink 1998). Data were analysed hierarchically by means of multiple linear regression models. All analyses were corrected by sex, age, schizotypal personality and anxiety levels.

Results: Childhood abuse was positively and significantly associated with positive ($B=0.15$; $SE=0.04$; $p=0.001$) and negative PEs ($B=0.11$; $SE=0.05$; $p=0.007$). Main genetic effects were only found in negative PEs ($B=0.11$; $SE=0.30$; $p=0.004$). A significant gene-environment interaction was detected between childhood abuse and the FKBP5 gene with regard to positive PEs ($B=0.16$; $SE=0.06$; $p=0.006$). Homozygotes for the T allele presented significantly higher scores of positive PEs when exposed to childhood abuse compared to homozygotes for the C allele; heterozygotes were in an intermediate position.

Discussion: The main finding of the present study was that the rs1360780 SNP of the FKBP5 gene moderated the relationship between childhood abuse and positive PEs. The T allele is associated with enhanced expression of FKBP5 leading to a prolongation of the activation of this system. Our findings suggest that this dysregulated stress response may be involved in the pathophysiology of subclinical psychosis. Furthermore, this result is in line with the recently reported gene-environment interaction effect (Collip et al 2013). Interestingly, although this gene-environment effect was not observed in negative PEs, a main genetic effect was found on this dimension presenting the T carriers higher scores on negative PEs compared to CC genotype carriers. Further research and replication is needed to establish the role of this HPA axis gene in the vulnerability and etiology of psychosis. Supported by the Ministry of Science and Innovation (SAF2008-05674-C03-00; PNSD2008-I090; PNSD2009-I019), the Institute of Health Carlos III, CIBER of Mental Health (CIBERSAM), the Comissionat per a Universitats i Recerca, DIUE, Generalitat de Catalunya (2009SGR827) and Fundació Caixa Castelló-Bancaixa (P1• 1B2010-40 and P1• 1B2011-47).

Poster #T7

FAMILIAL LIABILITY, THE BDNF-VAL66MET POLYMORPHISM AND PSYCHOTIC-LIKE EXPERIENCES

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Background: Familial liability to both severe and common mental disorder predicts psychotic disorder, psychotic symptoms and psychotic-like experiences (PLe). However, the relation between familial liability and psychosis outcome may be associated with genetic variation. We investigated the influence of familial liability on PLe in a nonpsychotic, general population based group, and the potential moderating effect of the BDNFVal 66Met polymorphism.

Methods: PLe and familial liability were assessed in 313 individuals (mean age 38.6 ± 13.3 ; gender: 43% males). Familial liability was obtained using the questions from Family Interview for Genetic Studies and dichotomized to none or at least one mental disorder in the first degree relatives (parents and siblings). PLe (visual and auditory hallucinations) were assessed through relevant questions in CIDI 2.1 G section on psychotic disorders. The sample underwent clinical reinterviews with the Structured Clinical Interview for DSMIV. BDNF val66met (rs6265) was genotyped using standardized procedures.

Results: Familial liability was associated with PLe (OR=1.8; CI: 1.1–3.0; $p: 0.012$). The association between familial liability and PLe was significant in individuals with Val/Val allele (OR=2.2; CI: 1.2–4.1; $p: 0.009$) whereas there

was no evidence for an association between familial liability and PLe in Met carrier individuals.

Discussion: Individuals with a familial liability for mental disorders are more likely to report PLe. Val/Val genotype reported more PLe when exposed to familial liability than did individuals carrying Met allele. Therefore, the observed gene-environment interaction effect may be partially responsible for individual variation in response to familial liability.

Poster #T8

EFFICACY AND SAFETY OF OLANZAPINE LONG-ACTING INJECTION IN PATIENTS WITH SCHIZOPHRENIA: A POST-HOC ANALYSIS OF A 6-YEAR, MULTINATIONAL, SINGLE-ARM, OPEN-LABEL STUDY

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Background: The purpose of this post-hoc analysis was to assess the long-term efficacy and safety of olanzapine long-acting injection (LAI) in the treatment of schizophrenia, focusing on clinical trial data that is consistent and in accordance with stipulations from regulatory authorities and which, therefore, physicians would find relevant to their clinical practice.

Methods: This was a post-hoc analysis of an open-label extension study of olanzapine LAI in patients (male or female, 18 to 75 years old) with schizophrenia. Patients were flexibly dosed (45 to 405 mg, 2- to 4-week intervals). However, those patients receiving oral olanzapine supplementation whose total olanzapine dose was >20 mg/day equivalent were excluded from this post-hoc analysis. Efficacy was assessed with the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression-Severity of Illness (CGI-S) scale, and the Patient Satisfaction with Medication Questionnaire-Modified.

Results: A total of 669 patients were included in this analysis (44.7% completed the study). Patients were predominantly male (66.1%) and Caucasian (67.7%); mean age was 39.4 years. The mean duration of patient exposure was 1110 days (approximately 3 years); the longest duration was 2204 days (approximately 6 years). PANSS total scores did not change significantly from baseline to endpoint (-0.26 , $P=0.641$). Improvement in CGI-S scores was statistically, but not clinically, significant. A total of 73.7% of patients reported being satisfied with the treatment. 69.5% preferred olanzapine LAI compared with their last oral medication, and 74.2% thought there were fewer adverse events during treatment with olanzapine LAI. Mean weight increase from open-label baseline was 2.19 kg ($P<0.001$) with 40.8% increasing $\geq 7\%$ from baseline weight. Categorical changes from normal to high (fasting) were observed for glucose (2.4%), total cholesterol (3.6%), and triglycerides (9.3%). A total of 21.1% ($n=61$) of patients developed high prolactin levels. Mean changes in measures of extrapyramidal symptom were not clinically significant: Simpson-Angus Scale total score (-0.18 , $P=0.002$), Barnes Akathisia Scale score (-0.02 , $P=0.327$), and Abnormal Involuntary Movement Scale total score (-0.11 , $P=0.059$). During the observed period of this post-hoc analysis, 24 post-injection delirium/sedation syndrome (PDSS) events (0.07% of injections) occurred in 23 patients on olanzapine LAI. All patients recovered within 72 hours after receiving the injection.

Discussion: The results of this post-hoc analysis provide long-term efficacy and safety information for olanzapine LAI when used for the treatment of schizophrenia in a manner which is consistent and in accordance with stipulations from regulatory authorities. With respect to efficacy, patients showed very little change in PANSS total scores and CGI-S scores, suggesting that the long-term maintenance of treatment effect with olanzapine LAI was clinically successful. Significant decreases in these scores were not expected because patients entered directly from feeder studies in which most were already being treated for their schizophrenia. Patient satisfaction with olanzapine LAI was high. Safety information observed in this post-hoc analysis is generally consistent with the known safety profile of oral olanzapine, with the exception of injection site-related adverse events. Significant increases in prolactin, fasting glucose, cholesterol, triglycerides, and weight were noted. PDSS events occurred in approximately 0.07% of injections. In conclusion, olanzapine LAI appears to be a safe and effective long-term treatment option for schizophrenia, especially for those patients whose adherence and treatment compliance could be a clinical issue.

Poster #T9**THE GOTHENBURG RESEARCH AND INVESTIGATION IN PSYCHOSIS – GRIP – AN INTERDISCIPLINARY NATURALISTIC STUDY WITH THE MAJOR AIMS TO IMPROVE DIAGNOSTICS AND PREDICT OUTCOME IN PATIENTS BELIEVED TO BE SUFFERING FROM A PSYCHOTIC ILLNESS**

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Background: The Psychosis Clinic at Sahlgrenska University Hospital (PC/SU) is the only psychosis clinic within the Gothenburg region – a region with approximately 630 000 inhabitants. The clinic serves roughly 3000 psychosis patients. To make sure that all our patients receive a thorough investigation of the highest standard, an interdisciplinary clinical protocol is in place as of fall 2013. The aim is to improve diagnostics and provide the most adequate support for each patient. This clinical investigation is solely meant to benefit the patient, all parts are of clinical relevance and patients will not be required to perform any parts they are not comfortable with. The investigation consists of a standardized somatic examination, including blood tests, a spinal tap, magnetic resonance imaging (MRI), and a thorough neurological examination. Structured and semi-structured interviews with patients and family members are performed. The aim is to cover broad areas such as family history, patient history, substance habits, and includes well known clinical instruments such as M.I.N.I. and PANSS. We screen for neuropsychiatric diagnosis using BAARS-IV, RAADS-R, and ASSQ. Occupational therapists, physical therapists, psychologist and social workers contribute with validated test batteries. The Gothenburg Research and Investigation in Psychosis – GRIP – is a research project attached to the clinical investigation. Patients who are assessed using the clinical protocol are informed of the study. If the patient choose to give written informed consent, all data collected in the clinical protocol can be coded and used for research purposes. The only difference between patients who take part in the study and patients who do not, is that the blood and liquor from research subjects will be stored for future use (including genetic analyses). All patients will receive regular and structured follow-ups. The major aims of the GRIP study is to: 1. Improve diagnostics by trying to look past DSM-5 and ICD-10, break down diagnostics to smaller subgroups with similar phenotypes, this by combining structured clinical information with genetics, neuroimaging, and liquor analyses. 2. Predict outcome at an earlier stage than today, which we hope will be possible since patients usually remain in the clinic for long periods and will be followed up regularly. 3. Assess effects of interventions at follow-up. The major interest of the presenting author is to see to what extent a high quality MRI scan can provide help with differential diagnostic issues in the near future.

Methods: The GRIP study has been approved by the Swedish Ethics Committee and is conducted in accordance with the Declaration of Helsinki. The study design is naturalistic. We include all subjects given written informed consent and collect data regardless of working diagnosis. No interventions are suggested. The data set will later be sub-grouped depending on the questions analysed by group members with different expertise. The protocol and methods of collecting data will be presented in detail.

Results: So far, 62 patients have been enrolled in the clinical protocol. 10 patients have provided written informed consent, 9 male (mean age 28.2±7.3) and 1 female (age 42). 52 patients have not been asked yet. Preliminary results from the first study sample will be presented and discussed.

Discussion: Our preliminary data will be discussed, as will the protocol and study design in more detail. We hope that this presentation of a new and large study effort will spark a lively discussion leading to new ideas, and we would highly value input that would help us improve the protocol at this early stage.

Poster #T10**ACCEPTABILITY AND FEASIBILITY OF EXTENDED USE OF MOBILE PHONE TECHNOLOGY TO ASSESS PSYCHOTIC SYMPTOMS IN DSM-IV SCHIZOPHRENIA PATIENTS**

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Background: Use of mHealth technology to support experience sampling methods can improve assessment of clinical phenomena in a real world setting, yielding rich individual and cohort data over time. This method reduces retrospective recall bias and symptom averaging whilst providing essential information about context and greater sensitivity to change (Palmier-Claus et al., 2011; 2012). We aimed to demonstrate that use of an ambulant, real-time, self-report assessment method delivered via Smartphone application (ClinTouch) was acceptable, feasible and safe to use over an extended period of time.

Methods: Seven DSM-IV schizophrenia patients (2 female, 28.6%; 5 male, 71.4%), aged 31 to 57 years, ($M = 41.85$ years; $SD = 9.09$) completed 14 branching, self-report items assessing psychotic symptoms every day for six weeks. The item set was presented at pseudo-random times once daily following an alarm, generating up to 42 data points per participant. Face-to-face PANSS and CDS interviews were conducted at baseline, 3 and 6 weeks with rater blind to ambulant data.

Results: All participants displayed fluctuations in depressive and psychotic symptoms over six weeks as measured by self-report and PANSS. Compliance, defined as completion of greater than 33% of all data points over the first seven days, was met by 87.5% of the sample. A single non-compliant participant was removed before further analysis took place. Remaining participants completed 80.0% of all entries over six weeks. An earlier validation study sampling 36 DSM-IV schizophrenia, schizoaffective and prodromal participants for seven days established moderate to strong correlations between corresponding self-report items and PANSS or CDS scores (ρ 0.6–0.8) and reported a similar completion rate of 82% (Palmier-Claus et al., 2012). Completion rates peaked at weeks two, three and five. 83.3% of participants took less than two minutes to complete each item set. 83.3% thought they could make use of the system in their everyday life and that other people would find it easy to use. 66.7% thought this approach could help them or other service users. All participants found it easy to keep track of what was being asked.

Discussion: Ambulatory symptom monitoring using Smartphone application is a feasible, valid and acceptable method to use over an extended six week period of time. Longer system use does not significantly diminish response rate. The method yields data that is of use to researchers and clinicians. Further work should continue to establish long-term use of the system and trial it in a clinical setting.

Acknowledgements: ClinTouch development was funded by the UK Medical Research Council.

Poster #T11**REDUCTION IN THE USE OF SECLUSION WITH THE INTRODUCTION OF RECOVERY PRINCIPLES IN AN ACUTE PSYCHIATRIC UNIT**

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Background: Seclusion is often used to manage acute behavioural disturbance in people with psychotic disorders. Consumers report that being secluded is an extremely traumatic experience, so there has been considerable effort directed to finding alternative strategies to manage severely disturbed behaviour. One such strategy is to change the ward environment, and the interactions between staff and consumers, by introducing recovery-based practises. These practises include appreciation of the consumer perspective; clear, respectful communication; discussion of treatment options; preparation of safety care plans; and incorporation of feedback from consumers about their experience of seclusion as well as their overall experience of the unit.

Methods: This study took place in a 10 bed psychiatric intensive care unit

in Adelaide, South Australia. Seclusion was defined as placing the person in a defined area or room, which they were not permitted to leave. Between 2011 and 2013, measures were taken to reduce the use of seclusion including the introduction of safety care plans. Staff participated in education about the recovery model and recovery practices. A multidisciplinary seclusion and restraint minimisation committee, chaired by a peer specialist, reviewed all episodes of seclusion. All consumers who had been secluded were offered debriefing after each episode of seclusion. Rates of seclusion were measured in both 2011-2012 and 2012-2013.

Results: June 2012 393 people were admitted, of whom 109 were secluded, a rate of 28%. Some individuals were secluded more than once, so the total number of seclusions was 261. The mean duration of seclusion was 4 hours. The following year, July 2012-June 2013, 332 people were admitted and 49 were secluded, a rate of 15%. There were 125 episodes of seclusion, with an average duration of 4.2 hours.

Discussion: This study shows that rates of seclusion can be reduced if staff adopt a recovery focus, which includes greater attention to the lived experience of the consumer, support for recovery through strength-based assessment and treatment planning, and assistance in developing strategies to manage agitation and distress. Effective leadership, ongoing staff education and an organisational model that incorporates consumer feedback were essential elements in changing the philosophy and delivery of clinical services for people in the very acute phases of psychiatric illness.

Poster #T12

LIFETIME SYMPTOM DIMENSIONS AND THEIR CORRELATION WITH COGNITIVE FUNCTION, FUNCTIONAL LEVEL, AND TREATMENT RESPONSE IN CHRONIC SCHIZOPHRENIA PATIENTS

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Background: Subtypes of schizophrenia defined in previous DSMs have been eliminated from DSM-5 due to their limited diagnostic stability, low reliability, and poor validity. However, considering large diversity of clinical presentation of schizophrenia, it is still important to identify valid clinical subtypes or dimensions that might have homogeneous biological underpinning. The current study aimed to explore lifetime symptom-based dimensional phenotypes in chronic schizophrenia patients, and to investigate their correlation with cognitive functions and other clinical characteristics.

Methods: Lifetime-based symptoms and additional clinical variables were measured using the Diagnostic Interview for Genetic Studies and the Schedule for the Deficit Syndrome in 315 clinically stable patients with chronic schizophrenia. From 42 selected clinical indicators covering symptoms of prodromal, active and residual phases, suicidal ideas and attempts, deficit symptoms, and obsessive compulsive symptoms, phenotype dimensions were extracted through principal components factor analysis with multiple imputations for missing data. Comprehensive neuropsychological tests were administered for 103 out of 315 patients, and domain scores were calculated for cognitive domains defined in the MATRICS consensus battery. General cognitive ability and intra-individual variability (IIV) of cognitive scores were also generated.

Results: Eight dimensional phenotypes were obtained: "auditory hallucination factor", "Schneiderian first-rank symptom factor", "paranoid factor", "non-paranoid delusion factor", "somatic preoccupation factor", "prodromal impairment factor", "negative symptom factor", and "disorganization factor". "Non-paranoid delusion factor" including delusions of grandiose or religious nature, showed significant negative correlation with processing speed, working memory, attention/vigilance, and general cognitive ability, and positive correlation with IIV. "Negative symptom factor" showed significant negative correlation only with general cognitive ability. Those two factors were also negatively correlated with function levels measured by Global Assessment Scale (GAS), and associated with poor treatment responses. The "auditory hallucination factor" also showed weaker but significant correlation with poor treatment response.

Discussion: Symptom-based dimensional phenotypes of schizophrenia

measured on a lifetime basis showed discriminative correlation with cognitive function domains, global functioning level, and overall treatment responses, indicating their possibility as valid phenotype axes of schizophrenia having homogeneous biologic basis.

Poster #T13

THE EFFECT OF PREVIOUS DOSE OR ORAL ARIPIPRAZOLE (10 OR 30 MG/DAY) ON THE EFFICACY AND TOLERABILITY OF ARIPIPRAZOLE ONCE-MONTHLY: RESULTS FROM POST-HOC ANALYSES FROM TWO DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIALS

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Background: Aripiprazole once-monthly, a long-acting injectable formulation of oral aripiprazole, is the first dopamine partial agonist available as a long-acting injectable formulation. In two pivotal trials of stable patients with schizophrenia (Kane et al. 2012; Fleischhacker et al. 2012), aripiprazole once-monthly delayed time to, and reduced the rate of impending relapse compared to placebo or a low dose of aripiprazole once-monthly. The objective of this post-hoc analysis is to present the efficacy and tolerability of aripiprazole once-monthly in patients stabilized on 10 or 30 mg/day oral aripiprazole and then switched to aripiprazole once-monthly 400 mg.

Methods: Data from two pivotal double-blind, placebo- or active-controlled trials assessing the efficacy and safety of aripiprazole once-monthly (246, NCT 00705783; 247, NCT 00706654) were used for this post-hoc analysis. Detailed study designs have been reported previously (Kane et al. 2012; Fleischhacker et al. 2012). The analysis was conducted in patients stabilized on 10 or 30 mg/day oral aripiprazole and subsequently initiated aripiprazole once-monthly 400 mg treatment i.e. patients in the open-label aripiprazole once-monthly stabilization phase (246) and those from the double-blind maintenance phase (247), all of whom received at least one dose of aripiprazole once-monthly. Efficacy was evaluated by change from baseline in the Positive and Negative Syndrome Scale (PANSS) Total Score at four weeks after initiation of aripiprazole once-monthly. Tolerability was measured in terms of common ($\geq 5\%$) adverse events in this period. Results are reported for each study individually.

Results: A total of 841 stable patients (study 246: n=576, study 247: n=265) with schizophrenia were assigned to aripiprazole once-monthly 400 mg. Of these, 105 had been stabilized on 10 mg/day oral aripiprazole (study 246: n=75, study 247: n=30) and 212 had been stabilized on 30 mg/day oral aripiprazole (study 246: n=147, study 247: n=65). In the both studies, aripiprazole once-monthly 400 mg maintained stability of symptoms in the 4 weeks after initiation of treatment: 246 study, change in PANSS total from baseline to Week 4: 10 mg group = 0, 30 mg group = -0.18; 247 study, change in PANSS total from baseline to Week 4: 10 mg group = -1.03, 30 mg group = -1.83. The most common adverse events ($\geq 5\%$) were injection site pain (range: 9.3% [10 mg/study 246] to 0% [30 mg group/study 247]); insomnia (range: 9.2% [30 mg/study 247] to 2.7% [10 mg group/study 246]); weight increase (range 8.2% [30 mg/study 246] to 1.3% [10 mg/study 246]); agitation (range: 6.2% [30 mg/study 247] to 0% [10 mg group/study 247]); dizziness (range 5.3% [10 mg/study 246] to 0% [30 mg/study 246 and 10 mg/study 247]); akathisia (range: 7.7% [30 mg/study 247] to 2.7% [10 mg/study 246]); and anxiety (range 6.7% [10 mg/study 247] to 1.5% [30 mg/study 247]).

Discussion: Across two pivotal trials, aripiprazole once-monthly 400 mg maintained stability of symptoms in the month after initiation (as measured by change in PANSS total) regardless of whether patients had previously been stabilized on 10 or 30 mg/day oral aripiprazole. Adverse events occurred at similar rates (none exceeding 10%) for patients converted from oral aripiprazole 10 or 30 mg/day; both doses also were similar to the overall adverse events as reported for the entire study population (Kane et al. 2012; Fleischhacker et al. 2012). Overall, for patients stabilized on 10-30 mg/day oral aripiprazole, symptoms remain stable for the first 4 weeks after conversion to aripiprazole once-monthly 400 mg.

References:

- [1] Kane. J Clin Psychiatry 2012;73:617.
- [2] Fleischhacker. Poster presented at ACNP 2012.

Poster #T14**FACIAL EMOTION IDENTIFICATION IN EARLY-ONSET AND FIRST-EPISTODE PSYCHOSIS: A SYSTEMATIC REVIEW WITH META-ANALYSIS**

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Background: Facial emotion identification deficits are common in patients with chronic schizophrenia (Kohler et al., 2010) and are strongly related to impaired functioning (Irani et al., 2012). It is not yet known, however, if these deficits are trait-like: present at the onset of psychosis or a consequence of a chronic illness. The objective of this review was to determine whether facial emotion identification deficits are present and emotion specific in people experiencing early-onset or first-episode psychosis.

Methods: We searched the MEDLINE, PsychINFO, and PubMed databases for peer-reviewed studies of facial emotion identification in early-onset and first-episode psychosis, published in English between 1980 and March 2012. Studies were included if they (i) reported original empirical research, (ii) included patients with early-onset or first-episode psychosis and reported data of these patient groups separately when other patient groups were included, (iii) involved a control group and (iv) utilized measures of emotion identification. The PRISMA guidelines were followed in the extraction of relevant studies to ensure quality of reporting. In meta-analysis we examined the average mean difference between patients and controls on measures of facial emotion identification. Two researchers independently rated methodological quality of selected studies using The Newcastle-Ottawa Scale.

Results: Twelve studies were identified. A separate analysis of early-onset and first-episode patients was not possible due to the small number of studies. Across all studies, at the onset of psychosis patients were distinguished from healthy controls by significantly poorer accuracy of facial emotion expressions, with a large mean effect size ($d = -0.88$, $N = 378$, 95% CI = -1.42 to -0.32). Six out of 12 studies examined accuracy for identifying expressions of individual emotions. The magnitude of impairment was found to be (i) large for disgust ($N = 169$, $d = -1.94$, 95% CI -2.54 to -1.30), fear ($N = 197$, $d = -1.88$, 95% CI -2.44 to -1.28), and surprise ($N = 129$, $d = -1.31$, 95% CI -1.84 to -0.76), and (ii) medium for sadness ($N = 141$, $d = -0.73$, 95% CI -1.27 to -0.18) and happiness ($N = 130$, $d = -0.66$, 95% CI -0.18 to -0.12). No between groups mean differences were found for anger ($N = 169$, $d = -0.26$, 95% CI -0.73 to 0.21) or neutral ($N = 69$, $d = -0.40$, 95% CI -0.99 to 0.19) facial expressions.

Discussion: Our systematic review and meta-analysis reveals a generalized deficit in facial emotion identification at the first onset of psychosis. This finding is consistent with studies examining patients with chronic schizophrenia and suggests that emotion identification impairments represent a trait susceptibility marker, rather than a sequela of illness. Moreover, our review indicates that deficits in facial emotion identification may be emotion specific; present for some, but not all emotions. While findings of this meta-analysis should be taken with caution, given the small number of studies, predominantly cross-sectional designs, varied sources of control participants, the heterogeneous nature of early psychosis populations and the use of different facial emotion identification tasks, they are of high clinical importance. They signal the urgent need to treat emotion identification deficits at the onset of illness, which could improve functional outcomes.

Poster #T15**POSTNATAL MGLUR5 ABLATION FROM PARVALBUMIN-POSITIVE INTERNEURONS ALTERS THE RESPONSIVITY TO PSYCHOTOMIMETIC DRUGS**

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Background: Schizophrenia is associated with cognitive impairments, social dysfunction and altered responsiveness to psychotomimetic and psychomotor stimulant drugs. N-methyl-D-aspartate (NMDA) receptor antagonists, such as phencyclidine (PCP), and dopamine reuptake inhibitors, such as amphetamine, are often used to model various aspects of schizophre-

nia in experimental animals. GABAergic deficits, including impairments in parvalbumin-positive (PV+) circuits, may underlie the pathophysiology of schizophrenia. The metabotropic glutamate 5 receptors (mGluR5) are involved in the development of PV+ neurons. Mice lacking mGluR5 in PV+ interneurons (PV-mGluR5^{-/-} mice) exhibit reduced PV and GAD67 expression and reduced putative inhibitory synaptic contacts with pyramidal neurons. PV-mGluR5^{-/-} mice also show domain-specific cognitive impairments and increased repetitive behaviors.

Methods: Therefore, the present studies sought to determine whether PV-mGluR5^{-/-} mice exhibited altered sensitivity to PCP and amphetamine in the open field test for locomotor activity. Prepulse inhibition (PPI), a rodent analogue of sensorimotor gating, was also assessed in PV-mGluR5^{-/-} mice.

Results: In control mice, PCP treatment increased locomotor activity at doses 1–10 mg/kg, but not at the highest dose (15 mg/kg). PV-mGluR5^{-/-} mice displayed a diminished sensitivity to PCP-induced hyperlocomotor activity compared to control mice; higher (5–15 mg/kg), but not lower (1 and 2.5 mg/kg) doses of PCP increased locomotor activity. Amphetamine (1–4 mg/kg) increased locomotor activity in both groups of mice. However, the locomotor response to 2 mg/kg amphetamine was greater in PV-mGluR5^{-/-} mice compared to control mice, suggesting an increased sensitivity to amphetamine in PV-mGluR5^{-/-} mice. PPI was impaired in control mice when PCP (5 and 10 mg/kg) was administered. PPI was unaffected in PV-mGluR5^{-/-} mice at all PCP doses (1–10 mg/kg), indicating an attenuation of PCP-induced sensorimotor gating deficits in PV-mGluR5^{-/-} mice.

Discussion: In summary, postnatal ablation of mGluR5 from PV+ interneurons, previously shown to induce GABAergic alterations and reduce inhibitory drive, resulted in diminished sensitivity to PCP-induced behavioral disruptions. Considering that PCP appears to exert behavioral disruptions preferentially via NMDA receptors located on GABAergic interneurons, the blunted response to PCP in PV-mGluR5^{-/-} mice may be attributed to the reduction of synaptic contacts terminating on pyramidal cells, producing an existing state of disinhibition. This state of excitatory disinhibition may increase the sensitivity of sub-cortical dopaminergic neurons to exogenous stimulation, thus contributing to the increased responsiveness of amphetamine seen in PV-mGluR5^{-/-} mice. Therefore, the neurobiological dysfunctions characterizing PV-mGluR5^{-/-} mice may reflect similar impairments to those seen in schizophrenia.

Poster #T16**RELATIVES' EXPRESSED EMOTION, ATTRIBUTIONS AND EMOTIONAL STATE IN CLINICAL HIGH-RISK AND ONSET STAGES OF PSYCHOSIS**

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Background: The responsibility of providing care for a family member with psychosis can lead to elevated levels of distress, anxiety and depression in caregivers (Collins and Addington, 2006) which, in turn, may elicit a variety of responses in relatives, including higher levels of expressed emotion (EE) such as critical and Emotional Over-Involvement (EOI) attitudes. The mechanism underlying the development of relatives' EE in early psychosis is still poorly understood. Some findings have shown that relatives' cognitive representations of psychosis may play an important role in their emotional appraisals even at an early stage of the disorder (Onwumere et al., 2008). Besides, it has been demonstrated that highly critical relatives of First-Episode Psychosis(FEP) patients are more likely to believe that the disorder is controllable by the patient (Vasconcelos et al., 2013). However, the relationship between EE and relatives' illness attributions has been rarely addressed in high-risk stages of psychosis. This study aimed to: 1) characterize the profile of EE, illness attributions and emotional state in relatives of At-Risk Mental State (ARMS) and FEP patients; 2) examine the associations of criticism (CC) and EOI with relatives' illness attributions and emotional state, as well as the possible differences of these associations between ARMS and FEP groups; and 3) explore whether relatives' illness attributions are predictors of EE beyond the contribution of emotional variables in the at-risk and onset stages of psychosis.

Methods: 78 relatives (41 from ARMS and 37 from FEP patients) were included in the study and were assessed with measures of EE, attributions and emotional state. Relatives were selected if they had regular contact and/or the most significant relationship with the patient.

Results: Differences between groups of relatives were found on CC, with ARMS relatives showing higher scores than FEP relatives. No differences between groups were found on EOI, illness attributions or emotional state. CC and EOI were strongly associated with almost all illness attributions except for causal attributions, self-blame attributions and attributions of control. Furthermore, both EE components were strongly related with levels of anxiety and depression in both ARMS and FEP relatives. Group differences were found for the effect of anxiety on the EE components, so that anxiety was more strongly associated with CC in ARMS than in the FEP group, and it was associated with EOI in ARMS but not in the FEP group. Finally, anxiety, depression and attributions of blame toward the patient significantly accounted for variance in CC, whereas attributions of control by the patient and emotional negative representation about the disorder significantly account for unique variance in EOI.

Discussion: To the best of our knowledge, this is the first study that explores the relationships between EE, illness attributions and emotional state comparing groups of ARMS and FEP relatives. Findings showed that even in the early stages of psychosis, CC and EOI were highly associated with several types of illness attributions, which supports the idea that relatives' cognitive representations of (pre)psychosis are strongly linked to their emotional responses towards the patient's disorder. Furthermore, findings showed that higher levels of anxiety and depression, negative emotions about the disorder, and attributions of control and blame toward the patient predicted EE in early psychosis, suggesting that relatives' distress, concern and helplessness at early stages of psychosis could provoke negative emotional reactions towards the patient in the form of CC and EOI.

Poster #T17

PREVALENCE OF DISEASE RELEVANT NMDA RECEPTOR AUTOANTIBODIES IN REFRACTORY PSYCHOSIS

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Background: N-Methyl-D-Aspartate receptor (NMDA-R) autoantibodies have been reported in people with acute psychosis. We hypothesised that the presence of NMDA-R autoantibodies may be implicated in the aetiology of treatment refractory psychosis. This study sought to ascertain the point prevalence of NMDA-R antibody positivity in patients referred to services for treatment refractory psychosis.

Methods: The primary outcome measure was seropositivity for NMDA-R antibodies. A standardised cell based assay was used for the detection of serum IgG antibodies directed against the NR1 and NR2b subunits of the NMDA-R. This was performed by the department of clinical neurology, John Radcliffe Hospital, University of Oxford. Study approval was granted by the Psychosis Clinical Academic Group Audit committee at South London and Maudsley NHS Foundation Trust, London UK.

Results: The sample comprised forty-three treatment refractory patients (32 males and 11 females; mean age = 40.3 years (SD=11.1, range 20-69); schizophrenia, n=36; schizoaffective disorder, n=7). The mean duration of illness was 15.7 years (SD=9.4, range 2-37 years), and all met criteria for refractory illness. We found that 3 individuals in this patient group (n=43) were seropositive for IgG antibodies against NMDA-R, giving a point prevalence of 7.0%. All had low serum antibody titres (1:50, 1:50, 1:100) and none displayed the typical clinical course described in NMDA-R encephalitis.

Discussion: This study found that 3 out of 43 (7.0%) patients with chronic refractory psychosis were positive for NMDA-R autoantibodies. This prevalence is the same order of magnitude to that seen in first episode psychosis (4.3%) and in patients in the acute relapses of schizophrenia (9.9%). These results do not support our hypothesis that NMDA-R autoantibodies specifically underlie treatment refractory schizophrenia, although research in larger samples is needed. It is possible that some of the seronegative patients with chronic refractory psychosis were seropositive for NMDA-R

autoantibodies earlier in their illness - given recent evidence suggesting that seropositivity occurs in the acute phase of illness for those with chronic psychoses. It is also possible that antipsychotic treatment may have decreased antibody titres. Thus we cannot exclude the possibility that the patients had NMDA-R autoantibodies earlier in their illness, and that the effects of this persisted after NMDA-R antibody production had ceased. In all three of our seropositive cases, the antibody titres were low. The clinical significance of low titres in patients presenting with psychosis and no other clinical features remains to be determined. Our study findings do not support the hypothesis that NMDA-R autoantibodies are a common aetiology in refractory psychotic illnesses, although we cannot exclude a role for them in the pathoaeiology of a subgroup of individuals with refractory psychotic illnesses. At present, there is no evidence that this is a useful routine investigation in refractory psychosis. However, further investigation is needed, given that there is evidence that some people with psychosis respond to immunomodulatory therapy.

Poster #T18

ESTIMATING THE COST AND EFFECT OF EARLY INTERVENTION ON IN-PATIENT ADMISSION IN FIRST EPISODE PSYCHOSIS

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Background: Early intervention in psychosis is an accepted mental health policy internationally. In 2007, at the time of publication of "A Vision for Change" the national blueprint for mental health policy in Ireland only one service for early intervention in psychosis existed. In 2012 the National Clinical Programme Plan for mental health services identified early intervention in psychosis as one of three priorities for development on a national basis. Concurrently the national health budget has been reduced. This highlights the need for economic evaluation of all new mental health programme initiatives. Outcome measures used to evaluate early intervention in psychosis services include admission and readmission to hospital. However admission is also a cost, accounting for a large proportion of the direct cost of treating people with psychosis. Interventions which reduce admissions will decrease costs. The aim of the study was to investigate whether the introduction of an early intervention in psychosis service resulted in any change to the number and duration of hospital admissions in people with first-episode psychosis in the first year.

Methods: We examined two epidemiological cohorts of individuals presenting with first-episode psychosis to an urban community mental health service (population 172,000). The historical cohort comprised of individuals presenting between 1995 to 1998 and received treatment as usual (n=131). The early intervention cohort presented to the same catchment area between 2008 and 2011 (n=97) following introduction of an early intervention for psychosis service in 2005. Data were analysed using PSAW SPSS version 20. Chi squared tests, Mann-Whitney tests and independent t-tests were used to examine relationships between variables.

Results: 64% (n=106) of the historical cohort were admitted over the four period and 34% (n=55) of the early intervention cohort (EI) were admitted over the four year period ($p<0.001$). The total cost of admission first year in the historical cohort was estimated to be €2,052,694 compared with €914,190 in the early intervention cohort in 2011 prices. The average cost per admission was €19,365 in the historical cohort and €16,622 in the EI cohort applying 2011 prices. The median duration of admission was 44 days (IQR 39.5) in the historical cohort v 21 days (IQR 42) in the EI cohort ($p<0.001$). The total number of days spent in hospital by the historical cohort was 5,218, and the total number of days spent in hospital by the DETECT cohort was 2,308.

Discussion: The comparison pre and post early intervention demonstrated a cost saving consistent with other studies internationally. Key issues are whether the changes in admission pattern are due to the implementation of early intervention or are caused by other factors. Examination of local and national factors showed that the dominant effect was from the implementation of early intervention. It is difficult to generalize interventions shown to work in one country, as there are both local and national variations in

service structure and delivery. It remains important to evaluate whether individual policies are applicable within a local context. Limitations of this study are that the comparison is with a historical cohort and is confined to in-patient costs. Further research in this area is required with contemporaneous control groups. More detailed methods to capture community costs will reveal to what extent the savings in admission costs are balanced by increased costs of community service provision.

Poster #T19

ANIMAL MODELS OF SCHIZOPHRENIA SYMPTOMS: POLYDIPSIA FOLLOWING SUBCHRONIC MK-801, POST-WEANING SOCIAL ISOLATION OR AMPHETAMINE SENSITIZATION IN RATS

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Background: Polydipsia is observed in up to 20% of chronic psychiatric patients with a majority of cases (80%) occurring in patients with schizophrenia. Animal models of schizophrenia symptoms including subchronic treatment with a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist, post-weaning social isolation and amphetamine sensitization reproduce a number of symptoms including working memory impairments, increased locomotor responses to amphetamine and impaired sensory-motor gating. We evaluated the hypothesis that these models will reproduce polydipsia.

Methods: Young adult male rats were injected twice daily with the NMDA receptor antagonist MK-801 (0.5 mg/kg) or its vehicle for 7 days and then given a 4-day washout period. Post-weaning rats (age 21 days) were housed alone (socially isolated) or in groups of 4 for 6 weeks. Young adult male rats were injected with amphetamine (1.5 mg/kg) or its vehicle once daily for 5 days and given a 4-week withdrawal period. All rats were then restricted to food access for 2 hr per day. Drinking behavior was evaluated in 21 daily 2-hr sessions using the schedule-induced polydipsia (SIP) procedure in an operant chamber outfitted with a food hopper and a drinking spout; food pellets (45 mg) were presented according to a fixed time 1-min schedule during these sessions. The dependent variable was amount drunk.

Results: As reported previously by a number of researchers, animals exposed to the SIP procedure developed polydipsia over the course of testing. Similar animals given the food pellets all at once in a bowl at the beginning of the 2-hr test session did not develop polydipsia. Animals previously treated subchronically with MK-801, socially isolated during the post-weaning period or previously sensitized to amphetamine developed polydipsia but drank significantly more than their respective control groups. These treatments were not associated with a change in amount drunk in the home cage. Rats tended to spend most time at the drinking spout immediately following pellet presentations.

Discussion: Results supported previous findings showing that exposing food-restricted rats to intermittent food presentations at regular intervals leads to the development of excessive drinking. Providing the same amount of food all at once has no similar effect. There was remarkable convergence of effects of the three animal models of schizophrenia symptoms on polydipsia. Subchronic NMDA receptor blockade, post-weaning social isolation and amphetamine sensitization all led to significantly greater polydipsia than observed in the respective control groups. The mechanisms underlying this effect remain to be determined. Some evidence relates hippocampal dysfunction to polydipsia. Subchronic NMDA receptor antagonist treatment has been shown to affect hippocampal GABA neurons and post-weaning social isolation alters markers of GABA function in the hippocampus, providing a possible link. These treatments also lead to augmented dopaminergic neurotransmission as does amphetamine sensitization, implicating dopamine in the mechanism. It has been suggested that hyperdopaminergia in schizophrenia may be secondary to changes in hippocampal GABA function. The present results provide convergent evidence from three different animal models of schizophrenia symptoms suggesting that polydipsia may result from the same neuropathologies that lead to other schizophrenia symptoms. (Funded by a grant from the Ontario Mental Health Foundation)

Poster #T20

THE ASSOCIATION BETWEEN INFECTIONS AND GENERAL COGNITIVE ABILITY IN YOUNG MEN – A DANISH NATIONWIDE STUDY

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Background: Infections and inflammation have been shown to increase the risk of mental disorders with affected cognition. Furthermore, infections and immune components might also affect the developing brain and influence the cognitive ability in people without mental disorders. However, no large-scale study has previously investigated the effect of infections on the general cognitive ability in the general population.

Methods: Danish nationwide registers were linked to establish a cohort of all 161,696 male conscripts that were tested for cognitive ability during the years 2006–2012. Severe infections requiring hospitalization was the exposure and draft board general cognitive ability was the dependent variable, which was based on logical, verbal, numerical and spatial reasoning at a mean age of 19.4 years with converted test scores to a mean of 100.00.

Results: A prior infection was associated with significantly lower cognitive ability by a mean of 1.76 (95%CI: -1.92 to -1.61). The cognitive ability was affected the most with the temporal proximity of the last infection and with severity measured by days of admission. The cognitive ability decreased by the amount of infections exposed to, where the highest mean differences were found for ≥ 10 hospital contacts for infections (Mean: -5.54; 95%CI: -7.11 to -3.98), and for ≥ 5 different types of infections (Mean: -9.44; 95%CI: -12.6 to -6.26).

Discussion: Independent of a wide range of possible confounders, significant associations between infections and cognitive ability were observed. Infections or related immune responses might directly affect the cognitive ability; however, associated heritable and environmental factors might also account for the decreased cognitive ability.

Poster #T21

MATERNAL SMOKING DURING PREGNANCY AND SYMPTOM SEVERITY AMONG OFFSPRING DURING THEIR FIRST EPISODE OF PSYCHOSIS

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Background: Maternal smoking during pregnancy is associated with a number of negative effects for the fetus and later the child, including adverse neurodevelopmental and behavioral outcomes. Prenatal exposure to tobacco smoke has been reported to be associated with an increased incidence of attention-deficit/hyperactivity disorder, conduct disorder, and reduced cognitive ability. In animal studies, long-term prenatal nicotine exposure alters the development of a wide spectrum of neuronal systems, all of which potentially could induce vulnerability to schizophrenia. Epidemiological and clinical studies indicate that prenatal tobacco exposure is associated with various psychiatric symptoms, including psychotic symptoms, as well as the development of psychiatric disorders. Fetal exposure to maternal smoking during pregnancy might also impact illness manifestation among individuals with schizophrenia. Recent findings suggest that prenatal exposure to tobacco smoke increases risk for later schizophrenia and is associated with the development of more prominent negative symptoms.

Methods: We examined associations between maternal smoking during pregnancy, using retrospective data provided by mothers, and symptom severity of first-episode psychosis patients, rated by trained research staff using the Positive and Negative Syndrome Scale (PANSS). Among 93 first-episode patients, 19 (20.4%) had been exposed to prenatal tobacco smoke according to mothers' reports. The average number of cigarettes smoked per month during pregnancy was 113.7 (equating to 5.7 packs per month, or 1.3 packs per week).

Results: When examining six subscales derived from the PANSS, first-episode patients having been exposed to prenatal tobacco smoke had a lower severity of deficit symptoms, computed as (N1 blunted affect + N6 lack of spontaneity and flow of conversation) – (P7 hostility + G2 anxiety + G3 guilt feelings + G6 depression): -7.1 ± 3.1 compared to -4.0 ± 3.3 , $t=3.69$, $df=91$, $p<0.001$. They also had a greater severity of reality distortion (P1 delusions + P3 hallucinations + G9 unusual thought content): 13.6 ± 2.8 compared to 11.6 ± 3.0 , $t=2.65$, $df=91$, $p=0.01$. The latter finding appeared to be driven by greater severity of hallucinations (5.2 ± 1.3 compared to 4.0 ± 1.6 , $t=3.06$, $df=91$, $p=0.003$). Controlling for effects of patients' gender and smoking status (using factorial analyses of variance) attenuated but did not explain these effects, and no significant interactions were observed.

Discussion: Although these initial results require replication, there appears to be an association between fetal tobacco smoke exposure and lesser deficit symptoms and greater hallucination severity at the time of the initial hospitalization. Further research on this potential fetal environmental exposure among individuals with schizophrenia is warranted.

Poster #T22

EXPLORING THE IMPACT OF FAMILY INTERVENTIONS FOR PATIENTS PRESENTING A FIRST EPISODE PSYCHOSIS AND THEIR FAMILIES

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Background: Many studies have indicated that a good family functioning facilitates patient recovery (O'Brien et al., 2006). In this regard, some authors have underlined the importance of understanding patients' perception of family functioning considering it could predict their clinical outcome. Despite a positive effect of single family treatment in terms of patients' outcome, questions still remain regarding the degree and type of family involvement needed at various stages of a psychotic disorder, in particular the earliest ones. Moreover, very few studies have focused on outcomes for the relatives of people with psychosis (Lobban et al., 2013). On this background, we aimed to explore the link between family interventions, patients' clinical outcome and changes in family functioning as perceived by patients and family members. We also aimed to analyse which characteristics of family interventions are operating.

Methods: 16 young adults aged from 18 to 25 (mean=22.31) hospitalized for a first episode psychosis in our inpatient unit and their parents were included. Every family member attending the sessions rated separately, at admission and discharge, the general functioning subscale of the Family Assessment Device (FAD) (Epstein et al., 1983). Patients were assessed during the first week and before discharge for symptom severity with the BPRS-24 (Ventura et al., 1993). Pearson's correlation coefficient was calculated between FAD mean scores of a patient and his/her family members', between FAD mean scores and BPRS factor mean scores, as well as with the delay to first family session and the number of family sessions. Paired t-tests were used for comparison of BPRS mean scores at admission and discharge, as well as of FAD scores at admission and discharge. A subset of families were rated by therapists as to the usefulness of family interventions and family functioning improvement.

Results: When considering FAD items separately, only the item 31 "there are lots of bad feelings in the family" score decreased significantly for the patient group ($t = 2.38$; $p<0.05$). No other significant difference for perception of general functioning between admission and discharge was noticed for any of the three groups (patient, father, mother). We observed a significant positive correlation between perception of family functioning by the mother at admission and overall negative symptoms at discharge (.643; $p<0.05$). Moreover, we noticed a significant negative correlation between perception of family functioning by the mother at discharge and degree of manic symptom improvement during hospitalization (-0.892 ; $p<0.05$). Neither perception of family functioning, nor BPRS scores were significantly correlated to delay to first family session and to number of family sessions neither at admission nor at discharge.

Discussion: Our preliminary findings show some associations between perception of impaired family functioning by the mother and patient symptoms at discharge and changes of symptoms during hospitalization; it suggests that perception of good family functioning by family members may potentiate patients' recovery. Further patient recruitment and family assessment should help to better understand what type of interventions

is required for what early psychosis families and to better understand the interplay of psychopathology and family functioning.

Poster #T23

AFFECTIVE PROSODY IN REMITTED AND NON-REMITTED SCHIZOPHRENIA PATIENTS COMPARED TO HEALTHY CONTROLS

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Background: Affective prosody perception is impaired in schizophrenia patients and considered as an immanent symptom of this devastating disease. It is at least partially responsible for the poor functional outcome of these patients. This study investigates quantitative and qualitative differences of these deficits in remitted and non-remitting patients compared to healthy controls.

Methods: In this cross sectional study we enrolled outpatients between 19 and 65 years of age, who had been symptomatically stable for half a year under antipsychotic treatment. Remission was defined, following the remission criteria of Andreasen et al (2005). Affective prosody perception was investigated by using one subtest of the Comprehensive Affective Testing System (CATS). In this computer based assessment, subjects had listen to 22 spoke sentences and to judge each with regards to its emotion by ignoring its content. Subjects could choose between fear, anger, happiness, grief, and a neutral mood.

Results: All groups were comparable regarding sociodemographic characteristics. So far, we enrolled 42 patients (23 remitted and 19 non-remitting) with schizophrenia and 45 healthy controls. CATS total scores were significantly lower in non-remitting patients than in remitted patients and healthy controls. The last two of them were comparable. All schizophrenia patients showed lower scores in recognising anger compared to healthy controls. Grief and happiness were detected significantly worse in the non-remitting than in the remitted patient group.

Discussion: Our results confirm earlier findings and demonstrate deficits in affective prosody perception in acute episodes as well as during remission. Independently of the remission status the recognition of anger in the emotion of a voice seems to be impaired in both patient groups. To investigate the influence of these deficits on the functional outcome in schizophrenia patients, more studies are needed.

Poster #T24

THE IMPACT OF CONSANGUINITY ON RISK OF EXTENDED PSYCHOSIS PHENOTYPE

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Background: Familial liability to both severe and common mental disorder predicts psychotic disorder and psychotic symptoms. Consanguinity may be used as proxy in models examining the interaction between the genetic risk and the individual for psychosis.

Methods: In a representative general population sample ($n=4011$) in Izmir, Turkey, the full spectrum of expression of psychosis phenotype representing: (0) no symptoms, (1) subclinical psychotic experiences, (2) low-impact psychotic symptoms, (3) high-impact psychotic symptoms and (4) full-blown clinical psychotic disorder was assessed in relation to consanguinity (any marriage within the relatives as a proxy for familial liability). Consanguinity was assessed as: (0) not related, (1) first-degree cousins, (2) second or distant degree cousins. Statistical analysis included age, gender, years of education and any mental disorder within the family (parents and siblings).

Results: Any marriage between first-degree cousins was significantly associated with the extended psychosis phenotype ($\beta: 0.11$, 95% CI: 0.01–0.23; $p<0.05$), with a prominent impact on the syndromal end of the phenotype

(psychotic disorders). The association was in part correlated with age, since consanguinity was prevalent in older age groups. However the association was not modified by any mental disorder within the family. Any marriage between second or distant degree cousins was not associated with the outcome.

Discussion: These results are consistent with claims that inbreeding can contribute to the risk of psychosis phenotype. The parental consanguinity and family history are one of the main risk factors for the development of psychosis.

Poster #T25

ANOMALIES IN THE FABRIC OF THE PERINEURONAL NET AND SCHIZOPHRENIA PATHOPHYSIOLOGY

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Background: Perineuronal nets (PNNs) represent key reticular structures consisting of components of the extracellular matrix (ECM) that coat a variety of cells in the mature mammalian brain. Until recently, the functions of the PNN had remained enigmatic, but are now considered to be important in development of the central nervous system, neuronal protection and synaptic plasticity, all elements which have been linked to schizophrenia. Recent studies have reported an alteration in PNNs and the constituent elements of these structures in the prefrontal and entorhinal cortex in addition to the amygdala and olfactory epithelium of patients with schizophrenia. We therefore sought to further extend these observations by investigating and characterizing which extracellular elements necessary for PNN structural integrity are preferentially affected in the superior temporal gyrus (STG) of patients with schizophrenia. Because the STG has been associated with developmental mechanisms of brain lateralization and the pathogenesis of language-related schizophrenic symptoms this structure lends itself to investigation of developmental deviance in the onset of schizophrenia.

Methods: In this study we used single-cell gene expression profiling of laser-captured pyramidal neurons from layer 3 of the STG (Brodmann's Area 42) from patients with schizophrenia and a corresponding set of normal controls. Microarray data were confirmed by quantitative RT-PCR.

Results: Pyramidal neurons from patients with schizophrenia exhibited significant reductions in the expression of multiple components of the PNN including aggrecan ($p=0.03$, fold enrichment = -1.26), versican ($p=0.04$, fold enrichment = -1.13) and hyaluronan and proteoglycan link protein 1 ($p=0.05$, fold enrichment = -1.14). Significant changes in the expression levels of two families of endogenous extracellular metalloproteinases (viz. matrix metalloproteinase (MMPs), and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTSs)), which are enzymes involved in the breakdown and remodelling of the ECM were also detected. We specifically found the expression of MMP16 ($p=0.02$, fold enrichment = -1.17), MMP25 ($p=0.02$, fold enrichment = -1.14) and MMP24 ($p=0.01$, fold enrichment = 1.22) in addition to ADAMTS1 ($p=0.03$, fold enrichment = 2.56) and ADAMTS6 ($p=0.05$, fold enrichment = 1.15) to be significantly altered in schizophrenia.

Discussion: The current data indicate deficits in constituents of the PNN in pyramidal neurons of the STG from patients with schizophrenia. In addition, these data suggest that a dysregulation in the remodelling of the ECM may represent a genuine mechanism underlying the pathophysiology of schizophrenia. Changes in the dynamics of the ECM under pathological conditions may affect and disrupt the structural integrity of PNNs triggering a cascade of molecular events culminating in the neuronal damage and synaptic dysfunction associated with schizophrenia.

Poster #T26

A CROSS-SECTIONAL AND LONGITUDINAL STUDY OF GLOBAL CORTICAL MORPHOLOGY IN THE EDINBURGH HIGH RISK STUDY OF SCHIZOPHRENIA

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Background: Schizophrenia is associated with global brain abnormalities

that have been shown to be evident before disorder onset. Most structural studies of the cortex have restricted their analyses to gray matter volume, rather than its constituents of surface area and cortical thickness. This may obfuscate potentially unique contributions of these parameters in the pathophysiology of schizophrenia, as they have been shown to have distinct genetic underpinnings. At present it is also unclear whether generalized abnormalities that precede disorder onset are static, or become evident through aberrant development. Therefore, we investigated cortical thickness and surface area in a longitudinal study of individuals at high familial risk of schizophrenia, compared to healthy controls.

Methods: Subjects were recruited from the Edinburgh High Risk Study of Schizophrenia. At baseline, there were 146 High Risk (HR) individuals, and 36 Healthy Controls (HC). We used subsequent clinical assessments to investigate baseline measures as well as longitudinal change in global cortical thickness and surface area across high risk individuals that remained well during the course of the study: HR[well] ($n=72$), individuals that had transient psychotic symptoms but did not develop schizophrenia: HR[symp] ($n=57$), and individuals that developed schizophrenia: HR[ill] ($n=17$). Individuals that became ill before the second time-point were not offered rescanning. Groups were also compared against HCs. Structural images were acquired at two time-points (mean scan interval = 1.87 years), and processed using the surface-based stream in Freesurfer v 5.0. Statistical analysis was conducted using mixed effects models implemented in R.

Results: At baseline, there were no significant group differences in thickness. However, there were significant group differences in bilateral surface area, ($F=2.80$, $df=165$ $p<0.05$), which post-hoc tests showed were because HR[symp] and HR[ill] had significantly larger surface areas than HR[well], $p<0.05$. For the longitudinal comparisons in thickness, a significant group by time interaction emerged bilaterally ($F=4.35$, $df=338$, $p<0.001$). Post-hoc tests revealed that this was because HR[ill] group experienced significant thinning over the two scans, $p<0.05$, which no other groups did. A significant Group by time interaction emerged for surface area bilaterally, ($F=4.6$, $df=329$, $p<0.05$). Post-hoc tests revealed that the HC showed larger decreases in surface area, compared to all HR individuals, $p<0.05$.

Discussion: At baseline, HR[symp] and HR[ill] had significantly larger surface areas compared to HR[well]. Longitudinally we found that all HR groups had a preservation of surface area compared to HC. Together these results suggest that relatively larger surface areas, either at baseline or developmentally may serve respectively as a state marker of psychosis or a trait marker for the disorder. The cortical thinning in HR[ill] suggests that an additional brain insult occurs near to the time of disorder onset. Our study indicates that static and progressive abnormalities in surface area confer vulnerability to the disorder, whilst further progressive changes in thickness may be on the causal pathway for schizophrenia. Our results reinforce the importance of investigating surface area and thickness separately.

Poster #T27

ALTERED HIPPOCAMPAL GLUTAMATE FUNCTION IN PEOPLE AT ULTRA HIGH RISK FOR PSYCHOSIS

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Background: Altered glutamatergic neurotransmission is thought to play a key role in the pathophysiology of schizophrenia. Recent neuroimaging studies have shown that striatal and thalamic glutamatergic abnormalities are present before the onset of the disorder, thereby significantly contributing to the risk for psychosis. However, hippocampal glutamate function has been more difficult to study due to methodological constraints and, as such, it is unclear if hippocampal glutamate function is altered or if it is associated with symptomatology. Here we examined if subjects at Ultra High Risk (UHR) for psychosis show altered glutamate function in the hippocampus, and how this relates to symptomatology.

Methods: Thirty-three individuals who met UHR criteria and 20 healthy volunteers participated in the study. Levels of glutamate (Glu) and the combined measure of glutamine and glutamate (Glx) were assessed in the left hippocampus using proton magnetic resonance spectroscopy at 3.0 Tesla (PRESS: Point-RESolved Spectroscopy; TE=30ms; TR=3000ms; 96 averages; voxel size 20×20×15). All spectra were analysed using LCModel version 6.3-0A, and water-scaled Glu and Glx values were corrected for CSF content. Symptomatology was determined using the Comprehensive Assessment of At-Risk Mental State (CAARMS). Group differences were determined using independent samples t-test (two groups) or one-way ANOVA (three groups). Relationships between hippocampal glutamate function and symptom severity were determined using Pearson's correlation.

Results: There were no significant group differences in hippocampal Glu (controls vs UHRs 6.96±0.90 and 7.29±1.13) or Glx levels (controls vs UHRs 9.36±2.05 and 9.97±2.11). However, subdivision of UHR subjects according to the level of positive symptoms at presentation (median CAARMS positive symptoms score ≤7 and >7) revealed a significant effect for hippocampal Glu concentrations ($p=0.015$) and a trend towards significant differences in hippocampal Glx levels ($p=0.099$) across all three groups. Post hoc tests revealed higher Glu levels and a tendency towards higher Glx levels in more symptomatic UHR subjects compared to both UHR subjects with minimal positive symptoms ($p=0.013$ and 0.062, respectively) and healthy controls ($p=0.017$ and 0.077). No changes in Glu and Glx concentrations were shown between UHR subjects with minimal symptoms and healthy volunteers. In addition, hippocampal Glu levels were positively correlated with positive symptoms ($p=0.030$), and showed a trend towards a negative relationship with negative symptoms ($p=0.095$). No correlations were demonstrated with cognitive symptoms or between hippocampal Glx levels and symptomatology.

Discussion: These results indicate higher hippocampal glutamate function in subjects at UHR for psychosis, who exhibit higher levels of positive symptoms. These data are consistent with the theory that glutamatergic abnormalities are fundamental to the development of psychosis, and support the notion that glutamate dysfunction is involved in the vulnerability to psychosis.

Poster #T28

OBSSESSIVE COMPULSIVE SYMPTOMS AND PREMORBID ADJUSTMENT AS PREDICTORS OF TRANSITION TO PSYCHOSIS IN ULTRA-HIGH RISK (UHR) SUBJECTS

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Background: Identifying at-risk mental states of psychosis can reduce the duration of untreated psychosis and the rate of transition. Meanwhile, it may improve prevention strategies of suicide, substance abuse and anxiety disorders comorbidities. We aim to investigate the clinical symptomatology differences at baseline, especially in non-specific symptoms, between UHR patients who did or did not make a transition to psychosis. Sharpening UHR inclusion criteria may improve prediction of transition to psychosis.

Methods: The study included 85 young help-seekers (mean age= 20 y.o.) meeting UHR CAARMS' criteria. 46 were followed up over a period of 30 months and 27 of them were assessed in a comprehensive clinical interview. Out of 46 finally included UHR subjects, 11 (40%) made a transition to psychosis. Psychopathology was investigated with the Comprehensive Assessment of At-Risk Mental State (CAARMS), BPRS and GAF-score. To identify the most predictive variables of transition, we applied a stepwise logistic regression on CAARMS' criteria plus other variables (premorbid adjustment scale, cannabis use, subjective experienced life events, treatment and suicide).

Results: At baseline, premorbid adjustment and severity of CAARMS' Obsessive-Compulsive Symptoms (OCS) were found to significantly influence the transition: poor premorbid adjustment, associated with moderate level of OCS increased the sensitivity (72.7%) and the specificity (92.8%) of the prediction.

Discussion: Premorbid adjustment and level of OCS were predictive of transition in subjects at UHR. These characteristics could increase the level of prediction of psychosis.

Poster #T29

HOW TO PREDICT AND MEASURE MEDICATION ADHERENCE IN SCHIZOPHRENIA: TWELVE MONTHS OF ELECTRONIC MONITORING (MEMS®) IN THE SWEDISH COAST-STUDY

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Background: Non-adherence to antipsychotics increases the risk of relapse in schizophrenia. Non-adherence is most commonly measured through subjective clinician - and patient self-reports, but these measures may underestimate adherence. Most previous studies have been small and short. The aim was to compare objective and subjective measures of adherence and to investigate clinical predictors of adherence to antipsychotics in a larger naturalistic cohort of schizophrenia outpatients over 12 months between October 2008 and June 2011.

Methods: Antipsychotic medication adherence was monitored in 117 outpatients diagnosed with schizophrenia or schizophrenia-like psychosis according to DSM-IV criteria in a naturalistic prospective study. Adherence was determined by the Medication Event Monitoring System (MEMS®), pill count, plasma levels, and patient, staff, psychiatrist and close informant ratings. The plasma level adherence measure reflects adherence to medication and to lab visits. Relationships between MEMS® adherence and other measures were expressed as a concordance index and kappa (K). In 112 of the patients symptom burden, insight, psychosocial function (PSP) and side effects were rated at baseline. A comprehensive neuropsychological test battery was administered and a global composite score was calculated. The Drug Attitude Inventory (DAI-10) was filled in. A slightly modified DAI-10 version for informants was distributed as a postal questionnaire.

Results: Non-adherence (MEMS® ≤ 0.80) was observed in 27% of the patients. MEMS® adherence was highly correlated with pill count (concordance= 89% and K=0.72, $p<0.001$). Concordance and K were lower for all other adherence measures and very low for the relationship between MEMS® adherence and plasma levels (concordance= 56% and K= 0.05, $p=0.217$). Adherence measures were also entered into a principal component analysis that yielded three components. MEMS® recordings, pill count and informant ratings had their highest loadings in the first component, plasma levels alone in the second, and patient, psychiatrist and staff ratings in the third. In univariate regression models low scores on DAI-10 and DAI-10 informant, higher positive symptom burden, poor function, psychiatric side effects and lack of insight predicted non-adherence. No association was observed with global cognitive function. In multivariate regression models, low patient-rated DAI-10 and PSP scores emerged as predictors of non-adherence. A ROC analysis showed that DAI-10 had a moderate ability to correctly identify non-adherent patients (AUC = 0.73, $p<0.001$). At the most "optimal" cut-off of 4, one third of the adherent would falsely be identified as non-adherent. A somewhat larger AUC (0.78, $p<0.001$) was observed when the ROC procedure was applied to the final regression model including DAI-10 and PSP. For the subgroup with informant data, the AUC for the DAI-10 informant version was 0.68 ($p=0.021$).

Discussion: The strong agreement between MEMS® and pill count suggests that structured pill count might be a useful tool to follow adherence in clinical practice. The large discrepancy between MEMS® and the adherence measure based on plasma levels needs further study in clinical settings. Non-adherence cannot be properly predicted in the clinical setting on the basis of the studied instruments alone. The DAI-10 informant questionnaire needs further testing.

Poster #T30**LINK BETWEEN NEUROLOGICAL SOFT SIGNS AND POOR OUTCOME SCHIZOPHRENIA (KRAEPELINIAN SUB-TYPE): PRELIMINARY RESULTS**

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Background: Neurological soft signs (NSS) refer to subtle neurological abnormalities comprising deficits in sensory integration, motor coordination and sequencing of complex motor acts. Previous studies showed that NSS scores are correlated to schizophrenia, specifically among patients with poor premorbid functioning and with severe negative and disorganization symptoms. NSS could be a neurodevelopmental marker interesting to detect patients with a risk of poor prognosis. The kraepelinian schizophrenia sub-type, defined by Keefe's criteria (1987), refers to a very poor prognosis sub-group (severe dysfunction in self-care) on the basis of the longitudinal course of the illness. Studies on kraepelinian sub-group show differences with good outcome patients regarding pre-morbid functioning, negative and disorganized symptoms, impaired performance on specific cognitive and motor deficits (visual-motor processing, abstraction/flexibility, fine motor dexterity) (Albus and al., 1996; Bralet and al., 2006). The aim of our study was to explore the association between NSS and kraepelinian sub-type in order to understand better the etiopathogenic mechanisms underlying the kraepelinian sub-type.

Methods: In 2013, we recruited 2 samples of 15 schizophrenic patients, kraepelinians and no-kraepelinians, matched on sex, ages (± 5 years) and duration of illness (± 5 years) from the psychiatric departments in Picardie area (France), according to DSM-IV criteria and using Keefe's criteria. Several socio-demographical, pharmacological, clinical, cognitive (neurocognitive, theory of mind, facial emotion perception) and NSS (Krebs and al., 2000) were collected for each patient. To compare the 2 sub-groups we used first wilcoxon analysis then linear regression.

Results: Results showed worse NSS score among kraepelinian patients ($p < 7 \times 10^{-5}$) and no link with treatment (equi mg/day chlorpromazine). Linear regressions show that NSS is more explained by the kraepelinian status than the other variables ($p < 0.003$).

Discussion: This result adds a new data regarding the etiopathogeny underlying the kraepelinian sub-type. This sub-group probably refers to specific and complex neurodevelopmental mechanisms which could be markers of a poor outcome. We must confirm these results in a larger sample, check the duration of antipsychotic impregnation and explore the link with autistic spectrum disorders.

Poster #T31**PROTEOMIC INVESTIGATION AND CHARACTERISATION OF POST-TRANSLATIONAL MODIFICATIONS OF HISTONE PROTEINS PURIFIED FROM PRENATALLY STRESSED MOUSE BRAIN TISSUE**

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Background: Genetics and environmental factors contribute to the risk of developing schizophrenia, but the exact mechanisms underlying these effects are unknown. Epigenetic studies have begun to provide insights into these mechanisms. Epigenetic studies focus chiefly on modifications to the DNA, microRNAs, or histone proteins that lead to altered gene transcription. Most previous work has focussed on DNA methylation and a small number of specific histone post translational modifications (PTMs). In the current study we demonstrate for the first time the mass spectrometry based proteomic analysis of histones enriched brain allows the characterisation and quantitation of multiple histone PTMs.

Methods: Histone proteins were purified from mouse hippocampi using the Epigentek EpiQuik Total Histone Extraction Kit. The efficiency of the extraction was tested by comparing the histone yield obtained from

different amounts of starting material (20-200mg). Histones must be chemically derivatized before digestion by the protease trypsin in preparation for proteomic investigation. This propionylation derivatization prevents the trypsin from cutting the proteins into fragments that are too small and complicated for MS analysis. Samples were injected into the QExactive mass spectrometer and data was analysed using sophisticated bioinformatic techniques to identify PTMs.

Results: Histone proteins from mouse hippocampi have been successfully purified, derivatized, digested and preliminary analysed has been carried out. It has been shown that PTMs are retained throughout this process and can be characterised using bioinformatics. Mass spectrometry analysis on an animal model of prenatal stress and control brain tissue is currently being carried out.

Discussion: This study has indicated that histone proteins can be purified from small amounts of brain tissue and that multiple histone PTMs can be identified. These findings will have direct applications to the study of the epigenetic basis of schizophrenia using post-mortem brain and animal models of the disease.

Poster #T32**"PEOPLE WITH SCHIZOPHRENIA SOMETIMES TALK TO THEMSELVES, AND THAT'S OKAY": COMMUNITY-PARTNERED DEVELOPMENT OF ANTI-STIGMA MESSAGES**

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Background: Stigma toward individuals with schizophrenia is associated with psychosocial losses, social exclusion, reduced help-seeking, and difficulty in pursuing recovery. While gains have been made in reducing stigma toward persons with non-psychotic psychiatric illnesses such as depression, more research and development is needed on reducing stigma toward those with schizophrenia.

Methods: We partnered with a community advisory board in an urban, predominantly African American community to develop three anti-stigma messages, each one to be delivered on a series of three postcards. Messages focused on recovery ("Recovery From Schizophrenia is Possible"), illness manifestations ("People With Schizophrenia Sometimes Talk to Themselves, and That's OK"), and social acceptance/inclusion ("Accept People Who Have Schizophrenia"). To enroll members of the community to participate in the pre-intervention/post-intervention survey-based study, we partnered with local community organizations. Four hundred fourteen African American community members completed a survey assessing stigma from multiple perspectives, were randomized to one of three anti-stigma messages and received a series of three weekly postcards, and then completed a post-intervention survey. The survey used measures such as the Social Distance Scale, emotional experiences toward people with schizophrenia, the Attribution Questionnaire, and a new multi-dimensional stigma scale, among other measures.

Results: Statistically significant effects of time were observed for three measures of stigma and marginally significant effects of time were apparent for the remaining four measures. Group-by-time interactions were not observed, indicating no clear advantage of one anti-stigma message over the others. Because time effects could have resulted from having completed the pre-intervention survey rather than the postcard intervention itself, follow-up analyses examined effects of time and whether or not the participant reported having received 2–3 postcards. We observed a significant effect of time (but not intervention exposure) for two measures of stigma, and a significant interaction between intervention exposure and time for empathic emotions (e.g., compassion, empathy, respect).

Discussion: This project demonstrates the potential for the development of targeted anti-stigma campaigns that rely on brief, tailored messages. A community-partnered approach is likely to result in the selection of the most appropriate anti-stigma themes, messages, and slogans for local campaigns and educational approaches.

Poster #T33**CRIMINAL JUSTICE SETTINGS AS A POTENTIAL SITE FOR EARLY DETECTION OF PSYCHOTIC DISORDERS AND REDUCING TREATMENT DELAY**

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Background: Interventions to reduce the duration of untreated psychosis should target institutions and key figures who may interact with individuals with emerging or untreated psychosis. Criminal justice settings, such as jails and prisons, may come into contact with many such individuals. The purpose of the present report is to determine the frequency of incarcerations during patients' initial treatment delay for a psychotic disorder in an urban setting.

Methods: Retrospective data were collected from an urban, largely African American group of patients hospitalized for first-episode psychosis ($n=191$). Collected data included incarceration history, premorbid functioning, age at onset, symptom severity, and diagnosis.

Results: Some 37% of participants were incarcerated at some point during their duration of untreated psychosis. Patients with a history of incarceration during the initial period of untreated psychosis had a much longer treatment delay, greater positive symptoms and auditory hallucinations specifically, and poorer premorbid academic adjustment. Among those who were incarcerated during this period, the mean number of incarcerations during the duration of untreated psychosis was 2.0 ± 1.5 , the median number of days detained during this period was 30.5, and most were detained for non-violent, often petty, crimes.

Discussion: Interventions to detect young people with untreated psychosis in jails and prisons, and to refer these individuals to appropriate psychiatric care, may reach some who would otherwise have very long treatment delays. Pre-booking jail diversion programs, such as the Crisis Intervention Team (CIT) training of police officers, set a precedent for this kind of action and may serve as a model for early intervention services.

Poster #T34**INCREASED STABILITY OF MICROTUBULES IN CULTURED OLFACTORY NEUROEPITHELIAL CELLS FROM INDIVIDUALS WITH SCHIZOPHRENIA**

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Background: Microtubules (MTs) are hollow cylindrical filaments polymerized from α/β -tubulin heterodimers. As essential components of the cytoskeleton, MTs play critical roles in various neurodevelopmental processes and adaptive central nervous system functioning. In developing neurons, MTs steer growth cones contributing to growth-cone advance and turning in filopodia, and consequently govern axon guidance. MTs are also critical for ultrastructural changes that are integral to development of synaptic plasticity. During neurodevelopment, the roles of MTs figure significantly into current pathophysiologic theories of schizophrenia, including deficits of neuronal migration and outgrowth of axons and dendrites, two processes that depend, in part, on MTs. NMDA receptor hypofunction can lead to altered MT dynamics. To date, no study has directly investigated MT dynamics in schizophrenia.

Methods: We compared the stability of MTs in olfactory neuroepithelial (OE) cells between seven schizophrenia cases and seven comparison subjects matched for age and sex. We applied nocodazole (Nz) to cultured OE cells from tissue biopsies from these subjects. Nz allows MT depolymerization to be followed but prevents repolymerization, so that in living cells treated for varying time intervals, the MTs that are stable for a given treatment interval remain. Our readout of MT stability was the time at which fewer than 10 MTs per cell could be distinguished by anti- β -tubulin immunofluorescence. The percentage of cells with >10 intact MTs at specified intervals following Nz treatment was estimated by systematic uniform random sampling with Visiopharm software.

Results: Age (mean, SD) of the cases (47.3, 6.3) and controls (43.1, 10.8)

did not differ significantly ($p=0.40$, $t=0.87$, $DF=12$). Three of 7 (43%) cases and 5 of 7 (71%) controls were Caucasian ($p=0.59$); the remaining subjects were African-American. In nearly every matched pair, the percentages of OE cells with intact MTs at 10, 15, and 30 minutes after incubation with Nz were greater for the schizophrenia case than the nonpsychiatric comparison subject (Figure 1). The mean percentages of OE cells with intact MTs were significantly greater for schizophrenia cases than for the matched comparison subjects at each time point tested in the main analyses: 10 minutes [mean (SD) for schizophrenia cases and nonpsychiatric comparison subjects, respectively, were 60.2% (15.1) and 27.6% (11.7), $p=0.0007$, $t=4.50$, $DF=12$]; 15 minutes [43.0% (15.3) and 14.2% (8.0), $p=0.0008$, $t=4.42$, $DF=12$]; and 30 minutes [13.8% (10.1) and 3.7% (5.1), $p=0.036$, $t=2.36$, $DF=12$]. As expected, there were no group differences between schizophrenia cases and nonpsychiatric comparison subjects at baseline [87.3% (12.5) and 85.7% (8.1), $p=0.78$, $t=0.29$, $DF=12$], while at 60 minutes virtually no OE cells had intact MTs in either group [0.99% (2.2) and 0.15% (0.25), $p=0.35$, $t=1.02$, $DF=12$].

Discussion: These findings provide evidence that MT stability is increased in olfactory neuroepithelial (OE) cells of adult patients with schizophrenia. Specifically, we observed a significant decrease in depolymerization of MTs during a time course of nocodazole treatment in cultured OE cells derived from individuals with schizophrenia, compared with cells derived from nonpsychiatric comparison subjects. If our findings reflect similar neurobiological events among immature neurons during fetal development, or perhaps among newly generated cells destined for the olfactory bulb or hippocampal dentate gyrus, this would suggest a mechanism to explain observations in schizophrenia, from autopsy studies and in vivo imaging.

Poster #T35**THE EFFECT OF LIFESTYLE TREATMENTS ON BODYWEIGHT, CARDIOMETABOLIC RISK AND DEPRESSION IN PEOPLE WITH SEVERE MENTAL ILLNESS - A META-ANALYSIS**

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Background: Known side-effects of antipsychotic drugs are weight gain and other metabolic disturbances, which increases the risk of developing cardiovascular diseases. This risk is about four times higher in people with severe mental illness than in the general population. The aim of this study was to estimate the effects of lifestyle interventions on bodyweight and other cardiometabolic risk factors. In addition, the long-term effects on body weight and the effects on depressive symptoms were examined.

Methods: We searched multiple databases for randomized controlled trials (RCTs) from the year 2000 onwards, that compared lifestyle interventions aimed at weight loss or weight-gain-prevention to control conditions in patients with severe mental illness. The primary outcome was bodyweight change. Cohen's d was calculated to compare effect sizes among studies. We assessed the quality of the included studies using the 'Clinical Trials Assessment Measure' (CTAM) for psychological treatments.

Results: The search resulted in 24 RCTs showing an overall effect in favor of lifestyle interventions ($ES=-0.63$, $p<0.0001$). Lifestyle interventions were effective in both weight loss ($ES=-0.52$, $p<0.0001$) and weight-gain-prevention ($ES=-0.84$, $p=0.0002$). Both had significant long-term effects with a large effect ($ES=-0.85$, $p=0.0002$) for the weight gain prevention interventions and a moderate effect ($ES=-0.46$, $p=0.02$) for the weight loss studies. However, according to the CTAM only four studies were of high quality. We performed a sensitivity analysis with these four studies, which resulted in an ES of -0.55 ($p=0.008$). Lifestyle interventions showed significant improvements on cardiometabolic risk: favorable effects were seen on waist circumference, fasting glucose and insulin. No significant effects were found for systolic blood pressure and cholesterol levels. Additionally, lifestyle interventions reduced depressive symptoms ($ES=-0.57$, $p<0.0001$). An individual approach ($ES=-0.67$, $p=0.0004$) was more effective than a group-based intervention ($ES=-0.36$, $p=0.002$), but a combined approach showed the best results ($ES=-0.99$, $p=0.002$).

Discussion: There was high heterogeneity among the studies and according to the CTAM they were generally of low quality. Therefore the results have to be interpreted with caution. It was not possible to perform a sensitivity analysis for the cardiometabolic risk factors and depression, because not enough high quality studies reported these outcomes. Overall, lifestyle interventions are effective in treating and/or preventing obesity, and in reducing cardiometabolic risk and depressive symptoms. In patients with severe mental illness a combination of individual and group sessions seems most effective.

Poster #T36

GLOBAL METHYLATION LEVELS OF SCHIZOPHRENIA SUBJECTS SUPPLEMENTED WITH FOLATE: A PILOT STUDY

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Background: The atypical antipsychotics have many beneficial therapeutic effects in schizophrenia patients however they also carry a significant risk of metabolic side effects including weight gain, dyslipidemia, insulin resistance and metabolic syndrome. Ultimately, these side effects increase the risk of cardiovascular disease and result in life years lost. Aberrant folate metabolism is associated with metabolic syndrome in schizophrenia patients taking atypical antipsychotics. Hypomethylation of DNA, a process regulated by the folate cycle (through methyl donors), has also been linked to metabolic syndrome and antipsychotic use. This pilot study investigated whether folate supplementation in schizophrenia patients would increase global methylation levels. A change in methylation may serve as a predictor of folate response in future studies.

Methods: This study took place under a parent pilot study looking at the effect of folate supplementation on metabolic syndrome and endothelial functioning. Schizophrenia patients stable on antipsychotic medication for at least 6 months and having 3 or more metabolic syndrome criteria were given 5mg of folate daily for 3 months in a non-blinded, non-randomized fashion. Subjects had fasting labs taken at baseline and at 3 months. Physical activity was measured using a previously validated questionnaire at baseline and endpoint. Global methylation levels were analyzed using the LUMinometric Methylation Assay (LUMA).

Results: Thirty-five schizophrenia subjects were enrolled with an average age of 50, 66% were male, 80% were Caucasian and 86% were taking atypical antipsychotics. Baseline folate level was 17.9ng/ml. Folate levels increased to 24.9 ng/ml after supplementation. LDL, homocysteine, total activity score and IL-6 decreased (mean decrease of -2.5%, -14%, -15% and -13%, respectively) while BMI, fasting blood glucose, cholesterol and HDL increased (mean increase of +5.76%, +4.35%, +3.75% +3.14%, respectively) from baseline to endpoint. Of these changes, only the decrease in physical activity was significant ($p=0.03$). Global methylation levels significantly increased (72.1% versus 77.1% $p=0.0066$). Furthermore, a larger increase was seen in female patients (70.2% before versus 78.6% after). Finally, patients taking olanzapine and clozapine had the lowest methylation levels (69.6%) at baseline and had the largest average increase in methylation levels (5.8%).

Discussion: The results of this pilot study suggest that 3 months of folate supplementation has a significant effect on global methylation levels in schizophrenia subjects taking antipsychotics. Females and patients taking the most metabolically adverse antipsychotics, olanzapine and clozapine, had the lowest methylation levels at baseline along with the largest increase in methylation levels after folate supplementation. This may suggest that those patients taking the most metabolically adverse antipsychotics may receive the highest benefit as measured by methylation status. Our results also show that gender should be taken into account when conducting epigenetic studies. These results may help aid in the understanding of how folate supplementation influences antipsychotic-associated metabolic side effects. Methylation levels may also have potential as a future biomarker for folate response. This pilot study is the first to show an increase in global methylation levels in schizophrenia subjects supplemented with folate. Future prospective, randomized, placebo controlled trials taking into account folate metabolism pharmacogenetics will help confirm and provide further insight into the implications of this finding in schizophrenia therapy.

Poster #T37

FACIAL AFFECT RECOGNITION: THE IMPACT OF CULTURE AND SCHIZOTYPAL TRAITS

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Background: Facial affect recognition (FAR) is the ability to recognise one's facial expressions and it is one of many important aspects to successful social interactions. Factors such as cultural background and personality traits are influential. This study examined whether participants from cultural groups different to the cultural background of the posed photograph stimuli would perform worse than those groups from the same cultural background. In addition, the relationship between FAR and schizotypal personality traits was also explored.

Methods: A total of 124 Anglo-Australians, 225 Mainland Chinese, 290 Chileans and 111 Indians were recruited to identify six basic expressions of happiness, sadness, fear, anger, surprise and disgust displayed in photographs of Caucasian and Asian faces, and all completed the Schizotypal Personality Questionnaire-Brief (SPQ-B).

Results: The results of the current study found that Anglo-Australians and Chileans were equally as accurate in recognising the emotions displayed by Caucasian posers. Contrary to prediction, the Mainland Chinese group was not more accurate in identifying the emotions expressed by Asian posers than the other groups. Based upon the cultural out-group theory, the hypothesis that Chileans would be less accurate than Caucasian Australians and Mainland Chinese in recognising Caucasian and Asian expressions was not supported. However, findings supported that the Indian group would be less accurate than Caucasian Australians and Mainland Chinese in recognising both Caucasian and Asian expressions. The results did not support that SPQ factor scores being associated with low accuracy in emotion recognition across groups, but there were some associations between schizotypal traits within groups. Specifically, higher schizotypal traits were associated with lower accuracy in perceiving more ambiguous emotions, particularly when trying to identify those emotions in other cultures.

Discussion: The results of the current study suggest that there may be an interaction between schizotypal traits and cultural group which impacts upon perception of emotions.

Poster #T38

PREDICTION OF SYMPTOM OUTCOME IN CLINICAL HIGH RISK SUBJECTS USING THE ACOUSTIC STARTLE PARADIGM

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Background: Individuals at Clinical High Risk (CHR) for psychosis are characterized by the recent onset of subsyndromal psychotic symptoms along with negative, disorganized and general symptoms that do not reach the threshold of a first psychotic episode. Over a two year follow-up period, up to 35% of CHR subjects will develop a full psychotic illness while others will demonstrate a continued progression, no change, or a remission subsyndromal symptoms. As the field of early psychosis research moves toward pre-emptive intervention based on specific neural system dysfunction, it is increasingly important to identify biomarkers associated with disease outcome that can specify treatment. The acoustic startle paradigm allows the assessment of startle magnitude, latency, prepulse inhibition (PPI) and habituation; all important biomarkers in translational schizophrenia research with the potential to inform early psychosis research.

Methods: As part of the North American Prodrome Longitudinal Studies (NAPLS) consortium 321 CHR subjects and 218 Healthy Comparison (HC) subjects were assessed on the startle paradigm at baseline and received clinical follow-up within a 2 year period. Clinical outcome of CHR subjects was defined as in Remission (N=65), Symptomatically unchanged (N=106),

Progressed (N=112) or Conversion to psychosis (N=38). An acoustic startle paradigm was then administered that included 115dB stimuli intermixed with prepulse trials of 86dB (30, 60 and 120 ms interstimulus intervals). The association of startle indices with clinical outcome was then assessed by grouping CHR subjects into their outcome group.

Results: Increased startle latency ($p<0.002$), reduced magnitude ($p<0.05$) and increased PPI (trend level: conversion > progression > symptomatic > remission > HC) were all associated with progression of symptoms or conversion to psychosis at follow-up, while startle habituation ($p<0.05$) and magnitude ($p<0.06$) differentiated CHR from HC subjects at baseline. Increased startle latency was also associated with increases in disorganized ($p<0.002$) and negative ($p<0.05$) symptoms in the CHR group.

Discussion: Startle measures, and in particular startle latency, represent important biomarkers associated with clinical outcome in CHR subjects. Increases in startle latency are associated with dopaminergic dysregulation in animal studies suggesting the potential importance of this index in specifying treatment for the prodromal phase of illness. The startle paradigm is a relatively simple paradigm that could be easily translated into the clinic and potentially used to not only assess risk for symptomatic progression but inform treatment based on the parallel basic science studies in the burgeoning field of CHR research.

Poster #T39

AN ASSOCIATION STUDY OF RGS4 POLYMORPHISMS WITH CLINICAL AND NEUROCOGNITIVE PROFILES OF SCHIZOPHRENIA PATIENTS

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Background: Polymorphisms of the gene encoding the regulator of G protein signaling, subtype 4 (RGS4), may be associated with schizophrenia. Few studies have shown the association of RGS4 polymorphisms with clinical and neurocognitive profiles. Previous studies have found a relation between SNP1, SNP7 and SNP18 of RGS4 and memory dysfunctions including face memory, verbal memory and spatial memory. Also SNP4 and SNP18 were also associated with schizophrenia symptoms, especially negative symptoms. The aim of the study was to investigate the association of four RGS4 polymorphisms (single nucleotide polymorphisms [SNPs] 1, 4, 7 and 18) with clinical and neurocognitive profiles in patients with schizophrenia.

Methods: 104 schizophrenia patients diagnosed as DSM-IV schizophrenia criteria were included for this study. Patients were genotyped with four RGS4 markers (SNP 1, 4, 7 and 18). Severity of schizophrenia symptoms was assessed by using Positive and Negative Syndrome Scale (PANSS). All subjects were administered verbal learning memory, visual memory, executive functions, verbal fluency, attention and verbal working memory tests. Four RGS4 markers (SNP 1, 4, 7 and 18) were applied to DNA sequence analysis (Macrogen, Kore). Hardy-Weinberg equilibrium for RGS4 markers was checked. Normal distribution of the continuous variables for genotypes at each marker was examined using ANOVA test. The variables which don't have a normal distribution were examined using Kruskal Wallis test for genotypes at each marker.

Results: SNP1 and SNP7 heterozygote G/A were significantly associated with impairment trail making test part A and B error scores. There was a significant association between SNP1 homozygote AA, SNP4 homozygote GG, SNP7 homozygote AA and SNP18 homozygote AA and PANSS' g7 subscale (motor retardation) score (respectively $p: 0.011$; $p: 0.013$; $p: 0.048$; $p: 0.003$). Additionally SNP18 homozygote AA was associated with PANSS' n1 subscale (blunted affect) score ($p: 0.007$).

Discussion: All SNPs were associated with PANSS' g7 subscale score and only SNP18 was associated with PANSS' n1 subscale score. RGS4 polymorphisms may be associated with motor function and affective symptoms in schizophrenia. There was also a association between SNP1, 7 and impairment trail making test part A and B error scores. However other neurocognitive tests which measure executive functions, working memory and attention weren't significantly associated with all SNPs. RGS4 Polymorphisms may be related to motor retardation and blunted affect in schizophrenia.

Poster #T40

THEORY OF MIND AND PERSONALITY PATHOLOGY IN SCHIZOPHRENIA PATIENTS AND FIRST-DEGREE RELATIVES

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Background: Theory of mind (ToM) is the ability to attribute mental states to the self and others. Persons with schizophrenia have been shown to have deficits in ToM abilities, with mixed results found in first-degree non-psychotic relatives of schizophrenia patients. Preliminary research also shows evidence for personality pathology in both schizophrenia patients and their first-degree relatives, including affective lability, anxiousness, insecure attachment, intimacy problems, restricted expression, and submissiveness. Moreover, ToM abilities have been related to personality characteristics in general, such as agreeableness and neuroticism. No research has focused on the association between ToM deficits and personality pathology in a schizophrenia family study.

Methods: The Awareness of Social Inference Test (TASIT), a collection of videotaped interactions with sarcasm comprehension questions, and the Dimensional Assessment of Personality Pathology - Brief Questionnaire (DAPP-BQ) were administered to schizophrenia patients (n=30), first-degree relatives of patients (n=28) and healthy controls (n=27).

Results: Schizophrenia patients scored significantly lower on measures of simple sarcasm comprehension compared to relatives ($p=0.005$) and controls ($p=0.005$), and significantly lower on measures of paradoxical sarcasm compared to relatives ($p=0.003$) and controls ($p=0.049$). However, no differences were found in sarcasm comprehension between relatives and controls. Schizophrenia patients scored significantly higher than relatives and controls on affective lability ($p=0.002$ and $p=0.000$, respectively), anxiousness ($p=0.03$ and $p=0.000$), insecure attachment ($p=0.000$ and $p=0.000$), intimacy problems ($p=0.000$ and $p=0.000$), restricted expression ($p=0.03$ and $p=0.001$), and submissiveness ($p=0.01$ and $p=0.001$). In schizophrenia patients, ToM abilities were negatively related to affective lability ($p=0.03$), anxiousness ($p=0.05$), and insecure attachment ($p=0.005$), and moderately negatively correlated with intimacy problems, restricted expression, and submissiveness. ToM abilities were not associated with personality pathology in either first-degree relatives or healthy controls.

Discussion: Schizophrenia patients showed impairments in sarcasm comprehension (a practical measure of ToM reasoning) compared to both first-degree relatives and healthy controls. Conversely, first-degree non-psychotic relatives of schizophrenia patients did not show impairments in ToM reasoning on this more ecologically valid videotaped task. Similarly, schizophrenia patients endorsed responses associated with personality pathology (e.g., high levels of affective lability, anxiousness, insecure attachment, and intimacy problems), whereas first-degree relatives did not endorse the same degree of personality pathology compared to healthy controls. ToM abilities were correlated with personality pathology for schizophrenia patients only. Taken together, schizophrenia patients show deficits in ToM reasoning, and this may be related to personality impairments. In contrast, first-degree relatives of schizophrenia patients show intact ToM performance on a task where real-world social cues (such as voice intonation and facial cues) provide contextual information, and comparable personality traits to controls. Future research on the genetic liability of ToM deficits should utilize more ecologically valid tasks that are more closely related to real-world social functioning (e.g., videotaped tasks).

Poster #T41

DO REWARD-PROCESSING DEFICITS IN SCHIZOPHRENIA PROMOTE CANNABIS USE? AN INVESTIGATION OF RESPONSE TO NATURAL REWARDS AND DRUG CUES

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Background: Despite the accumulation of evidence indicating negative consequences of cannabis use in schizophrenia, there has been little progress in reducing cannabis abuse in this population. It may be necessary to better characterize factors promoting cannabis use in order to tackle this problem. Dysfunctional reward processing is present in schizophrenia and may

confer vulnerability to addiction. Our objective was to identify a deficit in schizophrenia patients on response to rewarding stimuli and see whether this deficit predicts cannabis use.

Methods: 35 schizophrenia patients and 35 non-psychotic controls were divided into cannabis users and non-users. Response to emotional and cannabis-associated visual stimuli was assessed using self-report, event-related potentials (using the late positive potential, LPP), motivated behaviour, facial electromyography, and skin-conductance response. Frequency of cannabis self-administration over the prior month was assessed on the test day and one month later.

Results: Schizophrenia-spectrum patients showed blunted LPP response to pleasant stimuli compared to controls ($p=0.003$) and blunted reward seeking of pleasant stimuli ($p=0.046$). Across measures, cannabis-using controls showed significantly greater response to pleasant stimuli than to cannabis stimuli whereas cannabis-using patients showed little bias towards pleasant stimuli. More frequent subsequent cannabis use was predicted by blunted LPP response to pleasant stimuli ($\beta = -0.24$, $p=0.034$) and blunted reward seeking of pleasant stimuli ($\beta = -0.34$, $p=0.006$).

Discussion: Reward processing deficits identified in schizophrenia may promote substance use and explain in part the common comorbidity of these two disorders. The LPP in particular shows potential as a biomarker related to schizophrenia which may be able to help identify patients at risk of heavy cannabis use. Targeting reward processing deficits may be a promising avenue in the development of interventions for reducing cannabis use in schizophrenia.

Poster #T42

DURABILITY OF REINFORCEMENT LEARNING CHANGES AFTER COGNITIVE REMEDIATION

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Background: Converging evidence suggests that individuals with schizophrenia show a marked impairment in reinforcement learning. Recent research showed that cognitive remediation (CR) can improve reward learning by altering sensitivity to reward and punishment. The aim of this study is to explore whether these gains can be sustained once therapy is finished and compare them to individuals assessed at the same intervals to assess whether practice has effects.

Methods: Using computational modelling, two reinforcement learning parameters based on the Wisconsin Card Sorting Test (WCST) trial-by-trial performance were estimated: R (reward sensitivity) and P (punishment sensitivity). The durability of the cognitive remediation (CR) improvements on these parameters was assessed 3-months after the end of therapy in a group of individuals with schizophrenia who received CR ($n=37$) and compared to a group receiving treatment-as-usual (TAU, $n=34$). Neuropsychological and symptom assessments were also conducted.

Results: Individuals in the CR group showed a significant reduction in both P and R gains at follow-up compared to TAU. In the CR group 14 participants maintained or improved in R levels at follow-up while 12 maintained or improved in P levels. Participants who maintain P levels had higher premorbid and actual IQ at baseline and working memory levels at follow-up compared to those who did not. The R retention sub-group was not associated with any variable measured. Most individuals in the TAU still failed to improve on both parameters at follow-up despite practice.

Discussion: Retaining reward learning gains after CR may be difficult if patients are not provided with additional support. Despite overall group worsening in the CR group about a third of the participants maintained R and P gains without additional interventions. Punishment sensitivity gains retention seems to be affected by IQ levels and working memory.

Poster #T43

AUTOMATIC SELF-STIGMA-RELEVANT ASSOCIATIONS IN PEOPLE WITH SCHIZOPHRENIA EXPERIENCING HABITUAL SELF-STIGMA: EVIDENCE FROM THE BRIEF IMPLICIT ASSOCIATION TESTS

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Background: While self-stigmatizing thoughts constitute a cognitive vulnerability factor for poor mental health, dysfunctional coping (i.e., experiential avoidance and lack of mindfulness) with self-stigma may pose an additional risk factor for this propensity by leading to frequent activation of self-stigmatization, which may then make self-stigmatizing thinking habitual and automatic (namely, a mental habit). This concept of habitual self-stigma points to the importance of understanding the automatic, implicit aspects of self-stigma. The present study aims to investigate the possibility of a pattern of more automatic self-stigma-relevant associations among people with schizophrenia having habitual self-stigma.

Methods: A community sample of 62 people with schizophrenia spectrum or other psychotic disorder was recruited in Hong Kong. Habitual self-stigma was assessed with the Self-stigmatizing Thinking's Automaticity and Repetition (STAR) scale. Considering that self-stigma refers to internalizing the negative attributes associated with the mental illness (MI) identity for the self, three different Brief Implicit Association Tests (BIATs) were used to assess the automatic processing of the "self-MI" association (i.e., high centrality of the MI identity to the self), the "MI-negative" association (i.e., negative attitudes toward MI), and the "self-negative" association (i.e., low self-esteem).

Results: The automatic "self-MI" association ($r=0.342$, $p=0.006$), but not the "MI-negative" association ($r=0.196$; $p=0.126$) and the "self-negative" association ($r=-0.079$; $p=0.544$), was correlated with stronger self-stigmatizing thinking habit. Repetitive self-stigma ($r=0.341$, $p=0.007$) and automatic self-stigma ($r=0.324$, $p=0.01$) were also correlated with more automatic processing of the "self-MI" association.

Discussion: While there has been extensive research on the demographic, clinical, and psychosocial correlates of self-stigma, there has been little research on its cognitive or information-processing profile. This study provides a direct test of the relevance of automatic evaluation in understanding the nature of automatic cognitive processing in habitual self-stigma. Our findings suggest that the mental illness identity may be more central to the self-definition of participants with stronger self-stigmatizing thinking habit. The significant correlation between the STAR scale and the automatic quality of response latencies in the BIAT strengthens the assumption that the scale does have validity in reflecting cognitive processes that take place automatically.

Poster #T44

THREE-YEAR OUTCOME COMPARISON BETWEEN PATIENTS PRESENTING WITH FIRST-EPIISODE PSYCHOTIC MANIA AND SCHIZOPHRENIA TO EASY PROGRAM IN HONG KONG

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Background: Early intervention for first-episode psychosis has been the focus of mental health care development worldwide in the past two decades. A majority of previous research focused mainly either on outcomes of a cohort of broad-spectrum psychotic disorders (first-episode psychosis) or patients with a more specific diagnostic entity, mostly schizophrenia. Despite the fact that bipolar affective disorder frequently occurs in late adolescence or early adulthood, and is associated with poor long-term functional impairment, relatively few studies have been conducted to examine the early course of the illness. In this study, we aimed to compare the 3-year clinical and functional outcomes between first-episode psychotic mania (FEPM) and first-episode schizophrenia (FES) in the context of early intervention program in Hong Kong.

Methods: Four hundred-twenty patients aged 15 to 25 years presenting with first-episode ICD-10 psychotic mania or schizophrenia to a territory-wide early intervention service in Hong Kong, namely Early Assessment Service for Young people with psychosis (EASY) between July 2001 and August 2003 and completed 3-year follow-up were included in the study. Socio-demographics, baseline and follow-up variables were obtained via systematic retrospective medical record review following standardized protocol. Symptom (CGI-S) and functional outcome (SOFAS) measures were

determined for each month in the 3 years following entry to EASY program.

Results: Of the 420 patients, 374 and 46 were diagnosed with FES and FEPM, respectively. At baseline, patients with FES had longer duration of untreated psychosis (DUP) ($t=8.4$, $p<0.001$), fewer hospitalization at entry ($\chi^2=29.0$, $p<0.001$), fewer positive symptoms ($t=-2.6$, $p=0.01$) and better functioning ($t=3.5$, $p=0.001$) than patients with FEPM. By the end of 3-year follow-up, FEPM patients had significantly fewer positive symptoms ($t=2.8$, $p<0.05$), fewer readmissions ($t=-3.9$, $p<0.001$), better functioning ($t=-2.9$, $p<0.05$), higher likelihood of achieving sustained employment ($\chi^2=4.6$, $p<0.05$) than FES patients. Multivariate regression analyses taking into consideration baseline between-diagnostic group differences revealed that diagnostic status (i.e., FEPM vs. FES) independently predicted total number of hospitalizations over 3 years ($p<0.05$), sustained employment ($p<0.01$), and global functional outcome at 3 years of follow-up ($p<0.01$).

Discussion: In a large representative cohort of Chinese young patients presenting with first-episode psychosis to early intervention service, our findings indicated that patients with FEPM had better 3-year clinical and functional outcomes than those with FES. More prospective research is required to investigate the longitudinal course and outcome predictors of bipolar affective disorder in its early illness stage.

Poster #T45

CHANGES IN BODY MASS AND METABOLIC PROFILES OVER 12 MONTHS IN PATIENTS WITH FIRST-EPISEDE SCHIZOPHRENIA WITH ASSURED ANTIPSYCHOTIC ADHERENCE

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Background: Patients with schizophrenia are at increased risk of weight gain and metabolic syndrome, and antipsychotic medications are a major contributor.

Methods: We investigated the changes in body mass, fasting blood glucose, lipids and prolactin in 107 antipsychotic naïve or minimally treated patients with first- episode schizophrenia who were treated according to a standard algorithm with long-acting injectable flupenthixol decanoate over 12 months.

Results: Eighty-three (78%) participants completed the 12 months of treatment, and 104 (97%) received 100% of the prescribed injections during their participation. Linear mixed effect models for continuous repeated measures indicated statistically significant increases in BMI ($p<0.0001$), waist circumference ($p=0.0006$) and triglycerides ($p=0.03$) and significant decrease in HDL ($p=0.005$), while systolic ($p=0.7$) and diastolic blood pressure ($p=0.8$), LDL ($p=0.1$), cholesterol ($p=0.3$), glucose ($p=0.9$) and prolactin ($p=0.3$) values did not change significantly over time. The triglyceride:HDL ratio increased by 91%. Baseline rates of metabolic syndrome were high ($n=17$, 16%), and increased at endpoint ($n=26$, 24%). Change in BMI was significantly correlated with change in triglycerides ($r=0.34$, $p=0.008$), but not with change in glucose ($r=0.1$, $p=0.3$), HDL ($r=-0.1$, $p=0.3$), LDL ($r=0.2$, $p=0.1$) or total cholesterol ($r=0.2$, $p=0.1$). BMI increase was not significantly related to endpoint flupenthixol dose ($p=0.1$). The only significant predictor of BMI increase was non-substance abuse ($p=0.002$).

Discussion: The risks of weight gain and metabolic syndrome associated with antipsychotic treatment in first- episode schizophrenia psychosis are not restricted to second generation antipsychotics and low-potency first-generation antipsychotics. This is a global problem, and developing communities may be particularly susceptible.

Poster #T46

COMPARISON OF THE RORSCHACH PERFORMANCE BETWEEN SCHIZOPHRENIA AND BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES

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Background: Although bipolar affective disorder is conventionally viewed as distinct from schizophrenia, differential diagnosis between these disor-

ders might be challenging in the clinical setting. Although the Rorschach test might provide additional information to investigate these disorders, the controversial findings were shown in previous studies for diagnostic validity based on Rorschach indices (Llonen et al., 1999). For example, although Thought Disorder Index (TDI) is related to schizophrenia, no published studies have proven significant validity for diagnoses of the disorder (Wood, Lilienfeld, Garb, & Nezworski, 2000). Moreover, few studies have reported comparison of Rorschach profiles in relation to thought disorder between schizophrenia and bipolar disorder with psychotic features. The aim of this study was to compare Rorschach performance between schizophrenia (SPR) and bipolar I disorder with psychotic feature (BPF).

Methods: Twenty-four patients with schizophrenia and 16 patients with bipolar I disorder with psychotic features aged 18 to 61 years (mean=33.9) were recruited from a hospital located in Seoul, South Korea. Medical records and raw data of the Rorschach Inkblot test (using the Comprehensive System; Exner, 1986) were reviewed. Individual variables of the Rorschach test were applied. Statistical analyses were run in SPSS 17.0. Independent-samples t test was computed to evaluate the difference between SPR and BPF.

Results: Results indicated that BPF reported more W, DR, FQu and higher Zf, EA, Sum6, WSum6 compared to SPR ($p<0.05$). SPR reported significantly higher Lambda and more Hd than BPF ($p<0.05$). Meanwhile, no significant differences in color responses (WSumC, CF+C, FC), Afr between SPR and BPF were found. The differences in Rorschach indexes, including TDI (TDI, DEPI, CDI, S-CON, HVI, OBS), were also not significant.

Discussion: Present findings demonstrated that bipolar I disorder with psychotic features show more ideational activities, cognitive resources and mental abilities, including planning and imagination compared to schizophrenia. Whereas, contrary to our expectations, the findings indicated that bipolar disorder with psychotic features show more cognitive slippage than schizophrenia along with no differences in SCZI. Also, the responses related to affect and emotion were not remarkable in psychotic bipolar group. As reported in a previous study that the utility of the Rorschach SCZI and DEPI in the differentiation of psychotic disorders and only non-psychotic depression, the findings in this study may provide further evidence for the view that psychotic bipolar is distinct rather than non-psychotic bipolar. Future researches would be suggested.

Poster #T47

SIMILAR AGE-RELATED DECLINE IN CORTICAL ACTIVITY OVER FRONTOTEMPORAL REGIONS IN SCHIZOPHRENIA AND HEALTHY INDIVIDUALS: A MULTI-CHANNEL NEAR-INFRARED SPECTROSCOPY STUDY

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Background: Although recent studies have demonstrated similar age-related decline in cortical thickness and cognitive function in patients with schizophrenia and healthy controls, it remains unclear whether the influences of aging on brain functions differ between those two groups when assessed using functional neuroimaging. This study investigated the age effects on regional brain cortical activity to determine whether there is similar age-related decline in cortical activity as those observed in cortical thickness and cognitive function.

Methods: A total of 109 patients with schizophrenia (age range: 16–59 years) and 106 age-, gender-, and IQ-matched healthy controls (age range: 16–59 years) underwent near-infrared spectroscopy (NIRS) while performing a verbal fluency test (VFT). Group comparison of cortical activity was examined using two-tailed t-tests, adopting the false discovery rate (FDR) method, and the relationship between age and cortical activity was investigated using correlational and multiple regression analyses adjusting for potential confounders. A two-way ANOVA was conducted to investigate differences in the age effects between diagnostic groups.

Results: The patient group exhibited significantly decreased cortical activity in several regions of the frontotemporal cortices. However, similar patterns

of age-dependent decreases in cortical activity were observed in patients and controls over the bilateral MFG, and the right IFG.

Discussion: Consistent with previous studies demonstrating similar age effects on cortical thickness and cognitive function in patients with schizophrenia and healthy controls, our study showed similar age-related decline in cortical activity, as measured by NIRS, over several frontal regions during a VFT in both groups. As previous MRI and neuropsychological studies suggested that pathological changes in brain morphology or cognition occur relatively early in schizophrenia, results of our study might also indicate decrease in cortical activity in a relatively limited period around illness onset rather than progressing over the course of the illness.

Poster #T48

INVESTIGATION OF THE PRO-MELANIN-CONCENTRATING HORMONE GENE IN ANTIPSYCHOTIC INDUCED WEIGHT GAIN

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Background: Second generation antipsychotic medications can effectively treat core symptoms of schizophrenia (SCZ). However, the development of severe side-effects, including substantial weight gain, may result in onset of metabolic syndrome in SCZ patients. The PMCH rs7973796 single nucleotide polymorphism (SNP) has been associated with a greater body mass index in olanzapine-treated SCZ patients (Chagnon et al., 2007). Thus, we investigated the potential role of PMCH single nucleotide polymorphisms (SNPs) in antipsychotic induced weight gain by using tagSNP software to capture further coverage of the gene.

Methods: The PMCH SNPs (rs10507145, rs11111206, rs7973796, rs11111203) were selected by tagSNP and assessed in 217 chronic SCZ patients. The SNPs were typed using Illumina GoldenGate Genotyping Assays. The percentage change in weight across genotypic groups was assessed. Analysis of covariance with duration as a co-variate was conduct to analyze weight change (SPSS 15.0).

Results: Genotypic associations were found between the PMCH polymorphisms and weight gain in a sub-sample consisting of European ancestry patients treated with either olanzapine or clozapine (n=82). The rs7973796 AA homozygote group gained more weight $8.11 \pm 7.2\%$ than the GG genotypic group ($4.17 \pm 4.8\%$) or the heterozygotes ($4.17 \pm 4.8\%$) ($p = 0.048$).

Discussion: In this study, we observed that one PMCH gene variant reached a trend for association with antipsychotic induced weight gain. This finding supports the previous association with PMCH in weight in olanzapine treated SCZ patients (Chagnon et al., 2007). The PMCH peptide has been shown to have a role in feeding behaviour of mice (Shimada et al., 1998; Mul et al., 2011), though its exact function in human obesity is less well known. Our findings warrant further investigation in larger sample sets. The PMCH gene may also be acting in tandem with other weight regulating genes to result in antipsychotic induced weight gain.

Poster #T49

HYPER-THEORY-OF-MIND IN CHILDREN WITH PSYCHOTIC EXPERIENCES

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Background: Impairments in Theory of Mind (ToM) is well established in schizophrenia, but the nature and extent of the impairment remains unclear, as do the role of ToM in the ontogenesis of psychosis. Converging evidence suggests that the general population-based samples of children

with subclinical psychotic experiences (PE) may constitute a valid population in which to study the etiology of psychosis and Schizophrenia. A few studies of children have documented that ToM impairments are associated with PE in general, suggesting that ToM impairments may play a role in the development of psychosis. Our Aim was to examine the specific patterns of the over-interpretative exaggerated type of ToM impairment (HyperToM) and PE in children. We hypothesized that 1) PE would be more frequent in children with HyperToM than in those without, 2) HyperToM would be stronger associated to paranoid delusions compared to PE without paranoid delusions.

Methods: Hypotheses were tested in two independent samples: (I) a general population sample of 1630 Danish 11-12 y/o children and (II) a population-based sample of 259 Dutch 12-13 y/o children, pertaining to a case-control sampling frame of 7-8 y/o children with auditory verbal hallucinations. Multinomial regression analyses were carried out to investigate the associations between HyperToM and PE with and without paranoid delusions. Analyses were adjusted for proxy measures of general intelligence.

Results: HyperToM was significantly associated to PE in both sample I ($OR=1.8$, 95%CI 1.2-2.7) and II ($OR=4.3$, 95%CI 1.2-15.2). HyperToM was particular associated to paranoid delusions in both sample I ($OR=2.0$, 95%CI 1.1-3.7) and II ($OR=6.1$, 95%CI 1.6-22.8).

Discussion: The current study demonstrates detailed patterns of specific alterations in ToM being associated with specific types of psychotic experiences. HyperToM may index risk for developing psychosis and for paranoid delusions in particular.

Poster #T50

IS COGNITIVE REMEDIATION THERAPY AN EFFECTIVE INTERVENTION IN ENHANCING VOCATIONAL OUTCOMES FOR PEOPLE WITH SEVERE MENTAL ILLNESS?

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Background: People with severe mental illness (SMI) have reduced workforce participation, which leads to significant economic and social disadvantage. Cognitive Remediation (CRT) has been recognised as an intervention to improve employment outcomes by addressing cognitive impairments often experienced by patients. It is of critical importance to investigate the validity of these current international research conclusions in Australian settings. This pilot study aimed to determine whether CRT enhances cognitive, psychosocial and vocational functioning for jobseekers participating in a ten-session psychoeducational group program named HOPE, provided by Social Firms Australia (SOFA).

Methods: Fourteen participants with SMI (schizophrenia, bipolar disorder, major depression) (age $M=43.07$, $SD=7.00$) attended 20 individual sessions of CRT (CogPack). Patients were administered the MATRICS Consensus Cognitive Battery (MCCB), the PANSS, the MADRS at Baseline, 3 months and 6 months. They also responded to a Self-esteem scale, a Quality of Life scale and a vocational questionnaire, that obtained information of a number of vocational variables.

Results: Cognition: A 3 time points \times 7 cognitive domains repeated measure ANOVA demonstrated there was a main effect for time ($F(2,24)=4.9$, $p=0.016$), with overall cognition improving over the three time points. There was no main effect of cognitive domain and no interaction. This suggests that the different cognitive domains improved at the same rate. Vocational: A 3 time periods \times 2 work types (paid and volunteer) repeated measures ANOVA was run. There was no main effect of time ($F(2,24)=1.9$, $p=0.2$) or work type ($F(2,24)=0.5$, $p=0.5$) or interaction ($F(2,24)=1.6$, $p=0.2$). Although there was no statistically significant improvement in total number of hours worked, there was certainly a noticeable trend in the right direction between baseline and 3 months with a moderate effect size ($d=0.4$), with no change or minimal change noted between 3 and 6 months ($d=0.1$). Interestingly, 46% of patients initiated tertiary studies between baseline and 6 months.

Discussion: In accordance with previous studies, CRT succeeded in improv-

ing cognition and psychosocial performance. Although, vocational benefits were not reported, a large proportion of the sample initiated educational advancement. This pilot becomes highly relevant as it generates evidence on effective ways to enhance workforce access and participation for people with SMI.

Poster #T51

BIRTH WEIGHT AND IQ ARE ASSOCIATED WITH ADULT CORTICAL SURFACE AREA: ADDITIONAL EVIDENCES BASED ON A TWIN STUDY

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Background: Prior research indicates that low birth weight (BW) induces reductions in brain cortical surface area (SA) which would persist until at least early adulthood (Haukvik et al., 2013; Raznahan, Greenstein, Lee, Clasen, & Giedd, 2012; Walhovd et al., 2012). Besides, low BW has been linked to psychiatric disorders such as depression and psychological distress, and to altered neurocognitive profiles (Wojcik, Lee, Colman, Hardy, & Hotopf, 2013; McDaniel, 2005). In this study, authors aimed i) to test the BW-SA association in a middle-aged adult sample and ii) to assess if either depression/anxiety disorders or intellectual quotient (IQ) influence the BW-SA link, using a monozygotic (MZ) twin design to separate environmental and genetic effects.

Methods: High-resolution structural MRI scans of 48 twins were analyzed to calculate regional cortical surface areas, which were then evaluated with respect to BW, intelligence, and depression/anxiety in multivariate regression models.

Results: Smaller total cortical SA was associated with both lower BW and decreased IQ in the present adult sample. Regionally, lower BW lessens the right posteriorcingulate and paracentral surfaces, whereas decreased IQ correlated with reduced left temporal, cingulate and subcallosal areas. Within a twin pair, lower BW was related to smaller total cortical and regional left temporal SA, suggesting a strong effect of non-genetic prenatal conditions in modulating the BW-SA link. In contrast, MZ twin differences in SA were not related to differences in IQ. The aforesaid associations were not modified by depression/anxiety disorders.

Discussion: This study supports findings indicating that i) BW has a long-lasting effect on cortical SA, according to which a mix of familial and unique environmental interactions may influence both fetal growth and brain morphology; ii) environmental factors affecting BW have a specific effect on SA; and iii) higher IQ correlates with larger SA.

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Poster #T52

COMT MODERATION OF THE ASSOCIATION BETWEEN MOMENTARY STRESS AND PSYCHOTIC-LIKE EXPERIENCES IN DAILY LIFE

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Background: Daily life stressors play an important role in the expression of psychotic-like experiences (PLEs) and paranoid symptoms. Individual variation in PLEs in response to stressors is likely to be moderated by genetic variability. In particular, evidence suggests that the single nucleotide polymorphisms Val158Met (SNPs) on the Catecol-O-Methyltransferase (COMT) gene may moderate the association between momentary stress and psychosis. However, there is scant information regarding the role of COMT with the real-world expression of PLEs and paranoid symptoms. The present study employed Experience Sampling Methodology (ESM) to assess gene-momentary environment interactions in daily life in a non-clinical sample. Specifically, the current study examined (1) whether appraisals of stress in general, and social stress in particular, were associated with momentary PLEs and paranoia in daily life, and (2) whether COMT variability moderated the association of general and social stress with momentary PLEs and paranoia.

Methods: Two hundred and one nonclinical young adults who were oversampled for psychometric schizotypy were genotyped for COMT Val158Met and were prompted randomly eight times daily for one week to complete assessments of their current symptoms and experiences, as well as subjective appraisals of stress and contextual factors. A comprehensive daily life PLE index was based on eight ESM items.

Results: The results showed that stressful situations and social stress were associated with momentary PLEs and paranoia. The association between perceived social rejection and PLEs was higher for individuals with the Val/Val genotype as compared with those with the Met/Met genotype. Similarly, the association between perceived social rejection and paranoia was higher for individuals with the Val/Val genotype than for Met carriers. Additionally, results indicated that when participants were with others at the time of the signal, perceived social distance and preference to be alone were more strongly associated with PLEs for Val/Met than for Val/Val participants.

Discussion: As predicted by the stress-sensitivity model, momentary stress was associated with momentary PLEs and paranoid experiences. Genetic variability in the COMT moderated some of the associations of social stress with PLEs and paranoia, but not the associations with situational stress. Although a mixed pattern emerged in terms of the genotypic profile conferring a higher psychotic-like response to social stress appraisals, the findings seem to be consistent with the increasing relevance given to socially defeating schemas in the experience of reality distortion.

Poster #T53

THE KUMON METHOD FOR COGNITIVE REMEDIATION OF INDIVIDUALS WITH SCHIZOPHRENIA: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL

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Background: Cognitive deficits are an integral part of the clinical picture of schizophrenia. Various studies seek cognitive training (cognitive remediation) methods to improve those deficits, poorly responsive to pharmacological treatment. Clinical trials of cognitive remediation training use a variety of techniques, with the stimulation of several cognitive domains simultaneously. Many of them employ the “errorless learning” technique. Recent research indicates that some cognitive domains underlying mathematical learning (attention, executive function and working memory) are also impaired in schizophrenia. However, no cognitive remediation studies were found focusing on arithmetic training in individuals with schizophre-

nia. The arithmetic calculation method proposed by Kumon employs the errorless learning technique and is widely used for supplemental education. Two randomized trials of cognitive remediation using the Kumon Method (arithmetic calculation) with healthy elderly subjects as well as with elderly subjects with Alzheimer's disease showed cognitive function improvement with this intervention. The present study evaluated the effectiveness of the arithmetic calculation of the Kumon method as cognitive remediation for working memory, executive function and attention in patients with schizophrenia.

Methods: 51 subjects with a diagnosis of schizophrenia (DSM-IV), male and female, literate, aged between 18-55 years, were included in the trial and randomized to arithmetic calculation training by the Kumon method (experimental group) or recreational activities (placebo-control group). The subjects received 48 intervention sessions over the course of 6 months. The subjects were evaluated through a neuropsychological battery; the clinical outcome was assessed by the Positive and Negative Syndrome Scale (PANSS), and functioning was evaluated using the Personal and Social Performance (PSP) scale at baseline, at 6 months (discontinuation of interventions) and after 6 months without interventions.

Results: The experimental group showed a trend to improvement in sustained attention ($p=0.075$), yet this was not maintained after 6 months without interventions. Both groups showed improvements in selective attention and executive function at 6 months, which were not maintained after one year, with no differences between groups. No differences were found in social functioning between the groups and throughout the 12 months of follow-up. The factor analysis of the 5-factor PANSS (as proposed by Van der Gaag, 2006) showed no significant change in the factors "positive", "negative", "disorganization" and "emotional distress" over time and between groups. Only the placebo group exhibited a significant improvement in the factor "excitement" after 6 months compared with the experimental group, which was not maintained after 6 months without interventions.

Discussion: The cognitive arithmetic training by the Kumon method tends to improve sustained attention after 6 months, with no impact on either executive function or working memory. This trend was not sustained after 6 months without interventions.

Poster #T54

INCREASING THERAPEUTIC ACTIVITIES ON ACUTE PSYCHIATRIC WARDS

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Background: Introduction Service users have often reported that there are very few therapeutic activities for them to engage in while they are on inpatient acute wards, in spite of numerous reports and professional bodies (e.g., NICE) recommending talking therapies to be provided on inpatient wards, and specifically those who have a diagnosis of schizophrenia. Nurses often report that solving crises and administrative tasks often prevent them. The aims were twofold. Firstly to determine if executing such a programme is feasible in a busy inpatient environment. Secondly, to investigate in detail the difference that increasing therapeutic activities makes on the environmental milieu and how this is perceived by service users and staff. **Methods:** Method Sixteen wards took part, and they were randomised in turn to receive a structured training programme aiming to equip nurses to be able to run therapeutic groups independently. The main outcomes were perceptions of staff and patients and secondary outcomes of service user symptoms, length of stay and cost of care.

Results: Results The project demonstrated that nurses are able to independently deliver therapeutic activities. The view that this would be beyond their abilities undersells their skills. The uptake of the therapeutic groups also demonstrates the receptiveness of acutely unwell people to such interventions. The analysis of service user and nurse perceptions, ward atmosphere as well as costings are currently under analysis.

Discussion: Discussion/Conclusion The enthusiasm of for these evidence based group therapies by both staff and service users demonstrates their feasibility even in challenging environments. We look forward to presenting further data, when it becomes available, which demonstrates whether the implementation of these ward activities leads to a significant improvement in ward atmosphere, patient and staff perceptions.

Poster #T55

EFFECT OF LURASIDONE ON DEPRESSIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA

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Sunovion Pharmaceuticals, Inc

Background: Clinically significant depressive symptoms are common in schizophrenia, and are associated with greater functional impairment and worse outcomes. The aim of the current post-hoc analysis was to evaluate the efficacy of lurasidone in patients with a DSM-IV-TR diagnosis of schizophrenia who presented with significant depressive symptoms.

Methods: Pooled data were analyzed from 4, six-week, double-blind, placebo-controlled schizophrenia trials, with available Montgomery-Asberg Depression Rating Scale (MADRS) data. Patients with an acute exacerbation of schizophrenia were randomized to fixed once-daily doses of lurasidone ($n=902$), in the dosing range of 40-160 mg, or placebo ($n=439$). LOCF-endpoint data were analyzed using ANCOVA. MADRS remission was defined as an endpoint score <10 .

Results: At baseline, 45.0% and 24.5% of subjects had a MADRS score of ≥ 12 , and ≥ 16 , respectively. Treatment with lurasidone was associated with significantly greater improvement in the MADRS at LOCF-endpoint compared with placebo in the total sample (-2.8 vs. -1.4 ; $p<0.001$), and in each baseline depression severity subgroup: MADRS ≥ 12 (-6.7 vs. -4.8 ; $p<0.005$), and MADRS ≥ 16 (-9.3 vs. -6.3 ; $p<0.005$). Overall, the largest effect size was observed for the 160 mg dose of lurasidone (0.43). For the subgroup with MADRS ≥ 16 at baseline, higher depression remission rates were observed for lurasidone 160 mg (47.8%) compared with lurasidone 80 mg (38.6%) and lurasidone 40 mg (28.6%).

Discussion: In this pooled post-hoc analysis, once-daily doses of lurasidone, in the dosage range of 40-160 mg, significantly reduced the severity of depressive symptoms in patients with schizophrenia. Daily doses of 160 mg demonstrated the largest effect size. These results warrant further evaluation of the efficacy of lurasidone in patients with schizophrenia who present with co-morbid depression. Sponsored by Takeda Pharmaceuticals International, Inc., and Sunovion Pharmaceuticals Inc. (a US subsidiary of Dainippon Sumitomo Pharma, Ltd.)

Poster #T56

LEARN BEFORE YOU BURN: THC IMPAIRS ENCODING BUT NOT RETRIEVAL OF VERBAL INFORMATION

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Background: Cannabis and agonists of the brain cannabinoid receptor (CB1R) such as $\Delta 9$ -Tetrahydrocannabinol (THC), produce acute memory impairments in humans. The most well-studied acute effects of THC, the main psychoactive component of cannabis, in humans are on declarative verbal memory. However, the extent to which THC impairs encoding and/or retrieval in humans is not clear. This is important to know given how widely used cannabis is and also because the legalization of cannabis continues to spread.

Methods: Healthy subjects, recruited from the community were administered the Rey-Auditory Verbal Learning Test (AVLT) a measure of verbal memory, either 1) before they were administered THC (experiment #1) ($n=38$) or 2) while they were under the influence of THC (experiment #2) ($n=57$). Immediate as well as short and long delayed recall were compared across both experiments. Subjects received intravenous THC in a placebo-controlled, double-blind, randomized manner at doses known to reliably produce behavioral and subjective effects consistent with known effects of cannabis.

Results: There was a large, statistically significant drug-by-experiment interaction such that total immediate free recall, short delayed free recall, and long delayed free recall was lower (worse) with THC compared to placebo only in experiment #2, i.e. when the AVLT was first administered under the influence of THC.

Discussion: THC acutely interferes with encoding of verbal memory without significantly interfering with retrieval. These data suggest that it may be difficult to learn new information while under the influence of CB1R agonists. Future studies will be necessary to determine whether THC impairs encoding of non-verbal information, to what extent THC impairs memory consolidation, and the role of other cannabinoids in the memory-impairing effects of cannabis.

Poster #T57

CHARACTERISTICS OF COGNITIVE DEFICIT IN SCHIZOPHRENIA AND MAJOR DEPRESSION (IN TERMS OF DIFFERENTIAL DIAGNOSTIC)

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Background: Patients with schizophrenia and major depression are cognitive impaired. The purpose of our pilot research is differential psychological diagnostics of cognitive deficiency of these two groups of patients from schizophrenia and affective disorders. The experimental group consisted of 13 intellectually safe patients. 5 from them were with diagnosis "Major depression" and 8 with "Paranoid schizophrenia". Average age of the sample 32 ± 2.87 years. Average age of the beginning of a disease of patients with schizophrenia was 24.25 ± 1.82 years (with average duration of the disease 9.13 ± 2.68 years). Patients with major depression was 25.6 ± 6.03 years (lasting 4.40 ± 1.36 years). It should be noted that in both groups of patients there was high percent of a burdened heredity (about 46.2%).

Methods: For an assessment of cognitive deficiency Brief Assessment of Cognition in Schizophrenia scale was used.

Results: At a quantitative assessment statistically significant distinctions were found in the verbal memory subtest ($p < 0.05$). At quality analysis of the same data the following results tuned out (considering the conditional standardized selection): speed of mental functions of patients with schizophrenia (sch) qualitatively differed from patients with a major depression (MD) ($p < 0.001$). Subjects with schizophrenia had the lower score than patients with MD who performed at normal level (sch < MD=Norm). Other parameters had only quantities distinctions: motor speed, working memory sch = MD < 0.01).

Discussion: Since only the first investigation phase was completed it seems hard to make final conclusions. Small sample doesn't give a chance to speak about reliability of data therefore in future there is a task to increase sample, and also to find interrelations with other clinical scale. The obtained data might be considered as predictive factors when carrying out medical-social examination, and also might be important for psychotherapy and rehabilitation.

Poster #T58

LOWER ANTERIOR CINGULATE VOLUME IN SERIOUSLY VIOLENT MEN WITH ANTISOCIAL PERSONALITY DISORDER OR SCHIZOPHRENIA AND A HISTORY OF CHILDHOOD ABUSE

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Background: Antisocial personality disorder (ASPD) and schizophrenia, as well as childhood abuse, are associated with violent behaviour, and show marked volumetric reduction in the anterior cingulate (AC), a brain region implicated in regulation of violence through its involvement in decision-making, empathy, impulse control and emotion regulation. The present study examined, for the first time to the authors' knowledge, the grey matter volume of the AC in relation to seriously violent behaviour and childhood psychosocial deprivation (including physical and sexual abuse) in the context of a mental disorder (schizophrenia or ASPD).

Methods: Fifty-seven men [14 with ASPD and a history of serious violence; 13 with schizophrenia and a history of serious violence (VSZ); 15 with schizophrenia without a violence history (SZ); 15 non-violent healthy participants] underwent whole brain magnetic resonance imaging and were rated on the presence of physical abuse, sexual abuse, neglect, extreme poverty, foster home placement, criminal parent, severe family conflict, and

broken home (collectively "psychosocial deprivation"). Symptom ratings, measurement of IQ and level of violence were made. Stereological volumetric ratings of the AC were examined for group differences and their association with childhood psychosocial deprivation.

Results: A higher proportion of ASPD and VSZ patients had suffered psychosocial deprivation as children, in particular severe physical abuse, relative to SZ patients and healthy participants. ASPD and VSZ, but not SZ, patients had significantly lower AC volume relative to healthy participants. AC volumes correlated negatively with (total) psychosocial deprivation as well as physical and sexual abuse ratings. Group differences in AC volume became non-significant when psychosocial deprivation ratings were co-varied for.

Discussion: Violent mentally-disordered individuals with ASPD or schizophrenia suffer from a significant AC volume loss and this deficit, at least in part, is explained by their histories of stressful childhood experiences. An Anterior cingulate deficit may retard the effectiveness of relevant cognitive behavioural therapies that make use of AC-modulated cognitive processes to prevent the occurrence of future violence in these populations. Thus, current/future therapies aiming to reduce violence in such populations would benefit by attending to biological (and other) correlates of childhood abuse.

Poster #T59

RELATIONSHIP BETWEEN THE BDNF VAL66MET POLYMORPHISM, CHILDHOOD TRAUMA, SCHIZOTYPY AND PSYCHOTIC-LIKE EXPERIENCES

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Background: Previous studies have analyzed the effect of the BDNF Val66Met polymorphism on schizotypy dimensions or psychotic-like experiences showing negative results (Ma et al. 2007). However, the variability of this gene has been involved on the relationship between childhood trauma and psychotic-like experiences in the general population (Alemany et al. 2011), although a very recent study has not replicated these findings (Ramsay et al. 2013). The present study aimed to analyse: i) whether the BDNF Val66Met genotype moderate the prediction of interviewed measures of symptoms by positive and negative schizotypy dimensions and ii) whether the BDNF Val66Met genotype moderate the prediction of schizotypy dimensions and symptoms by trauma.

Methods: The sample consisted of 547 participants that completed self-reported questionnaires assessing the positive and negative dimensions of schizotypy (Wisconsin Schizotypy Scales, WSS) and childhood adversity (Childhood Trauma Questionnaire, CTQ). A subset of 214 individuals (123 with elevated schizotypy and 91 with standard scores) underwent structured interviews assessing the psychosis prodrome (The Comprehensive Assessment of At-Risk Mental States, CAARMS). The BDNF Val66Met was genotyped for all participants.

Results: Our results showed a trend for the interaction between BDNF Val66Met polymorphism (Met carriers vs. Val/Val) and positive schizotypy to predict CAARMS Positive Symptoms ($\beta = -0.56$, s.e.=0.30, $p=0.06$), even though main effect of BDNF was not significant. No effect was found for the negative schizotypy dimension. We also found a moderating effect of this polymorphism on childhood abuse on predicting CAARMS Positive Symptoms ($\beta = -0.19$, s.e.=0.08, $p=0.013$). No significant results were observed for childhood neglect.

Discussion: The BDNF Val66Met polymorphism showed a moderating effect between childhood abuse and the development of positive symptoms in healthy individuals. Our results support the previous findings suggesting a role of childhood adversity as a risk factor underlying the development of psychotic symptoms in the general population, adding that this risk depends on the genotype of the BDNF Val66Met polymorphism. More studies assessing the moderating role of genetic factors in the development of psychotic symptoms are needed to better understand the differences between people exposed to the same risk factors.

Poster #T60**SERVICE SATISFACTION AND SPIRITUAL WELL-BEING AS PREDICTORS OF QUALITY OF LIFE AMONG PATIENTS WITH SCHIZOPHRENIA: A LONGITUDINAL STUDY USING A STRUCTURAL EQUATION MODEL APPROACH**

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Background: Background. During the past decades, several cross-sectional studies have investigated the relationship between the subjective quality of life (QOL) of people with severe mental disorders and their socio-demographic, psycho-social and clinical characteristics. Nevertheless, little is known about the impact of other subjective variables on self-reported QOL of patients with schizophrenia, such as satisfaction with care received and spiritual and religious well-being, especially in Residential Facilities (RFs). The current study was conducted within the framework of the PERDOVE study – (Epidemiological Project on Patients Discharged from Residential Facilities and Outcomes Evaluation), the first prospective study carried out in Italy aimed at collecting comprehensive data about the course and outcomes of patients living in RFs. Our primary objective was to determine predictors of QOL at one point in time among a selected PERDOVE sample of patients with a diagnosis of schizophrenia. Our secondary objective was to test the longitudinal correlations between baseline predictors (including spiritual well-being) and QOL scores at 1-year follow-up.

Methods: Methods. In order to detect clinically meaningful changes in QOL measures, we dichotomized each subscale score at the median value, in order to classify individuals in lower (below the median) or higher (above the median) subjective QOL. Logistic regression models were adopted to evaluate the association between WHOQoL-Bref scores and potential determinants of QOL at baseline. In addition, all variables significantly associated with QOL domains in the final logistic regression model were included by using the Structural Equation Modeling (SEM).

Results: Results. We selected those participants who completed the QOL assessment at both time points, obtaining a final sample of 139 patients with a diagnosis of schizophrenia spectrum. In the final logistic regression model level of activity, social support, age, service satisfaction, spiritual well-being and symptoms' severity were identified as predictors of QOL scores at baseline. Longitudinal analyses carried out by SEM showed that 40% of QOL follow-up variability was explained by QOL at baseline. Moreover, transforming the regression coefficients in terms of odds ratio, we identified service satisfaction and social support as effective predictors of QOL at baseline with OR=1.67 (1.20-2.39) and OR=1.35 (1.03-1.78), respectively. Weak relationships were observed for spiritual well-being (OR=1.22, 95%CI [1.01-1.50]), activity level (OR=1.30, 95%CI [1.02-1.66]) and age (OR=1.22, 95%CI [1.01-1.42]). Moreover, a mutual correlation ($r=0.30$, $p<0.001$) between service satisfaction and spiritual well-being was found. Although none of the QOL predictors at baseline had a significant direct relationship with QOL at follow-up, the analysis of indirect effects, pointed at a relationship between predictors and QOL also at 1-year follow-up. In particular, through a high correlation between QOL at baseline and QOL at follow-up ($r=0.69$, $p<0.002$), service satisfaction and social support were related to the latent QOL at follow-up with $r=0.23$ ($p<0.001$) and $r=0.15$ ($p<0.05$), respectively.

Discussion: Discussion. This study shows that improving service satisfaction toward care received and enhancing social relationships might help enhance self-perceived QOL. Moreover higher spiritual well-being may indirectly affect QOL at baseline through an impact on service satisfaction. For this reason, the assessment of spiritual well-being should be included in recovery-oriented interventions delivered in RFs.

Poster #T61**PATTERNS OF HABITUATION TO NOVELTY IN FIRST EPISODE SCHIZOPHRENIA AND CONTROL SUBJECTS**

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Background: The P3a event-related brain potential (ERP) is elicited by highly salient, "novel" rare stimuli in the oddball paradigm and is characterized by habituation, where its amplitude decreases after repeated exposure to the stimuli. There is also evidence that the amplitude of the P3b evoked by rare target stimuli also habituates. Here we examined habituation effects on ERPs in auditory "classic" and "novelty" oddball tasks in first episode schizophrenia (FE) and healthy control subjects (HC).

Methods: Subjects were 21 HC and 16 FE. The electroencephalogram was recorded at 71 scalp sites and re-referenced to averaged mastoids. In the classic oddball task, subjects counted rare target tones (36) interspersed among standard tones (144). In the novelty oddball task, rare novel sounds (36) were also presented. Habituation was evaluated by averaging EEG segments to the first 1/3 (A1), the second 1/3 (A2), and the last 1/3 (A3) of the target (P3b), novel (P3a), and standard (N100) stimuli.

Results: The amplitude of the P3a in the novelty oddball task ($p<0.05$) and the target-evoked P3b in the classic oddball task ($p<0.001$) was reduced in FE compared to HC. P3a and P3b amplitude habituated in HC ($p's <0.01$ but not FE ($p>0.8$).

Discussion: This study confirms habituation of P3a and P3b in healthy individuals. These habituation patterns are missing in first episode schizophrenia, suggesting deficits in processes related to attentional orienting and contextual updating.

Poster #T62**DISTINCT EFFECTS OF LITHIUM CHLORIDE AND CLOZAPINE IN PREVENTING SUICIDE-RELATED BEHAVIORS IN A TWO-HIT MODEL OF SCHIZOPHRENIA**

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Background: Schizophrenia patients show a high rate of premature mortality by suicide (5%). The pathophysiological mechanisms of these suicidal behaviors in schizophrenia do not appear to involve serotonergic neurotransmission, as suicidal risk in general population. To gain a better understanding of suicide risk in a context of schizophrenia, we developed an *in vivo* double-hit model of schizophrenia with a prenatal immune challenge (PIC) followed by post-weaning social isolation (SI). It has been reported that SI induces suicide-related behaviors such as aggressiveness, impulsivity, anxiety and hopelessness.

Methods: We opted for a two-hit model: C57BL/6 gestational mice were injected with polyIC (20 mg/kg) (PIC) or with saline at gestational day 12. Pups were submitted, or not, to social isolation (SI) for 4 weeks after weaning. The last week of SI and 30 min before behavioral testing, mice received vehicle, lithium chloride (LiCl) (200 mg/kg) or clozapine (3 mg/kg). All drugs were given intraperitoneally. LiCl is well known for its suicide preventive effects in the non-schizophrenic population, while clozapine is the antipsychotic with the best-established suicide preventive effect. Prepulse inhibition (PPI) of acoustic startle was measured to validate the schizophrenia-like phenotype. The resident-intruder test and the elevated plus maze evaluated aggressiveness/impulsivity and anxiety, respectively.

Results: We observed that PIC/SI mice exhibited significant PPI deficits and were more aggressive/impulsive. Also, the same mice showed an increased anxiety. In PIC/SI mice, clozapine prevented PPI deficits, while had no significant effect. Also, clozapine treatment significantly decreased the aggressive/impulsive behaviors and reduced the anxiety in PIC/SI mice, while LiCl had no preventive effects.

Discussion: These findings support the hypothesis that post-weaning SI contributes to the development of suicide-related behaviors in a model of schizophrenia primed by PIC. Our results suggest that the mechanisms of suicide-related behaviors diverge between general and schizophrenic populations, since the usual clinical suicide preventive treatment with LiCl was shown to be ineffective in the *in vivo* model in opposition to clozapine. This *in vivo* model could be useful in the development of new drugs to optimize the treatments of schizophrenia patients.

Poster #T63**THE IMPACT OF A NCAN GENE POLYMORPHISM ON MEMORY AND WHITE MATTER MICROSTRUCTURE IN HEALTHY INDIVIDUALS: A DIFFUSION TENSOR IMAGING STUDY**

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Background: The NCAN gene codes for Neurocan, a chondroitin sulfate proteoglycan that is found in the extracellular matrix of the central nervous system. It is interacting with various cell surface structures and proteins of the extracellular matrix, by which it is believed to have an influence on neurite outgrowth and neuronal adhesion. In recent genome-wide association studies, it was identified as a susceptibility gene for bipolar disorder and schizophrenia. It was shown that the A-allele in the NCAN SNP rs1064395 is associated with these disorders. In the present study we investigated the impact of the NCAN SNP rs1064395 on white matter microstructure as well as on verbal learning and memory in healthy individuals.

Methods: In a large sample ($N > 100$) of healthy individuals (age 18–55 years), we used Tract-Based Spatial Statistics (TBSS) to examine the impact of the NCAN SNP rs1064395 on the fractional anisotropy (FA) in major fiber tracts. Furthermore, all participants completed a verbal learning and memory test (VLMT).

Results: In the VLMT genotype was significantly associated with memory recall performance. Risk allele carriers showed a poorer memory recall (after 30 min delay) performance compared to non-risk allele carriers. The TBSS analysis revealed widespread clusters of reduced FA in risk allele compared to non-risk allele carriers located in uncinate fasciculus, superior longitudinal fasciculus, corpus callosum, longitudinal inferior-occipital fasciculus, and anterior thalamic radiation.

Discussion: Our findings demonstrate that genetic variation in the NCAN SNP rs1064395 is associated with poorer memory recall performance in risk allele carriers compared to non-risk allele carriers. According to the white matter microstructure we found FA reductions in fiber tracts that have previously been shown to be reduced in patients with schizophrenia. Furthermore, some of these fiber tracts have been associated with verbal memory.

Poster #T64**SPECTRAL ENTROPY MODULATION DECREASE IN PATIENTS WITH SCHIZOPHRENIA DURING P300 EVOCATION**

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Background: There are evidences of brain activity disorganization under cognitive demands in patients with schizophrenia. Spectral or Shannon entropy (SE) is a wave complexity parameter that has been proved to be useful for quantifying the global regularity of the electroencephalographic (EEG) activity. However, this parameter has been barely used in schizophrenia research comparing resting and cognition-related EEG activity.

Methods: 31 patients with schizophrenia and 38 controls underwent clinical and cognitive assessment and an EEG recording during a P300 oddball paradigm to calculate SE for resting baseline [-250 0] ms and active task [150 550] ms windows. Contrasts in SE were performed between- (patients vs controls) and within-groups (resting vs active). Median frequency (MF) and relative power (RP) in each frequency were also calculated in order to assess the correlates of the possible SE differences.

Results: In comparison to patients, controls showed a significantly larger decrease in SE (i.e., in the difference between active and resting states; $p < 0.0029$), which points to a greater signal regularity in this group during the cognitive task. This was accompanied by an equivalent statistically

significant decrease in MF, which means a lower-frequency activity in controls than in patients during the same condition. In patients, the SE difference measure was inversely correlated to positive and total symptoms scores. Low frequency RP increase and high frequency RP decrease between conditions were also significantly larger in controls than in patients.

Discussion: SE may be a relevant parameter for the study of cortical processing and clinical status in schizophrenia.

Poster #T65**IMAGE-BASED AUTOMATED DETECTION OF FIRST-EPIISODE SCHIZOPHRENIA: THE IMPORTANCE OF SPATIAL RESOLUTION OF MORPHOLOGICAL FEATURES AND ENSEMBLE LEARNING**

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Background: Machine learning methods are increasingly utilized for automated classification and diagnosis in various areas of medicine. In schizophrenia, however, the straightforward approaches fail. Perhaps due to heterogeneity of the disorder and its manifestations, or due to a complex pattern of relatively discrete local brain changes that might be difficult to capture by classification algorithms. There is, therefore, continuing search for optimal set of feature encoding strategies and robust classification approaches that would render the image-based classification useful in the clinical setting. The aim of the presented study was to address the problem by using combination of two methods: 1) multiresolution image data representation for extracting features on multiple spatial scales and 2) classification based on ensemble learning providing desired robustness.

Methods: 52 first episode-schizophrenia (FES) patients and 52 healthy controls were scanned by 1.5T MR device. The resulting T1-weighted images were spatially normalized and segmented into tissue types. In order to reduce noise and obtain succinct representation of contained information, discrete wavelet transform (DWT) was applied to the gray matter tissue segments and only coefficients surpassing chosen threshold were retained. The ensemble classification algorithm based on 1000 independent support vector machines (SVM) was trained and its performance was tested by stratified 52-fold cross validation. Features crucial for the correct classification were extracted and projected backwards onto corresponding brain areas to visualize brain structures important for classification.

Results: Combination of the DWT preprocessing and SVM ensemble classification achieved accuracy of 78% while maintaining balanced values of sensitivity and specificity. This result was superior to settings in which either ensemble classification was used without preceding DWT feature extraction or DWT feature extraction was followed by simple SVM classification. Visualization of the significant features showed that anatomical regions important for correct classification included dorsolateral prefrontal cortex, medial prefrontal cortex and anterior cingulate, orbitofrontal areas, mediotemporal structures, temporal neocortex, caudate head, mediodorsal part of thalamus, and cerebellum. Retaining of sufficiently fine wavelet coefficients was crucial for the quality of the classification.

Discussion: The proposed methods for feature extraction and classification achieved accuracy comparable to state-of-the-art MRI-based classification of FES. Furthermore, visualization of the features important for classification enables us to look inside the “black box” classifier and interpret its biological relevance. The validity of the approach is substantiated by the fact that the described pipeline and its results depend on biologically meaningful morphological features, since the whole pattern of relatively tiny local features covers the pattern of changes detected in schizophrenia. The study was supported by research grants of the Ministry of Health CR No. NT 13437, NT 13359 and MH CZ-DRO FNBr 65269705.

Poster #T66**PREMORBID IMPAIRMENTS IN CHILDHOOD-ONSET SCHIZOPHRENIA**

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Background: The general model of schizophrenia as a neurodevelopmental disorder is widely accepted. This model is supported by research that has demonstrated aberrant motor, speech/language, and social development in individuals who later became schizophrenic. Childhood-onset schizophrenia (COS), a severe form of the illness that is clinically and neurobiologically continuous with the adult onset disorder, and requires onset of psychosis before age 13. Aberrant neurodevelopment may be more salient in cases of COS, presumably because the early onset cases are closer to the developmental roots of the disorder. Previous examination of premorbid developmental difficulties in 47 COS revealed abnormalities in the domains of speech/language (55%), motor (57%), and social (55%) development several years before the onset of psychotic symptoms. This study attempts to confirm and extend these findings while providing a 12 year update on our expanded COS sample. We hypothesize that, consistent with the neurodevelopmental model of the schizophrenia and our previous findings, a significant portion of the cohort will have experienced premorbid impairments.

Methods: This study was approved by the Institutional Review Board of the National Institute of Mental Health and has been ongoing since 1991. The diagnosis of schizophrenia was made in a cohort of 118 patients according to DSM criteria with good reliability ($K=0.77$) using clinical and structured interviews, and prolonged inpatient observations by the research team. The cohort consisted of 49 males, 69 females; 52% – Caucasian, 28% – African American, and 20% – other. The mean onset of psychosis was 9 years 10 months. Premorbid development was assessed through review of previous medical records, including clinician notes, original pediatric, psychiatric, psychological, and educational reports and records. We also used information gleaned from clinical interviews with parents. Diagnosis of a pervasive developmental disorder was made using a clinical interview, the autism-screening questionnaire, and observations by the research team.

Results: Of the 118 children in the cohort, 65 (55.08%) had premorbid academic impairments, 85 (72.03%) had premorbid social/behavioral impairments, 60 (50.85%) had premorbid language impairments, 52 (44.07%) had premorbid motor impairments, and 24 (20.34%) screened positive for pervasive developmental disorder. The average number of abnormalities (15 domains) in each child was 3.89 and 103 (87.29%) of the children had premorbid impairment in at least one domain.

Discussion: Rates of premorbid developmental impairments were similar to those found in other studies of childhood-onset schizophrenia. Direct comparisons with studies of adult-onset schizophrenia are problematic because of variable methods but suggest that premorbid impairments are more common and severe among patients with childhood-onset than adult-onset schizophrenia. Although pronounced in children and adolescents who later develop schizophrenia, premorbid abnormalities are neither sensitive nor specific to childhood-onset schizophrenia. These impairments are seen in the early histories of patients who later develop a variety of other mental illnesses and the vast majority of patients with developmental impairments do not develop schizophrenia in adolescence or adulthood. However, given the high rate of the schizophrenia in a study of adults who had had severe language abnormalities as children, premorbid impairments may be an early manifestation of the neurodevelopmental abnormalities underlying schizophrenia. Limitations of this study include a lack of a healthy comparison group, sampling and recall biases, and variability in quality of premorbid records.

Poster #T67**ARE PATIENTS WITH SCHIZOPHRENIA ABNORMALLY SENSITIVE TO PAIN?**

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Background: Patients suffering from schizophrenia have often been described as hypoalgesic and even though such a lack in pain sensation can cause various and severe health issues, only a few experimental studies have been conducted. Our aim was to investigate whether pain perception is impaired in stabilized patients.

Methods: For pain assessment we used electric stimulations and measured objective (EEG) and subjective reactions (rating scale). In order to consider the other dimensions of pain perception such as cognition emotion and stress, we also measured ACTH and cortisol levels, reactions to aversive emotional pictures and subjects' performances in tasks exploring attention and anticipation.

Results: ACTH and cortisol levels were slightly higher for patients and they also rated emotional stimuli as more arousing. The subjective as well as the objective measurements of pain perception show that the patients in our study are more sensitive to pain compared to a matched control group. After painful stimulations and aversive emotional picture presentation, the amplitude of the early related potential P50 was larger in patients than in controls.

Discussion: We propose that, consistent with deficient sensory gating in patients, the hyperalgesia observed in the present study is due to impaired ability to anticipate negative emotional stimuli.

Poster #T68**BRAIN SYSTEMS REGULATING FOOD-INTAKE AND BODY MASS CHANGES DURING ACUTE ANTIPSYCHOTIC TREATMENT IN FIRST-EPIISODE SCHIZOPHRENIA**

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Background: Morphological brain changes have been reported during acute antipsychotic treatment, as well as in obesity. We investigated whether changes occurred in brain regions responsible for body-weight homeostasis during acute treatment, and if so, whether they were related to changes in body mass and metabolic profile.

Methods: Twenty-two antipsychotic-naïve patients with first-episode schizophrenia or schizopreniform disorder received treatment over 13 weeks with either risperidone long acting injection or flupenthixol decanoate and were compared by structural MRI with 23 matched healthy volunteers at weeks 0, 4 and 13. Images were reconstructed using fully-automated whole brain segmentation which included a longitudinal processing stream. The ventral diencephalon (DC) and prefrontal cortex were selected to represent the homeostatic and non-homeostatic food intake regulatory systems respectively. Body mass was measured at weeks 0, 7 and 13 and fasting glucose and lipid profiles at weeks 0 and 13.

Results: From a mixed linear random regression coefficients model, significant reductions were observed in the patient group in L and R ventral DC volume respectively ($p=0.05$ and $p=0.03$), which were significantly correlated with body mass increase ($r=-0.78$, $p<0.0001$ and $r=-0.68$, $p<0.005$), HDL-cholesterol reductions ($r=0.49$, $p<0.05$ and $r=0.66$, $p<0.005$) and for the R ventral DC with blood glucose increase ($r=-0.6$, $p<0.01$). No significant changes were found in prefrontal cortical thickness bilaterally, as well as in global cortical thickness and subcortical gray matter volumes.

Discussion: These findings implicate the ventral DC, and likely the hypothalamus, in the adipogenic effects of antipsychotic medication. They also provide a possible explanation, at least in part, for reports of progressive cerebral volume reductions in schizophrenia.

Poster #T69**NEGATIVE SYMPTOM SUBGROUPS HAVE DIFFERENT EFFECTS ON CLINICAL COURSE AFTER FIRST EPISODE OF SCHIZOPHRENIA: A 24-MONTH FOLLOW-UP STUDY**Ceylan Ergul¹, Alp Üçok²¹Istanbul Faculty of Medicine, Department of Psychiatry; ²Istanbul Faculty of Medicine

Background: Recent factor analytic studies show that negative symptoms in schizophrenia have two subgroups: expressive deficit (ED) and motivation-pleasure deficit (MPD). The aim of this study is to assess the factor structure of negative symptoms in first-episode schizophrenia (FES), and to examine the relationship of these factors with clinical course and functioning of patients during the two-year follow-up.

Methods: We assessed 174 drug-naïve patients with FES using the Brief Psychiatric Rating Scale, the Scale for the Assessment of Negative Symptoms, the Scale for the Assessment of Positive Symptoms, the Global Assessment of Functioning (GAF) Scale, the Premorbid Adjustment Scale (PAS) and an 8-item cognitive battery at admission. Symptom rating scales were repeated at monthly outpatient visits for two years. We also recorded patients' functioning levels, remission and work status at the 12th and the 24th months.

Results: A two-factor structure was found at the baseline, whereas only one factor was found in the 12th and the 24th months. ED factor consisted of alogia and blunted affect, and MPD factor consisted of avolition and anhedonia. The patients who met the remission criteria during the 24-month follow-up had lower ED factor scores (14.4 ± 11.9 vs. 18.7 ± 12.1 , $Z=1.92$, $p=0.05$) than others. The early-onset group had a higher ED factor score (22.2 ± 15.9 vs. 16.2 ± 12 , $t=2.54$, $df=162$, $p=0.01$), and the score was negatively correlated with the age of onset ($r=-0.15$, $p=0.05$). ED factor score was also negatively correlated with duration of education ($r=-0.21$, $p=0.006$) and cognitive test scores ($r=-0.37$, $p=0.01$). No relationship was found between MPD factor score and neurocognitive test performance. MPD factor score was correlated with duration of untreated psychosis ($r=0.16$, $p=0.04$). Participants with a history of schizophrenia in first and second-degree relatives ($n=19$) had higher MPD factor scores (26.8 ± 8.9 vs. 22.8 ± 9.8 , $t=2.1$, $p=0.03$). Patients who could work/study during the month before their first admission and at their second year of follow-up had lower MPD factor scores (20.5 ± 9.7 vs. 25.1 ± 9.1 , $Z=-3.1$, $p=0.003$; 20.1 ± 9.1 vs. 24.4 ± 9.7 , $Z=-1.8$, $p=0.05$ respectively). Baseline GAF score was correlated with ED and MPD factor scores ($r=-0.24$, $p=0.004$; $r=-0.25$, $p=0.004$ respectively). The linear regression analysis showed that MPD factor is the only independent variable that contributes to the GAF score. There was no correlation between the factors and PAS scores. However, when we analysed by gender, we found that school performance in adolescence was correlated with both ED ($r=0.44$, $p=0.01$) and MPD factor scores ($r=0.37$, $p=0.03$) in women but not in men. Participants who dropped out before completing 12 months of follow-up had higher ED factor scores than the completers (23.1 ± 12.3 vs. 15.3 ± 6.8 , $t=3.51$, $df=174$, $p=0.001$), but no difference was found between the MPD factor scores of the two groups.

Discussion: Our findings support the opinion that the negative symptoms are heterogeneous. We found that ED and MPD factors are both related to premorbid characteristics and clinical variables. The finding that MPD factor score is higher in patients with a family history of schizophrenia implies that genetic factors are more important in MPD factor. In summary, the two factors have different aetiologies and impacts on the early course of illness.

Poster #T70**THE EFFECTS OF PSYCHOSOCIAL STRESS INDUCTION ON THE JUMPING TO CONCLUSIONS BIAS IN PEOPLE WITH CLINICAL RISK FOR PSYCHOSIS**

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Background: Studying people with vulnerability for psychosis, without the confounds of medication or severe illness is essential for understanding how environmental factors and psychological processes contribute to the formation and maintenance of psychotic symptoms. One of the reasoning

biases most consistently found in people with delusional beliefs is the so-called jumping to conclusions (JTC) bias. We compared the effects of stress induction on this information gathering bias in people with at risk mental states (ARMS) and healthy volunteers. Our study was the first to investigate the effects of stress induction on people with high clinical risk for psychosis. Our hypothesis was that stress would decrease information gathering in both groups, but especially so in people with ARMS. Our aim was to explore how emotional and reasoning processes combine and interact in mental illness, which can inform theoretical understanding of psychosis and in the future lead to reliable predictions and/or interventions.

Methods: 20 people with ARMS and 20 controls matched for age, gender and education were recruited. The JTC bias was assessed during two visits, with and without stress induction; using a modified version of the beads task with the outcome variable of how many draws participants took before reaching the decision. Stress was induced with the Trier Social Stress Task – the standardised social evaluation stress task with elements of uncontrollability that reliably induces moderate stress in laboratory conditions. Saliva samples were collected two days before each assessment and throughout the testing sessions. Blood pressure and pulse were monitored. Symptoms were assessed using the Clinical Assessment of the At Risk Mental States scale. Depressive symptoms were assessed using Beck Depression Inventory. Other questionnaires used were: stress rating, State-Trait Anxiety Inventory, Peters Delusional Inventory.

Results: After stress controls took significantly fewer draws to decision than before stress ($t(20)=2.851$, $p=0.010$), while in ARMS there was a trend to increase the information sampling, although not statistically significant ($t(18)=-1.113$, $p=0.282$). There was a significant stress by group interaction ($F(1)=7.293$, $p=0.010$). In the stressed condition controls had significantly fewer draws to decision compared to ARMS. Both groups felt equally stressed by the TSST, so the results could not be attributed to the failure to induce stress in the ARMS group. There was no effect of gender or whether the stress induction was done on the first or second day. Trait anxiety had no effect on the number of draws to decision.

Discussion: Our study was the first to investigate the effects of stress induction on jumping to conclusions task in people at high clinical risk for psychosis. The main finding was that stress influences data gathering in healthy volunteers and people with ARMS differently. In healthy controls, stress induction had a significant impact on reasoning. Hasty decision making might be one of the stress regulation strategies e.g. decreasing cognitive load to improve coping. Previous studies had contradicting results, so our contribution was to clarify that stress induces hasty decision making in healthy people. In contrast, people with ARMS did not change their reasoning style. Theoretical accounts of the delusion formation and maintenance should take into account the interaction between emotional and reasoning processes, rather than consider them in isolation.

Poster #T71**OXIDATIVE STRESS IS RELATED TO NEUROCOGNITION BUT NOT SOCIAL COGNITION IN PATIENTS WITH SCHIZOPHRENIA**Aysen Esen-Danaci¹, Cristina Gonzalez-Liencres², Cumhur Tas³, Elliot C. Brown⁴, Soner Erdin⁵, Ece Onur⁵, Zeynep Cubukcoglu⁵, Omerr Aydemir⁵, Aysen Esen-Danaci¹, Martin Brüne²¹Department of Psychiatry, Celal Bayar University; ²Ruhr University; ³Uskudar University; ⁴Maryland University; ⁵Celal Bayar University

Background: Schizophrenia is a severe mental disorder that has devastating effects on the brain development of the affected individuals. Several studies have highlighted the presence of oxidative stress in patients with schizophrenia. In general, higher quantities of pro-oxidants and lower anti-oxidants have been related to schizophrenia cases. However, oxidative stress has also been found in other chronic medical diseases and thus the specific effects of these quantitative differences on illness-related deficits in schizophrenia are not yet clear. Therefore, the aim of this study was to examine the role of oxidative stress molecules on the well-defined social cognitive and neurocognitive deficits of schizophrenia patients.

Methods: Cases with chronic medical diseases such as diabetes, obesity and hypertension were excluded following the recruitment, and the study was completed with forty one schizophrenia patients and forty three healthy controls. We assessed the peripheral levels of several molecules associated with oxidative stress, namely nitric oxide (NO), malondialdehyde (MDA),

glutathione (GSH), homocysteine, superoxide dismutase (SOD) and neurotrophin 4 (NT4). A battery of tests to measure neurocognition and social cognition were also administered to the schizophrenia group.

Results: We found that the schizophrenia group presented higher quantities of the pro-oxidants NO and MDA, and decreased levels of the anti-oxidants GSH, SOD and NT4. Interestingly, the levels of NT-4, which has been shown to have anti-oxidant effects, correlated with executive functioning as measured with the Wisconsin Card Sorting Test (WCST) ($r=-0.474$; $p\leq0.01$) and the Trail Making Test A (TMT-A) ($r=-0.333$, $p=0.047$). Lastly, social cognition and symptom severity were not found to be associated with oxidative stress.

Discussion: In agreement with previous studies, we found that schizophrenia patients present higher levels of oxidative stress than healthy controls, as revealed by elevated quantities of pro-oxidants and reduced levels of anti-oxidants. Notably, correlation analyses revealed relationships between NT-4 and neurocognition in the clinical group, most specifically executive function (WCST), and visual attention and task switching (TMT-A). We therefore propose a protective role of NT4 to oxidative stress which appears to also have a potentially beneficial impact on neurocognition but not on social cognition in schizophrenia.

Poster #T72

DNA METHYLATION AND GABAERGIC PATHOLOGY OF SCHIZOPHRENIA

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Background: Schizophrenia is characterized by disturbances originate in neuronal development and a subtle brain pathology in which deficits in specific GABAergic neuronal subtypes are apparent. This is demonstrated by decreases in markers of GABAergic neuronal functions, such as expression of the synthesizing enzyme glutamic acid decarboxylase (GAD) and parvalbumin, a protein present in a subgroup of GABA-containing interneurons. Several animal paradigms, such as isolation rearing, sub-chronic PCP administration and neonatal inflammatory challenge, that model aspects of schizophrenia also result in deficits of parvalbumin, indicative of GABAergic pathology underlying the abnormal behaviours in these models. Recent studies have demonstrated abnormalities in DNA methylation in various indicators of GABAergic function in schizophrenia. These abnormalities include both indicators of a general hypermethylation in brain regions important in the pathology of the disease, and effects on specific components of GABAergic neurons. These findings suggest that a hyperfunctional DNA methylation may be responsible for deficiencies in GABAergic neurotransmission. There is also evidence suggesting that such effects may be ameliorated by antipsychotic drug treatment. As yet, however, these effects have not been investigated in the animal models that mimic aspects of schizophrenia. The main of this work was to evaluate if there is a hypermethylation the parvalbumin gene in brain tissue from different areas from subjects with schizophrenia that relates to the parvalbumin deficit seen in the disease and if there is a hypermethylation the parvalbumin gene in brain tissue from chronic animal models associated with parvalbumin deficits.

Methods: For this we used brain tissue from post-mortem samples of patients with schizophrenia ($n=25$) and control subjects ($n=15$). Methylation levels (as a percentage for each subject) at each CpG site within the sequence chosen were determined following bisulphite reaction and pyrosequencing. We investigated DNA methylation in brain tissue (different areas) of animals treated chronically with PCP administration (7 days; $n=10$ each group), which we find to induce a long-lasting decrease in parvalbumin-positive cells, and behavioural effects reminiscent of some symptoms of schizophrenia. In both species (human and rat) the correspondent sequences analysed were chosen according to the most important transcription factors binding sites and CpG islands.

Results: Our results did not show any differences in the levels of DNA methylation in the CpG sites analysed of the promoter region for parvalbumin gene in hippocampus of rat brains undergoing chronic PCP administration when compared with control animals, the same was found in prefrontal cortex (PFC). The preliminary results from human brain samples did not show any alterations in PFC or hippocampus as well, but more experiments are doing to investigate different sequences in the promoter region of parvalbumin.

Discussion: These results indicate that there is another mechanism responsible to the reduction of parvalbumin in PCP rat model and schizophrenic brains, however we are investigating if there are some alterations in the methylation levels of the promoter region of GAD1 in the same samples. More studies are necessary to understand the mechanism that underlie the suppression of parvalbumin expression as well as other GABAergic changes in both the disease and rat models.

Poster #T73

JUMPING TO CONCLUSIONS, NEUROPSYCHOLOGICAL FUNCTIONING, AND DELUSIONAL BELIEFS IN FIRST EPISODE PSYCHOSIS

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Background: Individuals with delusions have a tendency to jump to conclusions (JTC). This means that they request less information before making a decision, and are therefore more likely to reach an inaccurate decision. This construct is often measured using a probabilistic reasoning task, called "The Beads Task". Using data from a case-control study of first-episode psychosis (FEP), we aimed to establish the prevalence of JTC in FEP, and its relationship to delusions and neuropsychological functioning.

Methods: 108 FEP patients and 101 age-matched controls completed assessments of delusions, general intelligence (IQ), working memory (WM), and JTC (the probabilistic reasoning "Beads" task). We used two versions of the Beads Task: 85:15 and 60:40. In both versions, participants are required to seek information in order to make a decision. Jumping to conclusions was defined on the Beads Task as making a decision after two or fewer items. Clinical and subclinical symptoms as well as Neurocognitive performances were assessed and compared with the presence of the JTC bias in both the clinical and non-clinical groups.

Results: Half the FEP participants jumped to conclusions on at least one task, compared to 25% of controls (OR range 2.1–3.9; 95% CI range 1.5–8.0, p values <0.05). Delusion severity was significantly associated with the tendency to JTC on the 85:15 task (OR=1.3, $p=0.03$, 95% CI 1.0 to 1.7), but did not reach significance on the 60:40 task; no association between subclinical symptoms and JTC was found in the non-clinical control group. IQ and WM were significantly associated with JTC in the FEP group (IQ: 0.96, 0.9 to 1.0, $p=0.009$; WM: 0.8, 0.7 to 0.9, $p=0.008$ – 85:15 task; IQ: 0.9, 0.9 to 1.0, $p=0.002$; WM: 0.8, 0.7 to 1.0, $p=0.04$ – 60:40 task), and in the control group (IQ: 0.96, 0.9 to 1.0, $p=0.01$; WM: 0.8, 0.7 to 1.0, $p=0.03$ – 85:15 task; IQ: 0.9, 0.9 to 1.0, $p=0.006$; WM: 0.7, 0.6 to 0.9, $p=0.007$ – 60:40 task). Both delusion severity (OR 1.4, 95% CI 1.0 to 1.9, $p=0.03$) and IQ (OR 0.9, 95% CI 0.9 to 1.0, $p=0.002$) were independently associated with JTC.

Discussion: JTC is present in first episode psychosis. The specific association of JTC with clinical delusions supports a state, maintaining role for the bias. The associations of JTC with neuropsychological functioning indicate a separable, trait aspect to the bias, which may confer vulnerability to psychosis. The work has potential to inform emerging interventions targeting reasoning biases in early psychosis.

Poster #T74

ENGAGEMENT WITH PSYCHO-SOCIAL INTERVENTIONS WITHIN AND AN EI PSYCHOSIS SERVICE

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DETECT Early Intervention in Psychosis Service

Background: Disengagement from treatment in patients with serious mental illness is a major concern for services. The benefit of an early intervention service is dependent on the willingness of the patient to engage in a sustained manner. Disengagement is of particular concern in an EI service for psychosis as long term treatment can improve symptoms, functioning and reduce relapse in individuals experiencing a first episode psychosis. Furthermore disengagement has been emphasized as key performance measure in the evaluation of an early intervention service. The focus of this

paper was to examine in detail the levels of engagement within an early intervention service for individuals experiencing a first episode psychosis.

Methods: We examined the rates of engagement with a prospectively identified epidemiological cohort of patients with a first episode of psychosis who were assessed and treated by the DETECT early intervention for psychosis service, the Irish national pilot early intervention in psychosis service. We established the rates of engagement of all those who were referred to the service between 2006 and 2012. We also sought to explore the rates of engagement with constituent parts of the early intervention service, i.e. psycho-social interventions provided by DETECT: Carer Education; Group Cognitive Behavioural Therapy (CBT) for Psychosis and Occupational Therapy.

Results: The number of suspected cases for first episode psychosis (FEP) referred to DETECT between 2006 and 2012 was 1,131. Of that number 9.6% (n=109) did not engage with the assessment process and are considered "true non-engagers". Of the 1,022 people who engaged with the assessment 49.4% (n=505) had a confirmed diagnosis of FEP. 80% (n=400) of this group were invited to avail of psycho-social interventions. Overall 31.6% (n=131) did not engage with any psycho-social intervention 68.4% (n=283) engaged with at least one intervention: 42% (n=174) engaged with at least two interventions and; 39.2% (n=111) engaged with just one intervention. With regards specific interventions: 49.3% (n=154) people who were offered the Carer Education engaged with the intervention. 50% of those offered group CBT engaged with the intervention and 60% (n=130) of people offered individual Occupation Therapy engaged with the programme.

Discussion: This study reports an overall disengagement rate of a third from psycho-social interventions within an EI service for psychosis. Our findings are consistent with international rates that approximately 30% of individuals with FEP disengage from services. Thus, even when receiving specialised treatment from an FEP service, the risk of an individual disengaging remains high.

Poster #T75

PRENATAL EXPOSURE TO MATERNAL IMMUNE STIMULATION LEADS TO CHANGES IN MYELIN PROTEINS IN THE ADULT RAT PREFRONTAL CORTEX WHICH CAN BE PREVENTED BY RISPERIDONE IN ADOLESCENCE

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Background: Epidemiological evidence indicates that maternal infections during pregnancy are associated with an increased risk for schizophrenia. Research has validated gestational exposure to immune stimulation in rodents as a means to reproduce schizophrenia-like neuroanatomical and behavioural abnormalities. Myelin and glial abnormalities are amongst the most robust neuropathological changes observed in schizophrenia. Preliminary evidence suggests that prenatal inflammation may play a role as investigations of such animal models have demonstrated white matter atrophy and reductions in myelin specific genes. It has been proposed that atypical antipsychotics may act to normalise myelination changes in schizophrenia by increasing gliogenesis. Poly(I:C), an analog of double-stranded RNA which mimics the viral response, is used for the identification of neurobiological mechanisms underlying prenatal inflammation as well as exploring preventative methods. We specifically hypothesized that myelin protein expression changes would be induced in the prefrontal cortex (PFC) by prenatal Poly(I:C) and that these changes would be reversed in adulthood by adolescent treatment with the atypical antipsychotic Risperidone.

Methods: On gestational day 15, pregnant dams given a single intravenous injection of 4 mg/kg Poly(I:C) or saline. On postnatal day (PND) 21, the pups were weaned and preventative treatment was given on PND 34–47 representing adolescence. Offspring of Poly(I:C) or saline dams were injected daily intraperitoneally with 0.045 mg/kg Risperidone or saline. Adult offspring were sacrificed on PND 120 and the PFC dissected, solubilised and digested for mass spectrometry. Each sample was analysed in triplicate by LC-MS/MS. Data analysis was carried out by label free quantitation (LFQ) in the MaxQuant software. The cut off for the false discovery rate for peptide and protein identification was 1%. The LFQ score for proteins

were log2 transformed and a 2-way ANOVA was performed giving fold changes as measures of treatment effects. Pathway analysis was carried out with Ingenuity Pathway Analysis. Ethical approval was granted by RCSI (REC-585bb) and the University of Tel Aviv.

Results: Over 1000 proteins were identified across all groups. Pathway analyses implicated changes in core metabolic pathways, including the tricyclic acid cycle, glycolysis and oxidative phosphorylation, following prenatal Poly(I:C) exposure compared to saline controls. Some, but not all of these protein changes were absent in the prefrontal cortex of Poly(I:C) treated offspring that received risperidone treatment in adolescence. Reductions in myelin specific and myelin related proteins were observed in offspring exposed to Poly(I:C) but increased in the prefrontal cortex of Poly(I:C) treated offspring that received Risperidone in adolescence.

Discussion: Our data extends previous studies by demonstrating that prenatal Poly(I:C) exposure leads particularly to dysregulation of core metabolic and myelin associated protein expression. We suggest that prenatal maternal inflammation may contribute to an increased risk for schizophrenia through mechanisms involving metabolic function and myelin formation and that Risperidone in adolescence may in part prevent or reverse such changes. Our findings have implications for the understanding of mechanisms of antipsychotics and the identification of new treatment targets. Additionally, they indicate that molecular abnormalities produced by prenatal inflammation are not always permanent but could be rectified by early drug treatment.

Poster #T76

BEHAVIOURAL ECONOMICS OF EFFORT-BASED REWARD-DRIVEN CHOICE IN SCHIZOPHRENIA

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Background: Individuals with schizophrenia demonstrate reduced goal-directed behaviour relative to healthy individuals, a hallmark of poor functional outcome in schizophrenia, particularly amotivation. In the present study, we employed an objective paradigm to examine effort-based cost-benefit decision making in individuals with schizophrenia while concurrently assessing for other reward-related variables.

Methods: Sixteen stable outpatients with schizophrenia and sixteen matched healthy control subjects completed an effort-based decision making task that accounts for individual differences in motoric ability. Briefly, subjects were presented with a series of trials where they may choose to expend a greater amount of effort for a larger monetary reward versus less effort for a smaller reward. High versus low value trials were categorized following a median split of trial expected value, which was calculated as the product of monetary payoff value and probability of reward receipt.

Results: Patients with schizophrenia opted to expend greater effort significantly less than healthy controls for trials of high incentive value (Cohen's $d=1.2$, $p=0.003$), which was related to clinical amotivation/apathy ($r=-0.40$, $p=0.02$) and neurocognitive deficits ($r=0.49$, $p<0.05$). Lower willingness to expend effort during high value trials was also related to poorer functional status ($r=0.41$, $p=0.02$). Healthy controls chose to expend greater effort for high versus low value trials ($d=2.8$, $p<0.001$), a result that was found in attenuated form in patients with schizophrenia ($d=1.0$, $p=0.004$; group difference: $d=1.3$, $p=0.001$). Group differences in effort expenditure during trials of high value were not due to differences in reward learning, reward valuation or hedonic capacity.

Discussion: These results suggest that patients with schizophrenia have impairments in effort-based reward-driven choice. During cost-benefit economic decision making involving effort costs, individuals with schizophrenia fail to maximize utility. Such computational abnormalities manifest clinically as apathy and undermine real-world functioning.

Poster #T77**PERCEIVED STRESS IS ASSOCIATED WITH THE RISK OF HOSPITALIZATION IN EARLY PSYCHOSIS: 1-YEAR PROSPECTIVE STUDY**

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Background: Stress impacts negatively in the outcome of subjects with a psychotic disorder. The risk of readmission is a prognostic variable related to the severity of the illness, which impairs the quality of life of patients. Although the relationship between stress and the onset of psychosis is well-known, there is less information regarding whether stressful life events or perceived stress could play a role in the risk of readmission in subjects at early stages of the psychotic illness. The main aim of our study was to assess whether stress variables are predictors of admission risk in subjects attending to an Early Psychosis Program.

Methods: We studied 46 patients (aged between 18 and 35 years old) who attended the Early Psychosis Program from Reus (Hospital Universitari Institut Pere Mata, Spain): 36 first episode of psychosis (FEP) and 10 at-risk mental states (ARMS). All participants were followed-up for a period of one year. Stress measures were assessed prospectively at three visits (baseline, 6 months, 12 months). Holmes-Rahe Social Readjustment Scale was used to evaluate stressful life events in the previous 6 months of each assessment. Perceived Stress Scale (PSS) was used to assess the perception of psychological stress. Mean values for each stress scale over the follow-up period have been calculated. Hospitalizations prior or during the follow-up period were registered. Antipsychotic treatment during the follow-up period was also registered, and converted to chlorpromazine equivalents (in mg/day). The duration of untreated psychosis was assessed by clinical interview at baseline. Cannabis use during the follow-up period was registered. Statistical analyses were performed with SPSS v. 19.0. T-test (or U-Mann Whitney when needed) was used to compare continuous data between groups (FEP vs ARMS). Chi-square was used to compare categorical data. Survival analysis with Cox regression was conducted in all participants to assess whether stress measures are associated with a risk of hospitalization while controlling for covariates.

Results: FEP patients had been more frequently admitted before inclusion in the follow-up study, when compared to ARMS (66.7% vs 20%, p=0.012). There were no significant differences in the risk of admission during the follow-up period (27.8% FEP vs 30% ARMS). No differences were found in Holmes-Rahe or PSS scores over the follow-up period between diagnostic groups. FEP patients received more antipsychotic treatment (p<0.001) and reported more cannabis consumption (p=0.004). In the survival analysis, perceived stress, but not stressful life events, was associated with a risk of hospitalization over one year. This Cox regression model was adjusted for cannabis use, antipsychotic treatment, duration of untreated psychosis, previous admissions, gender or diagnosis.

Discussion: In a sample of young subjects with an early psychosis, perceived stress (but not stressful life events) is a risk factor of hospitalization during the first year of the illness. These results suggest that it is more important the psychological repercussion of stress rather than the presence of stressful life events. To our knowledge, there are no other studies that have related PSS with admission risk in early psychosis subjects. The main limitation of the study is the small sample size, which limits the possibility of conducting separate Cox Regression models for diagnostic groups. The main strength is the prospective design with repeated assessment of two different aspects of stress during a follow-up period of one year. If these results are confirmed in future studies with larger samples, preventive strategies may be implemented to reduce perceived stress in order to avoid hospitalization.

Poster #T78**DETERMINANTS OF POOR DIET AMONG A LARGE SAMPLE OF PEOPLE LIVING WITH A PSYCHOTIC ILLNESS**

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Background: Low fruit and vegetable intake has been identified by the World Health Organisation (WHO) as a risk factor contributing to mortality. People with severe mental illness die prematurely compared to the general population, and whilst they are subject to other risk factors such as smoking, poor diet may also contribute to the reduction in life span. We investigated compliance with WHO guidelines for fruit and vegetable intake, in a large, nationally representative sample of people living with psychotic illness. We aimed to identify factors associated with poor diet, to enable effective design and targeting of interventions.

Methods: Data was collected from 1285 people who took part in the second Australian national survey of psychosis. People were aged 18–64 living with a psychotic disorder. All participants had provided a fasting blood sample. Dietary guidelines in terms of fruit and vegetable intake from the WHO were sought, to determine whether this psychosis population met these guidelines. Variables that may be related to diet and nutritional intake were investigated and these included: demographics, health outcomes, financial difficulty, physical activity, metabolic syndrome and substance use. The sample was stratified by gender, age and BMI to determine any differences for fruit and vegetable intake and a regression analysis was performed to identify any predictors of failing to meet dietary guidelines.

Results: Approximately 75% of participants did not have adequate fruit and vegetable intake according to WHO guidelines. Failure to meet this standard was associated with lower BMI (75% vs 81%), financial difficulty (29% vs 22%), eating less frequently, drinking whole milk instead of low fat milk and adding salt to food (54% vs 46%). People who failed to meet dietary guidelines spent an extra 47 minutes sedentary compared to those who met guidelines. Substance use was high among people who did not consume sufficient fruit and vegetables compared to people who met dietary guidelines; 69% were current smokers' vs. 50%, 35% were at harmful risk of alcohol use vs. 22%, 37% used cannabis compared to 21% and 13% used amphetamines compared to 6% who met dietary guidelines. Male gender, younger age (18–34) and lower BMI were also associated with lower fruit and vegetable intake. Results from a logistic regression analysis showed that being a current smoker, drinking alcohol, and using cannabis in the past year were all significant predictors of failing to meet dietary guidelines for fruit and vegetable intake. The adjusted odds of someone not meeting these guidelines were one and a half times higher if they smoked tobacco or used cannabis. However, eating more meals or snacks during the day was protective against failing to conform to dietary guidelines.

Discussion: The majority of Australians living with a psychotic illness failed to meet dietary guidelines for fruit and vegetable intake. Substance use appears to be a major factor influencing eating behaviour. Along with this, poor diet is accompanied by a constellation of other unhealthy behaviours which has important implications for development of effective interventions.

Poster #T79**COGNITIVE BIASES, PERSONALITY AND DIMENSION OF PSYCHOTIC-LIKE EXPERIENCES IN THE GENERAL POPULATION**

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Background: Although the prevalence of psychotic-like experiences (PLEs) in the general population is well documented, specific mechanisms re-

main unclear. Some recent study has suggested that personality and meta-cognition contribute to hallucinatory-like experiences (Gawęda and Kokoszka, 2013). This finding provided the data for more comprehensive model of psychotic-like experiences. In this study we aim to explore the relationship between three dimensions of psychotic like experiences (i.e. positive, negative and depressive symptoms) and Cloninger's temperament and character dimensions and cognitive biases. Further, we tested whether cognitive biases mediated the relationship between temperament and character and psychotic-like experiences.

Methods: This correlational study consisted of 348 (59 men) healthy participants, largely recruited amongst university students. None of them reported a history of being diagnosed with or treated for a psychiatric or neurological disorder and relatives being diagnosed with psychiatric disorders were exclusion criteria. The CAPE scale (Community Assessment of Psychic Experiences, Stefanis et al., 2002) was utilized to assess three dimensions of psychotic-like experiences (i.e. positive – delusions and hallucinations; negative – social withdrawal, blunted affect; depression). Cloninger's et al. Temperament and Character Inventory (TCI) was used in order to investigate the personality traits. TCI includes four temperament dimensions (1 - novelty seeking (NS); 2 - harm avoidance (HA); 3 - reward dependence (RD); and 4 - persistence (P)) and three character dimensions (1 - self-directedness (SD); 2 - cooperativeness (CO); and 3 - self-transcendence (ST)). Cognitive biases was assessed with the DACOBS (Davos Assesment of Cognitive Biases Scale,), that is a multidimensional measure of cognitive biases associated with psychosis. It includes seven subscales, but for the purpose of this study we included only four cognitive biases subscales: 1 – Jumping to Conclusion (JCT); 2 –Belief Inf flexibility (BI); 3 – Attention for Threat (AT); 4 – External attribution (EA). A mediation analysis was performed according to the four-step regression presented by Baron and Kenny (1986).

Results: Mean age was 22.38 (SD= 2.73). Positive dimension of the PLEs was related to ST ($r=0.50$, $p<0.001$), RD ($r=-0.19$, $p<0.001$), SD ($r=-0.17$, $p<0.01$) and HA ($r=0.11$, $p<0.05$). Negative dimension was related to HA ($r=0.42$, $p<0.001$), SD ($r=-0.39$, $p<0.001$) and P ($r=0.15$, $p<0.01$). Dimension of depression was related to HA ($r=0.51$, $p<0.001$), SD ($r=-0.43$, $p<0.001$) and ST ($r=0.16$, $p<0.01$). All the cognitive biases considered were associated to the three dimensions of the PLEs. However, only the positive dimension was related to JCT. Cognitive biases significantly, but partially mediated the relationship between ST and positive PLEs. Linkage between negative PLEs and HA and SD was partially mediated by AT and EA. Very similar results were obtained for depression dimension.

Discussion: Our results suggest different pathways between personality and PLEs in that temperamental traits impact negative and depressive dimensions of the PLEs, whereas positive dimensions is rather related to character. Cognitive biases play a role in the relationship between personality and PLEs. Jumping to Conclusion plays a specific role the positive PLEs. Cognitive biases mediate the relationship between PLEs and personality.

Poster #T80

INVESTIGATION OF THE RELATIONSHIP BETWEEN COGNITION AND ANATOMICAL NETWORKS IN SCHIZOPHRENIA

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Background: Schizophrenia has long been described as a disease affecting cognition. Kraepelin's term "dementia precox" indicated a change in cognition that occurs at an early age. Bleuler followed this work and coined the term "schizophrenia", implying that there was a "split" between a person's thoughts, behaviors and emotions. Focus had been aimed at understanding differences in brain volumes to describe the lack of integration for major elements in thought disorders. It has now been recognized that this split could stem from a lack of integration due to abnormalities in brain circuitry. The dysconnectivity hypothesis has been supported by multiple functional and diffusion imaging studies. It was the aim of the project to understand if correlations existed between cortical volumes or white matter connectivity and cognition scores in individuals with chronic schizophrenia vs. controls. **Methods:** Data was collected from 29 chronic schizophrenics and 29 healthy controls including structural (T1), resting state functional (6min in length, TR 2s, TE 30ms), and diffusion weighted (30 non-collinear, bval 1000s/mm²) magnetic resonance imaging. Images were preprocessed

with standard pipelines. Freesurfer was used to generate cortical volumes. White matter tractography files were generated and anatomical connectivity matrices were made containing the count of white matter streamlines connecting each ROI to ROI combination. Standard parametric statistical methods were applied. A priori knowledge of areas known to be important in schizophrenia was utilized. These areas were analyzed for differences in brain volumes and white matter tractography and compared to measures of cognition

Results: In probands, attention and memory subscores were decreased (diff 3.6724 $p < 0.0001$, diff 5.7644 $p < 0.0001$). Left hemisphere parsorbitalis, left hemisphere postcentral area and right hemisphere superiorfrontal area volumes trended towards significance (diff 105.4828, $p = 0.0895$; diff 968.2414, $p = 0.0760$; diff 1087.1034, $p = 0.0409$). None of these areas correlated with either memory or attention subscores. A priori analysis was completed and focused on white matter connectivity of left to right cuneus and left to right precuneus. Both cuneus and precuneus had statistically significant differences in white matter connectivity between probands and controls (diff 38.5862, $p = 0.0291$; diff 153.9310, $p = 0.0106$). Again, neither of these areas had a significant correlations to memory or attention subscores

Discussion: Cognition is a primary outcome measure in schizophrenia and a paramount factor in quality of life. Thus, understanding the correlation between both brain volumes as well as white matter connectivity with cognition scores is of specific interest. No statistically significant correlations were found between brain volume and cognition subscores. Additionally, the primary target of white matter connectivity investigated the connectivity between both left and right cuneus and precuneus nuclei. While both had statically significant differences in connectivity, neither correlated with cognition scores. These nuclei were chosen as they are both important nodes. It is interesting that, although cognition and memory scores were strikingly different between controls and probands, neither of these central hubs correlated to cognitive subscores. Further investigation of individual tracks will be completed to further elucidate the variations in cognitive tests.

Poster #T81

FREQUENCY AND CHARACTERISTICS OF THE ATTENUATED PSYCHOSIS SYNDROME AND DELINEATION TO OTHER RISK PROFILES IN A SAMPLE OF HELP-SEEKING INDIVIDUALS

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Background: High-risk research in the field of early recognition of psychosis led to the inclusion of the Attenuated Psychosis Syndrome (APS) in Section III of DSM-5. Although fiercely discussed, the DSM-5 work group also placed APS under the "Other Schizophrenia Spectrum and other Psychotic Disorder" category in the diagnostic Section II. The present study examines the frequency and characteristics of APS in individuals seeking help for a variety of mental disturbances, including mood symptoms, and the delineation of APS to other risk profiles.

Methods: A consecutive cohort of help-seeking individuals underwent extensive assessments in an early recognition program for schizophrenic and/or affective psychosis in the region of Zurich, Switzerland. Attenuated positive psychotic symptoms were identified using the Structured Interview of Prodromal Syndromes (SIPS) and considered as APS according to DSM-5. Excluding participants with frank or brief intermittent psychotic symptoms, correlates of APS were assessed and compared to non-APS subjects. The

non-APS group comprised two main subgroups: 1) participants meeting basic symptom criteria based on cognitive disturbances and/or cognitive-perceptive symptoms, and 2) participants defined as at-risk for bipolar disorder (at-risk bip) based on depressive and hypomanic symptoms, as assessed with the Hamilton Depression Scale and the Hypomania Checklist. **Results:** Of 213 participants (age=21.02±6.02, range 13-35 yrs, female=38.5%), 94 (44.1%) met and 119 (55.9%) did not meet APS criteria. In the non-APS group, 81 (38.0%) subjects fulfilled basic symptom and 33 (15.5%) at-risk bip criteria. Compared to non-APS, APS-status was significantly associated with younger age (23.18±5.90 vs. 18.29±4.98, p<0.0001), more obsessive-compulsive (p=0.022) and posttraumatic stress disorder (p=0.004), and less general anxiety disorder (p=0.027). In addition to APS defining positive scores, total SIPS negative, disorganized and general symptom scores were significantly higher in APS than non-APS, basic symptom and at-risk bip subjects. Whereas all positive symptoms differed between the groups, two negative symptoms (avolition, decreased experience of emotions and self), one disorganized (impairment in personal hygiene) and one general symptom (dysphoric mood) did not differ between APS and at-risk bip. Lifetime and current suicidality were more frequent in APS but corrected for age, the difference remained significant only for current suicidality. Higher Clinical Global Impression Scales Severity (CGI) and poorer current Global Functioning (GAF) were associated with APS and significantly correlated with all SIPS-symptom domains. Treatment with antipsychotics was numerically more frequent, whereas treatment with antidepressants was significantly less frequent in the APS group.

Discussion: In a sample of individuals with a broad range of mental symptoms enrolled in a high-risk project, 44.1% fulfilled the DSM-5 criteria for APS and could therefore be diagnosed as primary or secondary diagnosis under the rubric of "Other Specified Schizophrenia Spectrum and Other Psychotic Disorder". APS was associated with greater functional impairment and suicidality, emphasizing the need for clinical care. However, the APS group was significantly younger, exposing individuals during a vulnerable developmental phase to potentially immediate negative consequences of labeling and treatment, requiring follow-up studies to evaluate the outcomes and benefit/risk ratio of early recognition and intervention.

Poster #T82

SOCIAL STRESS AND PSYCHOTIC SYMPTOMS IN THE DAILY LIFE OF YOUNG ADULTS WITH HEARING IMPAIRMENT

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Background: Increased lifetime prevalence of psychotic symptoms and elevated psychosis risk have been reported in people with hearing impairment. Hearing loss, even when compensated with modern hearing aids, can hinder participation in conversations and result in feelings of exclusion and loneliness. We hypothesize that sensitization of the stress system through chronic exposure to social stress is an important mechanism leading to increased psychosis risk in the hard of hearing. This pilot study assesses if hard of hearing individuals show increased stress responses in daily life.

Methods: Fifteen participants with serious hearing impairment and 19 controls (age range 18-30) were examined using the Experience Sampling Method, which employs repetitive random sampling of momentary emotions and social context. Multilevel regression analyses were used to examine emotional and symptomatic reactivity to social stress.

Results: Participants with hearing impairment reported higher levels of negative affect ($\beta=0.47\pm0.19$, p=0.01) and psychotic symptoms ($\beta=0.25\pm0.097$, p=0.009) in daily life. Additionally, when faced with a stressful social situation participants with hearing impairment responded with a stronger increase in negative affect ($\beta=0.17\pm0.040$, p<0.001) and in psychotic symptoms ($\beta=0.090\pm0.017$, p<0.001) compared to control subjects.

Discussion: These preliminary results suggest greater reactivity to social stress in individuals with hearing impairment. The finding is consistent with earlier reports on hearing impairment and psychotic symptoms and provides ground for further investigation of the relation between social exclusion and stress reactivity in the development of psychotic disorder.

Poster #T83

GENETIC VARIATION IN ARRB2 IS ASSOCIATED WITH B-ARRESTIN2 EXPRESSION AND STRIATAL ACTIVITY DURING WORKING MEMORY

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Background: Recent studies have suggested a role of the D2 cAMP independent signaling pathway in phenotypes related to schizophrenia. A crucial factor of this pathway is β -arrestin2, which is coded by the ARRB2 gene. This protein participates with phosphatase 2A in a macromolecular complex which allows Akt1 dephosphorylation after stimulation of dopamine D2 receptors by dopamine. Here, our aim was to investigate association of single nucleotide polymorphisms (SNPs) in ARRB2 with multiple phenotypes ranging from molecular to brain imaging and behavioral correlates and including β -arrestin2 mRNA expression, working memory related brain activity and its relationship with behavior.

Methods: Prefrontal mRNA expression and genotypes of ARRB2 SNPs were evaluated in 112 Caucasian healthy subjects using the BrainCloud database, available online (<http://braincloud.jhmi.edu/>). In particular, one-way ANOVA was used to investigate the association between mRNA expression and genotypes of 55 SNPs with Minor Allele Frequency (MAF) ≥ 0.03 . Results were adjusted with Bonferroni correction. Based on mRNA expression findings, SNP rs733099 was genotyped in 606 healthy subjects in order to investigate its association with working memory processing. With this aim, 412 healthy individuals (21AA; 153 AG; 238 GG) underwent 3T fMRI while performing the 2-back working memory task. Groups were matched for age, sex, handedness and IQ. fMRI data were analyzed using Statistical Parametrical Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk>). Random effects models with a statistical threshold of p<0.05 and minimum cluster size (k)=5 were used for statistical analysis. Finally, BOLD responses were extracted from significant clusters using MarsBar (<http://marsbar.sourceforge.net/>). Spearman's correlations were performed between BOLD responses in relevant clusters and behavior as a function of genotype.

Results: One-way ANOVA indicated that rs733099 (10 AA; 48 AG; 54 GG) was associated with ARRB2 expression in prefrontal cortex (p=0.001). In particular, subjects with the AA genotype had lower mRNA levels than subjects with the AG genotype (p=0.0003) and GG genotype (p=0.002). SPM analysis indicated a main effect of genotype on striatal activity (FWE small volume corrected p=0.035). Parameter estimates extracted from this cluster indicated greater activity of AG subjects compared to GG individuals in right putamen (Fisher's post-hoc p=0.0001). Spearman's test indicated a positive correlation between BOLD responses in the striatum and reaction time at the 2-back in AA subjects (right putamen Rho=0.56 p=0.008). Such correlation was not present in the other genotype groups (all p>0.1).

Discussion: These results suggest that rs733099 is associated with molecular and imaging phenotypes as well as with the relationship between brain activity and behavior during working memory. Given the relevance of physiological and behavioral correlates of working memory for schizophrenia, these findings call for further investigation of the relationship between genetic variation in ARRB2 and this brain disorder.

Poster #T84**SEMAPHORINS AND PLEXINS GENE EXPRESSION IS ALTERED IN THE PREFRONTAL CORTEX OF SCHIZOPHRENIA PATIENTS WITH AND WITHOUT AUDITORY HALLUCINATIONS**

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Background: A focused brain area of study in schizophrenia is the PFC, a complex structure with altered connectivity, cell populations and functions in patients with schizophrenia. The PFC has been associated with auditory hallucinations, a positive symptom of this disease that means a clear endophenotype among the total schizophrenic spectrum. The endophenotype study facilitates the detection of specific alterations associated with this trait of the disease. The main aim of this project is to study the gene expression in the human PFC between schizophrenic patients with and without auditory hallucinations compared to healthy controls.

Methods: In this study we have analyzed the gene expression of fourteen postmortem brains of schizophrenic patients with and without auditory hallucinations in relation to brains of control individuals. Firstly, we have studied the complete transcriptome of the PFC of three individuals of each group, to identify altered pathways or genes. After the identification of the Axon Guidance pathway as one of the most differentially expressed pathways we have performed, in the total brain sample, a qRT-PCR of several genes involved in Axon Guidance, such as semaphorin family and the semaphorin receptors, the plexin family, in order to fathom differences in gene expression.

Results: Microarray results indicated the Axon Guidance pathway as potentially altered network between the three groups. The quantitative gene study pointed several differences in the expression of PLXNB1, SEMA3A, SEMA3C and SEMA4D genes between schizophrenic patients with and without auditory hallucinations. Furthermore, different gene expression of PLXNA1, SEMA3D, SEMA3E, SEMA6C and SEMA7A was seen in schizophrenic patients without auditory hallucinations compared to healthy controls.

Discussion: The plexin-semaphorin signaling system is widely involved in neural development and brain plasticity and has been previously implicated in the etiology of schizophrenia. In our study of prefrontocortical postmortem brains we have found several alterations in Axon Guidance pathway and concretely the expression of some semaphorin and plexin genes in schizophrenic patients without auditory hallucinations and other in common with patients with auditory hallucinations.

Poster #T85**THE EFFECTS OF MOTIVATIONAL INCENTIVES ON COGNITION IN PATIENTS WITH SCHIZOPHRENIA AND NEGATIVE SYMPTOMS – A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY**

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Background: Patients with schizophrenia suffering from negative symptoms show a persistent reduction of goal-directed behavior. A putative mechanism for this apathetic behavior is a dysfunctional integration of abstract representations of motivationally salient events (e.g., future rewards) with higher order cognitive operations (e.g., goal maintenance/updating). The goal of the current study is to examine the relationship between cognitive and motivational deficits in patients with schizophrenia and negative symptoms in a functional magnetic resonance imaging (fMRI) study using a n-back working memory task with monetary incentives dependent on performance.

Methods: Thus far, 19 medicated patients with schizophrenia and 14 healthy control subjects were included in the study. At the conference, data

from the full sample of 30 participants in each group will be presented. All subjects participated in three sessions, consisting of an extensive psychopathological assessment, a neuropsychological test battery and the fMRI session. Negative symptoms were assessed with the Brief Negative Symptom Scale (BNSS) and the Scale for the Assessment of Negative Symptoms (SANS). The incentivized verbal n-back task was presented in a 2×2 factorial design with the factors reward (reward vs. no reward) and cognitive load (2-back vs. 0-back).

Results: In the preliminary analysis we found no significant differences in reaction time or performance between both groups. On the neural level, the main effect of cognition showed a significant increase in the BOLD signal in fronto-parietal regions across all subjects. As a main effect of reward, we found significant activation in the bilateral thalamus. The interaction cognition x reward yielded a significant increase in BOLD signal in the left superior frontal and middle gyrus and the right anterior cingulate. With the current sample size, no significant differences between groups were found for any contrast. Furthermore, the interaction contrast values in the left superior frontal gyrus and the left anterior cingulate were negatively correlated with global negative symptoms, i.e. more negative symptoms were associated with less activation.

Discussion: The incentivized version of the verbal n-back task differentiates neural effects of cognition, reward and the cognition x reward interaction. Thus, it seems to be a good operationalization for measuring motivation-cognition interaction in a clinical sample. Until now, we found no significant differences in the behavioral or neural measures between patients with schizophrenia and healthy controls. This is a first hint that patients with schizophrenia are able to use motivational goals to drive current behavior. However, we found a negative association of negative symptoms with BOLD related activity in prefrontal regions. This negative correlation suggests that the neural "enhancement" of regions associated with goal-directed behavior due to secondary rewards is reduced with increasing negative symptoms. A dysfunctional coupling of motivation and cognition could be a promising pathway for investigating the neural basis of negative symptoms.

Poster #T86**STRUCTURAL MRI IN FIRST EPISODE PSYCHOSIS: AN INTERNATIONAL COLLABORATIVE MEGA-ANALYSIS OF INDIVIDUAL ADULT PATIENT DATA**

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Background: Meta-analysis is the most widely used method for averaging statistical effect sizes from different studies and is usually based on combining effect sizes from published literature rather than analysing pooled individual patient data, however it is associated with several methodological problems, the most significant of which are the frequent inclusion of studies that are heterogeneous in nature. In this international collaborative mega-analysis examining regional brain structures in individuals with First Episode Psychosis (FEP) compared to healthy controls, we pooled individual patient data and consequently were able to adjust for between-study differences, enabling us to compare regional brain measurements of individuals with FEP to those of healthy controls, whilst co-varying for relevant confounds, not possible in conventional meta-analysis.

Methods: Published brain volumetric studies were identified through systematic database searches for articles published between 1980 and 2012. Consequently we invited 43 international research groups who had employed robust methodology in MRI data acquisition in relation to individuals with FEP or healthy controls to participate in this study. MRI and clinical data (e.g. age, gender, duration of untreated psychosis, psycho-active substance use, age of onset of illness, diagnosis, medication usage) was provided by 21 international research groups on 1068 individuals with FEP and 941 controls. Linear mixed effects regression models were used where research centre was incorporated as a random effect to account for the correlation due to individuals within each research centre and possible heterogeneity between research centre. Gender was included as a fixed factor and age as a co-variates. We repeated the analysis including intracranial volume as an additional co-variante.

Results: The most common FEP diagnosis was schizophrenia (n=730), followed by schizoaffective disorder (n=93), bipolar disorder (n=78),

major depressive disorder (n=55) and schizo-affective disorder (n=45). A greater proportion of patients compared to controls were male (57% v. 44%, p<0.001) and the mean age of patients was younger (26.62 (SD=7.88) v 28.60 (SD=9.12), p=0.001). Brain regions with reduced volume in individuals with FEP compared to controls (before controlling for intracranial volume) included total Grey Matter ($F=21.96$, p<0.001), total white matter ($F=14.51$, p<0.001), left hippocampus ($F=4.91$, p=0.03) and amygdala ($F=5.58$, p=0.02). Brain regions with increased volume in individuals with FEP compared to controls included cerebrospinal fluid (total) ($F=4.376$, p=0.037), lateral ventricles ($F=4.725$, p=0.03) and caudate ($F=14.57$, p=0.001). When we controlled for intracranial volume white matter and caudate volume were no longer significantly different between the groups. Individuals with schizophrenia displayed similar brain structural differences compared to healthy controls group, but had a more marked reduction in hippocampal volume, including total ($F=6.682$, p=0.010), left ($F=12.43$, p=0.001) and right hippocampal volume ($F=6.950$, p=0.009).

Discussion: Similar to meta-analyses of aggregate data, we demonstrated that individuals at their first episode of psychosis have brain abnormalities compared to healthy controls, including ventricular enlargement and hippocampal volume reduction. This data tentatively further supports a reduced total brain volume at the onset of illness. Unfortunately, insufficient research groups (≤ 3) had examined certain brain regions (e.g. orbitofrontal cortex and corpus callosum) for us to accurately ascertain if there were differences in these structures between individuals with FEP or healthy controls.

Poster #T87

ONCE MONTHLY PALIPERIDONE PALMITATE – TOLERABILITY AND TREATMENT RESPONSE IN RECENTLY DIAGNOSED VERSUS CHRONIC NON-ACUTE SCHIZOPHRENIA PATIENTS SWITCHED FROM PREVIOUSLY UNSUCCESSFUL TREATMENT WITH ORAL ANTIPSYCHOTICS

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Background: To explore tolerability and treatment response of flexible doses of once monthly paliperidone palmitate (PP) in recently diagnosed versus chronic adult non-acute schizophrenia patients previously unsuccessfully treated with oral antipsychotics.

Methods: International prospective 6-month open-label study exploring non-acute but symptomatic patients, stratified by years since diagnosis [recently diagnosed (≤ 3 years) or chronic (> 3 years)]. Outcomes were changes from baseline to endpoint in Positive and Negative Syndrome Scale (PANSS) total score, Clinical Global Impression-Change Scale (CGI-C), Extrapyramidal Symptom Rating Scale (ESRS) and adverse events (AEs).

Results: N=233 recently diagnosed (63.9% male, mean age 32.2 ± 10.3 years, mean time since diagnosis 1.2 ± 0.9 years) and n=360 chronic patients (62.5% male, mean age 42.4 ± 11.0 , mean time since diagnosis 13.9 ± 9.3 years) were included in the analyses. 77.7% and 72.5% of the patients, respectively, completed the study. Mean mode maintenance doses of PP were comparable between subgroups (100.6 ± 33.0 mg eq and 105.1 ± 32.6 mg eq). 71% of recently diagnosed and 59% of chronic patients showed a response measured by decrease of $\geq 20\%$ in PANSS total score at endpoint. Mean change in PANSS total score at endpoint (-15.1 ± 15.6 and -9.6 ± 15.7 , respectively), but also in PANSS positive (-3.6 vs. -2.3), negative (-4.4 vs. -2.9) and general subscores (-7.1 vs. -4.4) was numerically but consistently higher in recently diagnosed patients. At endpoint, 52.4% of recently diagnosed patients were rated much or very much improved on CGI-C compared to 38.1% in the chronic group. TEAEs identified in $\geq 5\%$ in both subgroups (recently diagnosed vs. chronic) were injection site pain (12.9% vs. 11.9%), insomnia (9.9% vs. 7.8%), anxiety (6.4% vs. 6.9%), and headache (6.0% vs. 5.3%).

Discussion: These data suggest that recently diagnosed and chronic patients previously unsuccessfully treated with oral antipsychotics may benefit from paliperidone palmitate, with recently diagnosed patients showing consistently higher treatment response, and lower disease severity at endpoint.

Poster #T88

THE EFFECTS OF MATERNAL IMMUNE ACTIVATION AND MK-801 ON MISMATCH RESPONSES IN AWAKE, FREELY MOVING RATS

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Background: Reduced amplitude of mismatch negativity (MMN) of the ERP to rare deviant sounds is one of the most robust neurophysiological endophenotypes observed in patients with schizophrenia and is believed to be primarily due to impaired NMDA receptor signalling. In recent years, research has shown that MMN is just one of a number of auditory ERPs components that exhibit deviance detection, with numerous earlier middle latency components also modulated by sound deviance. The purpose of this study was to investigate whether deviance detection effects on auditory ERPs are affected in an animal model of schizophrenia, the maternal immune activation (MIA) model, and how such deviance detection effects are impacted by administration of MK-801, an NMDAR antagonist.

Methods: Pregnant rats were given an i.v. administration of either a viral mimetic, Poly (I:C) (4mg/kg) or saline; at one of two gestational ages: gestational day (GD) 10, or GD19. In adulthood, stainless steel screw electrodes were surgically implanted over five cortical locations in MIA and control offspring (n=7-10). After recovery, a wireless transmitter (Multichannel systems MCS GmbH) was attached to the recording electrodes and the EEG recorded while the rat was presented with two oddball sequences with either a high or low frequency deviant (standard 87.5%, deviant 12.5%) and a control sequence of randomly intermixed frequencies (each 12.5%) that controlled for adaptation effects and physical features of the deviant. The difference between responses to the deviant and the same frequency sound from the control sequence was used as an index of deviance detection and human-like mismatch responses in the rat. GD19 MIA and control rats were then given escalating doses of MK-801 (0.1, 0.3 and 0.5mg/kg).

Results: Five components of the ERP were identified and measured: P13 (11-15 ms), N18 (15-22 ms), and P30 (22-43 ms) followed by a negative shift with two broad peaks, N-early (43.5-65.5ms) and N-late (65.5-105.5ms) that seem to resemble MMN in humans. For control rats (saline-treated), adaptation-independent deviance detection (a significant difference between the response to the deviant and control stimuli) was observed at P13, N18, N-early and N-late for high frequency, but not low frequency deviants. MIA and MK-801 had different effects on deviance detection, depending on the component measured. Deviance detection at P13 was increased by MK-801, an effect which was potentiated in MIA-exposed rats. MIA and low-midrange MK-801 also increased deviance detection at N18, and MIA and high-dose MK-801 did the same at P30. Mid-high doses of MK-801 reduced deviance detection, while MIA had no effect on deviance detection evident in the N-early component. MIA increased deviance detection over the N-late range, which was normalised by MK-801.

Discussion: In this rat model, deviance detection evident in the N-early component most closely resembles human MMN in terms of sensitivity to NMDAR antagonists. However, MIA in rats did not reduce deviance detection of this component. Findings from other components suggest that both MK-801 and MIA increased deviance detection responses, indicating that the pharmacology and neurobiological underpinnings of separate deviance-detection components are distinct. The findings of increased deviance detection in MIA-exposed rats indicate that schizophrenia-related MMN impairments are not recapitulated in this model. However, for several components, the effects of MIA and MK-801 were similar and in some cases, potentiated each other, indicating that MIA and MK-801 may be converging on similar neurobiological systems.

Poster #T89**DO COMMUNITY TREATMENT ORDERS KEEP PEOPLE OUT OF HOSPITAL? THE INFLUENCE OF THE LEVEL OF COMMUNITY CARE**Anthony W. Harris^{1,2}, Joe Garside¹, Grant Sara³¹*University of Sydney*; ²*Westmead Millennium Institute*; ³*InforMH, Mental Health and Drug and Alcohol Office, NSW Health, North Ryde, Australia*

Background: The use of community treatment orders (CTO) to enforce involuntary community treatment has been a source of considerable debate in Australia and internationally. Several large cohort studies have found that CTOs reduce re-hospitalization rates for individuals compared with their pre-CTO baselines. However three randomised controlled trials have produced conflicting results. In this study we examine the effectiveness of CTOs in New South Wales (NSW), a state of Australia, using a large population-based sample with sufficient power to control for demographic and diagnostic variables as well as the pattern and intensity of care prior to CTO initiation.

Methods: All persons (n=8961) receiving CTOs in NSW (n=26972 orders) from 2003-2009 were identified using data from the NSW Mental Health Review Tribunal Mental Health. Inpatient and community mental health care in the 30 months prior to each individual's first CTO was compared with service use during and after CTO initiation using the Health Information Exchange that records all admissions and outpatient care within the public mental health services. Case controls were identified using propensity score matching on demographic, clinical and prior care variables. Impact of CTOs on re-hospitalisation was examined using repeated measures survival analysis.

Results: CTOs were associated with increased community care and reduced hospital admission. These impacts were greatest in people with high levels of inpatient care and low levels of community care prior to their first CTO. However the level of community care clearly affected the success of this intervention.

Discussion: CTOs may be effective in preventing re-hospitalisation, however this assumes the availability of appropriate intensive community care.

Poster #T90**EFFECT OF LIFETIME STRESS ON RESISTANCE TO ANTIPSYCHOTIC TREATMENT**

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Background: Approximately 20-30% of Schizophrenia patients fail to respond to antipsychotic medications. The burden of treatment resistant (TR) patients is between 60 to 80% of the total cost of schizophrenia. In addition, there is evidence that TR patients have more severe symptoms, more co-morbidities, higher suicidal risk and lower quality of life than non TR patients. Several studies showed that all types of childhood trauma increase the risk of psychosis. Furthermore, other studies revealed that the incidence of stressful events is higher prior to the psychosis onset. However, to date, the relationship between the number of stressful events and resistance to antipsychotics has not been investigated. The aim of this study is to compare the prevalence of traumatic events in TR and non TR schizophrenia. Association between resistance and high number of traumatic events has been found in other mental illnesses such as major depression.

Methods: We recruited 71 participants diagnosed with schizophrenia spectrum disorders through the Center of Addiction and Mental Health (CAMH), a Canadian teaching hospital located in Toronto. The diagnosis of schizophrenia was ascertained by the means of the SCID-I/P and the presence of adverse life-events was assessed using the Stressful Life Events Screening Questionnaire (SLESQ) and the Childhood Trauma Questionnaire (CTQ). Medical charts were reviewed for determining the history of failure of two antipsychotic trials, or more, of adequate duration using the criteria of the American Psychiatric Association for refractory schizophrenia.

Results: According to the APA criteria, in our sample 49.3% of the participants were defined as TR and 50.7% as non TR. Higher numbers of lifetime stressful events were reported by TR participants compared to non TR patients ($p<0.001$). Also, there was a significant correlation between the CTQ and TR ($p=0.016$).

Discussion: Higher numbers of stressful and traumatic events are found in TR schizophrenia patients, therefore predicting a poorer outcome. Unresolved repeated exposures to childhood and adulthood traumatic events perpetuate psychosis. Thus, TR schizophrenia patients require a personalized bio-psycho-social approach to improve the success of the therapeutic intervention.

Poster #T91**CHILDHOOD ABUSE AND BRIEF LIFE EVENTS IN POSTPARTUM PSYCHOSIS**Katie M. Hazelgrove¹, Carmine M. Pariante², Astrid M. Pauls¹, Susan Pawlby³, Costanza Vecchio¹, Paola Dazzan³¹*Department of Psychosis Studies, Institute of Psychiatry, King's College of London*; ²*Department of Psychological Medicine, Institute of Psychiatry, King's College London*; ³*Department of Psychological Medicine, Institute of Psychiatry, Kings College London*

Background: Individuals with and at risk of psychosis, unrelated to gestation, report higher levels of childhood trauma and stressful life events compared to healthy controls (Mondelli et al., 2010; Tikka et al., 2013). However, to the author's knowledge, no research has been carried out in women with or at risk of postpartum psychosis (PP). The aim of this study was to investigate childhood abuse and recent stressful life events in a sample of women with and at risk of PP.

Methods: 50 women were assessed on average 15 weeks following delivery (range 3 - 43). 13 women had PP, 16 were at risk of PP and 21 were controls. Women's experience of life events over the previous 6 months was assessed using the Brief Life Events Questionnaire (BLE: Brugha & Cragg, 1990). Women were also asked questions from the Childhood Experience of Care and Abuse Questionnaire (CECA-Q: Bifulco et al., 2005) about any adverse childhood experiences before the age of 17.

Results: There were no significant group differences in weeks following delivery. Using the Kruskal-Wallis non-parametric test, there was a significant difference between the groups in the number of BLE experienced ($N=50$, $\chi^2_{(2)}=7.99$, $p=0.02$). Post-hoc analyses showed a significant difference in the number of BLE between women with PP and controls, with women with PP having more BLE than controls ($M=1.23$, $SD=1.2$ versus $M=0.24$, $SD=0.5$, respectively; $U=71.00$, $N_1=13$, $N_2=21$, $p<0.01$). There were no other significant differences between groups. A significant difference was also found between groups in whether they experienced childhood abuse, with 9.5% of controls, 56.3% of women at risk of PP and 23.1% of women with PP experiencing physical and/or sexual abuse ($N=50$, $\chi^2_{(2)}=10.05$, $p<0.01$). Post-hoc analyses showed a significant difference between controls and women at risk of PP with women at risk being more likely to have experienced childhood abuse than controls ($N=37$, $\chi^2_{(1)}=9.49$, $p<0.01$). Women at risk of PP were no more likely than women with PP to have experienced childhood abuse. There was no significant difference between controls and those with PP. There was a significant difference between groups in whether the women experienced physical abuse, with women at risk of PP experiencing more physical abuse than women with PP or controls ($N=50$, $\chi^2_{(2)}=7.81$, $p=0.02$). The numbers experiencing sexual abuse were very small. No controls, 25% of women at risk ($N=4$) and 15.4% of women with PP ($N=2$) experienced sexual abuse. Using Pearson's Chi Square, physical abuse was significantly correlated with sexual abuse with 38.5% of women experiencing both physical and sexual abuse ($N=50$, $\chi^2_{(1)}=11.65$, $p<0.01$). There was no significant difference in duration of illness (years) between women at risk of PP and those with PP. Compared with women who did not experience childhood abuse, those who did had a longer duration of illness ($M=3.06$, $SD=5.7$ versus $M=6.92$, $SD=7.3$, respectively; $U=141.00$, $N_1=35$, $N_2=13$, $p=0.03$).

Discussion: In line with previous literature the results of this study show that compared to healthy women, women who developed PP experienced more recent stressful life events. There was no difference in the length of illness nor in the experience of childhood abuse reported by women at risk of PP and those who developed PP. However, compared to healthy women, the women who were at risk of PP were more likely to have experienced childhood abuse whereas this was not the case for the women who did develop PP.

Poster #T92**N-ACETYLCYSTEINE PREVENTS INCREASED SENSITIVITY TO AMPHETAMINE IN SOCIAL ISOLATION-REARED MICE**

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Background: The cost-benefit of early intervention in individuals considered to be at high risk to develop schizophrenia is currently on debate. Clinical and pre-clinical data placed N-acetylcysteine (NAC) as a potentially useful drug in the treatment of various psychiatric disorders, including schizophrenia. NAC is a precursor of cysteine that increases brain glutathione levels and modulates glutamate transmission through the astrocyte cystine-glutamate antiporter. NAC has also been considered as a potential medication to counteract the pathological processes that precede full-blown schizophrenia, thus preventing or delaying the onset of psychosis. However, studies addressing this possibility are lacking. The aim of this study was to investigate the effects of chronic NAC in adolescent mice reared in social isolation, an established neurodevelopmental model of schizophrenia. Specifically, we report the effects of NAC on amphetamine sensitivity, a behavioral correlate of schizophrenia positive symptoms.

Methods: C57BL/6 male mice were weaned at postnatal day 21 and randomly assigned to isolation or social (3-5 animals per cage) rearing groups. Mice were treated (daily, i.p.) with saline or NAC (60 or 120 mg/kg) during postnatal days 42 to 70. Behavioral testing started after 1-week washout. The locomotor response to amphetamine challenge (2.5 mg/kg, i.p.) was assessed in open field arenas (40×40×40 cm). Animals were treated with saline and placed in the arena for 30 min; after briefly removed and treated with amphetamine, subjects returned to the arena for 60 min. Experiments were video recorded and analyzed with the ANY-Maze tracking software.

Results: No significant differences were observed in baseline locomotion (habituation after saline) between groups. However social isolation-reared mice showed increased locomotor response to amphetamine in comparison to controls. While NAC did not modify the response to amphetamine in the social-reared group, it (at both doses) prevented the enhanced sensitivity to amphetamine in the social isolation group. Statistical support for these results was provided by three-way repeated measures ANOVA, which yielded a significant main effect of bins ($F_{11,440}=59.4$, $p<0.0001$) and a significant housing condition x treatment group x bins interaction ($F_{22,440}=1.64$, $p<0.05$).

Discussion: We report here the first set of data supporting the proposal that NAC can be useful for early intervention in individuals at risk to develop psychosis. The mechanism by which NAC exerts this preventive effect is yet to be defined. The protective mechanism is likely to be multifaceted given that, besides its antioxidant and glutamatergic properties, NAC affects other relevant neurochemical pathways, including neurotrophic, apoptotic and inflammatory signaling. Clinical studies are ultimately needed to evaluate the benefits of NAC to treat subjects in prodromal stages, though diagnosis of the prodrome is polemic and criteria vary across research groups. Safety and tolerability in early intervention is even more important considering the high rates of false-positive predictions. The optimal profile of NAC in terms of safety and tolerability is thus a considerable advantage in comparison to current antipsychotics. Complementary data on the neuroprotective effects of NAC in this context are thus warranted to subsidize clinical trials.

Poster #T93**CONCORDANCE RATES AND HERITABILITY IN SCHIZOPHRENIA, DATA FROM A DANISH TWIN STUDY**

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Background: Schizophrenia is a serious brain disease with a prevalence of approximately 1%. In a meta-analysis of 12 previous twin-studies heritability was estimated to 81% (Sullivan et al, 2003). Differences in methodological procedures across the studies might influence the estimate. **Methods:** We linked the Danish twin register, which contains information on all Danish twins born 1951-1981, to the Danish Central Psychiatric Research Register including information on all psychiatric admissions in

Denmark since 1969, and out-patient contacts since 1995 (N=19539). The heritability of schizophrenia (DF 20.xx) and schizophrenia spectrum (DF 2x.xx) was estimated using Structural Equation Modeling. Furthermore, we investigated the heritability for males vs. females and early onset (<22 years) vs. late onset (≥ 22 years).

Results: The heritability according to additive genetic effects was higher for schizophrenia (75.0%) than for schizophrenia spectrum (69.4%). Furthermore, the heritability of schizophrenia spectrum according to additive genetic effects was higher among females (74.3%) than males (61.4%). When studying both schizophrenia and schizophrenia spectrum the heritability due to additive genetic effects was higher among early onset (80.9%, 84.0%) than late onset (71.1%, 64.4%).

Discussion: We found modified heritability estimates for schizophrenia in this large twin study, still with a substantial genetic component. The higher heritability among females speaks for a larger environmental component being involved in the male cases when looking at schizophrenia spectrum. Furthermore, the increased heritability in early onset cases indicates a larger genetic component for early onset (<22 years).

Poster #T94**OPTIMIZING TREATMENT AND SIGNAL DETECTION WITH EVP-6124 IN A CIAS PHASE 2B STUDY**

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Background: A number of factors can potentially impact the ability to both accurately assess cognition longitudinally in a clinical trial and to detect the potential effects of a procognitive agent in patients with CIAS. The effects of circadian rhythm fluctuations in cognitive abilities may impact the ability to detect a drug effect; the hourly variation in cognition during the course of the day may obscure a potential treatment effect. An additional factor in demonstrating a drug effect may be the decreased ability of CIAS patients above a certain age to have adequate neural plasticity to respond to a procognitive agent.

Methods: We examined the results of a recently completed Phase 2b CIAS study to address these questions. A 3-month, dose ranging (0.3 and 1 mg vs placebo) study in stably treated (all atypical antipsychotics except clozapine) CIAS patients (n=317, ages 18-55yo) in the United States and Europe was conducted. The primary endpoints of cognition (CogState) and clinical function (ScoRS) were positively met with the 1 mg dose group showing the greatest change from baseline versus placebo.

Results: In the U.S., patients (n=140) were also assessed by MCCB cognition testing. These patients (18-55 yo) had a change in the MCCB composite score in the 1.0 mg group vs placebo of ES= 0.28, $p=0.069$; in patients <50 yo (n=108), ES=0.48, $p=0.058$; in patients <45 (n=74), ES=0.67, $p=0.032$, and in patients <40 yo (n=48), ES=1.0, $p=0.01$. Patients that had the final MCCB testing done within the same two hour time block as the baseline testing had a cognition ES=0.64, $p=0.044$. This effect was substantially larger than the effects observed in patients that had the final MCCB testing at a different time of day, ES=-0.07, $p=0.805$.

Discussion: These results suggest that two controllable factors may impact treatment optimization and signal detection in CIAS trials: age and consistent time-of-day administration of cognitive testing.

Poster #T95**EXCESS MORTALITY IN MENTAL DISORDERS ATTRIBUTABLE TO SUBSTANCE USE DISORDERS**

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Background: Abuse of alcohol, cannabis, or other illicit substances are

highly prevalent in people with mental disorders such as schizophrenia. While these comorbid substance use disorders are known to be related to poor prognosis within a range of outcomes, their influence on mortality is not well-understood. Alcohol and hard drugs are shown in the background population to increase mortality, but at least one study has found no association between alcohol and mortality in schizophrenia. The same study even found that cannabis was protective against early death. The combination of a relatively small sample size and short follow-up period makes it highly important to attempt to replicate this study in a larger population with longer follow-up. In particular, people with mental disorders are an important group in which to investigate this question. First of all because substance use disorders already appear to play a prominent part in many mental disorders; and second of all because it is likely that substance use disorders are less under-diagnosed in people with mental illness than in the background population. The presence of nationwide Danish registers allows us to conduct this study on all people in Denmark who have ever received treatment for a psychotic disorder. The aim of the present investigation is to examine the link between substance use disorders and mortality in people with either schizophrenia spectrum disorders, bipolar disorder, or depression.

Methods: We linked data from the following Danish registers: The Psychiatric Central Research Register, The National Patient Registry, The Civil Registration System, The Cause of Death Register, The National Prescription Registry, The Substance Misuse Register, and Statistics Denmark. The study population consisted of all people born in Denmark 1955 or later who have ever received a diagnosis of schizophrenia or similar disorders.

Results: In unadjusted analyses, all types of substance use disorders increased the risk of dying compared to people without the respective types of substance use disorders. When the different types of substance use disorders were mutually adjusted, the association between cannabis use disorders and mortality completely disappeared. Alcohol use disorders may be protective against dying from suicide in people with psychosis. This effect was not observed in people with depression, where alcohol use disorders increased mortality, and cannabis use disorders decreased mortality. Alcohol use disorders also increased the risk of dying from cardiovascular causes. All types of substance use disorders, even after mutual adjustment, increased the risk of dying from chronic obstructive pulmonary disease (COPD) or other non-infectious, non-cancerous respiratory causes.

Discussion: Alcohol use disorders increased all-cause mortality and many cause-specific mortality rates as well. Cannabis use disorders were only associated with all-cause mortality when analyses were not adjusted. Cannabis use disorders were a strong predictor of dying from respiratory causes such as COPD. Since cannabis use disorders were not associated with death from cardiovascular causes or malignant tumors, it is unlikely that there is much residual confounding due to unmeasured tobacco smoking. This is also confirmed by the high rates of tobacco smoking in people with mental illness who do not use other substances - if almost everybody smokes tobacco, any effects that are observed for substance use disorders must be beyond the effect of tobacco. The findings from this study are important both in establishing the overall harm of substance use disorders (probably regardless of mental illness); and give important clues to prevention of early death in people with severe mental illness.

Poster #T96

MEASURING THE GAP BETWEEN COGNITION AND FUNCTIONING: EVALUATING AWARENESS OF THE BRIDGE BETWEEN COGNITION AND EVERYDAY BEHAVIOUR VIA THE ASSESSMENT OF BRIDGING STRATEGIES OF THINKING TO REAL-WORLD ACTIVITIES (ABSTRACT)

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Background: Substantial evidence suggests that cognitive remediation (CR) improves cognition, thus, it is efficacious. However, its effectiveness, the magnitude and manner with which cognitive improvements translate to gains in functioning, is less clear. In addition to cognitive training, many forms of CR include bridging, whereby individuals learn to use multiple strategies to apply thinking skills to real-life situations. Yet, there remain many unanswered questions about the mechanisms, or "key ingredient", of CR. This study pilots a new measure entitled the Assessment of Bridging Strategies of Thinking to Real-world Activities (ABSTRACT). ABSTRACT is

designed to evaluate an individual's ability to use strategies to solve cognitive tasks and think about how these cognitive skills are applied in the real-world, a critical component of CR.

Methods: ABSTRACT entails three brief cognitive tasks of short-term memory (List Memory), visual attention and information processing (Bells Task), and executive functioning (Amusement Park Task). In List Memory, participants complete two trials of recalling 10 words. In the Bells Task, participants find bells amongst distracting pictures in a limited amount of time. And in the Amusement Park Task, individuals find the fastest route to visit locations at an amusement park. Next participants sort cards inscribed with specific everyday real-world activities into one of three bins (List Memory, Bells Task, or Amusement Park) by determining which cognitive skills best correspond to the skills needed to perform that activity. Participants' sort 30 cards into the bin they believe use most of the same thinking skills. Scoring procedures for sorted behavior cards were established using a two-step validation process by which (1) five CR therapists sorted cards through consensual agreement, and then (2) 35 healthy subjects completed ABSTRACT. The sample presented here includes individuals with schizophrenia and mood disorders (n=21) and healthy controls (n=21). To evaluate criterion validity, senior clinicians rated bridging capabilities of a subsample of individuals who completed CR (n=7).

Results: Findings suggest that there is a significant difference in performance between a clinical sample and healthy controls ($p=0.002$). We observed a positive correlation between performance on the cognitive tasks and total score on the sorting task (r range = 0.38 to 0.57; $p<0.05$), demonstrating that individuals with higher performance on the cognitive tasks have better bridging capabilities, but that these are not completely overlapping constructs. Further, senior clinician ratings of bridging abilities were highly correlated with participants' performance on ABSTRACT ($r=0.68$ and 0.93).

Discussion: Preliminary findings support the utility of ABSTRACT to discriminate between groups on bridging cognitive skills to real-world behaviors. Further, performance on ABSTRACT is only moderately related to cognition and correlates significantly with clinician ratings, suggesting that ABSTRACT has external validity. The following additional data will be also presented: (1) individuals completing CR at multiple sites including the Toronto Centre for Addictions and Mental Health and (2) the association between ABSTRACT performance and contributions to bridging discussions in-session during CR. Evaluation of the mechanisms that promote gains in CR is critical to furthering research on the effectiveness of CR as an evidence-based treatment. This project is an important step toward understanding how individuals learn during CR and how treatments can be streamlined to better serve individuals with cognitive deficits, particularly those struggling with "bridging".

Poster #T97

TREC-SAVE: A RANDOMISED TRIAL COMPARING MECHANICAL RESTRAINTS WITH SECLUSION FOR AGGRESSIVE PATIENTS IN PSYCHIATRIC HOSPITALS

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Background: TREC-SAVE is the third of the TREC studies in Brazil. The first two evaluated commonly used drug treatments for management of people with psychosis who have become acutely aggressive. TREC-SAVE address issues of seclusion or restraint of this same group. It is the first randomised trial addressing this question.

Methods: This pragmatic trial was designed after close consultation with all involved. Participants were anyone aggressive or violent in the emergency wards of a large psychiatric hospital in Rio de Janeiro (Psychiatric Institute Philippe Pinel) for whom some kind of restriction was indicated by nursing and medical staff, and for whom staff were unsure whether seclusion or restraint would be best. People were randomised to use of four-point restraint (strong cotton banding to edge of bed) or use of a minimally furnished seclusion room with open but barred windows onto the nursing station. All participants used medication as prescribed. Protocol and analysis plan was published and main outcomes chosen by clinicians

and managers, the local ethics committee approved the study. Data were analysed by intention-to-treat. Trial registration: ISRCTN4945427

Results: Recruitment started in July 2010 and ended Jan 2011. 105 participants were included (restraints = 51; seclusion = 54) with similar demographic and clinical data across groups. People allocated to the least restrictive option (seclusion room) were at greater risk of needing an early change of their treatment to restraints compared with those allocated to restraints (RR 1.96 95% CI 1.02-3.80). However, even taking into account the move out of seclusion into restraints, this study provides evidence that this care pathway does not increase overall time in restriction of some sort (RR Not restricted - by 4 hours 1.10 CI 0.74-1.63). Participants tended to be less satisfied with their care in the restraints group (42.2% vs 27.7%) but this did not reach conventional levels of statistical significance.

Discussion: This study suggests that opting for the least restrictive option in circumstances where there is clinical doubt does not harm or prolong coercion. This is one small trial of short duration but its outcomes and circumstances of conduct apply to very great numbers of people who are at risk of maltreatment. These most coercive parts of health care have been under-researched and researchers have not employed randomized trials. For the first time, a randomised pragmatic clinical trial was undertaken to illustrate how objective evaluation of these techniques can, humanely and ethically, be applicable worldwide.

Poster #T98

USING PROGRESSIVE RATIO RESPONDING IN MICE TO DEMONSTRATE PHARMACOLOGICAL ATTENUATION OF DEFICITS IN MOTIVATION

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Background: Given the lack of progress in discovering novel treatments for psychiatric disorders, there is a drive to place greater emphasis on the pathophysiology of psychiatric diseases. The NIMH has launched the Research Domain Criteria (RDoC) initiative which is intended to consider domains of function and how these are affected in different disorders. The five domains are Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Systems for Social Processes, and Arousal/Regulatory Systems. Deficits in Positive Valence such as reduced motivation are common to a range of disorders, including schizophrenia and depression. Here we describe the use of the progressive ratio assay in mice to demonstrate deficits in motivation and their reversal by pharmacological agents. Deficits in motivation were induced pharmacologically using mechanisms which have been shown to induce dysphoria in humans (Astrup et al., 2007; Pfeiffer et al., 1986). In addition the motivation level of a mouse model (Df(16)1+/-; Paylor et al., 2001) of the human 22q11 deletion syndrome, which dramatically increases the risk of schizophrenia, was also studied. The NR2B antagonist, CP-101606, which treated anhedonia in treatment resistant depression patients (Preskorn et al., 2008) was tested for its ability to restore normal levels of motivation in these deficit states.

Methods: Male mice were food restricted to 85% of their free feeding body weight over the course of 1 week. Mice were then trained to nose poke for food rewards on a progressive ratio schedule until they achieved a stable baseline level of responding. For drug studies C57bl6/J mice were dosed with the D1 receptor antagonist, SCH-23390 (0.032-0.1 mg/kg) or the kappa opioid receptor (KOR) agonist, spiradoline (0.32-10 mg/kg) to identify a dose which consistently decreased motivation. In subsequent experiments, the optimal dose of each disruptor was combined with the NR2B antagonist, CP-101606 (5.6-7.5 mg/kg) to determine whether the disruption could be restored. The level of motivation of 22q11 heterozygous (HET) mice and their wild type (WT) littermates was also assessed by monitoring the acquisition of the task and the stable baseline level of responding. CP-101606 was tested for its ability to restore motivation in this genetic deficit model. **Results:** The D1 receptor antagonist, SCH-23390 (0.032-0.1 mg/kg; F(3,31)=18.25; P<0.01) and the KOR agonist, spiradoline (0.32-10 mg/kg; F(5,66)=; P<0.05) produced dose-dependent decreases in motivation as measured by decreased number of rewards. CP-101606 significantly attenuated the motivational deficit induced by both mechanisms (SCH-23390 vs CP-101606 + SCH-23390, P<0.05; spiradoline vs CP-101606 + spiradoline, P<0.05). 22q11 HET mice exhibited reduced motivation compared to WT controls, as seen by increased time to reach a stable level of performance and a lower level of performance overall (F(1,22)=11.63; P=0.003). This

deficit in the HET mice was significantly attenuated by acute administration of CP-101606 (5.6 mg/kg; CP-101606 vs veh P<0.05 in HET mice). Performance of the WT mice was not affected at this dose of CP-101606.

Discussion: The progressive ratio assay represents a useful tool for assessing the effects of drugs on motivation. The bidirectional modulation of motivation using drugs known to affect human behavior increases our confidence in using this assay to profile agents with putative utility in treating deficits in motivation associated with depression, schizophrenia or other CNS disorders.

Poster #T99

THE RELATION BETWEEN LIFETIME ANTIPSYCHOTIC MEDICATION AND COGNITIVE PERFORMANCE IN SCHIZOPHRENIA AT AGE 43 YEARS – THE NORTHERN FINLAND BIRTH COHORT 1966

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Background: The effects of long-term antipsychotic medication on cognition in schizophrenia are unclear. Most studies in this area are short-term clinical trials. The effects of lifetime antipsychotic treatment on cognition have been studied very little if at all. Naturalistic samples offer an optimal setting for investigating the long-term effects of medication (Wang P. et al., Textbook in Psychiatric Epidemiology 2011). The aim of this study was to analyse the association between cumulative lifetime antipsychotic dose and cognition in schizophrenia at the age of 43 years.

Methods: Fifty-five (31 males) schizophrenia spectrum subjects from the Northern Finland Birth Cohort 1966 were assessed at the age of 43 years both diagnostically and cognitively, including California Verbal Learning Test (CVLT), Abstraction Inhibition and Working Memory task (AIM), Visual Object Learning Test (VOLT), Vocabulary (WAIS-III), Visual series (WMS-III), Digit Span (WAIS-III), Grooved Pegboard, Matrix reasoning and Verbal fluency. The mean time since onset of illness was 18.6 years (range 5 to 27 years). Illness severity was estimated by using total symptom score of Positive and Negative Syndrome Scale (PANSS) and Andreasen's remission criteria. Data of the subjects' cumulative lifetime antipsychotic doses in chlorpromazine equivalents were collected from treatment records and interviews. A factor analysis was performed based on nine selected representative variables of all the different cognitive tests. The factor analysis of cognitive tests resulted in one cognitive factor (cognitive composite score). The association between dose-years of antipsychotics and cognitive composite score of the factor analysis was analysed by linear regression model.

Results: According to the preliminary results higher dose-years of antipsychotics were statistically significantly associated with poorer cognitive composite score at the age of 43 years when adjusted for gender and onset age ($\beta=-0.38$, $p=0.005$). When we adjusted also for remission, the effect remained statistically significant ($\beta=-0.45$, $p=0.038$). After adjusting for gender, onset age and total PANSS score, the effect was no longer statistically significant ($\beta=0.03$, $p=0.90$).

Discussion: Previous cross-sectional studies have found an association between higher antipsychotic doses and poorer cognitive performance in schizophrenia (Elie D. et al., J Psychopharmacol 2010; Torniaisen M. et al., J Nerv Ment 2012). To our knowledge, there are no previous reports of an association between cumulative lifetime antipsychotic dose and cognition in midlife in schizophrenia. Based on this data, the use of high doses of antipsychotics may relate to poorer global cognitive functioning in schizophrenia after twenty years of illness. These results do not support the view that antipsychotics prevent cognitive decline or promote cognitive recovery in schizophrenia.

Poster #T100**MINOCYCLINE ADD-ON TO HALOPERIDOL BLUNTS HALOPERIDOL-MEDIATED EXPRESSION OF EARLY GENES IMPLICATED IN GLUTAMATERGIC NEUROTRANSMISSION IN BOTH VEHICLE AND KETAMINE-TREATED RATS**

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Background: Minocycline is a second-generation tetracycline with neuroprotective potential, recently proposed as an add-on to traditional antipsychotics. In NMDA receptor hypofunction models of schizophrenia, minocycline was found effective in reverting psychotic-reminiscent behaviors. In this study, we investigated whether minocycline add-on to haloperidol may affect the expression of two early genes, Homer1a and Arc, implicated in glutamatergic signaling and synaptic remodeling. We carried out this investigation in rats exposed or not to ketamine, thus mimicking acute "glutamatergic" psychosis or naturalistic conditions, respectively.

Methods: Male Sprague-Dawley rats (n=7) were assigned to the following groups: Vehicle+Vehicle (VEH+VEH); Vehicle+Haloperidol 0.8mg/kg (VEH+HAL); Vehicle+Minocycline 45mg/kg (VEH+MYN); Vehicle+Haloperidol 0.8mg/kg+Minocycline 45mg/kg (VEH+HAL+MYN). In the second experiment, Vehicle was replaced by Ketamine 30mg/kg, resulting in the following treatment groups: KET+VEH; KET+HAL; KET+MYN; KET+HAL+MYN. Drugs were administered by i.p. injection. Gene expression was evaluated by means of *in situ* hybridization histochemistry. The Analysis of Variance was performed to evaluate significant changes (set as p<0.05) among treatment groups.

Results: No significant differences in baseline Homer1a expression were observed (i.e. VEH+VEH-mediated expression vs. KET+VEH). In the vehicle experiment, Homer1a expression was not significantly affected in the cortex, with the exception of the insular cortex. In this region, both haloperidol and minocycline (alone or in combination) significantly reduced Homer1a expression compared with vehicle ($p=0.0042$). In striatum, gene expression was significantly induced by haloperidol in almost all subregions. Minocycline per se did not affect gene expression. When added to haloperidol, minocycline either not affected or reduced haloperidol-mediated gene expression. In the ketamine experiment, cortical Homer1a expression was significantly reduced by haloperidol+minocycline in the medial agranular cortex and in the motor cortex compared with vehicle. In striatum, haloperidol significantly induced Homer1a expression in the ventrolateral caudate-putamen only. Minocycline limitedly reduced haloperidol-mediated Homer1a expression. No significant differences in baseline Arc expression were observed (i.e. VEH+VEH-mediated expression vs. KET+VEH). In the vehicle experiment, cortical Arc expression was reduced by haloperidol+minocycline combination compared with vehicle. Arc expression was significantly higher by haloperidol or minocycline alone compared with their combination. On the contrary, in striatum, both haloperidol and haloperidol+minocycline significantly induced Arc expression compared with vehicle, while minocycline alone significantly reduced it. The profile of expression observed in the vehicle experiment was confirmed also in the ketamine step.

Discussion: Minocycline reduced Arc expression (mostly in striatum), while poorly affected Homer1a expression. In combination with haloperidol, it blunted haloperidol-mediated cortical Arc expression and cortical/striatal Homer1a expression in both vehicle and ketamine-treated rats. Notably, both Homer1a and Arc genes are induced by activation of dopaminergic and glutamatergic transmission. Minocycline has been described to affect distinct signaling pathways operated by the NMDA receptor and to attenuate the increase in dopamine levels after NMDA receptor blockade. Therefore, minocycline may attenuate haloperidol's acute effect on dopaminergic and glutamatergic signaling, which may be relevant for therapeutic efficacy and side effects.

Poster #T101**POSTNATAL DEVELOPMENT OF THE ISLANDS OF CALLEJA: ACHILLES' HEEL IN THE ONSET OF PSYCHOSIS?**

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Background: Numerous susceptibility genes for schizophrenia, such as neuregulin-1, regulate not only embryonic neurogenesis, but also postnatal and adult neurogenesis. On the other hand, schizophrenia shows a "late", juvenile onset of symptoms. Therefore, pathologic changes during postnatal/juvenile development may be critical in triggering the delayed manifestation of schizophrenia. It is unclear if and how disturbed neurogenesis at juvenile stages could induce neurotransmitter (e.g. dopamine) dysregulation associated with schizophrenia.

Methods: Fate-mapping studies, time-lapse imaging and BrdU birthdating in wildtype and transgenic mice that allow the *in vivo* labelling of newborn neurons migrating from the subventricular zone (SVZ)

Results: Numerous neuroblasts were identified migrating from the early postnatal SVZ into subcortical areas, nucleus accumbens and ventral striatum, forming the ventral migratory mass (VMM). Some SVZ-derived neuroblasts appear to reorganize and aggregate into spheroidal and ellipsoidal structures of GABAergic granule cells, the Islands of Calleja (ICj). The ICj receive dense dopaminergic projections from the ventral tegmental area and substantia nigra, expressing high levels of dopamine D3 receptors. Moreover, they are activated by antipsychotic treatment with clozapine.

Discussion: We present here data and our hypothesis (Inta et al., Schizophr Bull, 2010) according to that, "late", postnatal impairment of the ICj could represent the point of convergence for genetic and environmental influences leading to dopamine dysfunction in the ventral striatum and the onset of psychosis.

Poster #T102**IDENTIFICATION OF A SUSCEPTIBILITY LOCUS IN A CONSANGUINEOUS FAMILY WITH MULTIPLE SCHIZOPHRENIA-AFFECTED MEMBERS**

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Background: Schizophrenia is a complex disorder with multiple genetic and environmental factors interacting in its aetio-pathogenesis. Genome-Wide Association Studies (GWAS) have unveiled some common risk polymorphisms but a large portion of the heritability remains unknown. One possibility would be the existence of recessively-inherited mendelian alleles in discrete families and isolated population groups. To test this hypothesis we used homozygosity mapping coupled to exome-sequencing strategy in order to identify such risk alleles in a large endogamic and consanguineous family with multiple schizophrenia affected.

Methods: DNA and RNA samples from peripheral blood were taken from a family composed of 4 first-cousin marriages and 6 schizophrenia patients between their offspring. The family is from south-asian ethnicity and all the cases met the DSM-IV criteria. Genome-wide SNP genotyping on the Affymetrix 6.0 SNP chip and autozygosity mapping were performed to find shared homozygous regions in 4 of the affected members. Common homozygous regions were checked using microsatellites genotyping in the rest of the family. Whole-exome sequencing using an Illumina HiSeq2500 platform was performed in one patient in order to find possible mutations in the homozygous regions. Real-Time and RT-PCRs were also performed in the genes located in the homozygous regions to see differences in the expression and processing between patients and controls.

Results: A common 5Mb homozygous region was found in 13q31-32 in all the patients. This region contains 13 coding genes and 2 miRNAs. The whole-exome sequencing, after filtering out the synonymous changes and

common SNPs, showed only a 5'-prime UTR polymorphism in CLN5 gene. RT-PCR and qPCR showed no differences in the processing or mRNA levels of this gene between controls and patients. However, when the experiment was expanded to the 13 genes, a significant downregulation in the homozygous patients was found in comparison to heterozygous unaffected in SPRY2. This gene is involved in signal transduction and it has been shown to have a role in multiple processes, including axon growth and brain development.

Discussion: Alternative approaches to GWAS are needed to unravel some of the missing heritability in schizophrenia. Homozygosity mapping has been a powerful strategy to identify the genes responsible for many Mendelian diseases but our results suggest it may also be useful in complex diseases like schizophrenia when coupled to next-generation sequencing. A decreased expression of SPRY2 in schizophrenia post-mortem brains has already been described (Pillai, 2008) and our results confirm it. Nevertheless, further research is necessary to clarify whether the differential expression in SPRY2 is a byproduct of antipsychotic drugs or a genuine cause of pathogenic disease.

Poster #T103

STRESS-REACTIVITY AS POSSIBLE PREDICTOR FOR SOCIAL FUNCTIONING IN A SAMPLE OF PSYCHOTIC PATIENTS, UNAFFECTED SIBLINGS AND HEALTHY CONTROLS

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Background: Higher levels of stress-reactivity have consistently been associated with symptomatic outcome, both in the onset as well as the course of psychotic symptoms. The effect of stress-reactivity on functional outcome however is less clear. The present study therefore set out to determine the longitudinal association between stress-reactivity at baseline and social functioning at three-year follow-up in a sample of 45 patients with psychotic disorder, 44 siblings of patients with psychotic disorder and 62 healthy controls.

Methods: Individual values (beta's) of stress-reactivity were calculated by regressing negative affect on the subjective appraisal of activity and event related stress, measured with the experience sampling method (ESM). In order to assess whether stress-reactivity at baseline predicts social functioning at follow-up, multilevel random regression models were estimated with individual level stress-reactivity as dependent variable and social functioning (measured with the Social Functioning Scale) as independent variable. To assess whether the association differs between controls, siblings and patients, the interaction with group was tested.

Results: No association was found between stress-reactivity at baseline and social function at follow up. When assessing the subgroup that participated in experience sampling at follow-up however (N=84), significant associations were present between both activity-related stress-reactivity at baseline and social functioning at follow-up ($B=-12.87$, $P=0.023$, 95% CI = -23.94 ; -1.80) and between event-related stress-reactivity at baseline and social functioning at follow-up ($B=-6.67$, $P=0.043$, 95% CI = -13.14 ; -0.20). No significant interaction with group was present.

Discussion: Findings on the association between stress-reactivity and social functioning are inconclusive. A significant association was present but only in a subsample consisting of subjects who participated in the ESM study at both time points. In the group of subjects who participated in the ESM study at baseline but not at follow-up, this association was not present. Post hoc analyses aimed at elucidating the difference between these groups (e.g. age, sex, iq, symptom level) were not successful in finding distinctive factors at baseline. Nonetheless, a causal role of stress-reactivity in functional outcome is found in this subsample, and future research in larger samples should elucidate the role of stress-reactivity in social functioning and identify possible distinctive factors in this association.

Poster #T104

BRAIN IMAGING IN PATIENTS WITH SCHIZOPHRENIC SPECTRUM DISORDER

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Background: Background: Although schizophrenic patients are only marginally more violent than the healthy population, violence represents a main cause of hospitalization of schizophrenic patients in forensic, security wards. The dominant factors associated with violence are major mental illness, substance abuse, and psychopathy. It remains to define the contribution of each of these factors to the symptomatology. We examined in retrospect the results of imaging studies in a selected population. Imaging has shown that 60% of schizophrenic have definite cerebral atrophy most often as ventricular enlargement. Furthermore, temporal volume reduction appears to be common both in schizotypal personality disorder and chronic schizophrenia. The aim of the study was to compare SPECT, MR and CT findings in schizophrenic patients with and without violence.

Methods: Methods: A total of 34 inpatients fulfilled the DSM-IV criteria for schizophrenic spectrum disorder and had been examined with SPECT. Average age was 31.7 years, range 20-65 years. 21 patients were in a forensic unit, 13 patients without any violent history was in an open ward. The length of the stay differed from one to twelve years. Any history of substance abuse was taken from the records. Patients with known violence were additionally examined with HCR-20 risk assessment scheme. For brain scintigraphy we used 99mTc-HMPAO single photon emission computed tomography (SPECT) in the study.

Results: Results Neither CT nor MRI revealed pathological findings. SPECT defined areas of changed perfusion in 25 of 34 patients. Among the patients with violence (n=21) SPECT was positive in 18 patients (86%). In the non-violent group (n=13), SPECT var positive in 7 patients (54%). There was significant difference ($p=0.040$) between the groups. Hypoperfusion was mainly seen in the temporal lobe and in the amygdale area, but also in the parietal and occipital lobes. Chronic substance abuse was documented in 20 patients (59%). In the violence group 15/21 (71%), and 5/13 (38%) in the non-violent group (n.s.). In the violence group 18 of 20 patients scored higher than 20 on HCR-20

Discussion: Discussion SPECT describes perfusion in different mental illnesses and has the ability to detect changes early on in the course of disease, before structural changes are noted in anatomical imaging modalities as MRI. The negative MR/CT in our study may be explained by the protocol, which primarily focused on tumour detection. The reason for the hypoperfusion among our patients is uncertain and further, prospective studies are needed to differentiate the process behind the mental disorder from the toxic influence of abused substances.

Poster #T105

PREVALENCE AND PROFILE OF COGNITIVE DEFICITS IN A COHORT OF FIRST-EPIISODE ANTIPSYCHOTIC-NAÏVE SCHIZOPHRENIA PATIENTS

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Background: Cognitive deficits are considered a core feature of schizophrenia with prevalence estimates ranging from ca. 75-85%. These deficits are present in the early phase of the illness; however in most first-episode schizophrenia studies the patients are receiving antipsychotic medication, which can affect the results on specific domains such as processing speed. As part of the PECANS project (Pan European Collaboration on Antipsychotic Naïve Schizophrenia) the aim of the present study is to establish the prevalence and profile of cognitive deficits in a cohort of first-episode antipsychotic-naïve schizophrenia patients, without the potential confounding effects associated with medication and chronicity.

Methods: The overall design of the PECANS project is a 2-year longitudinal case-control study with assessment at baseline and follow-ups after 6 weeks, 6 months, 1 and 2 years. Sixty first-episode antipsychotic-naïve

schizophrenia patients and 60 matched healthy controls have been examined at baseline. The study uses several instruments, including BACS (Brief Assessment of Cognition in Schizophrenia) and CANTAB (Cambridge Neuropsychological Test Automated Battery). Premorbid intelligence is estimated using DART (Danish Adult Reading Test) and current intelligence is estimated from 4 subtests from WAIS-III (Wechsler's Adult Intelligence Scale, 3rd ed.). Psychopathology ratings are obtained using PANSS (Positive and Negative Symptom Scale).

Results: Preliminary analyses show significant deficits in almost all cognitive domains assessed with effect sizes ranging between 0.5 to 1.2 standard deviations below the average of the healthy controls. The prevalence and profile of these deficits and their relation to psychopathology will be presented in further detail.

Discussion: Comprehensive cognitive deficits across several cognitive domains are prevalent in schizophrenia patients from the time of their first episode, before initiation of antipsychotic medication.

Poster #T106

PSYCHOPATHOLOGY, LEVEL OF FUNCTIONING AND SOCIOECONOMIC STATUS: A DESCRIPTIVE STUDY OF 42 SUBJECTS FROM AN ULTRA HIGH-RISK COHORT

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Background: Most of the ultra high-risk subjects do not have transition to psychosis. Only a few studies present results on pathology and demographics of the non-transitional group. From various studies, it is clear that these patients have low level of functioning, meet the criteria of non-psychotic illness and present with a variety of symptoms. Still we do not know which treatment they benefit from. The first step towards proper treatment is to make a thorough characterization of the psychopathology and demographics of a cohort, which is what this study aims to do.

Methods: We included 42 ultra high-risk (UHR) patients assessed with CAARMS (the Comprehensive Assessment of At-Risk Mental States); among the inclusion criteria were also age between 18-40 and a chronically low level of functioning or a recent deterioration in functioning measured by SOFAS. The UHR subjects went through elaborate interviews assessing their co-morbidity, psychopathology, family history of psychiatric disease or substance abuse, own substance abuse and socio-economic status by means of several different interview instruments and scales.

Results: The UHR subjects met criteria of averagely four diagnoses each, for the major part within anxiety, depression, substance abuse and eating disorders. Also 48% was diagnosed with schizotypal personality disorder and 19% with borderline personality disorder. Men generally had lower level of functioning and more accentuated negative symptoms compared to women, reflected in a significantly lower score on the Cornblatt social functioning scale (males: 5,3 ($\pm 1,3$); females: 6,1 ($\pm 1,0$); p=0,045) and total SANS (males: 9,6 ($\pm 3,1$); females: 7,4 ($\pm 3,0$); p=0,025); on the other items there were no significant differences. As expected level of function was low, which is reflected in a SOFAS score of 43 and Cornblatt's social and role functioning scale scores of respectively 5,8 and 4,6. For 36% highest level of education corresponded to elementary school; in addition 47% were unemployed and 29% on sick leave. 55% relied financially on public support, and an additional 26% received State Educational Grant.

Discussion: This study shows that the ultra high-risk group had low function on many different levels. Both socially and educationally plus they met several diagnoses including a high level of previous substance abuse. This suggests that the UHR group requires pharmacological and non-pharmacological psychiatric treatment regarding particularly depression and anxiety related disorders, and furthermore requires vocational guidance and support.

Poster #T107

CIGARETTE SMOKING IS ASSOCIATED WITH REDUCED CINGULATE AND INSULAR THICKNESS AMONG PATIENTS WITH PSYCHOSIS AND BIPOLAR SPECTRUM DISORDERS

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Background: Magnetic resonance imaging (MRI) studies show reduced cortical thickness among patients with schizophrenia and bipolar disorder. These subtle brain abnormalities may provide insights into illness mechanisms. However, environmental and lifestyle-related factors such as cigarette smoking may also affect brain structure. Cigarette smoking is highly prevalent in this patient group. In non-psychiatric samples, studies suggest smoking may be associated with reduced thickness in anterior and posterior cingulate cortex (ACC, PCC), insular cortex (Ins) and orbitofrontal cortex (OFC). This study compares cortical thickness in these regions between smokers and non-smokers among patients with psychotic and bipolar disorders and healthy controls.

Methods: Patients with schizophrenia, other psychotic disorders or bipolar disorders (n=506; 49% smokers) and healthy controls (n=237; 20% smokers) participating in the Thematically Organized Psychosis (TOP) study, Oslo, Norway, were included. MRI scans obtained on a 1.5T Siemens scanner were processed in FreeSurfer version 5.3.0. Main effects of smoking status were tested using ANCOVA models with age, sex, and diagnosis as covariates. Age X smoking interaction terms were added to examine if age-slopes of regional thickness differed between groups. Whole-brain analyses of cortical thickness were performed using the general linear model function in FreeSurfer.

Results: As significant group X smoking status interactions were found in left rostral ACC and left Ins, patients and controls were analyzed separately. Smokers showed reduced cortical thickness in rostral ACC and PCC bilaterally and left Ins among patients. A reduction was found in left lateral OFC. After adjusting for potential confounders, which included substance use, only findings in left rostral ACC, left PCC and left Ins remained significant. No differences were found between light, moderate, and heavy smokers. No main effect of smoking status was found among controls. Significant age X smoking interactions indicated patients who smoked had thinner cortices with higher age compared to non-smoking patients in caudal ACC bilaterally, left PCC and Ins, and right lateral and medial OFC. In the control group, interaction models indicated reduced cortical thickness in right rostral ACC and medial OFC bilaterally among younger smokers compared to non-smokers, but not among older smokers. Whole-brain cortical analyses revealed limited effects of smoking outside of the regions described above. After FDR-correction, only reduced thickness in left Ins, and in addition an age X smoke interaction effect indicating thinner cortex with higher age in the occipital lobe among controls, remained significant.

Discussion: The main finding was reduced cortical thickness in regions in the cingulate and insular cortex among smoking patients. These brain areas have been shown to contain high densities of nicotine receptors, and been implicated in smoking addiction in functional studies. However, the mechanism behind the reductions remains unclear. Among controls, no main effect of smoking was observed. Several explanations are possible: We lacked data for smoking intensity among controls and they likely smoked less. The control sample was smaller and with fewer smokers. However, it cannot be ruled out that the differences between patients and healthy controls are related to an illness-specific vulnerability. Our findings suggest cigarette smoking may affect the age-related trajectory of cortical thickness in specific regions, but this needs further longitudinal study.

Poster #T108**THE RELATIONSHIP BETWEEN LANGUAGE ABILITY AND COGNITIVE FUNCTION IN PEOPLE WITH SCHIZOPHRENIA**

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Background: It is well-known that cognitive dysfunction in people with schizophrenia is common. The cognitive deficits has generally been started in the early stages of illness and prolonged across many decades. The severity of cognitive deficits of patients with schizophrenia is related to age of onset. Several studies show patients with schizophrenia have difficulties with interpretations of figurative language and reduced comprehension accuracy for information in sentences. And they perform particularly poorly on tasks using verbal materials. This study was performed to assess the use and comprehension ability of the Korean language and to find the correlation between language ability and cognitive function in the Korean patients with schizophrenia.

Methods: Eighty six patients with schizophrenia, who are clinically stable, and twenty nine healthy individuals in a control group were recruited. We assessed the clinical symptoms and cognitive functions including Korean language ability. For the clinical symptoms, the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression – Schizophrenia scale (CGI-SCH), the Social and Occupational Functioning Assessment Scale (SO-FAS) were performed. For the Korean language ability assessment, a portion of the Korean Broadcasting System (KBS) Korean language test was used. For other cognitive functions, the Short-form of Korean-Wechsler Adult Intelligence Scale (K-WAIS), the Korean version of the UCSD Performance-based Skills Assessment (K-UPSA) and the Wisconsin Card Sorting Test (WCST) were performed. Chi-square test, t-test and Wilcoxon rank sum test were used to data analysis.

Results: No significant differences between groups were found in age and years of education. On the KBS Korean language test and K-UPSA, schizophrenic patients received a significant lower score than the control group in the total and subscale score ($p<0.001$). The PANSS scores have a negative correlation with the reading domain of the KBS Korean language test, and the CGI-SCH was correlated with the total score and reading domain of the KBS Korean language test. The SOFAS showed a positive correlation with the reading domain of the KBS Korean language test. The WCST showed a positive correlation with the listening domain, creative domain and the total score of the KBS Korean language test. A part of the K-UPSA also has a significant correlation with the KBS Korean language test.

Discussion: In this study, significant difference was found on the Korean language ability between the patients with schizophrenia and the healthy control group. This study revealed the correlation between Korean language ability and several clinical symptoms and cognitive functions in Korean patients with schizophrenia. Additionally among cognitive function tests, WCST and K-UPSA revealed to have a correlation with Korean language ability.

Poster #T109**ASSOCIATION OF FAMILY HISTORY OF PSYCHOSIS TO SOCIAL, OCCUPATIONAL AND GLOBAL OUTCOME IN SCHIZOPHRENIA: SYSTEMATIC REVIEW AND META-ANALYSIS**

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Background: We aimed to investigate associations between family history of psychosis and long-term occupational, social and global (i.e. combined occupational, social and clinical) outcome in schizophrenia.

Methods: A systematic search to identify potentially relevant studies was conducted using seven electronic databases and by manual literature search. Only observational studies with a follow-up period of at least two years were included.

Results: The search identified 3,860 unique potentially relevant articles of which 14 studies met our inclusion criteria. The presence of family history of psychosis associated statistically significantly to poor occupational ($n=3$; $r=0.17$, 95% confidence interval, CI 0.05–0.29; $p=0.008$), and global

(combined occupational, social and clinical) outcome ($n=11$; $r=0.13$, 95% CI 0.05–0.21; $p=0.002$).

Discussion: This was the first systematic review on effects of family history of psychosis on occupational and social aspects of outcome in schizophrenia. Based on the review the presence of family history of psychosis has a relatively small but statistically significant association on the long-term occupational and global outcome.

Poster #T110**CLASSIFYING SCHIZOPHRENIA USING JOINT MULTIVARIATE PATTERN RECOGNITION ANALYSIS OF BRAIN FUNCTION AND STRUCTURE**

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Background: Previous studies have shown that structural brain changes are among the best-studied candidate markers for schizophrenia along with global functional connectivity alterations of resting-state networks. So far, only few studies tried to combine these data domains to outperform unimodal pattern classification approaches. Therefore, this study aimed at distinguishing patients with schizophrenia from healthy controls at the single-subject level by applying multivariate pattern recognition analysis to both gray matter volume and functional connectivity measures. Our method may potentially inform the generation of robust diagnostic classifiers allowing for a more objective identification of patients with schizophrenia in future biomarker-based diagnostic workflows.

Methods: The resting-state functional and structural MRI data from 74 healthy controls (HC, 35.8 (11.5) age; 31% female) and 71 patients with schizophrenia (SZ, 38.1 (13.9) age; 19.7% female) were obtained from the publicly available COBRE database (1000 Functional Connectomes). 160 seed-regions with a 4 mm³ radius were defined based on a recent study using machine learning classifiers on adolescent brains (Dosenbach et al., 2010) to identify neural hotspots on which discrimination could be performed. Time-series for every voxel within the seed-region were averaged and mutual information matrices (MIM) were created for each subject corresponding to each individual's resting-state scan. Following machine learning pipeline wrapped into repeated nested cross-validation was used to train a multi-modal diagnostic system and evaluate its generalization capacity in new subjects. First, dimensionality reduction and feature selection was performed by applying principal component analysis (PCA) to the structural imaging data (normalized GM volume maps) and F-score-based feature selection to the MIM. Further, the obtained uni-modal feature sets were used to train separate L2-regularized logistic regression models. Ultimately, the predictions of the uni-modal classification systems were combined into multi-modal classifier ensembles, which provided a final group membership prediction through majority voting.

Results: Both functional and structural classifiers were able to distinguish between HC and SZ patients with similar accuracies. The resting state classifier was showing a slightly higher accuracy (75%) comparing to GM volume classifier (74.4%). Ensemble-based data fusion outperformed pattern classification based on single MRI modalities by reaching 76.6% accuracy, as determined by cross-validation. Further analysis showed that resting-state classification was less sensitive to age-related effects across the life span than gray matter volume, indicating that functional connectivity-based biomarkers derived from resting-state fMRI may provide more stable classification results across adult life.

Discussion: Our findings suggest that age plays an important role in discriminating SZ patients from HC, but that resting-state is more robust towards age-differences compared to GM volume. Single neuroimaging modalities provide useful insight into brain function or structure, while multimodal fusion emphasizes the strength of each (compensating for lower accuracy of single modality) and provides higher accuracy in discriminating SZ patients from HC. Future work may further enhance the complementarity of information extracted from different imaging data in order to further increase diagnostic performance.

Poster #T111**ASSOCIATION STUDY BETWEEN ANTIPSYCHOTICS-INDUCED RESTLESS LEGS SYNDROME AND POLYMORPHISMS OF MEIS1 GENES IN SCHIZOPHRENIA**

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Background: The pathophysiology of restless legs syndrome (RLS) has not been fully elucidated, but many promising theories involve genetic causes. The recent genome-wide association studies of RLS identified variants within intronic or intergenic regions of MEIS1, BTBD9, and MAP2K5/LBOXCOR1. This study aimed to investigate whether the MEIS1 genes are associated with antipsychotic-induced RLS in schizophrenia.

Methods: All of the subjects were diagnosed with schizophrenia by board-certified psychiatrists using the Korean version of the Structured Clinical Interview for DSM-IV. We assessed antipsychotic-induced RLS symptoms in 190 Korean schizophrenic patients using the diagnostic criteria of the International Restless Legs Syndrome Study Group. Genotyping was performed for the rs2300478 and rs6710341 polymorphisms of the MEIS1 gene.

Results: We divided the subjects into two groups: those with RLS symptoms ($n=96$) and those without RLS symptoms ($n=94$). The genotype frequencies did not deviate from Hardy-Weinberg equilibrium (rs2300478 $\chi^2=2.17$, $p=0.141$; rs6710341 $\chi^2=1.85$, $p=0.174$). There was no significant difference in the genotype (rs2300478 $\chi^2=1.38$, $p=0.503$; rs6710341 $\chi^2=1.04$, $p=0.596$) and allele frequencies (rs2300478 $\chi^2=0.48$, $p=0.489$; rs6710341 $\chi^2=0.34$, $p=0.561$) of two polymorphisms investigated between these two groups.

Discussion: These data do not suggest that rs2300478 and rs6710341 polymorphisms of the MEIS1 gene are associated with antipsychotic-induced RLS symptoms in schizophrenia. There is possibility of different genetic mechanism between the antipsychotic-induced RLS and primary RLS. A larger-scale association study is needed in the future in order to confirm these results.

Poster #T112**IDENTICAL PATTERN OF HEDONIC AND AFFECTIVE REACTIVITY TO DAILY-LIFE SOCIAL STRESS AMONG PATIENTS WITH PSYCHOTIC DISORDER AND HEALTHY INDIVIDUALS**

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Background: Altered sensitivity to stress confers risk for the development of the positive symptoms of psychosis. Recent reports of reward-related effects of social stress, however, suggest a putative role for stress in precipitation and maintenance of the negative symptoms as well. In order to explore this premise, we investigated the pattern of fluctuation in hedonic and affective experience as a function of various forms of daily stress in individuals with psychotic disorder and healthy controls.

Methods: Using the experience sampling method (ESM), 6 days of subjective ratings of momentary affect and context as well as the appraisals of recent events were collected from 118 patients with psychotic disorder and 139 healthy controls. At each time point, the change in intensity of positive affect (PA), negative affect (NA) and pleasantness of an event (PE) were computed in two time-lagged directions: i) backwards, as the difference between the current (t0) and most recent (t-1) appraisals and ii) forward, as the difference between the current (t0) and subsequent (t+1) appraisals. Lagged PA, NA and PE were entered as independent variables into separate multilevel analyses, with ratings of social stress (SS) as a predictor.

Results: In patients and controls alike, the backward-looking analyses revealed that increase in social stress at t0 was associated with significant decrease in PA (patients: $B=-0.19$, $p<0.001$; controls: $B=-0.18$, $p<0.001$) and PE (patients: $B=-0.16$, $p<0.001$; controls: $B=-0.14$, $p<0.001$) and increase in NA (patients: $B=-0.19$, $p<0.001$; controls: $B=0.07$, $p=0.001$) at

t0 compared to t-1. The forward-looking analyses showed that in both groups, the higher the stress at t0, the greater the increase in PA (patients: $B=0.14$, $p<0.001$; controls: $B=0.19$, $p<0.001$) and PE (patients: $B=0.12$, $p=0.001$; controls: $B=0.21$, $p<0.0001$) and decrease in NA (patients: $B=-0.14$, $p<0.001$; controls: $B=-0.09$, $p<0.001$) at t+1 relative to t0.

Discussion: These findings indicate identical patterns of stress-related attenuation in hedonic experience and positive affect and potentiation of negative affect among patients and controls. Critically, patients matched controls in the extent of improvement of hedonic and affective experience post-stress, demonstrating intact restoration of affective state. These findings provide initial evidence for a lack of a direct role of stress in the etiopathogenesis of hedonic deficits in psychosis.

Poster #T113**SALIENCE ATTRIBUTION IN SCHIZOPHRENIA PATIENTS AND DELUSION-PRONE SUBJECTS**

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Background: Schizophrenia patients have been hypothesized to attribute aberrant salience to irrelevant events which might contribute to the formation of hallucinations and delusions (Heinz, 2002; Kapur, 2003). Following the continuum hypothesis, subclinical psychotic experiences also appear in the general population (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009) and those delusion-prone subjects might have an intermediate position with regard to aberrant salience between controls and schizophrenia patients. The Salience Attribution Test (SAT), recently developed by Roiser and colleagues (Roiser et al., 2009), allows to assess both adaptive and aberrant salience on an explicit and implicit dimension. Here, we tested if schizophrenia patients and delusion-prone individuals displayed higher aberrant salience compared to controls

Methods: 28 schizophrenia patients, 24 healthy delusion-prone participants and 51 healthy controls completed the SAT (Roiser et al., 2009). Subjects were instructed to increase their wins by rapid responses to a cue that was preceded by conditioned stimuli. The latter varied on two dimensions: a relevant dimension with one reinforced and one non-reinforced manifestation and an irrelevant dimension with two equally reinforced manifestations. During the experiment, subjects were asked to estimate the likelihood of reinforcement for each conditioned stimulus type. Salience attribution was measured implicitly via reaction time differences and explicitly by the estimations on a visual analogue scale. Whereas aberrant salience was calculated using the absolute differences between equally reinforced conditioned stimuli, adaptive salience was calculated for reinforced compared to non-reinforced conditioned stimuli. Analyses of variance were performed for these four measures of salience attribution including age as covariate.

Results: Implicit aberrant salience showed significant group differences ($F=3.379$, $p=0.038$) due to higher values in schizophrenia patients compared to healthy controls ($p=0.011$) while delusion prone participants displayed an intermediate value. The three groups did not differ regarding the explicit measure of aberrant salience ($F=0.886$, $p=0.416$). Concerning adaptive salience, for the implicit measure both delusion-prone subjects and schizophrenia patients displayed reduced values ($F=5.089$, $p=0.008$), while for the explicit measure of adaptive salience only schizophrenia patients revealed reduced values ($F=13.067$, $p<0.001$). The group effects for implicit aberrant salience remained when including implicit adaptive salience as an additional covariate ($F=5.383$, $p=0.006$).

Discussion: In line with the aberrant salience hypothesis, we found that schizophrenia patients showed higher implicit measures of aberrant salience in the SAT. Aberrant salience attribution was less marked in the delusion-prone group than in schizophrenia patients compatible with a dimensional approach. Measures of adaptive salience, which is relevant for dissociating reinforced from non-reinforced conditioned stimuli, were reduced in both schizophrenia patients and delusion-prone individuals similar to previously described reinforcement learning deficits in psychotic patients (Murray et al. 2008; Schlagenhau² et al. accepted). While previous studies (Roiser et al., 2009, 2012) found higher measures of explicit aberrant salience attribution in schizophrenia patients and ultra-high risk

subjects our results may indicate that implicit measures are more sensitive to measure group differences potentially due to lower explicit cognitive demands and strategies. Our results demonstrate that the SAT is able to detect group differences in implicit salience attribution between controls and subjects with psychotic experiences.

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Poster #T114

EARLY DETECTION AND INTERVENTION PROJECT FOR YOUNG PEOPLE AT RISK FOR DEVELOPING PSYCHOSIS IN UCHINADA

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Background: Whilst interventional services are currently being established internationally, services working at the pre-psychosis "at-risk" stage are in their infancy. Recent evidences have suggested that indicated prevention of "at risk mental state (ARMS)" is most promising approach to identify people at risk of developing psychosis. The Outpatient clinic for Assessment, Support and Intervention Services in Uchinada (OASIS-Uchinada) for ARMS is a newly-established specialized clinical setting to study and treat young people (aged 15-30 years) at risk for developing psychosis. The OASIS service was launched in October 2012 by the Kanazawa Medical University Hospital in cooperation with the Ishikawa Prefectural Mental Health Centre. **Methods:** The consultation service is offered free of charge at the Mental Health Centre by psychiatrists or psychologists to people referred as being suspected to be at risk for psychosis. It accepts self-referrals, as well as referrals made by surrounding people. An initial non-psychiatric setting for consultation is intended to promote access. Individuals considered fulfilling the criteria for ARMS are then referred to the monitoring and support service at the University Hospital for further evaluation. The specialized clinic in the University Hospital provides detailed assessment of clinical symptoms by means of the Comprehensive Assessment of At-Risk Mental States (CAARMS) and other instruments, supplying information about the risk of psychosis, clinical case management, and treatment by cognitive behavior therapy and/or need-based low dose medication regimens. Individuals who give informed consent at intake undergo evaluations by neuropsychological tests, magnetic resonance imaging, electroencephalography, etc.

Results: So far we have interviewed 5 clients: Of the 5 subjects, 1 met a criteria for the first episode of schizophrenia and 1 met criteria for ARMS. One first episode patients has never received antipsychotic medication and subsequently received antipsychotic medication and clinical follow-up. One client who met ARMS criteria had temporary received antipsychotic medication and returned to his job after one year of rehabilitation period. Remaining 3 clients, 1 clients are receiving clinical follow-up and cognitive psychotherapy. Other 2 clients have been receiving only psychological intervention.

Discussion: A pragmatic approach in which symptom-based indicators, alongside family history, are evaluated is rational to provide a clinical

service for people with prodromal symptoms. It is important to encourage referrals from a wide range of sources, in order to allow for a diversity in case presentation. It is convincing that most of the clients, even who had already been psychotic, may have not visited psychiatric hospitals directly at the time point they consulted our service. Therefore it is suggested that the specialized service for help-seeking individuals at risk for developing psychosis can promote early detection and intervention.

Poster #T115

KANIZSA SHAPE PERCEPTION AND CONTOUR INTEGRATION IN SCHIZOPHRENIA: WHAT IS THE ROLE OF SPATIAL FREQUENCY?

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Background: Patients with schizophrenia exhibit a reduced ability to distinguish Kanizsa shapes and integrate oriented elements (Gabors). Patients also poorly process low spatial frequencies (SFs), which may reflect dysfunction along the magnocellular pathway. Here, we ask: Will patients' perceptual organization deficits disappear when low SFs are removed from the stimuli?

Methods: To address the foregoing question, we tested chronic patients and healthy controls on two classic paradigms. In the contour integration task, subjects identified the screen quadrant in which a closed chain of co-circular Gabors appeared among randomly oriented noise Gabors. The stimulus was scaled to produce two SF conditions (4 and 12 cycles/deg) and an adaptive staircase determined the number noise Gabors needed to yield threshold accuracy (75%). In the discrimination task, subjects determined on each trial whether four pac-men formed a fat or thin Kanizsa shape (illusory condition) or whether four downward-pointing pac-men were rotated left or right (fragmented condition). The pac-men were presented with all SFs (broadband) or with low SFs reduced. In all cases, task difficulty depended on the amount by which the pac-men were individually rotated, with more rotation making for an easier discrimination. An adaptive staircase estimated the rotational magnitude needed to produce threshold accuracy (79.7%). Illusory shape perception was measured as the difference between the thresholds in the illusory and fragmented conditions.

Results: Patients were worse at both illusory shape perception and contour integration, and this impairment was not ameliorated with higher spatial frequency stimuli. Moreover, the worse that patients were at discriminating illusory shapes relative to fragmented shapes, the worse that they were at contour integration, suggesting a common underlying mechanism.

Discussion: The ability to perceive Kanizsa shapes and detect gabor chains is reduced in schizophrenia, perhaps as a result of a disturbance to a common underlying mechanism. Crucially, illusory shape discrimination and contour integration deficits in SZ cannot be explained in terms of poor low SF processing, and therefore probably cannot be explained in terms of magnocellular dysfunction.

Poster #T116

INTERACTION BETWEEN PARENTAL PSYCHOSIS AND DELAYS ON EARLY MOTOR DEVELOPMENTAL MILESTONES IN SCHIZOPHRENIA - THE NORTHERN FINLAND 1966 BIRTH COHORT STUDY

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Background: Our aim was to investigate how age of achieving early motor developmental milestones differ among subjects with and without a history of parental psychosis and whether parental psychosis may alter the effects of the age of achievement on the risk of schizophrenia.

Methods: The study sample comprised 10,307 individuals from the prospective Northern Finland 1966 Birth Cohort. A total of 139 (1.3%) cohort members suffered from schizophrenia by the age of 44 years. Out of them 19 (13.7%) had a parent with a history of psychosis, while among the non-psychotic cohort members this figure was 524 (5.2%).

Results: Out of eight different motor milestones investigated, parental psychosis associated ($p < 0.05$) with later learning of holding head up, grabbing object, being capable to stand up (lift themselves up) and walking without support. In the parental psychosis group, significant risk factors for schizophrenia included later learning of holding head up and touch thumb with index finger. In the non-parental psychosis group risk estimates were lower and statistical significant milestones were different i.e. turning over, standing up, standing and walking without support. No statistically significant interaction was found between the early motor development and parental psychosis in respect to risk of schizophrenia.

Discussion: In our research we found that parental psychosis does not explain the interaction between late achievement of motor milestones in the first year of life and risk for schizophrenia later in adulthood. Although parental psychosis associated with delays in motor milestones, we found no interactions.

Poster #T117

CHILDHOOD NEURODEVELOPMENTAL DISORDERS, IQ AND SUBSEQUENT RISK OF PSYCHOTIC EXPERIENCES IN ADOLESCENCE: A POPULATION-BASED LONGITUDINAL STUDY

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Background: The neurodevelopmental hypothesis of schizophrenia posits abnormal brain development as a cause of this illness, which is supported by longitudinal studies showing an association between subtle alterations in motor, cognitive, language and social development in the early life and the risk of adult schizophrenia. It has been suggested that adult schizophrenia and neurodevelopmental disorders (ND) that commonly manifest in childhood may share overlapping pathogenic mechanisms under-laid by aberrant brain development. Yet longitudinal studies of psychotic outcomes among individuals with childhood ND are limited. An increased risk of psychotic outcomes in the future among individuals with childhood ND will be consistent with the neurodevelopmental view of schizophrenia. Childhood psychotic experiences (PE) may be important antecedents of adult psychotic illness. These are associated with the risk of psychosis in the adult life as well as a number of risk factors for schizophrenia. Cognitive deficit during premorbid period and after illness onset are important features of schizophrenia as well key determinants of functional outcome. Childhood PE is also associated with cognitive deficit previously in childhood. Therefore, longitudinal studies of the effect of cognitive function on the association between childhood ND and later psychotic outcome may help to elucidate developmental pathways to psychosis. Using data from the population-based Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, we report associations between six common childhood ND (dyslexia, dyspraxia, dysgraphia, dysorthographia, dyscalculia, and Autism Spectrum Disorder or ASD) up to age 9 years, neurocognitive performance assessed as IQ, short term memory, working memory between ages 9 and 11 years, and the risk of PE at age 13 years. We predicted that ND would increase the risk of PE, and intermediary neurocognitive deficits would explain this association.

Methods: Parent-completed questionnaire data was used to determine the presence of ND at age 9 years. IQ was measured by the Wechsler Intelligence Scale for Children (WISC III) at age 9 years. Digit span subtest of the WISC III was used as a measure of short-term memory. Working memory was measured by the computerized counting span task at age 11 years. The outcome of PE (any, i.e. suspected or definite, and definite only) were assessed by the semi-structured psychosis-like symptoms interview (PLIKSi) at age 13 years. Linear regression calculated mean difference in cognitive scores between those with and without ND. The association between ND and PE was expressed as odds ratio (OR); mediating effects of cognitive deficits (IQ and working memory, separately) were examined. Potential confounders included age, gender, social class, ethnicity, and maternal education.

Results: Out of the 8,220 children, 487 (5.9%) were reported to have a ND at age 9 years in ALSPAC. Dyslexia was the most common (4.4%). Children with ND, compared with those without, as a group performed worse on all cognitive measures; adjusted mean difference in total IQ 6.8 (95% CI 5.0–8.7). The association between total IQ and ND was consistent with the left-shift of entire distribution of IQ scores in ND ($p < 0.0001$). The risk of PE was higher in those with, compared with those without ND; adjusted OR for definite PE 1.76 (95% CI 1.11–2.79). IQ (but not working memory) deficit partly mediated this association, 17% (95% CI 10%–25%).

Discussion: Childhood PE have a neurodevelopmental facet to their origin. The emergence of these experiences, at least in some individuals may be related to IQ deficit.

Poster #T118

HISTOLOGICAL RESPONSE ON DIFFERENT MODEL OF SCHIZOPHRENIA

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Background: Schizophrenia is a complex disorder, characterized by both genetic and environmental factors and their interactions. It is a severe mental disorder with episodic positive symptoms such as delusions, hallucinations, paranoia. The pathophysiology of schizophrenia is poorly understood but researcher suggested neurotransmitter signaling role in several areas of the brain. NMDA receptor pathways indicated potential treatments for various main neurological disorders as Schizophrenia. Dysfunction of NMDA receptor is hypothesized to be adequate to generate various symptoms, which traditionally addressed as schizophrenia.

Methods: In the present study 21 Wistar juvenile rats (65–80 gr) were used. Animals were classified in three groups as MK-801 treated Social isolation, and Sham. Histological assessments were used to determine various model of Schizophrenia. Mean number of injured cell in hippocampus brain region between groups were compared.

Results: Histological studies indicated that neural cell death have significantly increased in both model of Schizophrenia in investigated area, however there was no significant changes in comparison of two group.

Discussion: This suggested that Schizophrenia could cause cell damage, however various model of disease have same neurological response in brain tissue.

Poster #T119

REWARD SYSTEM DYSFUNCTION AND NEGATIVE SYMPTOM DIMENSIONS IN SCHIZOPHRENIA

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Background: The negative symptoms of schizophrenia – such as apathy and diminished expression – strongly contribute to impairments in social and occupational functioning. In neuroimaging research, increasing evidence suggests that negative symptoms are associated with altered hemodynamic activation of subcortical regions in the mesolimbic reward system and cognitive control regions in the prefrontal cortex. This study examines the neural correlates of negative symptom total and factor scores during a reward processing task emphasizing task performance for obtaining rewards.

Methods: So far 20 patients with schizophrenia and 11 healthy controls were included in this ongoing study. At the conference data from the full sample including 30 participants in each group will be presented. Negative symptoms were assessed with the Brief Negative Symptom Scale (BNSS) and the Scale for the Assessment of Negative Symptoms (SANS). In addition, participants completed the Positive and Negative Symptom Scale (PANSS) and the Calgary Depression Scale (CDS) as well as a neuropsychological test battery. Both groups performed a modified version of the monetary incentive delay task emphasizing task performance for obtaining rewards.

Functional Imaging Data were acquired on a Philips Achieva 3.0T magnetic resonance (MR) scanner and analyzed using SPM8. Group analyses were performed according to the random effects procedure using individual participant contrast images as input. Within-group activation was compared using a one sample t-test and between-group activation using a two sample t-test. Correlation analyses were performed with respect to negative symptom ratings.

Results: In the preliminary analysis we focused on the contrast "anticipation of a high reward versus anticipation of no reward". Across groups we observed significant activation in the ventral striatum and substantia nigra/ventral tegmental area. There were no significant differences between groups during anticipation of a reward at the current sample size. Correlation analysis yielded a negative correlation between the BNSS total score and activation in the right dorsolateral prefrontal Cortex (dIPFC -BA 9/46-) during anticipation of reward. This negative correlation was more pronounced with respect to the BNSS motivation and pleasure factor (i.e. apathy). Hence, high negative symptom scores were associated with decreased right dIPFC (BA 9/46) activation.

Discussion: Our performance-emphasizing reward task robustly activated regions known to be involved in reward processing in both patients with schizophrenia and healthy controls. Preliminary data suggest a specific association between activation in the right dIPFC and negative symptoms, which is consistent with the classical concept of hypofrontality as a putative mechanism for negative symptoms. However, our findings were not obtained in a primarily cognitive task, but in a reward paradigm. Recently, it has been proposed that the dIPFC is a crucial point of entry in a neural network, through which reward information gains access to subcortical reward regions. Dysfunctions in this network possibly lead to reduced incentive salience attribution and the clinical expression of apathy in schizophrenia.

Poster #T120

DOES RTMS HELP TO IMPROVE NEGATIVE SYMPTOMS IN SCHIZOPHRENIA? RESULTS FROM A RANDOMIZED CONTROLLED TRIAL IN THE NETHERLANDS

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Background: Negative symptoms in schizophrenia are very invalidating and an important predictor of clinical outcome. To date, adequate pharmaceutical treatment options have been limited. Techniques such as repetitive Transcranial Magnetic Stimulation (rTMS) might be helpful in reducing negative symptoms. Previous studies have, however, reported inconsistent results on the efficacy of rTMS treatment for negative symptoms of schizophrenia. This study aimed to investigate whether 3 weeks of 10 Hz bilateral stimulation of the dorsolateral prefrontal cortex (DLPFC) enhances treatment effects.

Methods: In this multicenter trial, 32 schizophrenia patients with moderate to severe negative symptoms were randomized over either active (n=16) or sham (n=16) 10 Hz rTMS treatment. The bilateral dorsolateral prefrontal cortex (DLPFC) was stimulated for 3 weeks (week days only), twice daily for 20 minutes at 90% of the motor threshold. The primary outcome was total score of negative symptoms as measured with the Scale for the Assessment of Negative Symptoms (SANS) and the negative subscale of the Positive and Negative Syndrome Scale (PANSS). Secondary outcome measures included cognition, insight, quality of life and mood. Subjects were evaluated at baseline, end of treatment, at 4 weeks and at 3 months follow-up. For analysis of the primary outcome measure, a mixed effects linear model was used, with baseline scores and Montgomery Åsberg Depression Rating Scale (MADRS) scores as covariates.

Results: SANS scores significantly reduced in the active group compared to the sham group until 3 months after treatment (reduction=15%; p<0.05). Treatment effect on the PANSS negative subscale did not reach significance in the entire group. However, an exploratory analysis of the more severe patients (PANSS negative subscale ≥20; n=15) did reveal a significant treatment effect (reduction=13%; p<0.05). Of all the cognitive measures, patients in the active group only improved on the semantic Verbal Fluency Task (p<0.05). Another exploratory analysis on quality of life, excluding patients with very poor insight, found a significant improvement (n=28; p<0.05) on the self-reported overall perception of health in the active group as compared to the sham group.

Discussion: Bilateral high frequency rTMS significantly improved negative symptoms as measured with the SANS in the active group up to three months compared with sham treatment. This improvement is a proof-of-principle of rTMS treatment for negative symptoms. Future studies should focus on enhancing treatment effects by optimizing treatment parameters in larger patient samples, and combine rTMS treatment with psychosocial interventions.

Poster #T121

SOCIAL COGNITION DYSFUNCTION AND ABNORMALITY OF THE BRAIN STRUCTURE

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Background: Social cognition dysfunction is a hallmark characteristic of schizophrenia. There were many meaningful studies about the relationship between structural or functional abnormalities of brain and social cognition dysfunctions in patients with schizophrenia; however these findings might still have limitation that only specific domains of social cognition were examined. The purpose of this study is to determine which brain areas are involved in social cognition dysfunction in patients with schizophrenia. The secondary purpose is to reconfirm that the video based social cognition assessment can be a valid tool for evaluation of social cognition in schizophrenia research.

Methods: In this study, 23 schizophrenia patients, recent onset within 5 years and 13 healthy controls were recruited. Brain image data was measured by statistical parametric mapping 8 (SPM 8), Freesurfer. IQ and social cognition scores were measured by the short form of WAIS, the video based social cognition assessment and false belief task. Especially, the video based social cognition assessment was developed and revised in Asan Medical Center, consisting of 20 video clips portraying interactions which were socially unnatural and patients were asked to indicate which parts of social interaction were awkward. The reliability and validity of the assessment were proved (Goh, Hyun et al. 2008).

Results: Patients with schizophrenia showed lower IQ and also scored significantly lower in both 2 social cognition tasks compared with healthy controls. In addition, the scores of video based social cognition assessment were positively associated with those of well-validated false belief task. In the brain imaging analysis, the total score of social cognition measured by the video based social cognition assessment was positively correlated with the thickness of grey matter in left superior frontal, right supramarginal gyrus.

Discussion: We reconfirmed that the video based social cognition assessment could be useful instrument for evaluating social cognition in schizophrenia. Findings from this brain imaging study are also consistent with previous studies regarding "theory of mind" related brain regions. Although there are still limitations including small sample size and analyzing the thickness of grey matter alone, our results add to previous findings about brain correlates of social cognition.

Poster #T122**WHITE MATTER STRUCTURE IN SUBJECTS WITH FAMILIAL RISK FOR PSYCHOSIS – THE OULU BRAIN AND MIND STUDY**

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Background: According to the disconnectivity model, disruptions in neural connectivity play an essential role in the pathology of schizophrenia. There are few studies evaluating white matter structure in subjects with familial risk for psychosis, with somewhat conflicting results. In order to determine whether these abnormalities are present in young adults with familial risk for psychosis in the general population, we used diffusion tensor imaging (DTI) to study a population-based birth-cohort sample.

Methods: We used the Finnish Hospital Discharge Register to detect psychiatric inpatient treatments in parents of the members of the Northern Finland Birth Cohort 1986. We invited subjects with familial risk for psychosis and control subjects to a field study conducted between 2007–2010 when the subjects were aged 20–25 years. During the study DTI, cognitive test battery, and background questionnaires were completed. We used DTI and tract-based spatial statistics (TBSS) to compare fractional anisotropy (FA), mean diffusivity (MD), and axial and radial diffusion of 47 individuals (17 males) with familial risk for psychosis and 51 controls (17 males). We separately analysed subjects with familial risk for schizophrenia (N=13) and compared to 13 gender-matched controls.

Results: Groups were comparable regarding demographic variables such gender, age, handedness and educational level. We found no significant difference between groups in intelligence, Global Assessment of Functioning (GAF) or alcohol use. In the TBSS group comparison analyses we did not find any significant differences in FA, MD, axial or radial diffusion between subjects with familial risk for psychosis and controls. There was also no difference in FA in a subgroup of subjects with familial risk for schizophrenia.

Discussion: Contrary to our expectations we did not find differences in white matter structure between familial risk and control groups. This suggests that white matter abnormalities may not be a genetic feature for risk of psychosis and preceding onset of psychosis. Our findings do not support the theory of disconnectivity as a primary sign of psychosis in the brain in young adults.

Poster #T123**A TRANSGENIC RAT MODEL OF DISC1OPATHIES: BRAIN DISORDERS CHARACTERIZED BY DISC1 AGGREGATES AND ABERRANT DOPAMINE HOMEOSTASIS**

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Background: A neuropathology and molecular neurobiology of chronic mental illnesses (CMI) such as schizophrenia or the recurrent affective disorders has remained elusive. We reported the presence of biochemically defined insoluble aggregates of the Disrupted-in-schizophrenia 1 (DISC1) protein in a subset (ca. 15%) of cases with CMI (Leliveld et al., 2008, J Neurosci 28:3839) suggesting that this subset may represent a distinct, biologically defined mental illness category. Disrupted-in-schizophrenia 1 (DISC1) is a major gene of behavioral control that has been genetically linked and associated to various CMI across ethnicities. Furthermore, various animal models expressing mutant DISC1 support a key role of DISC1 in regulating mammalian behavior. We were interested in investigating the role of NON-MUTANT DISC1 protein in an assembled multimeric conformation in behavioral control, particularly related to dopamine homeostasis as a major neurotransmitter system dysregulated in CMI.

Methods: To model aggregation of human DISC1 and its role in DA homeostasis *in vivo* we generated a transgenic rat model overexpressing full length, non-mutant DISC1. We performed immunohistochemical stainings of post mortem human brains with mental illnesses and normal controls using the Stanley Medical Research Institute's Consortium Collection (cingulum and frontal cortex). To address the interplay between DISC1 and interplay *in vitro*, we generated a tetracycline-inducible, full length non-mutant human DISC1 neuroblastoma cell line. We analyzed DISC1 multimerization by imaging and biochemical purification, and dopamine kinetics by HPLC and a reporter assay.

Results: Transgene expression led to the abundant and widespread deposition of neuronal perinuclear DISC1 assemblies. Similarly, and corroborating our earlier data on biochemical purification of insoluble DISC1 from post mortem human brains, we demonstrate perinuclear DISC1 assemblies in human cases with mental illness by immunohistochemistry. Upon extensive behavioral phenotyping, the most prominent symptom of the DISC1 transgenic rat (*tg*DISC1 rat) was its hypersensitivity to amphetamine, indicating dysregulation of dopamine homeostasis *in vivo*. Furthermore, *tg*DISC1 rats were impaired on the rotarod test but without deficits in object recognition paradigms. When expressed recombinantly in an inducible SHSY5Y cell line or in primary neurons generated from the *tg*DISC1 rat, DISC1 formed distinct perinuclear and reversible aggregates and led to a characteristic high molecular weight immunoreactive band in Western blots. On a functional level, DISC1 induction suppressed clearance of extracellular dopamine clearance, an effect that was potentiated by the formation of DISC1 aggregates. These effects were mediated through a functional interaction with the dopamine transporter (DAT).

Discussion: The *tg*DISC1 rat displays a specific behavioral phenotype consistent with a dysregulation of dopamine homeostasis and therefore is a valid animal model for DISC1-related behavioral disorders, termed DISC1opathies. Our *in vitro* data indicate that DISC1 has a cell-autonomous function in regulating dopamine homeostasis. Our demonstration of DISC1 aggregates in human post mortem brains in a subset of patients with CMI further strengthens the role of DISC1 aggregates as both a pathogenic event and molecular marker of DISC1opathies.

Poster #T124**CLINICAL AND BRAIN STRUCTURAL PREDICTORS OF 'TRANSITION TO PSYCHOSIS' OR 'RISK REMISSION' IN INDIVIDUALS AT ULTRA HIGH-RISK FOR SCHIZOPHRENIA**

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Background: Specific criteria have been developed in order to identify individuals at ultra high-risk (UHR) of developing a psychosis since early intervention may delay or even prevent overt disease. These criteria combine a significant drop in function and either attenuated psychotic symptoms or genetic predisposition. Early studies found that 30–50% of the UHR individuals developed a psychosis within 1–2 years, but more recent studies have reported a steady decline in transition rates to around 10–16%. Previously focus has been on the UHR individuals who develop a psychosis, thereby ignoring the large proportion of UHR individuals who continue to display the same severe psychopathology and drop in function but do not develop a psychosis. The few studies that assessed the UHR individuals who did not develop a psychosis suggest that 50–75% remit from their initial UHR status within 1 to 3 years. Stratification of UHR individuals into subgroups such as "transition to psychosis", "risk remission" or "continuous risk" permits comparison of the three subgroups and allows for identification of specific markers that predict risk status. Brain structural abnormalities are well known in schizophrenia patients. Abnormalities are also seen in UHR individuals, and seem to be associated with transition to psychosis. We wish to compare the longitudinal changes in brain structure in the

UHR subgroups, and to investigate if brain structure at baseline can predict risk status at one-year follow-up. Since the pathogenesis of schizophrenia is complex, we also employ a multivariate model that identifies complex patterns in large datasets. By inserting brain structural, functional, and neuropsychological data from each UHR individual in a multidimensional space, the multivariate model creates a model for categorizing future UHR individuals.

Methods: 60 UHR individuals who meet the criteria of the Comprehensive Assessment of at-Risk Mental States (CAARMS) will be recruited from Mental Health Services in the Capital Region of Denmark. They must not have been exposed to more than 50 mg haloperidol (or equivalent) as a lifetime dose. The UHR individuals will be examined longitudinally throughout a year by: • Structural magnetic resonance imaging (MRI) scans using a 3 Tesla Philips scanner. • Diagnostic and psychopathological tests: SCID-I, CAARMS, SANS, SPI-A, MADRS, YMRS, SPI-A, SOFAS, GAF. • Neuropsychological tests: BACS, CANTAB and DART, WAIS III At 1-year follow-up the individuals will be stratified into subgroups based on whether or not they have transition to psychosis, remain at risk, or remit from risk.

Results: Inclusion of UHR individuals is ongoing and results are expected in the Spring 2015.

Discussion: Risk stratification of UHR individuals offers a unique insight into the course of the attenuated psychotic symptoms and permits identification of predisposing as well as protective factors to developing a psychosis. Moreover identification of specific markers that predict if an UHR individual eventually converts to psychosis or remits from symptoms, facilitates early and personalized intervention targeting individuals who are at continuous risk, while offering assurance to those who are mislabeled.

Poster #T125

EFFECTS OF URBAN UPBRINGING ON BRAIN STRUCTURE AND NEUROPSYCHOLOGICAL FUNCTIONING – A MULTIMODAL DTI AND VBM STUDY

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Background: Urban upbringing is one of the best replicated environmental risk factors in schizophrenia. While effects of urban upbringing on neural correlates of social stress experience have been demonstrated, there is a lack of data on urban upbringing and structural brain changes as well as neuropsychological functioning. The aim of the present study was to identify potential effects on these markers.

Methods: A sample of 280 healthy subjects was investigated with diffusion tensor imaging (DTI) and T1-weighted sequences in a Siemens 3-Tesla Tim Trio scanner. In addition, they were tested with several neuropsychological tests outside the scanning environment.

Results: Urban upbringing was correlated with grey matter reductions in the bilateral dorsolateral prefrontal cortex and reduced fractional anisotropy in several fiber-tracts, such as the fasciculus uncinatus. Furthermore, levels of reduced executive functioning were correlated with urban upbringing.

Discussion: In this study we could demonstrate a significant influence of urban upbringing on local grey matter volume and white matter integrity that was accompanied by lower executive functioning. The brain areas found to be affected have very often been demonstrated to be reduced in patients with schizophrenia and they also show lower levels of activation during a variety of tasks, especially during working memory tasks. Grey matter reductions in these areas might render subjects more vulnerable to stress, as these areas serve as filters during data processing. As can be demonstrated by levels of reduced executive functioning in the present cohort, this could be one of the pathways how urban upbringing could lead to psychosis.

Poster #T126

HEAD MOVEMENT SYNCHRONY IN SOCIAL INTERACTIONS OF PATIENTS WITH SCHIZOPHRENIA INDICATES SYMPTOMS, COGNITION AND SOCIAL FUNCTIONING

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Background: Disturbed interpersonal communication is a core problem in schizophrenia. Patients with schizophrenia often appear disconnected and “out of sync” when interacting with others. This may involve perception, cognition, motor behavior, and nonverbal expressiveness. Although well-known from clinical observation, mainstream research has neglected this area. Corresponding theoretical concepts, statistical methods, and assessment were missing. In recent research, however, it has been shown that objective, video-based measures of nonverbal behavior can be used to reliably quantify nonverbal behavior in schizophrenia. Newly developed algorithms allow for a calculation of movement synchrony. We found that the objective amount of movement of patients with schizophrenia during social interactions was closely related to the symptom profiles of these patients (Kupper et al., 2010). In addition and above the mere amount of movement, the degree of synchrony between patients and healthy interactants may be indicative of various problems in the domain of interpersonal communication and social cognition.

Methods: Based on our earlier study, head movement synchrony was assessed objectively (using Motion Energy Analysis, MEA) in 378 brief, videotaped role-play scenes involving 27 stabilized outpatients diagnosed with paranoid-type schizophrenia.

Results: Lower head movement synchrony was indicative of symptoms (negative symptoms, but also of conceptual disorganization and lack of insight), verbal memory, patients' self-evaluation of competence, and social functioning. Many of these relationships remained significant even when corrected for the amount of movement of the patients

Discussion: The results suggest that nonverbal synchrony may be an objective and sensitive indicator of the severity of symptoms, cognition and social functioning.

References:

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Poster #T127

CARDIOVASCULAR RISK FACTORS AND METABOLIC SYNDROME IN PEOPLE WITH SEVERE MENTAL ILLNESS – A UK CROSS-SECTIONAL STUDY

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Background: Individuals with psychotic illnesses are at an increased risk of developing cardiometabolic risk factors which significantly contribute to excess cardiovascular morbidity and mortality in this population.

Methods: We conducted a cross sectional study to assess the prevalence rates of cardiovascular disease (CVD) risk factors and metabolic syndrome in a study cohort of 453 individuals with psychotic illnesses. These individuals were recruited as part of the IMPACT study, a RCT of a lifestyle intervention in severe mental illnesses (SMI). We sought to examine the relationship be-

tween illness severity, negative symptoms of psychosis, functional impairment and CVD risk. The International Physical Activity Questionnaire (IPAQ) was used as a measure of physical activity. Descriptive measures were used, along with the student-t test for parametric data. Analysis of variance (ANOVA), with post hoc analyses using Tukey's post hoc criterion for significance was conducted to compare the frequency of CVD risk factors with measures of clinical characteristics such as the PANSS, and the GAF scale.

Results: The mean age of the patients (n=453) was 43.5 years (Range 19-65 years; Standard Deviation (SD) =10.0) and the mean duration of illness was 15.7 years (SD=10.3). Fifty seven percent (n=259) of the population were male. Fifty four percent (n=239) of the total IMPACT study population were of Caucasian ethnicity, while 34% (n=147) were of Black African or Black Caribbean ethnicity. The total study population was made up of 301 (71% of the total study population) individuals with a diagnosis of paranoid schizophrenia. 50.4% (n=209) of the total study population were obese ($BMI > 30\text{kg}/m^2$). Sixty percent (n=250) of the study population had 3 or more CVD risk factors, while 28% (n=118) had four or more CVD risk factors. Sixty two percent (n=268) of the population were cigarette smokers. There were no significant associations identified between the frequency of CVD risk factors and illness severity (as measured by the PANSS total score) ($F=0.894$, $p=0.468$) and between the frequency of CVD risk factors and negative symptoms (as measured by the PANSS negative symptom subscale) ($F=0.395$, $p=0.812$). An analysis of variance (ANOVA) showed significant differences in the mean GAF scores between those individuals with four CVD risk factors and those with two CVD risk factors (mean difference (MD) in GAF scores= 6.2, $p=0.07$) and between those with four CVD risk factors and one CVD risk factor (MD=6.8, $p=0.034$). 57% of 295 individuals with laboratory measures met the criteria for metabolic syndrome (MetS) (IDF) (n=167). The prevalence rate of MetS in the bipolar affective disorder subgroup was 68% (n=26), while 55% (n=108) of individuals with schizophrenia met the criteria for MetS. Forty four percent (n=200) of individuals engaged in low intensity physical activity, while only 12% (n=53) participated in high intensity physical activity.

Discussion: The overall rate of the cardiovascular risk factors in this cohort of individuals with psychotic illnesses is higher than that observed in UK general population studies. These findings indicate that those who were more functionally impaired had significantly higher frequency of CVD risk factors. We didn't identify any such associations between the frequency of CVD risk factors and illness severity and negative symptoms of psychotic illness. This study findings confirm high rates of metabolic syndrome (CVD) risk factors, with between 40% (with a fasting serum glucose $> 5.6\text{mmol/L}$) to 83% (with a waist circumference $> 94\text{cm}$ if male and $> 80\text{ cm}$ if female) of individual risk factors meeting the criteria prevalence. Strengths of this study include the large sample size of individuals with SMI and the diversity of ethnic backgrounds from which patients were recruited, adding to the generalisability of the study findings. We intend to follow up the cohort prospectively as part of the original study protocol, in order to assess metabolic changes over the course of a one year period and the response to the study intervention.

Poster #T128

MULTITASKING CAPACITIES IN PERSONS DIAGNOSED WITH SCHIZOPHRENIA: A PRELIMINARY EXAMINATION OF THEIR NEUROCOGNITIVE UNDERPINNINGS AND ABILITY TO PREDICT REAL WORLD FUNCTIONING

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Background: Difficulties in everyday life activities are core features of persons diagnosed with schizophrenia. Moreover, patients seem to demonstrate particular difficulties during complex and multitasking activities, such as cooking a meal (Semkovska et al., 2004). Multitasking refers to activities where the person has to: carry out and alternating between different tasks that vary in terms of priority, difficulty and duration; define the tasks' targets; and where the person is faced with unexpected problems during the realization of these tasks (Burgess, 2000). However, at present, patients' multitasking capacities have not been adequately examined in the

literature due to an absence of suitable assessment strategies. We thus recently developed a computerized real-life activity task designed to take into account the complex and multitasking nature of certain everyday life activities where participants are required to prepare a room for a meeting – the Computerized Meeting Preparation Task (CMPT).

Methods: Twenty-one individuals diagnosed with schizophrenia and 20 matched healthy controls completed the CMPT. During the CMPT, participants found themselves in a virtual room that they must prepare for a meeting while respecting a list of instructions containing the placement of the guests, the needed objects, the desired drinks ... Patients were also evaluated with an extensive cognitive battery (assessing executive functions, attention, processing speed and memory), measures of symptomatology and real world functioning. To examine the ecological validity of the CMPT, 14 others patients were recruited and were given the computerized version and a real version of the meeting preparation task.

Results: Results demonstrated that performance on the CMPT significantly differentiated patients and healthy controls for the total time to complete task, the planning efficiency, and the respect of the instructions. Moreover, these variables were significantly correlated with executive functioning (i.e. cognitive flexibility and planning), suggesting the major implication of these cognitive processes in multitasking activities. Performance on the CMPT also significantly predicted up to 50% of real world functioning. Finally, performances on the computerized version and the real version of the meeting preparation task were highly correlated, suggesting the good ecological validity of the CMPT.

Discussion: In this study, we created a novel task involving the multitasking nature of real world activities. The results demonstrated that this approach provides a good indication of the real world functioning in patients diagnosed with schizophrenia. Moreover, results suggest a particular implication of executive functioning in multitasking activities of everyday life. These findings suggest the importance of evaluating multitasking capacities in patients diagnosed with schizophrenia in order to predict real world functioning.

Poster #T129

NEUROCOGNITIVE ARCHITECTURE OF SCHIZOTYPY IN AN ASIAN POPULATION

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Background: Neurocognitive deficits in schizotypy have been reported in the literature over the last two decades, albeit from fairly small samples, that are similar to those found in patients with schizophrenia. These similarities could represent shared vulnerabilities between schizotypy and schizophrenia, but broad based studies in large samples may be required to adequately capture deficits that represent an underlying phenotype. The current study was conducted to elucidate schizotypy in a non-clinical Asian population and investigate associations between schizotypy and neurocognition. The aim of this study was to, i) explore the presence of different schizotypy clusters and determine the sample structure of schizotypy in a non-clinical Asian population ii) to identify potential associations between schizotypy with neurocognition by in relation to gradations of schizotypy.

Methods: 1012 community-dwelling Singaporean Chinese adults aged 21-55 years completed the Schizotypy Personality Questionnaire (SPQ) and underwent aware administered a standard battery of neuropsychological tests. Participants with any history of psychosis were excluded from the study. Two stage hierarchical clustering, coupled with k-means clustering were conducted to identify individuals with high schizotypy. This was compared to a pre-determined cut-off of $SPQ \geq 30$. The methods demonstrated concordance.

Results: A two cluster solution – "high and low schizotypy scores" displayed greatest effect sizes across SPQ domains, and further hierarchical clustering of the "high scores" generated 3 solutions ($k=1, 2, 3$). Cluster solution $k=2$ seemed to be indicative of individuals with relatively high levels of schizotypy, consisting of 90% of individuals with "high schizotypy scores". Individuals in cluster $k=2$ (high schizotypy) performed significantly poorer on tests involving fluency and sustained attention when compared to the other 3 clusters (low schizotypy; $k=1, 3$). Further analyses of the

high schizotypy individuals revealed gender differences; males tended to perform worse on verbal fluency type tasks, while females performed worse on sustained attention type tasks.

Discussion: Cognitive performance may vary along a non-linear distribution with schizotypy severity. Gender differences in developmental trajectories may yield crucial clues as to how schizotypy and the psychosis spectrum are related.

Poster #T130

NEURAL MEDIATOR OF SCHIZOTYPY-ANTISOCIAL BEHAVIORS RELATIONSHIP: PREFRONTAL AND ORBITOFRONTAL GRAY

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Background: Prior studies have established an association between schizotypal personality traits (schizotypy) and antisocial behaviors, but it is unclear what neural factors mediate this relationship. The present study assessed the mediating effect of sub-regional prefrontal gray matter volume on the schizotypy- antisocial behaviors relationship.

Methods: Superior, middle, inferior, orbitofrontal, and rectal gyral gray matter volumes were assessed using structural magnetic resonance imaging in 108 adults from the community, together with schizotypy and antisocial behaviors.

Results: Schizotypy was positively associated with the antisocial behaviors and both of them were negatively associated with the total gray matter volumes in prefrontal and orbitofrontal cortices. Mediation analyses showed that prefrontal cortex gray, specifically the orbitofrontal cortex gray fully mediated the association between schizotypy and antisocial behaviors after controlling for sex, age, race, IQ, socio-economic status (SES), whole brain volume, and substance abuse/dependence.

Discussion: Findings are the first to document a neural mediator of the schizotypy – antisocial behaviors relationship, and suggest that functions subserved by the orbitofrontal cortex including impulsive control and inhibition, emotion processing and decision- making may help explain this comorbidity.

Poster #T131

AUTOBIOGRAPHICAL MEMORY DEFICITS IN PATIENTS WITH CHRONIC SCHIZOPHRENIA

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Background: Autobiographic memory represents the most advanced memory system and is considered to be crucial for the continuity and cohesion of the self and the development of personal identity. Although the respective functions are compromised in schizophrenia, few studies have investigated AM deficits with respect to important psychopathological symptoms, cognitive deficits and self-defining memories in patients with chronic schizophrenia.

Methods: 84 patients with chronic schizophrenia (mean age 49.8 years, SD=12.2; mean duration of illness 22.7 years, SD=12.9) and 50 healthy controls (mean age 52.3 years, sd=11.0) were included. Both, episodic and semantic AM was investigated by using a semi-structured interview (Erweiterter Autobiographisches Gedächtnis Inventar) in four different life periods. In addition, psychopathological symptoms and cognitive deficits were assessed on the scale for the assessment of negative symptoms and positive symptoms (SANS-SAPS) and a test battery covering relevant neurocognitive domains, respectively.

Results: In our preliminary analyses repeated measures ANOVAs consistently revealed significant main effects for group, with schizophrenic patients showing an impaired recall of personal semantic information and an impaired event recall. The analyses also revealed a main effect for epoch and an epoch x group interaction for the event recall measure (but not for the semantic measure). Independent t-tests revealed that schizophrenic patients recalled less specific episodes across all life epochs. In the same manner we analysed the recall of contextual details in the pool of the recalled specific episodes. These analyses revealed a lower scoring of the schizophrenic group only in the recent period.

Discussion: Taken together, our preliminary analysis replicated the known overgenerality of autobiographical memory in patients with schizophrenia, but did not demonstrate a general deficit of remembering contextual details of the recalled specific episodes. Such a preserved detail-recall could be a consequence of a “semantication process” and is in this regard independent of the impaired capacity of autoetic reliving during autobiographical event recall in schizophrenia.

Poster #T132

DIFFERENCES IN INSIGHT BETWEEN SCHIZOPHRENIC AND SCHIZOAFFECTIVE PATIENTS: IS AFFECTIVITY THE KEY?

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Background: Deficit in insight is a common phenomenon in psychosis. Some studies have found that patients with schizophrenia show more severe insight deficits than patients with schizoaffective or major depressive disorder with or without psychosis; and that better insight in schizophrenia is associated with low mood or depression. But data are contradictory and the link between affectivity and insight in psychotic disorders remains unclear. We aim to study differences of insight between schizophrenic and schizoaffective patients, and to analyze the relationships between affectivity and dimensions of insight.

Methods: Multicenter cross-sectional naturalistic study of 288 psychotic patients (250 schizophrenic and 38 schizoaffective) from different clinical settings was undertaken. Diagnosis was made following DSM IV criteria. The severity of psychopathology was assessed using Positive and Negative Syndrome Scale (PANSS) and Lindenmayer's Factors -Positive, Negative, Cognitive, Depressive and Excitement- were obtained. One Positive PANSS item (P5 Grandiosity), and three General PANSS items (G3 Guilt, G6 Depression, and G2 Anxiety) were used as specific affectivity symptoms measures. The deficit of insight and its three dimensions -awareness of illness, awareness of the effects of medication, awareness of the social consequences of the diseases- and the total awareness and total attribution of each different symptom- were evaluated by the Scale of Unawareness of Mental Disorders (SUMD). Bivariate analysis and non-parametric correlations were performed in order to make a multiple linear regression model of insight dimensions.

Results: There were no significant differences between schizophrenic and schizoaffective patients in any dimension of insight. No significant relationships were observed with Depression or Grandiosity in any of the three dimensions of insight. Regression analysis showed that all insight dimensions except attribution were mainly explained by the Positive Lindenmayer's factor and being inpatient - independently of clinical phase, severity, gender and age. Also Guilt and Anxiety was therefore independently related to better insight of the illness, better awareness of the social consequences of the disease, and better total awareness of symptoms. Schizoaffective diagnosis and less Disorganized with better awareness of effect of medication. Poorer total insight of symptoms was also independently related to Disorganized and Excitement Lindenmayer's factors and duration of illness. Finally, better attribution of symptoms was predicted by Anxiety, and less Disorganization.

Discussion: According to our data, Schizophrenic and Schizoaffective patients seem to be similar in their levels of insight, while severity of positive symptoms and inpatient clinical setting are important conditions. Nevertheless, a better awareness of the effects of medications is explained by Schizoaffective diagnosis. Guilt and Anxiety, but not Depression, are the affective symptoms associated to better insight, in accordance with other studies; however Anxiety but not Guilt were symptoms specifically related

to better attribution. Affective symptoms of psychotic patients as Anxiety and Guilt but not Depression seem to modulate the awareness of illness in some specific way related to dimensions of insight.

Poster #T133

UNDERSTANDING THE PHYSICAL ACTIVITY BEHAVIOR AMONG PATIENTS WITH PSYCHOSIS

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Background: Regular physical activity in reducing the risk of certain kinds of cancer, decreasing the chance of suffering chronic diseases, improving the cognitive and executive functioning and diminishing the severity of the mental illness are well developed [1–3]. However, the physical activity level among patients with mental illness was insufficient mainly due to the symptoms of the illness and the side-effect of the medication [4]. In order to successfully promoting regular physical activity in this population, examining the potential factors in predicting the change of physical activity behavior is needed to bring about change in physical activity habit.

Methods: A cross sectional survey questionnaires, which include stages of change, decisional balance, self-efficacy and processes of change, were used in measuring the physical activity behavior of the out-patients who are diagnosed with psychosis with an age between 18 and 64 at the out-patient clinic.

Results: Among 181 outpatients, the majority of the subjects were in contemplation stage (51.4%), followed by preparation stage (25.4%), pre-contemplation stage (17.1%) and action and maintenance stages (6.1%). Data in action and maintenance stages were excluded due to the small sample size. Over 64.2% of subjects were diagnosed as schizophrenia spectrum disorder. The mean age of the subjects was 29.2 years old and 55.3% were female. Except the cons of decisional balance and dramatic relief, significant findings were found on all factors. Significant differences were found on self-efficacy $F(2,167)=22.74$, $p<0.001$ and the pros of decisional balance $F(2,167)=12.21$, $p<0.001$. In the processes of change, consciousness raising $F(2,167)=13.90$, $p<0.001$, environmental reevaluation $F(2,167)=3.60$, $p=0.03$, self-revaluation $F(2,167)=23.42$, $p<0.001$, social liberation $F(2,167)=6.99$, $p=0.001$, counterconditioning $F(2,167)=22.61$, $p<0.001$, helping relationships $F(2,167)=7.69$, $p=0.001$, reinforcement management $F(2,167)=16.92$, $p<0.001$, self-liberation $F(2,167)=42.07$, $p<0.001$ and stimulus control $F(2,167)=23.69$, $p<0.001$ were also statistically significant.

Discussion: Examining the physical activity behavior among patients with psychosis in Hong Kong found significant difference across different stages of change, hence, the strategies in promoting physical activity could be based on these factors. The use of motivational interviewing, which focus on person-centered counselling, will also facilitate the change of physical activity behavior. However, further study is needed to test the utility of these factors in this population as action and maintenance stages were excluded in this study.

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Poster #T134

PERSISTENCE OF PSYCHOTIC-LIKE EXPERIENCES (PLES) IN THE GENERAL POPULATION OF HONG KONG

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Background: PLEs are poorly-understood phenomenon referring to sub-clinical psychotic symptoms that do not meet clinical criteria, reported by individuals in the general public without psychotic disorder. Most PLEs were reported as transient in previous studies, while persistent PLEs might increase the risk of developing psychosis. Examining persistent PLEs could provide insights on PLEs' role in the development of psychiatric disorders.

Methods: The present on-going study, which aims to examine the persistence of PLEs, is a 2-year follow-up on the 187 participants who reported PLEs in the Hong Kong Mental Morbidity Survey 2010 (HKMMS). HKMMS is a territory wide epidemiological study carried out in 2010–2013, targeted at general population aged 16–75 in Hong Kong. PLEs were assessed by the Psychosis Screen Questionnaire, where PLEs of a subject are counted as persistence when he/she endorsed ≥ 1 items in both baseline and follow-up.

Results: The mean age of the first 26 participants was 43.54 (SD=11.79), where 18 (69.23%) were female and 8 (30.77%) were male. PLEs persisted in 17 (65.38%) of them – in these 17 subjects, 4 (23.53) reported increased number of PLEs, 7 (41.18) reported decreased and 6 (35.29%) remained the same.

Discussion: Persistence rate of PLEs is higher in the current study when compared with previous literatures. A higher persistence rate might imply a higher rate of transition into psychosis but more data needs to be collected to make any conclusion.

Poster #T135

REDUCTION IN HOSPITAL STAY OF PATIENTS WITH SCHIZOPHRENIA AFTER THE LONG-TERM PSYCHOSOCIAL INTERVENTION

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Background: This study aimed to elucidate the effectiveness of long-term psychosocial intervention in reducing the disabling period of patients with schizophrenia by their rehospitalization status.

Methods: Of 210 patients with major psychiatric disorder, serviced by intensive or maintain psychosocial interventions (drug monitoring, social skill training, family therapy etc.) in Dobong Mental Health Center were recruited, 147 (140, schizophrenia and 7, schizoaffective disorder) were selected who had been followed up for more than 6 months with respect to rehospitalization. To obtain information about the same periods before and after the psychosocial intervention, a medical record review of these patients was conducted.

Results: The number ($z=-5.005$, $p<0.001$) and length ($z=-5.124$, $p<0.001$) of hospitalization of the patients significantly decreased after psychosocial intervention compared to the same period before intervention. The hospital days per year of the patients were also decreased significantly after intervention ($z=-5.124$, $p<0.001$). By analyzing 81 patients who were followed up for more than 5 years, it was suggested that the elongation in the community was substantially sustained for up to 5 years after psychosocial intervention.

Discussion: This study revealed that the number and length of hospitalization are significantly decreased by long-term psychosocial intervention and that this effect can positively affect the social outcome for patients with schizophrenia.

Poster #T136

POSITIVE AND NEGATIVE SYMPTOM SCORES CORRELATED WITH DIFFERENT BRAIN REGIONAL ACTIVATION DURING FACE EMOTIONAL PERCEPTION IN SCHIZOPHRENIA PATIENTS: A VOXEL-BASED SLORETA SOURCE ACTIVITY STUDY

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Background: Schizophrenia is one of the most devastating of all mental

illnesses, and has dimensional characteristics that include both positive and negative symptoms. One problem reported in schizophrenia patients is that they tend to show deficits in face emotion processing, on which negative symptoms are thought to have stronger influence.

Methods: In this study, four event-related potential (ERP) components (P100, N170, N250, and P300) and their source activities were analyzed using EEG data acquired from 23 schizophrenia patients while they were presented with facial emotion picture stimuli. Correlations between positive and negative syndrome scale (PANSS) scores and source activations during facial emotion processing were calculated to identify the brain areas affected by symptom scores.

Results: Our analysis demonstrates that PANSS positive scores are negatively correlated with major areas of the left temporal lobe for early ERP components (P100, N170) and with the right middle frontal lobe for a later component (N250), which indicates that positive symptoms affect both early face processing and facial emotion processing. On the other hand, PANSS negative scores are negatively correlated with several clustered regions, including the left fusiform gyrus (at P100), most of which are not overlapped with regions showing correlations with PANSS positive scores.

Discussion: Our results suggest that positive and negative symptoms affect independent brain regions during facial emotion processing, which may help to explain the heterogeneous characteristics of schizophrenia.

Poster #T137

"JOHYEONBYUNG (ATTUNEMENT DISORDER)": RENAMING MIND SPLITTING DISORDER AS A WAY TO REDUCE STIGMA OF PATIENTS WITH SCHIZOPHRENIA IN KOREA

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Background: The term schizophrenia, which comes from the Greek roots "skhizein" and "phren", was translated as "Jungshinbunyeolbyung" in East Asian Countries, including Japan, Korea, and China. The term literally means "mind-splitting disease". This term has generated a misconception of the disorder as an untreatable chaotic personality, thus instilling stigma and causing suffering in patients and their families. This socio-cultural connotation has impeded medical treatment of schizophrenia.

Methods: The Korean Committee for Renaming Schizophrenia conducted surveys for coining a new Korean term for schizophrenia and held workshops and symposia to change the Korean term for schizophrenia. Also, there was active collaboration with a Korean linguist.

Results: Accordingly, a new term, "Johyeonbyung (attunement disorder)", was coined in South Korea. This term literally refers to tuning a string instrument, and metaphorically it describes schizophrenia as a disorder caused by mistuning of the brain's neural network.

Discussion: This change helps to avoid the stigmatization derived from the name of the disorder. A South Korean study showed that the term johyeonbyung induced significantly less prejudice and stigma than did the term Jungshinbunyeolbyung. We expect that the term Johyeonbyung will incite less stigma and that its metaphoric description of the disorder may help patients to access medical treatment in the early phase. The name of a psychiatric disorder can influence others' attitudes toward patients; thus, discretion is crucial in naming psychiatric disorders.

Poster #T138

CAPACITIES FOR THEORY OF MIND, METACOGNITION, AND NEUROCOGNITIVE FUNCTION AS INDEPENDENTLY RELATED TO PERFORMANCE ON A TEST OF EMOTIONAL RECOGNITION

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Background: While it is recognized that many with schizophrenia experience difficulties understanding the feelings of others while engaging in social interactions, little is known about the psychological antecedents of these deficits. These deficits are of both theoretical and clinical interest in that they interfere with the ability to identify what others are feeling during social exchanges and thereby represent a unique impediment to social and vocational function above and beyond the effects of other aspects of illness, such as neurocognitive deficits. One issue concerns whether there are different factors whose interaction might create or sustain deficits in inferring the emotions others may be experiencing or trying to express. It is unclear whether deficits in emotion recognition are an entirely unique deficit or a function of impairments in a number of semi-independent psychological and cognitive phenomena. An understanding of the mechanisms underpinning the detection of emotions in complex social exchanges could be of considerable importance as it may well point the way to the development of treatments that might help address some of the root causes of these difficulties. In the current study we seek to examine whether three processes: mental state decoding, mental state reasoning, and metacognition; all of which are theoretically necessary for the recognition of affect in social experience, are related to the ability to detect emotion in others for those with schizophrenia and whether their relationships with affect recognition exist independent of one another.

Methods: To explore this issue we examined whether mental state decoding, mental state reasoning, and metacognitive capacity could predict performance on a task designed to measure emotion recognition in a simulated social interaction. Participants were 115 adults with a schizophrenia spectrum disorder in a non-acute phase of disorder. A psychiatric control group was recruited composed of 58 adults with substance use disorders but no history of a diagnosis of psychosis. All completed two Theory of Mind tests: the Eyes and the Hinting Test. Metacognitive capacity was assessed using the metacognitive assessment scale and emotion recognition was assessed using the Bell Lysaker Emotion Recognition Test.

Results: Results showed that schizophrenia patients performed more poorly than controls on tests of Theory of Mind and metacognition. Correlations revealed that for the schizophrenia group lesser capacities for mental state decoding, mental state reasoning, and self-reflectivity were related to lesser abilities to grasp another's emotional state depicted in a video clip. These relationships persisted after controlling for neurocognition and symptoms in a stepwise multiple regression.

Discussion: Results suggest that deficits in emotion recognition in schizophrenia may in part result from an interaction between impairments in the ability to judge the cognitive and affective states of others along with difficulties forming complex representations of self and others. Consistent with our prediction, greater deficits in all factors examined were linked to deficits in the ability to recognize emotion in a task that briefly simulated a social interaction. Results suggest that each factor affects emotion recognition differently, after controlling for education, flexibility of abstract thought, and negative symptoms. Specifically, we found that poorer performance on the BLERT first predicted by mental state decoding, then by the capacity for metacognition, and finally by mental state reasoning. These results are consistent with previous literature, suggesting that correctly inferring emotions in others on the basis of multiple channels of information requires a series of intact, semi-independent aspects of the metacognitive systems to work. These findings may have several clinical implications.

Poster #T139

GENOTYPIC VARIATION, CHILDHOOD LITERACY SKILLS AND RISK OF PSYCHOTIC EXPERIENCES IN EARLY ADOLESCENCE: FINDINGS FROM THE ALSPAC STUDY

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Background: Dystrobrevin-binding protein 1 (DTNBP1) have been shown to have a major role in the cognitive functioning of individuals presenting with schizophrenia. DTNBP1 is a protein that is involved in the modulation of glutamatergic neurotransmission in the human brain, thereby influencing prefrontal cortex function and associated cognitive processes (Fallgatter et al., 2010). Directed by findings from schizophrenia genetic association

studies, this preliminary study aims to examine distribution of reporting psychotic experiences in early adolescence in relation to the DTNBP1 genotypes. This study also examined the association of childhood literacy skills and psychotic experiences. Further, the interactive (additive) effect of genotypic risk indicators and low average literacy skills was explored in relation to presence of psychotic experiences.

Methods: This study examined data from n=6790 children from the Avon Longitudinal Study of Parents and Children cohort (The University of Bristol, UK) who participated in a semi-structured interview to assess psychotic experiences at age 12 (age range = 12.5–13.3 years). Based on this interview, psychotic experiences were classified as not present (n=5862, 86.3%), suspected (n=544, 8.0%) or definitely present (n=384, 5.7%). Literacy skills such as spelling, basic real and non-real word reading, and reading skills and comprehension were assessed (ages 7 – 9) by a research purpose-made spelling task, Wechsler Objective Reading Dimension, and the revised Neale Analysis of Reading Ability, respectively. Genotyping was performed by KBioscience (<http://www.kbioscience.co.uk>); single nucleotide polymorphisms were genotyped using the KASP-SNP genotyping system.

Results: DTNBP1 (rs4715984) combined rare homozygotes to the heterozygotes (G:A + A:A) was found to be a significant predictor of definite psychotic experiences (OR = 1.34, 95% CI = 1.0–1.80). Further, those endorsing definite psychotic experiences were more likely to have low average literacy skills (OR = 1.54, 95% CI = 1.13–2.09). However, in terms of an interactive effect, results showed that neither the DTNBP1 minor alleles (rs4715984; G:A + A:A) nor low average literacy skills increased the odds of reporting definite psychotic experiences. Though, exposure to both risk indicators was associated with a 2.54-fold increase in the odds of reporting definite psychotic experiences (95% CI = 1.36–4.74), 38% of which was attributable to the joint action of both risk indicators (additive interaction).

Discussion: While results found some evidence pertaining to the additive effect of genotype and literacy skills in predicting psychotic experiences in early adolescence, only small percentages were attributable to the additive effect of both exposures. Failure to replicate findings is a major limitation in investigating the genetic indicators of psychotic experiences. Nevertheless, from a biological function perspective, analyses of haplotypes are more plausible than single nucleotide polymorphism effects. Unlike this study, with the limitation of only examining single genotypes, haplotype analyses may have contributed to further consistent findings. Overall, the findings imply that schizophrenia and psychotic experiences are unlikely to be caused by a single gene. As yet, no studies have conclusively found a direct association between a single gene and schizophrenia. In terms of future research, ethnic background, gender, the inherent phenotypic heterogeneity of schizophrenia, epigenetic interactions, may contribute to genetic variations observed in psychotic conditions/symptoms (Sacchetti et al., 2013) and these are all worth pursuing in future research.

Poster #T140

THE ROLES OF VICTIMIZATION EXPERIENCES, PARANOIA AND SALIENCE MISATTRIBUTION IN PREDICTING PSYCHOSIS PRONENESS: THE TWINSCAN CHINA STUDY

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Background: Subclinical psychotic-like experiences (PLEs) are reported to be relatively common in the general population. One approach to support the dimensional continuum from PLEs to clinical psychotic symptoms is to identify their common risk factors. Previous studies have identified victimization in school bullying as a risk factor for schizophrenia, but its association with psychosis proneness is yet to be established. Bullying victimization may not be directly associated with PLEs, but rather its effects may be mediated through cognitive mechanisms such as paranoia and salience misattribution. Also, few studies have compared the effects of high-school bullying with elementary-school bullying in predicting psychosis vulnerability. The present study aimed to address these questions by hypothesizing paranoid ideation and salience misattribution as mediators in the victimization-proneness relationship.

Methods: The sample comprised 100 Chinese adolescents (male=52, mean

age=17.7, SD=1.95) who were recruited in Beijing and Hong Kong. Participants were normal, healthy individuals with no prior diagnostic history of mental illnesses. A set of three questionnaires and a computer-based task were administered to the participants. The Retrospective Bullying Questionnaire (RBQ) was used to measure the history of bullying in elementary school, high school and the workplace (Shaffer et al., 2004). Participants were asked to rate the frequency of bullying and describe their related experiences. Paranoid ideation was assessed using the Subscale PAR of Hopkins Symptom Checklist 90-Revised (SCL-90-R), which measures a general cynicism towards others (Derogatis, 1977). The Community Assessment of Psychic Experiences (CAPE) was used to assess psychosis proneness. It consists of 42 items which measure the frequency and severity of positive, negative and depressive PLEs. Salience misattribution was assessed by the White Noise Task developed by Galdos and colleagues (2011). Participants were randomly presented with 75 sound clips in this 15-minute task. These clips were made of different combinations of noise and sentences from the materials of (i) noise, (ii) clearly audible sentence and (iii) barely audible sentences. Participants were asked to indicate whether they heard something positive, negative, neutral, nothing or uncertain.

Results: Supporting our hypothesis, paranoia was found to be a significant partial mediator in the relationship between bullying victimization and psychosis proneness (p=0.0225). Results suggested that more recent victimization experiences (high school bullying) could significantly predict overall symptoms of PLEs (p<0.001), but earlier childhood victimization (elementary school bullying) could not (p=0.355). Nevertheless, elementary school bullying was a significant predictor of paranoid ideation (p=0.004). Results also showed that victimization experiences in high school could significantly improve prediction of positive, negative and depressive PLEs (p<0.001). However, correlations of salience misattribution were reported to be non-significant with any other variables of interest.

Discussion: This study may shed light on the association between victimization experiences, paranoia and psychosis proneness, suggesting a pathway from environmental to cognitive factors in predicting proneness. By studying PLEs in healthy adolescents, it also lends support to the psychosis-as-continuum model in the literature. The study has demonstrated the potential traumatic effects of high school bullying, suggesting the importance of intervention programmes in educational settings.

Poster #T141

SENSITIVITY TO MINOR STRESSORS MEDIATES THE RELATIONSHIP BETWEEN ENVIRONMENTAL RISK EXPOSURES AND PSYCHOMETRIC RISK FOR SCHIZOPHRENIA

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Background: Schizophrenia and associated liability states share common risk exposures, including economic and vocational disadvantage, minority status, spring birth, urbanicity, trauma, neglect, and substance use. It is unclear whether these risk exposures each contribute to schizophrenia liability and morbidity through distinct mechanisms of action, or whether the associations reflect the influence of a common mechanism such as sensitization to stress. We test the hypothesis that individual differences in stress sensitivity mediate the relationship between environmental risk exposures and schizophrenia risk.

Methods: Taxometrics-based classification was used to identify schizotypes among a cohort of undergraduates (n=741) who had completed the Schizotypal Personality Questionnaire and provided information on risk exposures (season of birth, ethnic minority status, birthplace density, solitude, cannabis use, sex, home moves during childhood) and stress sensitivity (perceived impact of minor hassles). Three risk classes, each with its own complement, were obtained in separate analyses: Positive (cognitive-perceptual) risk (risk n=52, complement n=689), disorganization risk (n=54), and negative (interpersonal) risk (n=111). Path analyses, repeated for each risk-complement structure, were used to examine three models: (a) a direct only model in which risk exposures and sensitivity are direct predictors of membership; (b) a full model where membership is predicted by risk exposures both indirectly (via sensitivity) and directly; and (c) an indirect effects model, where the effects of risk exposures on class membership are mediated by sensitivity. Analyses were conducted

using MPlus 7.11 and fit was evaluated using chi-square, RMSEA, CFI, and TLI.

Results: For each risk – complement comparison, direct only (9 free parameters) and full models (18 free parameters) did not generate valid chi-square statistics, suggesting misfitting models. In contrast, valid results were obtained for the indirect effects models (11 free parameters). Good fit was obtained for the indirect model for positive risk ($\chi^2=7.25$, df=7, $p=0.403$, RMSEA = 0.007, CFI = 0.995, TLI = 0.989, $r^2=0.121$), with cannabis (standardized estimate = 0.14, $p<0.001$), male sex (-0.13, $p=0.001$), and solitude (-0.08, $p=0.040$) predicting sensitivity; sensitivity predicting membership (0.27, $p=0.001$); and sensitivity mediated the effects of male sex (-0.03, $p=0.006$) and cannabis use (0.04, $p=0.003$). The indirect model of disorganization ($\chi^2=4.46$, df=7, $p=0.726$, RMSEA < 0.001, CFI = 1, TLI = 1, $r^2=0.071$) gave significant direct effects of male sex (-0.13, $p<0.001$) and cannabis use (0.14, $p<0.001$) on sensitivity; sensitivity on membership (0.15, $p=0.022$); and sensitivity mediated the effect of cannabis use (0.02, $p=0.048$). Finally, for the indirect model of negative risk, $\chi^2=14.17$, df=7, $p=0.048$, RMSEA = 0.037, CFI = 0.901, TLI = 0.787, $r^2=0.148$. In this model, male sex (-0.12, $p<0.001$), ethnic minority status (0.09, $p=0.036$) and cannabis use (0.14, $p<0.001$) predicted sensitivity; sensitivity predicted membership (0.32, $p<0.001$); and sensitivity mediated effects of male sex (-0.04, $p=0.003$), ethnicity (0.03, $p=0.046$), and cannabis use (0.05, $p=0.001$).

Discussion: Indirect models of risk class membership provided good fit to the observed data whereas full and direct-only models were problematic (possibly for technical reasons). Sensitization may provide a common-mechanism account for the relationship of environmental risk exposures with psychometric risk classifications, particularly those based on positive and disorganization features.

Poster #T142

SOCIAL COGNITION AND INTERACTION TRAINING-TABLET FOR OUTPATIENTS WITH SCHIZOPHRENIA: A PRELIMINARY STUDY

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Background: Deficits in social functioning (e.g., interpersonal effectiveness, community integration) are hallmark features of schizophrenia (SCZ) and arguably the most debilitating; SCZ patients have identified them as their greatest unmet treatment need (Coursey et al 1995 and Middelboe et al 2001). Current front-line treatments, including medications and psychosocial interventions, have only shown modest improvements in social deficits. In recent literature, social cognition has emerged as a promising treatment target because it is a strong predictor of social functioning (Couture et al., 2008; Fett, 2011). Most initial social cognitive treatment modalities have targeted specific social cognition domains (i.e. Emotional Perception (EP), Social Perception (SP), Theory of Mind (ToM), or Attributional Style (AS)) without integrating these individual components as a whole. While showing some improvements in the targeted domains, these gains largely have failed to generalize to social functioning improvements. Social Cognition and Interaction Training (SCIT) was designed to address the full range of social cognitive impairments with the hope of increasing gains in functional outcome. SCIT has shown modest, but promising evidence of improving EP, ToM, AS, and social functioning (Combs et al 2006). One problem with SCIT is that patients struggle to recall material from one week to the next, and to apply the material in their day-to-day lives. It is known that neurocognitive impairments are a rate limiting factor in patients' ability to benefit from psychosocial interventions. To minimize the effects of these impairments on SCIT treatment effects, we turned to the literature on learning and automaticity. Automaticity refers to behaviors displaying efficiency, lack of awareness, and lack of control (Lally 2009). Ma and colleagues have demonstrated that simple motor routines can be learned to the point of automaticity through 15 minutes of daily practice for four weeks, and that this results in increased functional efficiency in motor circuitry (Ma et al 2011). Applying this approach to social cognition, we condensed SCIT into a simplified social cognitive heuristic that patients could learn easily and practice daily on their own. This approach, which we call SCIT-Tablet, integrates emotion perception, ToM, and attributional style training within a single heuristic strategy. Specifically, patients learn to flexibly interpret others' thoughts and feelings in terms of three archetypal character styles:

My-fault Mary (who is sad and self-blaming), Easy Eddie (who is happy and never blames others), and Blaming Bill (who is angry and always blames others) (MEB). The goal of the current study was to test the feasibility and potential efficacy of SCIT-T.

Methods: The current study uses data from a randomized, waitlist controlled trial of SCIT-T. During the treatment phase, all participants were asked to complete 15 minutes of in-home training, 6 days a week for 28 days using the SCIT-T application on a tablet computer. The training material includes photographs, videos, and audio recordings teaching subjects MEB. Subjects received regular phone calls for reminders and troubleshooting. Feasibility data for the present study includes tablet recordings of participants' treatment adherence, number of participant withdrawals, number of lost or damaged tablets, and participant feedback. Efficacy data includes speed and accuracy of responses, as recorded by tablet computers during daily training, and participants' self-reported automaticity as recorded weekly using the Self-Report Habit Index (SRHI; Verplanken & Orbell 2003). The SRHI is a validated self-report measure of automaticity which includes items such as, "I do [the MEB strategy] without having to consciously remember", and "I start doing [the MEB strategy] before I realize I'm doing it". Using linear growth curve modeling, we hypothesized that over the course of training SCIT-T participants would demonstrate significant increases in response speed and accuracy and in self-reported automaticity.

Results: Results from the first 15 participants are generally in line with hypothesis. Over 95% of participants successfully completed all 24 modules of SCIT-T within one month, with only one withdrawal. No tablets were lost or damaged. Participants reported high levels of acceptability of SCIT-T. Initial efficacy analyses suggest possible small improvements in EP and ToM. Further analyses are in progress and will be included in the final poster.

Discussion: Data suggest that SCIT-T is feasible and potentially efficacious as outpatient treatment to improve social cognition in schizophrenia. The extremely high treatment adherence, low withdrawal and lack of hardware damage support ongoing development of tablet-based interventions for this population. Although efficacy analyses are ongoing, and this feasibility trial was underpowered for efficacy analyses, several explanations for modest efficacy data should be considered. First, participants completed each module within approximately 7 min, which is significantly less than the 15 minutes of daily motor training that Ma and colleagues have shown for change in neuro-circuitry to take place (Ma 2011). This may require an increase in the training intensity and/or training content in order to achieve sufficient practice and interaction time (>1 5min) with the program. Second, it cannot be ruled out that reliance on computer interaction may undermine the goal of SCIT-T to improve social interaction and social skills. In sum, the current results support continued study of SCIT-T and other tablet based interventions for scz, however it remains plausible that future research will conclude that human social interaction is needed to improve real world social cognition.

Poster #T143

INFLAMMATORY RESPONSE IN FIRST EPISODES OF PSYCHOSIS. MARKERS OF COGNITIVE IMPAIRMENT

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Background: Described various mechanisms involved in the pathophysiology of schizophrenia and other psychoses, as altered inflammatory processes. In a study that examines the physiological balance between the interrelated proinflammatory/anti-inflammatory pathways found plasma levels of the anti-inflammatory prostaglandin 15d-PGJ2 were significantly lower in FEP patients than those in the control subjects. Some studies suggest that certain inflammatory biomarkers could be used as markers of cognitive impairment, but there are no conclusive studies about the

inflammatory changes in first psychotic episodes and their involvement in cognitive function. The aim of this study is to determine the relationship between the anti-inflammatory mediator 15d-PGJ2 and premorbid intelligence in a sample of first episodes of psychosis (FEP).

Methods: Case-control study of 92 FEP patients and 80 gender, race and age matched controls. All subjects were administered Vocabulary subtest for measures of IQ (WISC-IV Vocabulary in child and WAIS-III in adult). The anti-inflammatory mediator 15d-PGJ2 were measured in plasma. All patients were administered the PANSS for psychopathology.

Results: A positive correlation is obtained between the anti-inflammatory mediator 15d-PGJ2 and measures of IQ ($r=0.222$; $p=0.042$) in patients sample. No correlation was found in healthy controls. Further analyses will be performed to evaluate the relationship between other inflammatory markers and cognition domains.

Discussion: The anti-inflammatory mediator 15d-PGJ2 might be used as plasmatic biomarker for first episodes of psychosis and can provide a better understanding of the physiological mechanisms involved in cognition. Because the high predictive power of cognition for psychosocial functional outcome, these results could allow early intervention to improve the prognosis and course of the condition.

Poster #T144

INTEGRATED GENOMIC AND PROTEOMIC EVIDENCE FOR THE POSTSYNAPTIC DENSITY IN SCHIZOPHRENIA

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Background: Recent advances in genomics have led to revealing insights in the possible neuropathology of schizophrenia. The proteomics field is now ready to make such a large-scale impact with the recent advent of high-throughput and targeted proteomic advances. In combination both genomic and proteomic research promises to elucidate the molecular and cellular basis of schizophrenia.

Methods: Proteomic studies in a schizophrenia experimental system – enrichment of the postsynaptic density (PSD) in human post-mortem brain tissue have implicated the PSD in schizophrenia. To test the genetic evidence for these findings, a gene based test was performed on the largest available genome-wide association study for schizophrenia to date from the Psychiatric Genetics Consortium, including 13,689 cases and 18,226 controls. We tested for association of proteomic priority genes at the single gene level and enrichment of the gene set.

Results: We report the enrichment of PSD genes, and long term potentiation and endocytosis pathways, with schizophrenia (FDR q-values <0.25), and highlight HIST1H1E ($p=1.9 \times 10^{-5}$) and MAPK3 ($p=0.000186$) in particular.

Discussion: We support new biological associations with schizophrenia, and demonstrate the complementary nature of proteomic and genomic research in biological psychiatry.

Poster #T145

"I AM HERE BECAUSE THE VOICES CAME BACK . . .": NARRATIVE EXPLORATION OF THE FUNCTION OF CONCEPT FORMATION IN ADULTS HOSPITALIZED DUE TO SYMPTOMS OF SCHIZOPHRENIA

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Background: Building upon Vygotsky's (1934) theorizing regarding the disturbance of the concept formation function in individuals suffering from schizophrenia, we conducted a 12 week-long narrative study which explores differences in concept formation and integration across various context of individual's life. The study was conducted with adults hospitalized at a large psychiatric hospital in New York City due to symptoms of schizophrenia. In order to explore the function of concept formation – operationalized in this study in terms of narrators' use and integration of evaluative elements across narrative dimensions – we asked the participants to narrate in response to a series of prompts varied for author-purpose-audience stances over time (i.e. letter to a friend outside of the hospital vs. letter to a doctor at the hospital)

Methods: Narratives – be they written, oral, real or imagined – often serve a function of establishing a point of personal interest for the narrator in relation to the social context of his/her activities. Because of this emphasis on personal interest of the narrator, narrative analysis was successfully employed by developmental researchers to explore processes of sense-making (Piaget, 1968; Bruner, 1986; Daiute, 2010; Daiute & Lucić, 2010; Lucić, 2013; Peterson & McCabe, 1983). Majority of these works build on Labov and Waletzky's (1967) narrative analysis scheme which distinguishes two distinct narrative functions: evaluative and referential. Referential function relates to actions frequently organized as canonical events (Bruner, 1990) and often involves pre-scripted ways of accomplishing an activity. Referential core of a narrative frequently carries a referential meaning – it answers the question of how something is done or what happens in general (Daiute & Nelson 1998). On the other hand, evaluative function in narrative serves to establish a point of personal interest for the narrator in relation to his/her activities. Evaluative devices individuate the narrative, by introducing specific and non-canonical unexpected happenings – they usually tell us why something is done. Given that evaluation is often self-referential and frequently implicit (Daiute, 2010) it is rarely stated explicitly. Thus, evaluation often appears through accidental, sporadic and unintended use (at least consciously) of narrative elements, such as negations, metaphors, causal connectors, cognitive or affective linguistic devices. Evaluation, as situated rather than absolute (Daiute & Nelson 1997) has embedded social function: it signals the meaning of narrative for the narrator.

Results: In this study we hypothesized that a) narrative functions would be better integrated when participants were engaged in sense-making of expressive genres b) better integrated when addressing social contexts outside of the hospital (friends) than social context of others with significant power over their daily functioning (doctors). We compare analyses of letters participants wrote to a doctor at the hospital and to a friend earlier (week 1 and 2) and later (weeks 9 and 10) in the study. Preliminary results indicate a clear difference in the use of evaluative elements in a direction of our initial hypothesis for hypothesis a) and in a direction opposite from our hypothesis b). The data reveal pronounced differences in narrative length, use of psychological states, use of causal connectors, and overall greater complexity in narratives towards the other-oriented genres and social context of others with significant power.

Discussion: Findings from this study indicate that individuals diagnosed with schizophrenia are able to vary their narrative responses across diverse context indicating flexibility of cognitive functions and suggesting avenues for the future narrative based cognitive interventions.

Poster #T146

DELAYS TO TREATMENT PREDICT PERSISTENT NEGATIVE SYMPTOM DOMAINS

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Background: Negative symptoms may be divided into expressivity and motivation/pleasure domains, although few studies have investigated the predictors of each domain. Several previous studies have found that delays to treatment are predictive of negative symptoms, including persistent negative symptoms (PNS). This study investigated the relationship between delays to treatment and PNS domains for expressivity and motivation/pleasure.

Methods: All individuals with suspected psychosis within a defined catchment area were interviewed following referral to the DETECT early intervention for psychosis service. Scale for the Assessment of Negative Symptoms (SANS) data were collected for 197 individuals with confirmed first episode psychosis diagnosis at both first presentation and again at a one year follow-up assessment. Delays to treatment, including duration of

untreated psychosis (DUP) and duration of untreated illness (DUI) were measured using the Beiser Scale. Regression models determined whether the delays to treatment relationship with PNS was specific to either negative symptom domain independent of confounders, including premorbid adjustment.

Results: Both DUP and DUI had a significant unadjusted relationship with both PNS domains. After controlling for confounders DUP no longer predicted either domain, while DUI significantly predicted expressivity domain. DUI also predicted motivation/pleasure domain following an imputation method which allowed for inclusion of individuals with missing premorbid adjustment data. In a post-hoc analysis there was evidence that the DUP relationship with both domains was stronger when the sample was restricted to individuals with a DUP of less than nine months.

Discussion: DUI predicted both negative symptom domains suggesting that a long duration of psychosis prodrome may contribute to early negative symptom development as well as a long DUP. The DUI relationship with negative symptoms may not be specific to either negative symptom domain. The findings also support previous evidence that a nine month cut-off threshold is important for the DUP relationship with negative symptoms.

Poster #T147 DECONSTRUCTING NEGATIVE SYMPTOM PREVALENCE IN FIRST EPISODE PSYCHOSIS

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Background: Previous studies in schizophrenia samples suggest negative symptoms are a highly prevalent feature of the illness. There has been less focus on negative symptom prevalence in psychotic diagnoses other than schizophrenia. This study aimed to investigate negative symptom prevalence in schizophrenia as well as other first episode psychosis diagnoses using a cross-sectional (negative symptoms present at one timepoint), persistent (negative symptoms present at two timepoints) and primary persistent (negative symptoms present at two timepoints in the absence of depressive and positive symptoms) negative symptom definition. The study objectives were to determine negative symptom prevalence in the recently described expressive and experiential domains and to determine the relevance of diagnostic shifts between baseline and follow-up on negative symptom prevalence.

Methods: All individuals with suspected psychosis within a defined catchment area were interviewed following referral to an early intervention for psychosis service. Scale for the Assessment of Negative Symptoms (SANS) data were collected for 197 individuals with confirmed first episode psychosis diagnosis at both first presentation and again at a one year follow-up assessment. Principal Components Analysis (PCA) was conducted with the baseline data and Confirmatory Factor Analysis (CFA) with the follow-up data to determine negative symptom structure. Negative symptom prevalence in each psychosis diagnosis was determined using standardised remission criteria.

Results: PCA at baseline indicated the expressivity and experiential domain structure was consistent in both schizophrenia spectrum and non-schizophrenia spectrum diagnoses. CFA at follow-up also supported this domain structure. Negative symptoms were most prevalent in schizophrenia using cross-sectional, persistent and primary persistent definitions, however negative symptoms were also present in other diagnoses. A similar pattern was found for both domains, although experiential domain was more prevalent in each diagnosis. Individuals whose diagnosis shifted from non-schizophrenia spectrum diagnoses at baseline to schizophrenia spectrum diagnoses at follow-up had relatively high negative symptom prevalence at follow-up.

Discussion: The study provides support for the specificity of primary PNS to schizophrenia, however negative symptoms were present in other diagnoses, particularly those whose diagnosis ultimately shifted to schizophrenia. The findings support the introduction of a negative symptom dimension when describing a range of psychotic illnesses. Further research investigating the evolution of negative symptoms in non-schizophrenia diagnoses is needed.

Poster #T148

RISK OF PSYCHOTIC DISORDER IN OFFSPRING OF PARENTS WITH SCHIZOPHRENIA: A META-ANALYSIS

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Background: A substantial historical literature identifies offspring of parents with schizophrenia and psychotic disorders as at higher risk of psychosis than the general population. The historical literature relied on family history samples, however an increasing number of population/registry studies and prospective high-risk cohorts with adult diagnostic data for the offspring generation offer an opportunity to update our estimates of offspring vulnerability to psychosis using case-control designs. We conducted a meta-analysis of the strength of association between a parental diagnosis of schizophrenia (non-affective psychosis) and a diagnosis of psychotic disorder in the offspring.

Methods: Following MOOSE guidelines, MEDLINE, EMBASE, PsycINFO and grey literature were searched from 1946 through to September 2013. The search terms were constructed from conjunctions of psychosis (PSYCHOTIC*, SCHIZO*, HALLUCINAT*, DELUSION*, PARANOI*), developmental risk (HIGH-RISK; CHILDREN; OFFSPRING; MOTHERS, PARENTS, DEVELOPMENT), and outcome (FOLLOW-UP; OUTCOME; CHARACTERISTICS; FUNCTIONING; DIAGNOSIS). Case-control studies from prospective cohorts or population/registry studies were eligible for inclusion. The relevant study statistics were converted to Odds Ratios (OR's). Given the a priori assumption of heterogeneity in the retrieved studies a random effects meta-analysis was fitted to the data using Der-Simonian Laird's method. Heterogeneity and sensitivity analyses were conducted. We also analysed the association between parental schizophrenia and diagnoses of bipolar disorder (affective psychosis) and Cluster C Personality disorder.

Results: Our analyses included k=17 studies representing N=18,258 offspring of parents with schizophrenia and N=487,874 control offspring. Of these k studies 11 were prospective case control studies, 2 adoption case-control studies and 4 population/registry cohorts. There was an overall effect of OR= 5.80 (95%CI = 3.22 – 10.42) for the association between parental schizophrenia and offspring schizophrenia spectrum disorder. There was significant evidence of high levels of study heterogeneity ($I^2 = 96.5\%$). There was a significant association between maternal diagnosis of schizophrenia and offspring non-affective psychosis was (OR= 5.74; 95%CI = 2.68 – 12.30) and the association between paternal diagnosis of schizophrenia was also significant (OR=4.11; 95%CI = 3.20 – 5.29). There were significant differences between summary effects from differing study designs. There was a significant association between parental schizophrenia and offspring bipolar disorder (OR= 3.10 (95%CI = 2.39 – 2.81); and between parental schizophrenia and offspring Cluster A personality disorder (OR=3.62; 95%CI = 1.92 – 6.80). Eggers test indicated no evidence of small study bias. Influence analyses indicated no study exerted undue influence on the main results of the study.

Discussion: The meta-analysis supports and extends historical evidence that offspring of parents with schizophrenia have increased vulnerability of psychotic disorders compared to controls. Consistent with a dimensional model of psychotic disorders this association was also evident for bipolar and Cluster C Personality Disorder. The high degree of heterogeneity in the analyses suggests methodological differences and environmental factors are also relevant to accurate identification of vulnerability to psychotic disorders.

Poster #T149**LINE1 POLYMORPHIC RETROTRANSPOSITIONS IN SCHIZOPHRENIA**

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Background: Genome-wide association studies (GWAS) have produced a growing number of replicated Single Nucleotide Polymorphism (SNP) associations in complex psychiatric diseases, including schizophrenia, autism, and bipolar disorder. In most cases SNPs, Insertions/Deletions (Indels) and Copy Number Variants (CNVs) associated with complex psychiatric traits are mostly found in non-gene/non-coding regions and map predominantly in association with regulatory elements, which include both Transposable Elements (TEs) and TE-derived elements, like for example long intergenic non-coding RNAs (lincRNAs) or microRNA (miRNAs). Evidence is slowly accumulating that TEs could be involved in structural genomic variants and can contribute to the genetic component of vulnerability to psychiatric disorders. Although findings have been mostly anecdotal and despite our still initial and limited knowledge, active retrotransposition of LINEs, Alus and SVAs has been identified in several different human brain regions. The provocative hypothesis that we can derive is that active mobilization and differential expression of TEs can be essential in normal brain development (and adult physiology), and possibly in psychiatric disorders.

Methods: We have sequenced the whole genome of ~1,000 SZ cases and matched controls from our large sample of cases and controls that we collected over several years and include some mid-size families where schizophrenia segregates. For both cases and controls we are characterizing their genomic architecture, with a special interest in non-coding regulatory regions that harbor the largest number of association signals with the disease. In addition to the already large number of positively associated SNPs that fall within already known TEs as we understand from the last release of the human genome annotation (hg19), we are also looking for new TE retrotranspositions. Building from our sequenced families and using the ad hoc pipeline we have developed, we can identify both retrotransposition polymorphisms (RIPs – Retrotransposon Insertion Polymorphisms, i.e. new TE insertions that are transmitted from parent to their children) and “de novo” TE insertions that can arise in affected children, but are not present in parents.

Results: We found that more than 70% of SNP association signals fall within already known TEs or lincRNAs rather than within the boundaries of coding genes. Moreover, in many cases, the associated SNPs are far away from “genes”. Thus, using these associations as proxies for genes should be considered only a consequence of our current practice of binning the whole genome into “gene” regions rather than based on a carefully annotated gene-mapping procedure. When looking at RIPs in the few families that we have available from sequencing, we have observed that new TE insertions are more common than we previously thought, for all TE classes. Gene network analyses suggest predominant dysfunctions in Neurodevelopment, supporting a developmental hypothesis for Schizophrenia.

Discussion: With next-generation whole-genome approaches, we expect that our understanding of the relationship between TEs and psychiatric disorders will greatly improve. Current technologies offer a unique opportunity to integrate DNA and RNA sequencing data to explain the potential effects of RIPs on gene expression. We believe that understanding the mechanisms that finely dysregulate the genome and transcriptome in psychiatric disorders is of pivotal relevance

Background: Depersonalization refers to phenomena in which subjects complain that their mental activities, bodies, and/or surrounding environments are changed in their quality, so as to be unreal and strange. The pathophysiologic mechanisms underlying depersonalization have long been historically discussed from various standpoints, however, the theory for core pathophysiology is still controversial. In the present study, we investigated the nature of depersonalization especially in the schizophrenia spectrum. Regarding depersonalization in schizophrenia, the phenomena is one of characteristic symptoms in early stages of the illness, and is regarded as the prototype of self-disturbances in schizophrenia. Neurobiological research of depersonalization recently focused on a profound disruption of self-awareness mainly characterized by feeling of subjective emotional numbing and feeling of disembodiment including sense of body-ownership and agency (Sierra 2011). We investigated the cognitive mechanisms of depersonalization from the perspective of sense of agency (SoA). SoA is defined as a feeling that a person causes and controls his/her own actions and their effects on the outside world, and it is one of the essential aspects of self-consciousness. Moreover, SoA has been recognized as an operational measure for evaluating self-disturbances in schizophrenia (Frith et al., 2000; Lindner et al., 2005; Maeda et al., 2012; 2013), and aberrant SoA in schizophrenia has been physiologically explained based on the forward model in self-monitoring for intentional actions.

Methods: We investigated patterns of SoA in the schizotypal subjects with depersonalization by means of our original task: sense of agency task (Keio method) (Maeda et al., 2012; 2013) which is a agency attribution task that evaluates explicit experience of the temporal causal relation between an intentional action (Key press) and an external event on the PC screen. Various temporal delays of 0 to 1,000 ms were randomly introduced in the computer manipulation.

Results: We demonstrated the specific patterns of strikingly attenuated SoA in no-delay condition in subjects with depersonalization, i.e., the lack of SoA in the current time of actions. This means that agentic “cleft” between self and the external world could exist during intentional actions. This could never be found in chronic schizophrenia in our previous studies. Therefore, these curious findings are supposed to be specific findings in subjects characterized with depersonalization in early stage of schizophrenia spectrum disorders.

Discussion: From the perspective of the Forward model, the lack of SoA in the current time of action could be due to delayed prediction signals. We hypothesized the delayed prediction signal would be the core pathophysiological mechanisms for the schizophrenia spectrum, and pure form of the inadequate predictions could be seen without any compensatory processes in the early stage of the illness. Clinically, clarifying the specific nature of the depersonalization in early stage of the schizophrenia spectrum disorders could have significant implications for a profound understanding of pathophysiology of schizophrenia and could have critical role in its precise diagnosis in early intervention.

Poster #T151**CHILDHOOD AND ADOLESCENCE SYMPTOMS PRECEDING FIRST EPISODE PSYCHOSIS IN A GENERAL POPULATION BASED NORTHERN FINLAND 1986 BIRTH COHORT**

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Background: The onset for psychotic disorder is often in adolescence. At least some of them are neurodevelopmental disorders. Prospective general population based reports are lacking on specific symptoms in childhood and adolescence predicting clinically treated first episode psychosis in youth

Poster #T150**DEPERSONALIZATION IN THE SCHIZOPHRENIA SPECTRUM: LACK OF SENSE OF AGENCY AT THE CURRENT TIME OF ACTION DUE TO IMPAIRED PREDICTION**

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and having as a control group also non-psychotic psychiatric cases, and in this way taking account specificity. We wanted to describe which kind of symptoms precede onset of psychosis when taking account specificity.

Methods: Members of the Northern Finland 1986 Birth Cohort (N=8258 for Rutter B2 and N=6514 for PROD-screen), an unselected general population based cohort, were examined in childhood and adolescence. The 8 -year field study included Rutter B2 questionnaire for teachers and subscales from Rutter A questionnaire for parents screening antisocial and neurotic symptoms. The 15 -year field study included a 21-item PROD-screen questionnaire screening prodromal symptoms for last six months. The Finnish Hospital Discharge Register was used to find out new cases of psychosis and non-psychotic mental disorders till the age of 23 years.

Results: High scores of antisocial and neurotic symptoms in Rutter B2 and in subscales of Rutter A did not associate with later psychosis. The highest prevalence of positive symptoms in the PROD-screen were in the group of adolescents who developed psychotic disorder (65% over the cut off) compared to group of subjects who developed hospital-treated non-psychotic disorder (36%, p<0.001), and to group of subjects without any disorder (27%, p<0.001). Respective figures for negative symptoms were 55% in the group of psychotic adolescents, 30% in the group of subjects with non-psychotic disorder (p=0.01) and 24% in the "healthy" (p<0.001).

Discussion: Antisocial and neurotic symptoms reported by teachers and parents at age 8 did not predict psychosis. Both positive and negative features were common in adolescents, especially in those who later developed psychosis. In this large prospective general population sample both positive and negative symptoms in adolescence associated specifically with development of hospital-treated first episode psychosis.

Poster #T152

PHENOTYPIC FEATURES OF PATIENTS WITH SCHIZOPHRENIA CARRYING DE NOVO GENE MUTATIONS

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Background: Rare Copy Number Variants (CNVs) and Single Nucleotide Variants (SNVs) have been found to contribute substantially to the aetiology of schizophrenia. In their de novo form, they carry high pathogenicity value. This study attempts to parse schizophrenia based on the presence of such mutations and attempts genotype-phenotype correlation. We compare patients who carry de novo CNVs, to patients who carry de novo SNVs, to patients carrying no detectable mutations and examine phenotypic variables across three categories: clinical variables, premorbid variables and disease course & functional outcome.

Methods: A subset of probands was recruited from a collaborative genetic study of schizophrenia in the Afrikaner population spanning >10 years. 24 patients were included (7 with de novo CNV(s), 8 with de novo SNV(s), and 9 with no detectable mutation). Follow-up evaluations were performed using the Diagnostic Interview for Genetic Studies (DIGS), Specific Level of Functional Assessment scale (SLOF: a multidimensional survey across 6 domains of current functioning and behaviour) and a Checklist on Early Deviant Behaviour (EDB: probing 7 areas of deviance before the age of 10). Statistical analysis consisted of comparison of means between groups and chi-square analysis of two-way tables. The mean SLOF scores and parental ages were compared by one-way analysis of variance (ANOVA). Permutation tests were done to confirm results or compare means in diminutive sample sizes. Pairwise comparisons were used to illicit significant differences. Fischer's Exact test was used to detect significant differences in EDB.

Results: The lifetime diagnoses originally assigned to the subjects remained stable across all 3 groups and there was no difference in diagnostic stability indicating that the presence of de novo mutations does not lead to a different diagnostic course over time. The average SLOF scores for the 3 groups showed a gradient of severity of dysfunction with the worst outcome in the group with CNVs and the best in the group with no mutation. Patients carrying de novo CNVs had a significantly lower score in the domain "work skills" indicating worse adaptability and capacity to function independently. A significant trend was observed for the group with de novo SNVs toward learning disability. Also, although not significant, an enrichment of EDB -

Social Dysfunction, was found among the de novo CNVs group. In agreement with literature, we find that parental age (specifically paternal age) at the time of proband's birth is significantly higher in the group with de novo SNVs. Clozapine use (as a marker of treatment resistance) showed no significant difference between the 3 groups.

Discussion: Lifetime diagnoses remained stable over a period of >10 years and higher paternal age at the proband's birth correlated with subjects carrying de novo SNVs. The functional outcome seemed to be worse in the group with de novo CNVs and the best in the group carrying no detectable mutations with work skills being mostly affected. EDB seemed to occur more in the group with de novo SNVs. Treatment resistance was not prominent in our findings. Our results suggest that there is merit in evaluating functioning for particular domains rather than globally and it is evident that the combined use of the SLOF and EDB has higher predictive value for underlying genetic vulnerability. This study highlights valuable phenotypic characteristics in patients with schizophrenia with de novo CNVs and SNVs.

Poster #T153

ABERRANT AFFECTIVE SALIENCE ATTRIBUTION AS A RISK FACTOR FOR PSYCHOSIS-PRONENESS: INSIGHTS FROM THE TWINSSCANCHINA STUDY

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Background: Individuals with psychosis are frequently affected by auditory hallucinations. These aberrant perceptual experiences might arise from mis-assignment of salience to irrelevant auditory stimuli. For example, it was previously shown that aberrant emotional-meaning assignment to white noise (affective speech illusion) was more prevalent in patients with a psychotic disorder than in healthy controls. Furthermore, there was a progressively greater incidence of affective speech illusion with increasing familial vulnerability to psychosis. It was also found that in healthy controls, any type of speech illusions was strongly associated with positive schizotypy, but not with negative schizotypy. This study seeks to clarify the relationship between affective speech illusion and psychotic experiences in a Chinese subclinical population. It is hypothesized that presence of affective speech illusion predicts higher positive schizotypy scores.

Methods: Data were collected from 72 pairs of healthy Chinese adolescent twins (Mean age = 16.75) with no known familial or personal history of mental disorder. White noise speech illusion was measured using the White Noise Task: participants rated white noise clips as being speech with positive, negative, neutral, or uncertain valence; or no speech. Endorsements of positive and negative speech indicated "affective" speech illusion. Psychosis proneness was measured using the Community Assessment for Psychic Experiences (CAPE): a self-report 42-item questionnaire designed to measure the frequency and level of distress of psychotic-like experiences in the general population. The CAPE includes dimensions of positive psychotic experiences, negative psychotic experiences and depressive experiences.

Results: Multilevel linear modelling revealed that "negative speech illusion" significantly predicted CAPE positive dimension scores ($b=0.26$, 95% CI = 0.022, 0.51; $p=0.033$). Participants who assigned negative meaning to white noise reported more positive psychotic experiences. Negative speech illusion was also a marginally significant predictor of CAPE total scores ($b=0.22$, 95% CI = -0.02, 0.46; $p=0.075$). Specifically, there was a trend for participants who assigned negative meaning to white noise to report more psychotic experiences overall.

Discussion: Negative speech illusion independently predicted positive psychotic experiences, as well as showed a marginal effect in predicting overall psychotic experiences. The finding suggests that negative-meaning attribution to random noise in incoming auditory information might be the mechanism underlying positive psychotic experiences such as auditory hallucination. Auditory hallucinations that carried a negative emotional value then had to be "explained", resulting in delusions over time and hence maintaining or exacerbating positive schizotypy symptoms. Through the use of a subclinical population, our findings suggest that negative speech illusion was not due to the illness experience in psychotic patients, supporting it as potential vulnerability markers for positive psychotic symptoms.

Poster #T154**THE INDEPENDENT EFFECTS OF TWO NOVEL SOCIAL-COGNITIVE REMEDIATION PROGRAMS FOR SCHIZOPHRENIA: EMOTION RECOGNITION TRAINING AND COMPLEX MENTAL-STATE REASONING TRAINING**

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Background: Impaired ability to make inferences about what another person might think or feel (i.e., social cognition impairment) is recognized as a core feature of schizophrenia and a key determinant of the poor social functioning that characterizes this illness. The development of treatments to target social-cognitive impairments as a causal factor of impaired functioning in schizophrenia is of high priority. In this study we sought to compare the independent effects of two programs to improve social cognition in schizophrenia: "SoCog" Mental-State Reasoning Training (MSRT) and "SoCog" Emotion Recognition Training (ERT).

Methods: Forty two participants with schizophrenia or schizoaffective disorder were entered into the study to receive SoCog-MSRT (n=18) or -ERT (n=12) or were assigned to a control group (n=11). MSRT and ERT comprised 12 twice-weekly sessions for six weeks. Participants underwent assessments of social cognition (emotion recognition and affective and cognitive theory of mind), neurocognition and symptoms at baseline, post-training and three-months after completing training or treatment as usual.

Results: Results showed independent effects of MSRT and ERT. MSRT improved social skills and attributional biases, while ERT improved emotion recognition. MSRT also improved theory of mind abilities, although ERT also generalized to improve theory of mind abilities. Trends were found for an effect of training dose (number of training sessions attended) on affective and cognitive theory of mind. A sense of enjoyment and choice on the Intrinsic Motivation Scale (Choi et al., 2010) was also positively correlated with improved cognitive theory of mind abilities.

Discussion: ERT and MSRT were, to some degree, distinguished by improvements in the abilities targeted by each of these SoCog programs: ERT improved the recognition of negative emotions, whereas MSRT improved investigator-rated social skills that underlie successful social interaction and ameliorated the tendency to blame others for negative outcomes. However, ERT unexpectedly generalized to also improve the same complex theory of mind abilities as did MSRT. Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12613000978763.

Poster #T155**FACTORS RELATED TO EMPLOYABILITY OF OUTPATIENTS WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDERS**

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Background: The importance of work for patients with schizophrenia and other serious mental illnesses is well established, although only a small percentage of this population is employed. Having a job has been associated with clinical and social functioning improvement and reduction of depressive symptoms among schizophrenic individuals. The low employment rates among these individuals have been understood as reflecting a combination of psychological, clinical and social barriers (such as the stigma that may be present among employers) associated with lack of support and vocational guidance. In Brazil, according to statistics from Social Security referring to workers with formal registration, the mental disorders occupy the 3rd position among the causes of granting social security benefits such as: social security benefits for absence from work for more than 15 days, and disability pensions. In descending order: major depression, schizophrenia, bipolar disorder, alcoholism and obsessive compulsive disorder. According to the Ministry of Health, these numbers refer to workers with formal jobs, not been computed those individuals who never worked due to mental health disorders. The aim of this study was to analyze factors related to employability of schizophrenic and schizoaffective outpatients over a year.

Methods: Outpatients with schizophrenia and schizoaffective disorders were enrolled in two healthcare services from São Paulo. Inclusion Criteria: Age 18-45 years; stable for the psychiatric symptoms for at least two months; good treatment adherence; be able for the job in accordance with the evaluation of the reference team. Exclusion criteria: Judicial disqualification or disability retirement; drug and alcohol abuse; Patients hospitalized due to psychiatric causes for more than two weeks during the study. Patients were referred by the staff and should demonstrate interest in having a job. Those enrolled in these study were asked to fill out a questionnaire to analyze socio-demographic and clinical data and were assessed with the following scales: Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale, Global Assessment of Functioning (GAF), Clinical Global Impression Scale (CGI), Personal and Social Performance Scale (PSP).

Results: Thirty patients were assessed with an average age of 34.53 ($SD \pm 6.83$), 19 (63.3%) men, 26 (89.7%) single, 23 (92%) had a diagnosis of schizophrenia, and the mean disease duration was 22.47 years ($SD \pm 5.82$), 12 (40%) completed high school. Patients who got jobs had lower scores on PANSS negative scale ($F=2.192$, $t=-2680$, $df=28$, $p=0.012$), PANSS general psychopathology scale ($F=0.245$, $t=-2201$, $df=28$, $p=0.036$); PANSS total score ($F=0.001$, $t=-2747$, $df=28$, $p=0.010$), PSP ($F=1.109$, $t=2.803$, $df=28$, $p=0.005$). The variables education, antipsychotics, "had some work experience throughout life" and social relations were not significant when comparing these two groups.

Discussion: The results suggest that the group that got a job had lower scores on PANSS symptom and social performance scales. Dealing with the difficulties inherent to work is not always an easy task, therefore, the treatment of patients with schizophrenia and schizoaffective disorder should consider counseling before and during this process, to assist in the search for strategies to deal with challenges, especially the management of stress and interpersonal relationships.

Poster #T156**DECREASED CORTICAL AND RIGHT PREFRONTAL CORTEX VOLUMES ARE CORRELATED WITH AN INFLAMMATORY MARKER (IL-6) IN PATIENTS WITH SCHIZOPHRENIA**

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Background: It is well established that cortical gray matter and prefrontal cortex volume are decreased in patients with schizophrenia (SZ). The factors that lead to tissue loss are not clear. One possible explanation is that the increased pro-inflammatory status in SZ is related to volumetric decrease of gray matter. The aim of this pilot study was to correlate serum type-1 (TNF α) and type-2 cytokines (IL4, IL6, IL10) with cortical, left and right prefrontal cortex volume in patients with schizophrenia and matched controls.

Methods: We selected 36 patients with SZ (28 males; age mean = 37.17 ± 12.05 ; years of disease 15.56 ± 11.75), 36 matched controls (24 males, age mean = 37.06 ± 11.17). Images were acquired by a Philips Achieva 1.5T MRI scanner at the Hospital de Clínicas de Porto Alegre, Brazil. All images were processed using the automated pipeline of FreeSurfer v5.1. Age, years of education, gender and intracranial volume were regressed out from total cortical and prefrontal volume.

Results: IL6 is negatively correlated with cortical volume ($p=0.027$; $\rho=-0.370$) and right prefrontal volume ($p=0.012$; $\rho=-0.42$) in patients with SZ. IL4 ($p=0.167$; $p=0.053$; $p=0.069$), IL10 ($p=0.111$; $p=0.114$; $p=0.224$) and TNF α ($p=0.239$; $p=0.205$; $p=0.246$) are not correlated with cortical, right and left prefrontal cortex volume. IL6 is not correlated with left prefrontal cortex volume ($p=0.215$). In controls serum cytokines are not correlated with cortical, left and right prefrontal cortex volume: IL4 ($p=0.090$; $p=0.096$; $p=0.286$) IL6 ($p=0.090$; $p=0.068$; $p=0.170$) IL10 ($p=0.556$; $p=0.540$; $p=0.882$) TNF α ($p=0.547$; $p=0.558$; $p=0.918$).

Discussion: Increased inflammation markers have been described in schizophrenia relating increased IL-6 to the disorder. In animal studies IL-6 have been associated to brain anatomical abnormalities. Our re-

sult suggests that the chronic inflammatory activation in patients with schizophrenia could be related to the volumetric decrease of cortical and prefrontal cortex.

Poster #T157

PROGRESSIVE REDUCTION OF VISUAL P300 AMPLITUDE IN PATIENTS WITH FIRST EPISODE SCHIZOPHRENIA

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Background: To understand the underlying dynamic neurophysiological changes over the course of schizophrenia, it is important to study subjects longitudinally from the early stage of the illness. We previously reported that visual P300 was already impaired in patients with first episode schizophrenia (FESZ). The present study demonstrates how the visual P300 findings changed at the 1-year follow-up after their initial measurement. The visual P300, to our knowledge, has not been previously examined in longitudinal studies of schizophrenia.

Methods: Visual P300 was recorded with the same experimental paradigm and acquisition protocol at both time points in FESZ (n=18) or healthy comparison subjects (HC) (n=24). Participants silently counted infrequent target stimuli ("x") amid standard stimuli ("y") presented on the screen while the 64-channel EEG was recorded.

Results: FESZ showed visual P300 amplitude reduction and latency delay at baseline. Furthermore, FESZ showed progressive visual P300 amplitude reduction in the course of the illness over the 1-year follow-up. P300 latency didn't change over time in either group. FESZ showed significantly reduced Spatial Span total score at both time points, and there was a significant negative correlation between P300 peak amplitude at Pz with the BPRS positive score at baseline.

Discussion: These data showed a visual modality P300 progression in the early stage of schizophrenia, unlike the unclear or absent progression in the auditory P300. These visual P300 findings support the concept of progression of schizophrenia, suggesting the usefulness of the visual P300 as a biological marker of progression in schizophrenia.

Poster #T158

A COMPARISON OF LONG-ACTING INJECTED MEDICATIONS FOR SCHIZOPHRENIA

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Background: Background: Haloperidol decanoate and paliperidone palmitate are both efficacious long-acting preparations of antipsychotic medications that can be injected monthly. Neither requires reconstitution or refrigeration; both can be injected in either deltoid or gluteal sites; both can be initiated via loading strategies. Paliperidone palmitate is substantially more expensive than haloperidol decanoate. No randomized, blinded comparison of these agents has been previously reported.

Methods: Methods: Adults diagnosed with schizophrenia or schizoaffective disorder who were considered to be at risk for relapse and likely to benefit from treatment with a long-acting injected antipsychotic medication were randomly assigned to receive haloperidol decanoate 25–200 mg or paliperidone palmitate 39–234 mg every 4 weeks for up to 2 years. The primary outcome measure was time to efficacy failure (determined by an independent, blinded adjudication committee). Key secondary outcomes included weight, lipids, glucose, prolactin, and extrapyramidal side effects.

Results: Results: Data are available for the 145 individuals in each group (total n=290) who received at least one injection of their assigned medication.

Discussion: Discussion: The ACCLAIMS trial represents the first independent comparison of a first-generation and a second-generation long-acting injected antipsychotic medication. The presentation at SIRS will be the first conference presentation of the primary results of the study, including

comparisons of time to efficacy failure and of adverse effects including weight, lipids, glucose, prolactin and extrapyramidal side effects.

Poster #T159

"IT IS HARD WORK TO BECOME EDUCATED IN ONE'S VULNERABILITY". PATIENTS' CONCEPTUALIZATION OF TREATMENT FOR FIRST EPISODE PSYCHOSIS: A QUALITATIVE STUDY

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Background: Young people treated in specialized early intervention services for first episode of psychosis may achieve a high rate of remission and recovery. It is essential for a positive outcome that the treatment matches young peoples' needs, their aspirations and thereby facilitates their motivation to adhere to treatment. The results of our study can provide the mental health care system with up-to-date knowledge about young patients' interpretation of treatment, and thus contribute to the improvement of first episode treatment. Aim: To explore young patients' perceptions of the specialized early intervention and to identify factors important for adhering to treatment.

Methods: Young patients with a first episode of psychosis represented the study sample (n=14). The patients participated in focus groups in the beginning the research period. They were thereby included in the process of identifying the topics and questions that served to guide the choice of theme for this study. The identified questions were subsequently used in individual in-depth interviews (n=10), which focused on young patients' experiences of factors deemed important for remaining in treatment. Data was analyzed within the framework of phenomenology and hermeneutics

Results: The psycho-educational and cognitively oriented content of the specialized early intervention service match young patients' experiences of being in an educational setting. This perspective on treatment can be understood as age-appropriate.

Discussion: Conceptualizing treatment for first episode psychosis as an education may facilitate motivation for staying in treatment over time and enhance empowerment for young patients.

Poster #T160

A STRATIFIED MODEL FOR PSYCHOSIS PREDICTION IN CLINICAL PRACTICE

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Background: Neurocognitive disturbances are regarded as a core component of psychosis; and patients symptomatically at risk of psychosis already exhibit several neurocognitive deficits. These neurocognitive baseline deficits are promising candidates for an estimation of the risk of conversion. Research on the value of neurocognitive testing for psychosis prediction mainly relies on study-specific sample means, which, different from broadly available general test norms, are difficult to translate into clinical practice. We explored the combined predictive value of at-risk criteria and neurocognitive deficits according to test norms with a risk stratification approach.

Methods: We investigated potential predictors of psychosis (neurocognitive deficits and at-risk criteria) over 24 months in 97 at-risk patients.

Results: The final prediction model included (i) at-risk criteria: attenuated psychotic symptoms (APS) plus subjective cognitive disturbances (COGDIS), and (ii) a processing speed deficit: Digit Symbol Test (DST). The model was stratified into the following four risk classes: (i) neither DST deficit nor APS+COGDIS (ii) only DST deficit (iii) only APS+COGDIS (iv) both DST deficit

and APS+COGDIS. The hazard rates for the four risk classes ranged between 0.0 (both predictors absent) and 1.29 (both predictors present).
Discussion: The combination of a processing speed deficit and at-risk criteria provides an optimized stratified risk assessment. Based on neuropsychological test norms, it can easily be applied in clinical practice.

Poster #T161**AN OPEN-LABEL TRIAL OF ADJUNCTIVE TOCILIZUMAB IN SCHIZOPHRENIA**

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Background: Schizophrenia is associated with impaired cognition, which persists despite current treatments, and is an important determinant of quality of life and overall function. Converging lines of evidence suggest that interleukin-6 (IL-6) may play a role in the pathophysiology of schizophrenia. We previously found that higher blood IL-6 levels were a significant predictor of greater cognitive impairment in schizophrenia after controlling for multiple potential confounding factors. We are conducting an 8-week open-label trial of adjunctive tocilizumab in schizophrenia. Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor, approved by the US FDA for the treatment of adults with moderately to severely active rheumatoid arthritis. Tocilizumab is administered as an intravenous infusion every 4 weeks.

Methods: Subjects in the trial are age 18–55, taking a non-clozapine antipsychotic, stable based on clinical judgment and no psychiatric hospitalizations in the past 3 months, and on the same psychotropic medications for at least 1 month. Following a screening visit, subjects receive a 4 mg/kg infusion of tocilizumab at baseline and again at 4 weeks. Cognition, as measured by the Brief Assessment of Cognition in Schizophrenia (BACS, using alternate forms) is assessed at baseline, and 2, 4, and 8 weeks.

Results: In the first 3 subjects, tocilizumab infusions were well tolerated without significant adverse effects. The mean improvement was 11% on the BACS composite score, including a mean 32% improvement (11 points) on digit symbol coding.

Discussion: These preliminary data suggest that anti-cytokine therapy may be a viable adjunctive treatment for cognitive impairment in schizophrenia.

Poster #T162**CAARMS IN THE COMMUNITY: ASSESSING THE PREVALENCE OF ULTRA-HIGH RISK SYMPTOMS IN THE GENERAL POPULATION**

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Background: Over the past two decades, there has been increasingly interest in the definition, identification and treatment of individuals presenting with symptoms indicating an ultra-high risk of developing psychosis. However, current understanding of these ultra-high risk syndromes for psychosis is based almost entirely on studies of clinical populations and it is unclear whether there is another population that is experiencing similar symptoms but is not seen by mental health services. Motivated by the question of whether the OASIS clinical service represents the true extent of ultra-high risk individuals in South London, we aimed to estimate the prevalence of ultra-high risk symptoms within a general population sample.

Methods: A random sample of 200 participants was obtained from within the South London boroughs of Lambeth and Southwark, using GP lists and the national postal address file as sampling frameworks. Clinical interviews were conducted, including the Comprehensive Assessment for the At Risk Mental State (CAARMS) to assess ultra high risk symptoms against the PACE clinic criteria and the nine-item Schizophrenia Proneness Instrument – Adult version (SPIA-9) to check for basic symptoms. Data relating to past psychotic experiences, common mental disorder, help-seeking behaviour, sociodemographic characteristics, and other potential confounders were also collected.

Results: Preliminary findings have shown the overall unweighted prevalence of ultra-high risk subjects within our sample to be around 19%, with over 16% of subjects meeting PACE criteria and around 6% meeting Basic Symptom criteria. We expect the remaining analyses to show that:

1. In accordance with the concept of a psychosis continuum, the prevalence of ultra-high risk symptoms in the general community is in between that of subclinical psychotic experiences (approximately 17–25%) and diagnosable psychotic disorders (approximately 3%).
2. PACE criteria and Basic Symptom criteria tend to identify different individuals within this ultra-high risk group.
3. Not all of those meeting ultra-high risk criteria are in contact with clinical services.
4. Compared to patients using the OASIS service, subjects who meet ultra-high risk criteria but have not sought clinical help are likely to have:
 - a. Higher levels of basic symptoms and/or affective symptoms, but lower levels of attenuated positive symptoms.
 - b. A higher level of global functioning.

Discussion: These findings are likely to have implications for clinical services, particularly in South London. Preliminary data support the idea that there may be a number of individuals within the general population who would meet ultra-high risk criteria in terms of symptoms but do not seek clinical help. Indeed the size of this group may even be higher than the predictions of previous studies. Any sociodemographic differences between community and clinical ultra-high risk groups may indicate a need for services to target particular areas of the community with more information, whereas differences in the symptomatic profile of clinical and community ultra-high risk groups may be seen as reassurance that OASIS is successfully meeting the demand of those who need it most. Follow-up studies of this general population group may be required to establish the true meaning of these criteria outside of clinical settings.

Poster #T163**ALTERED CONNECTIVITY IN THE HIPPOCAMPAL NETWORK AND HEIGHTENED COUPLING WITH THE SALIENCE NETWORK IN PEOPLE AT ULTRA-HIGH RISK FOR PSYCHOSIS**

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Background: Dopamine dysfunction may lead to psychotic symptoms through an effect on salience processing (Kapur, 2003). It has been suggested that this dopamine dysfunction is driven by hippocampal overactivity, which influences midbrain dopamine neurons via inputs through the basal ganglia (Lisman and Grace, 2005). On the other hand, independent research suggests that there is a "salience network (SN)" comprising the insula and anterior cingulate cortex (ACC). Its activity is not task-specific, but involved in switching between the default mode (DMN) and central executive networks (CEN) (Sridharan et al, 2008). We used neuroimaging to investigate functional connectivity within and across these two different "salience" networks in people at ultra-high risk for psychosis (at risk mental state, ARMS).

Methods: Resting state functional MRI (rsfMRI) data were acquired from 29 ARMS subjects and 25 age and gender matched healthy controls (HC), using T2*-weighted echo-planar sequences (TR=2s TE=31ms), on a 3T scanner. The rsfMRI data were analyzed by independent component analysis (ICA). Six networks of interest were identified: hippocampal network (HN), basal ganglia network (BGN), SN, CEN (right and left), and DMN. Group differences in intra-network connectivity analysis within each network were tested for both the ARMS > HC and HC < ARMS contrasts, using a clusterwise family wise error (FWE) correction across all 12 tests, yielding a threshold of $p < 0.0041667$ for each contrast. Group differences in inter-network connectivity were calculated by partial correlation between the time series of each network, controlling for the effects of all the other networks.

Results: ARMS participants had significantly decreased connectivity within the HN and within the dorsal prefrontal part of the right CEN, but increased connectivity within the ventral prefrontal part of the right CEN. ARMS participants showed a significantly increased partial correlation between the HN and the SN ($p < 0.05$, FWE corrected).

Discussion: The ARMS was associated with intra-network abnormalities in both the HN and right CEN, but not within the SN, and with heightened

coupling between the HN and SN. These data provide further support for the role of altered medial temporal connectivity in psychosis, but also implicate the insular-ACC salience network.

Poster #T164

EMOTION PROCESSING IN SCHIZOPHRENIA IS STATE-DEPENDENT

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Background: Substantial evidence exists about impairments on emotion processing (EP) in schizophrenia patients (Maat et al., 2013). However, whether this deficit is trait- or a state dependent in schizophrenia remains unclear.

Methods: This is a 3 year longitudinal study, in a large sample of schizophrenia patients (N=521, age: 27.34±7.33, 77% men, IQ: 96.82±15.23) and healthy controls (N=312, age: 30.13±10.73, 50% men, IQ: 111.70±15.61). At baseline (T1) and at follow-up (T2) EP was assessed with the Degraded Facial Affect Recognition task (van 't Wout et al., 2004) and remission was assessed using the PANSS remission tool (Andreasen et al., 2005). Patients were divided into 4 groups: remission T1 and remission T2 (RR); remission T1 and non-remission T2 (RN); non-remission T1 and non-remission T2 (NN) and non-remission T1 and remission T2 (NR). EP performance between patients and healthy controls was analysed using ANCOVA. Group × time interactions, using repeated measure analyses, were used to examine differences between the patient groups in EP performance over time. Age, gender and IQ were served as covariates.

Results: Schizophrenia patients performed worse on EP compared to healthy controls at baseline ($F(1,797)=10.272$, $p=0.001$). Group × time interactions were found between RR and RN, $F(1,235)=11.360$, $p=0.001$, and between NR and RN, $F(1,161)=4.202$, $p=0.042$. No group × time interaction was found between NN and NR, $F(1,248)=0.500$, $p=0.480$.

Discussion: Our study shows that EP performance in schizophrenia is not stable over time and relies heavily on the state of illness, i.e. remission or non-remission. This suggests that social cognition; in particular facial recognition is related to the symptomatology of schizophrenia and might be a target for novel (psychotherapeutic) interventions.

Poster #T165

ETHNICITY, SOCIAL DISADVANTAGE AND THE LONG-TERM COURSE AND OUTCOME OF PSYCHOSIS

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Background: In the UK, there is strong evidence that black Caribbean and black African populations have higher rates of psychosis and more negative interactions with specialist mental health services. In addition, it has been suggested that the clinical course and outcome of psychosis in these groups is more benign, with fewer individuals experiencing continuous and negative symptoms over time. We sought to test this in a ten-year follow-up of a large cohort of individuals with first-episode psychosis (n=557) (AESOP-10).

Methods: AESOP-10 is a multi-centre follow-up study at 10 years of a cohort of 557 individuals with a first episode of psychosis. At baseline, extensive data were collected on a range of social and biological risk factors. At follow-up, detailed information was collated on clinical course and outcome, social function and disability, and service use during the 10 year period since inception into the study.

Results: At follow-up, 39 (7%) had died and 30 (5%) had moved abroad. Of the remaining 488, we successfully followed and collated information on 392 (80%). In contrast to what we hypothesised, we found evidence that black Caribbean and, to a lesser degree, black African cases experienced worse outcomes across all domains compared with white British. For example, black Caribbeans took longer to first remission (Hazard Ratio 0.7, 95% CI 0.5–0.9), were over 3 times more likely to experience a continuous (vs.

episodic) course (Risk Ratio 3.4, 95% CI 1.6–6.9) and were over two times more likely to experience severe symptoms when unwell (Odds Ratio 2.4, 95% CI 1.3–4.8). With regard to service use, both black Caribbean and black African cases were more likely to be admitted to hospital (black Caribbean Incidence Rate Ratio [IRR] 1.3, 95% CI 1.2–1.5; black African IRR 1.3, 95% CI 1.1–1.5) and to be admitted compulsorily (black Caribbean IRR 2.2, 95% CI 1.8–2.6; black African IRR 2.3, 95% CI 1.9–2.8). Overall, at 10 years over 75% of black Caribbean and black African cases had been admitted to hospital compulsorily at least once, compared with around 50% of white British ($p<0.001$). When adjusted for an index of baseline social adversity, differences between ethnic groups across all domains were attenuated.

Discussion: These analyses do not support the proposition that outcomes of psychosis are more benign in black minority ethnic groups in the UK. They do, in fact, suggest outcomes are worse and again show high levels of compulsory admissions in these groups. Tentatively, high levels of social disadvantage and isolation at first presentation may contribute to these more negative outcomes among black Caribbean and black African groups.

Poster #T166

CAN THE MOTOR THRESHOLD BE PREDICTIVE TO RESPONSE TO RTMS TREATMENT IN SCHIZOPHRENIC PATIENTS WITH AUDITORY HALLUCINATIONS?

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Background: The treatment of resistant auditory hallucinations in schizophrenia by repetitive transcranial magnetic stimulation (rTMS) shows a high interindividual variability in the response, without clearly identifiable predictor. The motor threshold is an individual variable which depends also on the state of excitability of the cortex of the subject at a given time. The purpose of our study is to test the existence of a link between the motor threshold as a reflection of the state of cortical excitability and efficacy of rTMS treatment in reducing hallucinations in schizophrenic patients.

Methods: Sixteen schizophrenic patients whose hallucinatory symptoms were assessed by the scale Auditory Hallucinations Rating Scale (AHSR) before (D0) and after (D12) rTMS were included in this experiment. RTMS treatment consisted in a stimulation assisted by neuronavigation at 20 Hz, 80% of motor threshold of a functional target of the left temporal cortex in four sessions on two consecutive days (D1 and D2). We tested the existence of a correlation link between the motor threshold measured before treatment and the percentage change in the score of the AHSR as a reflection of the effectiveness of treatment.

Results: We have highlighted a correlation between the motor threshold and decreased auditory hallucinations after treatment ($r=-0.57$, $p<0.02$). The higher the motor threshold was, the greater the treatment appears to be effective.

Discussion: We demonstrated the existence of a link between clinical rTMS efficacy and motor threshold. This result could help to clarify the indications for the use of rTMS in the treatment of auditory hallucinations.

Poster #T168

BRAIN STRUCTURE IN SUBGROUPS OF PERSONS AT ULTRA HIGH-RISK (UHR) COMPARED TO FIRST-EPIISODE SCHIZOPHRENIA AND HEALTHY PERSONS

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Background: The at-risk mental-state (ARMS) has become an established concept in early psychosis intervention research. While several MRI studies have identified brain structural changes in ultra-high-risk subjects (UHR), they have mostly divided subgroups based on later conversion to psychosis. There is, however, little research into the heterogeneity of subgroups of UHR subjects, who might enter the ARMS state through either genetic predisposition, attenuated symptoms, or brief limited psychotic symptoms.

Here we provide a cross-sectional subgroup analysis based on subgroups of UHR subjects with genetic vs. attenuated symptoms, and compare those to healthy subjects and unmedicated first-episode schizophrenia subjects.

Methods: We obtained high-resolution 3 T MRI scans (1mm voxel dimensions) from a total of 116 subjects: 43 unmedicated ultra-high risk risk (UHR) subjects (11 with genetic predisposition, and 32 with attenuated symptoms), 24 unmedicated first-episode patients, and 49 healthy controls with no prior psychiatric history. UHR subjects were assessed using the CAARMS interview. Groups did not differ in age or gender distribution. All subjects provided written informed consent to a study protocol approved by the local ethics committee. We used voxel-based morphometry (VBM) to analyse grey matter density across the entire brain and compared the total UHR group as well as the two subgroups to healthy controls (HC) at $p < 0.001$, testing anatomical hypotheses focusing on the prefrontal and temporal cortices, and removing variance related to age and gender.

Results: UHR subjects compared to controls showed focal grey matter deficits in the left prefrontal cortex (PFC) and right lateral (superior and middle) temporal cortex. The attenuated symptoms UHR subgroup (UHR-as) showed grey matter deficits in the right lateral temporal cortical cluster only, as compared to healthy controls, but higher grey matter density compared to first-episode schizophrenia (Sz) subjects in right striatum and thalamus, left insula and putamen, as well as left hippocampus. The genetic liability subgroup of the uHR sample (UHR-gen) showed grey matter deficits compared to healthy controls in left PFC, right lateral/orbital PFC, right caudate and right medial temporal lobe/hippocampus, but no grey matter increase compared to Sz.

Discussion: These findings provide a first delineation of brain structural deficits in persons at high risk of developing schizophrenia, by demarcating effects in those subjects whose UHR state is based on genetic factors and those based on the expression of attenuated symptoms. While the former group shows multiple prefrontal and medial temporal deficits, resembling patterns seen in chronic and first-episode schizophrenia, the attenuated symptoms subgroup (UHR-as) shows only minor deficits in the right superior/middle temporal cortices. The latter might be related to the presumably higher heterogeneity of this subgroup, in which many persons might go on to develop either another psychiatric disorder (non-psychotic) or show symptoms in other dimensions. Hence, our results provide evidence for biological heterogeneity of UHR samples and the at-risk mental state.

Poster #T169

EFFECT OF LONG-TERM TREATMENT WITH LURASIDONE OR RISPERIDONE ON METABOLIC SYNDROME STATUS IN PATIENTS WITH SCHIZOPHRENIA

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Background: This post hoc analysis evaluated the effect of long-term treatment with lurasidone or risperidone on metabolic syndrome status in patients with schizophrenia.

Methods: Outpatients with clinically stable schizophrenia were randomized 2:1 to flexibly dosed, once-daily lurasidone (40–120 mg/d) or risperidone (2–6 mg/d) in a 12-month, multiregional, double-blind study that was followed by an open-label extension during which all patients received flexibly dosed lurasidone (40–120 mg/d) for up to 6 months. International Diabetes Federation criteria were used to evaluate metabolic syndrome, defined as elevated waist circumference (based on ethnic group-specific norms) or $BMI > 30 \text{ kg/m}^2$ (in patients without available waist circumference measurement) plus ≥ 2 of the following: triglycerides $\geq 150 \text{ mg/dL}$, HDL cholesterol $< 40 \text{ mg/dL}$ in men or $< 50 \text{ mg/dL}$ in women, blood pressure $\geq 130/85 \text{ mmHg}$, or blood glucose $\geq 100 \text{ mg/dL}$. Lurasidone and risperidone treatment groups were compared using a chi-square test. Double-blind and open-label data were analyzed using observed cases (OC) and study completers.

Results: The prevalence of metabolic syndrome at baseline of the double-blind phase was similar for the lurasidone group (32.5%; 134/412) and the risperidone group (32.7%; 65/199). After 12 months of treatment, the prevalence of metabolic syndrome (OC) was 31.5% (47/149) with lurasidone and 44.1% (41/93) with risperidone ($p < 0.05$). Among patients without

metabolic syndrome at baseline, 16.3% (16/98) of lurasidone-treated patients met criteria for metabolic syndrome after 12 months, compared with 27.1% (16/59) of risperidone-treated patients (OC, $p = \text{NS}$). Of the patients who satisfied criteria for metabolic syndrome at baseline, 36.7% (18/49) of patients in the lurasidone group no longer met criteria for metabolic syndrome after 12 months, compared with 28.1% (9/32) of patients in the risperidone group (OC, $p = \text{NS}$). For patients taking lurasidone in the double-blind phase who continued on lurasidone in the open-label phase ($n = 109$), the prevalence of metabolic syndrome was 33.3% at double-blind baseline and 26.6% after 18 months of treatment. In a similar analysis of patients switched to open-label lurasidone after 12 months of double-blind risperidone treatment ($n = 65$), the prevalence of metabolic syndrome was 42.9% at double-blind baseline, 48.4% at open-label baseline (after 12 months of risperidone), and 38.5% after 6 months of open-label lurasidone.

Discussion: Lurasidone treatment was associated with a lower risk of metabolic syndrome compared with long-term risperidone treatment. The prevalence of metabolic syndrome remained stable over 18 months of continuous treatment with lurasidone, in contrast to increases in the prevalence of metabolic syndrome over 12 months of treatment with risperidone. The prevalence of metabolic syndrome decreased in risperidone-treated patients who were switched to lurasidone for 6 months.

This study was sponsored by Sunovion Pharmaceuticals Inc. ClinicalTrials.gov identifier: NCT00641745.

Poster #T170

COULD REWARD-DISTURBANCES CAUSED BY ANTIPSYCHOTIC MEDICATION LEAD TO WEIGHT GAIN?

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Background: The reward system is known to be central to the regulation of appetite. Further, disturbances of the brain reward system are suggested to play an important role in the development of central psychopathological symptoms in schizophrenia. Antipsychotic medication partly acts by modulating the reward system and most antipsychotics cause some degree of weight gain. Recently, a relation between weight gain caused by one week of olanzapine treatment and change in reward signalling was found in healthy volunteers (Mathews et al. Arch Gen Psychiatry 2012;69:1226–1237). To our knowledge there are no previous studies examining how the effect of antipsychotic treatment on the reward system relate to weight gain in patients.

Methods: 50 antipsychotic-naïve first-episode patients with schizophrenia and 40 healthy controls were included in the study at baseline. 38 patients and 31 healthy controls were re-examined after six weeks where patients were treated with individual doses of Amisulpride. Weight gain was monitored during the period. At both baseline and follow-up the participants went through a functional Magnetic Resonance Imaging (fMRI) examination, while playing a monetary reward task (Nielsen et al. Arch Gen Psychiatry 2012;69:1195–1204). Relation between weight gain and the salience related activity in three parts of striatum was analysed.

Results: During the treatment period the patients received an average daily dose of 248 mg of Amisulpride and improved significantly in PANSS total, positive and general score (all $p < 0.001$). Further they had an average weight gain of 2.2 kilograms in the treatment period. Regarding fMRI a decreased activation in ventral striatum in the salience contrast was found in the patients at baseline. Further, patients with the most blunted fMRI response at baseline were the patients with the highest degree of weight gain during the next 6 weeks ($r = 0.412$, $p = 0.017$). At follow up, we found a correlation between weight change and the improvement of contrast signal in right putamen: The patients with the highest weight gain were the ones showing the most normalized BOLD response in right putamen ($r = 0.541$, $p = 0.001$). There was no relation between weight gain and treatment response or medication dose.

Discussion: As expected, antipsychotic treatment on average caused a moderate weight gain in the patients. The highest weight gain was found in the patients with the most aberrant fMRI anticipation signal at baseline, and the patients with the highest weight gain were also showing the highest increase in salience contrast signal over time. We do not know what this

change in BOLD response in striatum corresponds to at the neural level. However based on previous work, it seems reasonable to assume that it is related to changes in dopamine transmission. Thus our results suggest that by altering the dopaminergic transmission in putamen, antipsychotic medication might affect appetite regulation through its influence on the reward system and thereby, together with other mechanisms, lead to weight gain.

Poster #T171

PIERRE RIVIÈRE VS. ANDERS BREIVIK: IS HISTORY REPEATING ITSELF? RATIONALITY, MADNESS, AND PSYCHOPATHOLOGY IN THE 19TH AND 21ST CENTURY

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Background: In 2011 Anders Behring Breivik, ABB, slaughtered 77 civilians in a twofold attack on downtown Oslo and the island of Utøya. In the ensuing trial ABB's sanity or lack thereof was fiercely contested as two psychiatric evaluations arriving at radically different conclusions were drawn up. One found ABB to be suffering from paranoid schizophrenia whereas the other discovered no psychotic manifestations and instead diagnosed him with a narcissistic personality disorder with antisocial traits. Though unrivalled in the scope of its bestiality the case of ABB is not unique. In 1835 French peasant Pierre Marie Rivière, PMR, in a seemingly incomprehensible act of cruelty killed his immediate family with a pruning hook. Some contemporaries including Esquirol saw in PMR the traces of radical irrationality while others ascribed the deeds to an evil constitution. Thus a basic disagreement on the make-up of rationality and madness is seen to persist across the centuries and the advances made in all fields of psychiatry. It is the goal of this poster to clarify the nature of this divergence of opinions and to point a way forward.

Methods: In 1975 Foucault et al. published the book "I, Pierre Rivière, having slaughtered my mother, my sister and my brother ... A case of parricide in the 19th century" which contains a manuscript by PMR detailing the background for his actions, exempts from contemporary sources, and a number of analyses of the court proceedings and psychiatric evaluations that followed. During the trial of ABB the two psychiatric evaluations were leaked to the press, thus making it possible to carry out a phenomenologically informed, comparative, psychopathological reading of the documents using the case of PMR as a perspectival backdrop for understanding the disagreement at play.

Results: As were the case in 19th century France a certain grille de lecture influences the evaluations of ABB. Rather than being neutral case histories the evaluations tend to paint different portraits as pertinent omissions of certain facts are made. Thus the second evaluation manages to invoke an aura of rationality around ABB that allows for radically different interpretations of behaviour and statements that were initially considered indicative of psychosis.

Discussion: As the recent debate over the revision of the DSM quite clearly demonstrated current diagnostic praxis faces gross challenges. It appears to be this very fundamental crisis of both academic and clinical psychiatry that is encapsulated in the disagreement on the constitution of PMR and ABB. Across almost two centuries and the huge strides made by neurobiology and the cognitive sciences these two cases seem to have run a parallel yet somewhat misleading course. Prominent psychiatrists have called attention to the unintended consequences of adopting the diagnostic manuals as the ultimate authority on psychopathology. We suggest that a renewed interest in the continuation of a phenomenological psychopathology with a strong eye for context and Gestalt as opposed to mere "symptom-counting" is indeed called for as a sine qua non for a psychiatry that strives for both reliability and validity.

Poster #T172

PROJECT CHANGE: IT IS ABOUT LIFE. A RANDOMISED CLINICAL TRIAL INVESTIGATING THE EFFECT OF A SYSTEMATIC INTERVENTION FOR IMPROVING THE PHYSICAL HEALTH OF PATIENTS WITH SCHIZOPHRENIA

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Background: Schizophrenia is a life shortening disease, not only because of suicide but also because of increased mortality from natural causes of death. Patients with schizophrenia have a 20 years shorter life expectancy compared to the general population, and a 2-5 fold increased risk of death by coronary heart disease, respiratory diseases, lung cancer and endocrine and metabolic conditions. Part of the reason for this difference in health status is lifestyle factors and under treatment of somatic illness. With the project CHANGE, we want to investigate the effect of a systematic intervention aiming at improving lifestyle factors such as smoking, dietary habits and physical exercise.

Methods: We will include 450 patients with disorders in schizophrenia spectrum and randomise them to either treatment as usual plus treatment in CHANGE team or treatment as usual plus a care coordinator who will ensure contact to general practice or treatment as usual. The treatment provided by the CHANGE team will be affiliation of a life style coach to each patient, offering possibilities for participation in physical exercise adjusted to the needs and the abilities of the patient group, offering dietary advices and concrete help to change dietary habits, plus offering participation in a specialised smoking cessation program. Each patient will be affiliated to the team for one year, and the effect on risk for cardiovascular diseases will be measured by independent blinded researchers after one and two years. Secondary outcome measures will be smoking and sedentary lifestyle, perceived health, body mass index, waist circumference, waist circumference for a given BMI, resting blood pressure and heart rate, total blood cholesterol, LDL and HDL, triglycerides, fasting plasma glucose, and last week dietary intake of fibres, fat, fish, fruit, vegetables, and quality of life

Results: Baseline result for the 450 patients will be presented. Inclusion period will end in February 2014

Discussion: This trial is one of the first to investigate in a large group of patients whether the high risk of cardiovascular diseases can be reduced by life style interventions. The high mortality rates from cardiovascular diseases makes this kind of interventions necessary

Poster #T173

THE PROGNOSTIC SIGNIFICANCE OF EARLY REMISSION OF POSITIVE SYMPTOMS IN FIRST EPISODE PSYCHOSIS

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Background: Time to remission of positive symptoms has frequently been used as an important indicator of treatment outcome for patients with a psychotic disorder, but there has been little investigation of its significance for longer term outcomes. In this presentation we test the hypothesis that earlier remission of psychotic symptoms is associated with better symptoms and functioning outcomes at five year follow-up.

Methods: Time to remission of positive symptoms, other early characteristics and 5 year outcomes were assessed in a prospective study of 132 patients being treated for the first time for a psychotic disorder. Outcomes included assessment of positive and negative symptoms as well as weeks of competitive employment or studies and weeks on a disability pension.

Results: Just under 60% of patients showed remission of positive symptoms within 3 months. In comparison to later remitters, they showed lower levels of positive symptoms, greater likelihood of competitive employment and less likelihood of collecting a disability pension at five years.

Discussion: Early remission of positive symptoms may have prognostic significance for longer term symptoms and functioning outcomes. Possible mechanisms underlying this relationship will be discussed.

Poster #T174**GENDER DIFFERENCES IN THE COURSE OF SCHIZOPHRENIA ACROSS DIVERSE REGIONS OF THE WORLD**

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Background: Women with schizophrenia have been found to have a better course than men. Biological, social and cultural reasons have been proposed to explain these differences. We present a post-hoc analysis of the World-Schizophrenia Health Outcomes Study (W-SOHO) which explores the gender differences in the course of schizophrenia across regions

Methods: The W-SOHO study is a three year follow-up study on the outpatient care of schizophrenia that included 17,876 patients from 37 countries. Patients were recruited in W-SOHO by their treating psychiatrists when starting or changing antipsychotic medication. Evaluation was conducted during the normal course of care and was scheduled every six months after the baseline visit. Remission was defined adapting the Andreasen criteria to the CGI-SCH scale (Haro et al., 2008). Recovery was defined as two years of clinical remission with good social functioning. Patients were classified into 6 regions (North Europe, South Europe, Latin America, Asia, Central & Eastern Europe and Africa & Middle East). MMRM and GEE models were applied to account for the correlation between the visits of the same patient.

Results: Overall, differences in remission rates were small, with higher remission rates in women (58% versus 52% remission at 36 months; GEE OR, including all visits, 1.22 95%CI 1.14; 1.32). However, differences varied across regions. In South of Europe and Africa and Middle East, women had higher remission rates (OR 1.45; 95%CI 1.29; 1.62 in South of Europe; 1.36 95%CI 1.01; 1.84 in Africa and Middle East). In north of Europe, Central and Eastern Europe and Central Asia, remission rates in women were slightly higher, but differences were only marginally significant in the regression model (p value <0.1). There were minimal gender differences in Latin America. Recovery rates were much lower overall, with a frequency at 36 months of 17% for men and 12% for women. There were also regional differences. Gender differences in South of Europe were high, with 15% recovery rates at 36 months for women and 8% for men. Differences were also relevant for Latin America (23% vs 17%) and North of Europe (19% vs 15%). However, differences were non existant in Asia, Central & Eastern Europe and Africa and Middle East.

Discussion: Although overall women had higher remission rates than men, differences showed variation across regions. In all cases, women had higher remission rates than men, but the size of the difference varied.

Poster #T175**NPAS3: NEW GENETIC AND BIOLOGICAL FINDINGS WITH IMPLICATIONS FOR PROTEIN AGGREGATION AND SCHIZOPHRENIA**

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Background: Neuronal PAS Domain Protein 3 (NPAS3) was initially associated with schizophrenia through a balanced translocation. Subsequently, population studies associated NPAS3 with schizophrenia, bipolar disorder and antipsychotic efficacy. NPAS3 is a bHLH transcription factor that is important in the regulation of hippocampal neurogenesis. We sought to find and characterize additional mutations in this gene and to further characterize its biological properties.

Methods: NPAS3 exons and 3' and 5' flanking regions were sequenced using PCR and capillary electrophoresis in 34 probands (26 with schizophrenia, 8 with schizoaffective disorders) from a large genetic study of US pedigrees. Bacterially expressed and purified NPAS3 was subjected to an aggregation assay and mammalian expressed and purified NPAS3 was subjected to cold sarkosyl fractionation.

Results: We identified a nonsynonymous point mutation in NPAS3 that segregates with schizophrenia in a small American family. The mutation results in a valine to isoleucine (V304I) amino acid substitution located in the region between the two PAS domains, a potentially critical region for DNA binding and protein function. We have shown that NPAS3-V304I affects neurite outgrowth. Biochemically NPAS3 forms high molecular weight species in bacterial and mammalian systems suggestive of protein aggregation and the V304I mutation increases aggregation. In addition, the V304I mutation is located in a region critical for NPAS3 aggregation.

Discussion: Our study provides additional evidence for the role of NPAS3 in major mental illness. Like DISC1, NPAS3 appears to aggregate, suggesting that protein aggregation may contribute to the pathogenesis of psychiatric illness and provide a therapeutic target.

Poster #T176**THE INCREASED NUMBER OF PHOSPHOLIPID ABNORMALITIES OBSERVED IN THE ERYTHROCYTE MEMBRANE OF SCHIZOPHRENIA PATIENTS IS ASSOCIATED WITH INCREASED PSYCHOPATHOLOGY**

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Background: Neurotransmitter signalisation in brain is dependent on the biophysical and biochemical lipid membrane proprieties in particular at the membrane synapse level. The dopamine signalling dysfunction described in the physiopathology of patients with schizophrenia (SCZ) may partly result from these abnormalities.

Methods: Clinical characteristics and membrane lipid composition of chronic medicated patients with schizophrenia (n=75) have been examined and compared to a healthy control (HC) population (n=40). PANSS total as well as its positive and negative components were measured in the SCZ population. Red blood cell (RBC) membrane phospholipid (PL) and fatty-acid (FA) composition was identified by using LC-MS/MS method.

Results: Several highly significant differences were found in the PL and FA composition between patients and HC. A significant decrease of sphingomyeline (SM, p<0.0001) and phosphatidyl ethanolamine plasmalogens (PLG, p=0.001) as well as a significant increase of phosphatidylserine (PS, p<0.0001) was observed in SCZ patients. A total of 56.7% of the SCZ patients exhibited a decreased SM% versus 27.5% for HC. Furthermore, 82% of the SCZ patients exhibited an increase PS % versus 56% for HC. Patients' index of psychopathology increased with the number of PL RBC membrane abnormality. PANSS total and positive score were significantly higher in patients exhibiting concomitantly abnormal SM and PLG in comparison with SCZ patients without these abnormalities (p=0.01 and 0.03 for PANSS total and positive respectively). By contrasts, absence of membrane PL abnormality was significantly associated with low grade psychopathology (p=0.017 and 0.005 for PANSS total and positive respectively).

Discussion: An abnormal RBC PL composition was confirmed in a significant percentage of treated SCZ patients. Concurrent abnormal decrease in SM and plasmalogen is the RBC membrane was associated with the highest psychopathology severity scores in SCZ patients. The aberrant signalisation at the synapse level leading to increase psychopathology may be partly due to the abnormal lipid membrane composition and signalisation.

Poster #T177**RELATIONSHIP BETWEEN PSYCHOTIC SYMPTOMS AND JUMPING TO CONCLUSIONS: ARE THERE DIFFERENCES BY GENDER?**

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Background: The phenomenon known as "jumping to conclusions" (JTC) is a reasoning bias consisting in a tendency to make a decision about an event without having enough information about this. This feature has demon-

strated to be more present in people with schizophrenia, especially those with delusions (Garety et al, 1991; 2005). Moreover, gender differences in psychopathological assessment of people with schizophrenia have been demonstrated (Ochoa et al, 2012). So, the aim of the present study is to assess gender differences in the relationship between JTC and psychotic symptoms.

Methods: A total of 29 men and 14 women with schizophrenia were included in the study. JTC was assessed with the classical tasks of the beads in their three versions (task 1: probability 85:15; task 2: probability 60:40 and task 3: probability 60:40 with emotional component). The patients were assessed with the SANS and the SAPS for the assessment of clinical symptoms.

Results: In the case of men with schizophrenia, JTC in task 1 was explained by higher punctuations in distractible speech ($p=0.017$); while hallucinations ($p=0.036$) and illogically ($p=0.024$) explained JTC in task 2 and illogically ($p=0.042$) explained JTC in task 3. In the group of women pressure of speech ($p=0.004$) was related to JTC in task 1 and anxiety ($p=0.008$) explained JTC in task 2. No symptom variables were related to JTC in task 3 in women.

Discussion: In both samples, several items of positive formal though disorder were related to tasks of JTC. In the case of women anxiety was other specific symptom implicated in JTC while in men hallucinations were related to JTC. Specific interventions should be addressed different for women and men.

Poster #T178

LIFETIME EXPOSURE TO SEVERE TRAUMA, STRESS SENSITIVITY AND PSYCHOSIS IN A UK SAMPLE

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Background: There is increasing evidence which implicates social adversity in the development of psychosis. However, there remains a shortage of data on exposure to severe traumas and on the putative mechanisms involved and how these relate to experience of peoples' normal everyday life. One possibility is that stress sensitivity, defined as an increased intensity of psychotic or psychotic-like experiences in response to daily hassles, is elevated in those with prior exposure to severe trauma. In other words, increased stress sensitivity may lie on a pathway between exposure to severe trauma and development of psychosis. These possible mechanisms have not been investigated in relation to severe traumas and course of everyday life.

Methods: Data are drawn from an ongoing case-control study of first-episode psychosis (FEP) that overlaps with the EU-GEI study. Information on lifetime exposure to severe trauma (e.g. war) is being collected using the Harvard Trauma Questionnaire (HTQ). Experience Sampling Method (ESM) is used to assess daily hassles (defined as distinctive unpleasant events) and psychotic or psychotic-like symptoms occurring in the course of everyday life in cases and controls.

Results: To date, 28 cases and 36 controls have been assessed with the ESM and HTQ. Compared with controls, cases were more likely to be exposed to 3 or more traumatic events (OR 3.97, 95% CI 1.32-11.91, $p=0.014$). Cases reported higher levels of daily hassles ($B=0.31$, 95% CI -0.003-0.62, $p=0.052$) and psychotic experiences ($B=1.10$, 95% CI 0.70-1.50, $p<0.001$) than controls. Daily hassles were associated with an increased intensity of psychotic experiences in cases ($B=0.18$, 95% CI 0.05-0.30, $p=0.006$) and controls ($B=0.38$, 95% CI 0.03-0.13, $p=0.002$). We further observed that the association between daily hassles and psychotic experiences was similar in controls exposed to 3 or more traumatic events and in those exposed to less than 3 traumatic events (likelihood ratio test for daily hassles x traumatic event, $\chi^2=0.35$, $p=0.556$). By contrast, the association between daily hassles and increased intensity of psychotic experiences was stronger in cases exposed to 3 or more traumatic events ($B=0.55$, 95% CI 0.13-0.96,

$P=0.010$) compared with those exposed to less than 3 traumatic events ($B=0.14$, 95% CI 0.01-0.27, $P=0.038$) (likelihood ratio test for daily hassles x traumatic event, $\chi^2=3.32$, $P=0.069$).

Discussion: We found preliminary evidence that stress sensitivity may be an important mechanism that links exposure to severe trauma to an increased likelihood of psychotic or psychotic-like experiences. The potential moderating and mediating effects of cognitive schemas will be explored as the sample size of this study increases.

Poster #T179

ATYPICAL ANTIPSYCHOTICS NORMALIZE GAMMA EVOKED OSCILLATIONS IN PATIENTS WITH SCHIZOPHRENIA

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Background: The cognitive dysfunction and psychopathological symptoms of schizophrenia might be mediated by a disconnection syndrome both within and between different cortical areas. Changes in cortical oscillatory activity may be the functional correlate of this cortical network disconnection. Steady-state responses are an easy and consistent way to explore cortical oscillatory activity.

Methods: The use of a chirp-modulated tone (increasing the frequency of the modulation in a linear manner) allows a fast measure of the steady-state response to different modulation rates. We studied the auditory steady-state responses in two groups of patients with schizophrenia (7 drug-naïve and 23 treated with atypical antipsychotic drugs), in order to assess the differences in their responses with respect to healthy subjects, and study any potential effect of medication.

Results: Drug-naïve patients had reduced amplitude and inter-trial phase coherence of the response in the 30-50 Hz range, and reduced amplitude of the response in the 90-100 Hz range, when compared to controls. A shift of the frequency of maximal response from 42 to 49 Hz was also observed. In the treated patients group, the response in the 30-50 Hz range was normalized to values similar to the control group, but the reduction in amplitude in the 90-100 Hz range remained as in the drug-naïve group.

Discussion: These results suggest that gamma activity impairment in schizophrenia is a complex phenomenon that affects a wide band of frequencies and implies a shift in the frequency of preferred gamma oscillations. Treatment with atypical antipsychotic drugs can partially revert some of these alterations.

Poster #T180

THE COURSE OF COGNITIVE FUNCTIONING IN CLINICAL HIGH RISK AND FIRST-EPIISODE PSYCHOSIS INDIVIDUALS

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Background: Cognitive deficits form a prominent feature in psychosis patients as well as in individuals with an at-risk mental state (ARMS) for psychosis. It has been suggested that cognitive dysfunction in psychosis is caused secondary to abnormal brain development in early life, thus preventing the ordinary acquisition of such abilities in the first place. Alternative theories postulate that early neurodegenerative processes are taking place in adolescence or adulthood, provoking both the onset of psychosis as well as a progressive cognitive decline. However, evidence for this latter neurodegenerative model of disease is scarce as there is a lack of longitudinal studies examining the course of cognitive deficits before and after onset of psychosis. To test the neurodevelopmental model of psychosis, we investigated whether transition to psychosis and the prolonged course of the disorder are associated with a progressive cognitive decline over time.

Methods: The prospective longitudinal Basel Früherkennung von Psychosen (FePsy; English: Early Recognition of Psychosis) project, which aims to improve the early detection of psychosis, is well suited to examine the time

course of cognitive deficits in psychosis. In total, 27 ARMS individuals, 13 first-episode psychosis patients (FEP) and 15 healthy control subjects (HC) completed a comprehensive neuropsychological test battery. ARMS participants were clinically assessed at regular time intervals by experienced clinicians for up to seven years. During this period, 11 ARMS individuals developed psychosis (ARMS-T) while 16 did not (ARMS-NT). Cognitive function of ARMS subjects was reassessed either at the onset of psychosis or after a follow-up period of approximately five years. Neuropsychological performance of HC and FEP subjects was reassessed on average after four years and five years, respectively. Linear mixed effects models were used to compare performance on verbal learning and memory, working memory, attention and executive function longitudinally between the groups, adjusted for age, sex, education and neuroleptic medication. All p-values were fully corrected for multiple testing using the False Discovery Rate (FDR) procedure.

Results: Significant group-by-time interactions were found for verbal memory (California Verbal Learning Test; short delay free recall: $p \leq 0.023$, long delay free recall: $p \leq 0.023$) as well as cognitive flexibility (Wisconsin Card Sorting Test; total number of perseveration errors: $p \leq 0.026$). Post-hoc analyses showed that this effect was driven by the ARMS-T group displaying performance decreases in all of these cognitive domains over time as compared to the HC and ARMS-NT group (all $p \leq 0.05$). The ARMS-T group also showed significant cognitive flexibility decreases ($p=0.006$) as well as a marginally significant decline in verbal memory function (short delay free recall: $p=0.077$; long delay free recall: $p=0.067$) over time as compared to FEP individuals.

Discussion: Our finding of verbal memory and cognitive flexibility decreases over time in the ARMS-T group suggests that cognitive function declines in these cognitive domains are associated with transition to psychosis. Given that this effect was not detected for FEP individuals, our results do not support any evidence towards a continuous worsening of cognitive function after illness onset. Accordingly, our results only provide partial support for a neurodegenerative model of disease and rather implicate that circumscribed cognitive abilities are decreasing as a function of psychosis onset but do not further progressively decline during the course of illness.

Poster #T181

NEUROCOGNITIVE CHARACTERISTICS OF PSYCHOSIS RISK SYNDROME IN HELP-SEEKERS AND HEALTHY CONTROL CHILDREN AND ADOLESCENTS

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Background: Ultra-High Risk for Psychosis, also denominated At Risk Mental State or Psychosis Risk Syndrome (PRS) is characterized by the presence of several clinical indicators that reflect the patient vulnerability for developing a psychotic disorder. Previous studies have evaluated clinical criteria to help identify subjects with PRS, showing that about 35% of subjects with clinical high risk (HR) criteria developed a psychotic disorder at 12 months after completing any of the HR criteria, although the percentages vary in the different studies. Cognitive markers may be used to increase the predictive value of those HR criteria, being an early predictor of the risk to develop psychotic disorders, as a manifestation of impaired cerebral aging processes that occur prior to the appearance of the classic clinical symptoms. Several studies suggested cognitive impairment in patients with PRS, specifically in general intelligence, attention, executive functioning, verbal fluency, working memory, and verbal and visual memory. The aim of this study is to determinate the neurocognitive characteristics of PRS patients at baseline in a child and adolescent sample.

Methods: A prospective longitudinal study with SRP help-seekers patients and healthy controls (HC) of child and adolescent population (age 10-17). Help-seeking subjects who met PRS criteria were recruited from the Child and Adolescent Psychiatry and Psychology departments of Hospital Clinic and Hospital Sant Joan de Déu (Barcelona, Spain). Inclusion criteria were:

1) Attenuated positive or negative symptoms in the previous 12 months; 2) Brief intermittent psychotic symptoms; 3) First or second degree relative with schizophrenia or schizotypal disorder plus impairment of functioning. Exclusion criteria: IQ<70 and a diagnosis of neurodevelopmental disorder. The Semistructured Interview for Prodromal Syndromes and Scale of Prodromal Symptoms (SIPS/SOPS) were administered to assess prodromal symptoms. Neurocognitive Battery was used to assess cognitive performance in general intelligence, learning and verbal memory, visual memory, speed processing, visuospatial abilities, working memory, attention and executive functions. The same assessment was performed in the HC sample. Data was analyzed using SPSS 19.0 package.

Results: 46 PRS subjects (age 15.15, range 11-17; 39% male) and 20 HC (age 15.03; range 12-17; 25% male) were included. PRS subjects show significant differences in general intelligence (Wechsler Intelligence Scale: $p=0.025$), working memory (letter-number span: $p=0.001$), verbal memory (Test of Memory and learning. Immediate verbal memory: $p=0.000$; and late verbal memory: $p=0.000$), immediate visual memory (Wechsler memory scale. Visual reproduction: $p=0.008$), visuospatial abilities and planning (Rey-Osterrieth Complex Figure copy, $p=0.029$), executive functioning (TMT-B: $p=0.003$ and FAS: $p=0.001$), sustained attention (CPT. Omission: $p=0.001$; Comissions: $p=0.002$) and select attention (coding: $p=0.019$).

Discussion: Cognitive impairment was found in SRP patients compared to HC subjects. Child and adolescent PRS subjects show greater cognitive deficit in general Intelligence, attention, visual and verbal memory, working memory, visuospatial abilities and executive functions. No differences were founded in speed processing and verbal learning.

Poster #T182

CLINICAL PREDICTORS OF THE DIAGNOSTIC STABILITY OF BRIEF PSYCHOTIC DISORDER

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Background: There are scarce data about diagnostic stability and the clinical predictors of prognosis of brief psychotic disorder. The aim of this study was to investigate the diagnostic stability and the clinical predictors of prognosis of brief psychotic disorder.

Methods: This retrospective chart review was based on all BPD patients who had at least two admissions to the psychiatric ward of the Asan medical center, from 1988 to 2011. All clinical variables including demographic factors, clinical characteristics and outcomes are reviewed by experienced psychiatrist. And we compared the patients that maintain the diagnosis of BPD to the other patients that convert to other psychiatric diagnosis.

Results: Forty-four subjects met our inclusion criteria. The mean age at first admission with BPD was 33.4 ± 11.29 years and majority (72.7%) of patients was female. At a median follow up of 2577.18 ± 2104.25 days, 3.20 ± 1.83 episodes developed. Almost patients (91%) had own job and 70% of patients experienced symptoms in acute onset. Psychotic symptoms followed stressful event in about half of the patients (47%). 17 patients maintained the diagnosis of BP, and the overall stability rate was 38%. The diagnosis of the other patients was change to bipolar affective disorder (n=28), schizophrenia (n=10), schizoaffective disorder (n=2), recurrent major depressive disorder (n=1). Except for just two subjects, bipolar patient had no history of admission for depressive episode. They experienced only manic episode or mild depression. There is no predictive value of diagnostic stability in other demographic factors, however recurrent BPD patients have less psychiatric family history, sleep disturbance, number of total episode and more symptoms with acute onset.

Discussion: BPD patients had a high possibility of conversion to other psychiatric disorders. We investigated some factors that associated with diagnostic stability in BPD in this study. Subjects whose diagnosis was changed from BPD showed prominently better outcomes compared to patients who were originally diagnosed with schizophrenia or bipolar disorder.

Poster #T183**QUALITY OF PRESCRIBING FOR SCHIZOPHRENIA: EVIDENCE FROM A NATIONAL AUDIT FOR ANTIPSYCHOTICS - ORAL AND LONG-ACTING INJECTIONS (N=5055)**

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Background: The National Audit of Schizophrenia (NAS) examined the quality of care received in England and Wales. Part of the audit set out to determine whether six prescribing standards, set by the national clinical guidelines for schizophrenia, were being implemented and to prompt improvements in care.

Methods: Mental Health Trusts and Health Boards provided data obtained from case-notes for adult patients living in the community with schizophrenia or schizoaffective disorder. An audit of practice tool was developed for data collection.

Results: Of the 5,055 cases included in the analysis set, 5.2% were not prescribed a regular antipsychotic either in oral or long-acting injection formulation. Of the total sample, 36.5% were prescribed only one non-clozapine oral antipsychotic, and 24.0% were prescribed only one long-acting injection (predominantly first generation antipsychotic, 17.5%). Overall, 1590 patients (31.5%, 95%CI: 30.2-32.7) were prescribed an antipsychotic long-acting injection with comparatively higher rates for assertive outreach (240/610, 39.3%) and lower for early intervention teams (46/287, 16.0%). Most of the 5055 patients reviewed were receiving pharmacological treatment according to national guidelines. However, 15.9% of the total sample (95%CI: 14.9-16.9) were prescribed two or more antipsychotics concurrently and 10.1% of patients (95%CI: 9.3-10.9) were prescribed medication in excess of recommended limits. Overall 23.7% (95%CI: 22.5-24.8) of patients were receiving clozapine. Clozapine was prescribed as monotherapy (n=930, 18.4%) and also with augmentation by other antipsychotics (n=266, 5.3%). However, there were many with treatment resistance who had no clear reason documented as to why they had not had a trial of clozapine (430/1073, 40.1%).

Discussion: In conclusion, whilst most people were prescribed medication in accordance with nationally agreed standards, there was considerable variation between service providers. Antipsychotic polypharmacy, high dose prescribing and clozapine underutilisation in treatment resistance were all key concerns which need to be further addressed.

Poster #T184**VAGAL NERVE STIMULATION AS A NOVEL THERAPY FOR THE TREATMENT OF SCHIZOPHRENIA**

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Background: Vagal nerve stimulation (VNS) was approved for the treatment of epilepsy in the 1990's and for treatment resistant depression in 2005. Enhanced hippocampal activity has been observed in epileptic patients, and although the central effects of VNS have not been completely delineated, positron emission tomographic measurements of cerebral blood flow in humans have consistently reported that VNS stimulation induces bilateral decreases in hippocampal activity. Based on these observations and the fact that schizophrenia patients also have hyperactivity in the hippocampus, we propose to use VNS as a non-pharmacological therapy for schizophrenia. We have previously demonstrated that hyperactivity within ventral regions of the hippocampus (vHipp) actually drives the dopamine system dysregulation in the methylazoxymethanol acetate (MAM) rodent model of schizophrenia. Here we demonstrate the preclinical efficacy of VNS as a potential therapy for the treatment of schizophrenia.

Methods: MAM- and saline-treated rats were implanted with bipolar stimulating electrodes surrounding the left vagus nerve. The electrodes were connected to a subcutaneous stimulator pack (Cyberonics, Inc) while control rats received a dummy stimulator. Beginning 7 days after surgery, rats received continuous VNS (250 µs, 250 µA pulses at 20Hz for 30 s every 5 min). After 2 weeks of chronic stimulation, rats were anesthetized and

in vivo extracellular recordings of putative pyramidal neurons from the vHipp and mesolimbic dopamine neurons of the ventral tegmental area were performed.

Results: Here we demonstrate that VNS was able to reverse hyperactivity present in the vHipp of MAM-treated rats. Additionally, MAM-treated rats exhibit aberrant dopamine system function as measured by increased population activity. VNS was able to restore function to the mesolimbic dopamine system by reversing the increase in population activity.

Discussion: Because current therapies for schizophrenia are far from adequate, with a large number of patients discontinuing treatment due to low efficacy or intolerable side effects, it is important to explore alternative non-pharmacological treatments. These data provide evidence that VNS may be a possible non-pharmacological therapeutic approach for the treatment of schizophrenia.

Poster #T185**REFLEX: RESULTS OF A METACOGNITIVE GROUP TREATMENT TO IMPROVE INSIGHT IN PSYCHOSIS (CORRECT VERSION OF THE ABSTRACT, THIS REPLACES THE PREVIOUSLY SUBMITTED ABSTRACT ON REFLEX)**

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Background: This abstract replaces the previously submitted abstract on REFLEX! Many people with schizophrenia (50-80%) demonstrate impaired insight. A number of interventions aiming to improve insight have been proposed and evaluated, for example cognitive behavioral therapy and psycho-education. Results of these interventions leave room for improvement. Therefore, we proposed a new intervention to improve insight in people with schizophrenia: REFLEX. REFLEX focuses on insight in one's functioning in everyday life and changes in general functioning after psychosis by improving metacognitive acts necessary for insight (self-reflectiveness, idiosyncratic self-certainty) and reducing stigma-sensitivity. The primary objective was to improve insight. By improving insight, we hoped to improve functional outcome and symptoms.

Methods: 134 patients diagnosed with schizophrenia with poor insight (as defined as a) a score of <9 on the Psychosis Inventory (Birchwood et al., 1994) and b) impaired insight rated by a clinician) were included in a multicenter randomized controlled trial. REFLEX was compared to an active control condition consisting of group wise simplified drill and practice cognitive remediation training (CRT).

Results: Clinical insight as measured with the Schedule for Assessment of Insight-Expanded (SAI-E) improved significantly in the REFLEX condition, but also in the control group. Self-reflectiveness, idiosyncratic self-certainty and self-stigma did not change during treatment. Improved insight was associated with significantly less depression.

Discussion: REFLEX leads to better insight, but interestingly this effect was not specific. Given that previous studies have shown that impaired insight does not improve with treatment as usual, the insight increase in the control condition does not seem just an a-specific effect of time or attention in a treatment setting. It may be that our control condition of simplified CRT also stimulates insight. If confirmed, this could yield a low-cost, easy to implement, intervention to improve insight in psychoses.

Poster #T186**EFFECT OF 12 MONTHS OF TREATMENT ON WEIGHT IN PATIENTS WITH SCHIZOPHRENIA TREATED WITH LURASIDONE, RISPERIDONE, OR QUETIAPINE XR**

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Background: The prevalence of obesity and associated cardiometabolic co-

morbidity is significantly higher among patients diagnosed with schizophrenia compared to the general population (Mitchell et al. Schizophr Bull 2013;39:306-18). The aim of this analysis was to evaluate the effect of 12 months of treatment with lurasidone, risperidone, or quetiapine XR (QXR) on weight and body mass index (BMI) in subjects with schizophrenia.

Methods: A post-hoc, observed case (OC) analysis was performed on pooled data from 6 clinical studies that evaluated the safety of 12 months of treatment with lurasidone (40-120 mg/day; n=471), risperidone (n=89), and QXR (n=33).

Results: The mean weight at baseline in the lurasidone, risperidone and QXR groups was 72.8, 80.8, and 72.4 kg; with 18.5%, 32.6%, and 15.2%, respectively, meeting standard BMI criteria for obesity. The mean change in weight (kg) in the lurasidone, risperidone and QXR groups, respectively, was -0.5, +1.7, and +1.5 at 3 months; -0.4, +2.2, and +1.5 at 6 months; and -0.4, +2.6, and +1.2 at 12 months. A clinically significant increase in weight ($\geq 7\%$) occurred in the lurasidone, risperidone and QXR groups in 15.7%, 25.0%, and 15.2% of subjects, respectively, at 12 months; and a decrease of $\geq 7\%$ in weight occurred in 18.6%, 6.8%, and 9.1% of subjects, respectively at 12 months. Similar changes in BMI were observed at 12 months.

Discussion: The results of this pooled analysis of subjects with schizophrenia who completed 12 months of treatment suggest that lurasidone is associated with a low potential for clinically significant weight gain. Sponsored by Takeda Pharmaceuticals International, Inc., and Sunovion Pharmaceuticals Inc. (a US subsidiary of Dainippon Sumitomo Pharma, Ltd.)

Poster #T187

EFFICACY OF LURASIDONE IN THE TREATMENT OF SCHIZOPHRENIA WITH PROMINENT NEGATIVE SYMPTOMS: A POST-HOC ANALYSIS OF SHORT-TERM TRIALS

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Background: Negative symptoms in schizophrenia are associated with impairment in quality of life and functioning. The aim of this post-hoc analysis was to evaluate the efficacy of lurasidone in patients with prominent negative symptoms hospitalized for an acute exacerbation of schizophrenia. **Methods:** This post-hoc analysis utilized pooled data from three 6-week, double-blind, placebo-controlled trials (Meltzer et al. Amer J Psychiatry 2011;168:957-67; Loebel et al. Schizophr Res. 2013;145:101-9) of patients (N=1206) with an acute exacerbation of schizophrenia who were randomized to fixed, once-daily oral doses of lurasidone in the range of 40-160 mg. Patients with prominent negative symptoms at baseline were identified based on the following criteria: a PANSS negative subscale score ≥ 25 (median score); and a PANSS positive score < 26 (median score). MMRM analyses were performed for change in PANSS total, negative subscale and CGI-S scores. Responder status was evaluated for the PANSS total, defined as reduction from baseline of $\geq 20\%$, $\geq 30\%$, or $\geq 40\%$ (LOCF-endpoint).

Results: A total of 247/1206 (20.5%) patients met criteria for prominent negative symptoms. In the prominent (vs. not prominent) negative symptom group, baseline severity of illness was similar on the PANSS total score (96 vs. 97), higher on the PANSS negative subscale score (27 vs. 23), and lower on the PANSS positive subscale score (22 vs. 27). Treatment of the prominent negative symptom group with lurasidone (vs. placebo) was associated with significantly greater week 6 improvement in the PANSS total score (-23.1 vs. -16.2; p<0.01), PANSS-negative subscale score (-6.7 vs. -4.5; p<0.01), and CGI-S (-1.4 vs. -1.0; p<0.01). Treatment with lurasidone also demonstrated significant efficacy in the group with negative symptoms that were not prominent. Treatment of the prominent negative symptom group with lurasidone (vs. placebo) was associated with significantly greater endpoint response using the PANSS total 20% improvement criterion (71.3% vs. 52.5%; p<0.01), 30% criterion (55.1% vs. 37.5%; p<0.01), and 40% criterion (42.5% vs. 28.8%; p<0.05). Overall discontinuation, for lurasidone vs. placebo, respectively, was low in both the prominent negative symptom group (24.6% vs. 30.0%); and the group without prominent negative symptoms (33.3% vs. 41.7%). In the prominent negative symptom group, the 3 most common adverse events reported for lurasidone (and greater than placebo) were headache (22.2% vs. 18.8%), somnolence (22.2% vs. 2.5%), and akathisia (15.0% vs. 3.8%).

Discussion: Discussion: Patients who presented with prominent negative symptoms responded to treatment with lurasidone with significantly improved PANSS total and negative subscale scores. Treatment with lurasidone was well-tolerated in the prominent negative symptom group.

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Poster #T188

COMPARING CHANGES IN FUNCTIONAL ACTIVATION AND NEURAL CONNECTIVITY FROM COGNITIVE REMEDIATION IN SCHIZOPHRENIA

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Background: Cognitive remediation training (CRT) for schizophrenia has been shown to improve cognitive and psychosocial functioning. Previous findings have demonstrated that improvements from CRT are associated with changes in prefrontal brain activation and functional connectivity. However, these CRT evoked changes have never been directly compared to one another, and it is unclear whether changes in one of these forms of activity better demonstrates neural plasticity. Emerging findings indicate that neural dysconnectivity may underlie the cognitive deficits observed in schizophrenia. As such, we hypothesize that changes in functional connectivity will more strongly demonstrate neural plasticity and support changes in cognition and psychosocial ability from CRT. To date, 26 schizophrenia patients have undergone fMRI before and after participating in a randomized controlled CRT trial.

Methods: Patients are randomized to undergo either 48 hours of a working memory focused CRT or 48 hours of a computer skills training control condition. Trainings are conducted at the Minneapolis VA, and are matched on factors related to exposure to computers, clinician contact, and intrinsically motivating content. Before and after treatment, patients complete a fMRI scan as well as neurocognitive testing. To measure neural change in working memory, scanning procedures include two n-back tasks. Additionally, patients undergo an 8-minute resting scan to determine whether changes generalize to intrinsic brain activation. Analyses will be conducted blind to group status. Currently, 15 patients have been randomized into Group A and 11 have been randomized into Group B. To test the hypothesis that neural plasticity from CRT is better characterized by changes in functional connectivity as opposed to activation, analyses will compare groups at Time 2 versus Time 1 using a general linear model (GLM) and independent components analysis (ICA). GLM analysis will be limited to voxels in the prefrontal cortex, while the ICA will examine two task-related networks: the default mode network (DMN) and fronto-parietal executive network.

Results: Preliminary findings demonstrate neural change in a group by time interaction for both activation measured in a GLM and connectivity measured by ICA. Changes in functional activation were observed in the lateral prefrontal cortex, while connectivity changes were demonstrated in both the fronto-parietal executive network and the default mode network. Changes in connectivity were also observed at rest. Forthcoming analyses will compare the relative effects of change between functional activation and functional connectivity.

Discussion: Findings will be discussed in terms of whether they offer more support for change in functional activation or functional connectivity in response to CRT. This study will offer insights into the mechanisms that support cognitive training. Furthermore, these results will serve to direct future cognitive interventions to engage neural processes that preferentially support changes in functional activation or connectivity.

Poster #T189

DEVIANT NEURAL OSCILLATIONS AND LAGGED PHASE SYNCHRONICITY IN PATIENTS WITH AN AT-RISK MENTAL STATE FOR PSYCHOSIS

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Background: Converging evidence has shown that neural oscillations co-

ordinate activity across distributed brain areas, a process that seems to be perturbed in patients with schizophrenia. In particular, neuronal oscillations in the beta (13–30Hz) and gamma (30–50Hz) frequency bands were repeatedly found to be disturbed in schizophrenia. Both frequencies coordinate neuronal activity in small scale networks through phase synchronization, but the beta band phase synchronization has been shown to be primarily responsible for coordinating widely distributed neocortical regions. As schizophrenic psychoses usually do not start abruptly but often have preceding symptoms, our goal was to investigate whether patients with an at-risk mental state for psychosis with later transition to psychosis (ARMS-T) demonstrate abnormal oscillations in both the high gamma and beta frequency bands when compared to at-risk patients, who did not make the transition (ARMS-NT) and compared to healthy controls (HC). We hypothesized in particular that in ARMS-T phase synchronization of beta oscillation, the long-range coordinator, would be augmented in small-scale networks compared to large-scale networks.

Methods: As part of the Basel Früherkennung von Psychosen (FePsy) study, 23 ARMS-T, 40 ARMS-NT and 29 HC were measured by clinical EEG at resting state. EEG data were analyzed by the new neuroimaging technique eLORETA to first assess the group differences in current source density of neuronal oscillations in different frequency bands across brain areas. Next, current source density at those regions of interest that differed between ARMS-T and HC were correlated with cognitive performance measures that were known to be associated with activity in these regions. Second, we assessed lagged phase synchronization of oscillations in small and large scale networks using a new, robust, non-linear and non-biased measure of lagged phase synchronicity.

Results: Current source density of neuronal oscillations did not significantly differ between HC and ARMS-NT and between ARMS-T and ARMS-NT in any frequency band and brain area. However, ARMS-T showed a significantly higher current source density of gamma oscillations in the medial prefrontal cortex (mPFC) compared to HC. Moreover, this activity was positively correlated with cognitive performance on a non-verbal intelligence questionnaire in ARMS-T ($p < 0.001$), but not in HC. We also revealed a higher beta1 lagged phase synchronicity in small scale neural networks in ARMS-T compared to both ARMS-NT and HC ($p < 0.001$). In ARMS-T, but not in ARMS-NT and HC, this phase synchronicity increased with increasing positive and negative symptoms (as indicated by significant interaction effects $p < 0.001$).

Discussion: A heightened gamma activity in the mPFC in ARMS-T patients could potentially reveal the neural underpinnings for an abnormal cognitive integration. Moreover, the increased small-scale lagged phase synchronicity in the beta1 frequency suggests anatomical abnormalities that could be hindering the proper communication between various cortical areas. These findings provide strong evidence that patients who will later make the transition to psychosis are characterized by impairments in neural oscillations already at baseline.

Poster #T190

EFFECTIVE CONNECTIVITY IN SCHIZOPHRENIA – DYNAMIC CAUSAL MODELLING OF THE MISMATCH NEGATIVITY

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Background: Schizophrenia is increasingly thought to be due to abnormal neural connectivity, or dysfunctional integration between hierarchically organised brain regions. According to the predictive coding framework, backward (top-down) connections relay predictions from higher to lower cortical areas, and forward (bottom-up) connections transmit prediction errors from lower levels to higher. The mismatch negativity (MMN) is a pre-attentive brain response to changes in the environment (elicited during the oddball task) and patients with schizophrenia consistently show reduced MMN amplitudes compared to controls. Dynamic Causal Mod-

elling (DCM) estimates effective connectivity (how one neuronal system influences another), and can be used to investigate the neural dynamics underlying the MMN. Specifically, DCM can be used to test hypotheses about the modulations of forward and backward connectivity in response to the standard and deviant stimuli of the oddball task. This study aimed to investigate effective neuronal connectivity in response to the mismatch negativity in patients with schizophrenia, their healthy relatives, and healthy controls. Relatives of patients were included to further investigate the role brain dysfunctions underlying MMN deficits play in the development of schizophrenia, and whether such brain abnormalities are related to a genetic predisposition to the illness.

Methods: A total sample of 99 participants included 25 patients with schizophrenia, 35 of their healthy first degree relatives, and 39 healthy controls. EEG was collected from 21 electrodes, using the oddball paradigm to elicit the mismatch negativity (MMN). Dynamic Causal Modelling (DCM) was used to compare effective connectivity in response to the standard and deviant tones, between the three groups. The underlying sources of the MMN generation were obtained from previous research and included primary auditory cortex, superior temporal gyrus, and inferior frontal gyrus. DCM models were specified that differed in modulations of extrinsic (backward and forward) and intrinsic connectivity in response to the MMN task. Bayesian model selection was conducted to compare the different models, followed by quantitative connectivity analysis evaluating possible group differences in connection strengths.

Results: Results confirmed that patients show reduced MMN compared to healthy controls, consistent with previous findings. Healthy relatives of patients did not differ in MMN amplitudes compared to controls. Preliminary DCM findings indicate that patients with schizophrenia show altered extrinsic and intrinsic connectivity in response to the MMN task, compared to healthy controls. The winning model of the Bayesian model selection differed between the groups, and there were group differences in connectivity parameters. Patients showed decreased backward and intrinsic modulations compared to healthy controls. Relatives did not differ in connectivity strengths compared to controls.

Discussion: Our preliminary findings support the dysconnectivity model of schizophrenia, with patients showing altered effective connectivity (both extrinsic and intrinsic) in response to deviant stimuli in the oddball task, compared to healthy controls. Relatives did not show abnormalities compared to controls, indicating that abnormalities in patients might not be related to a genetic predisposition for the illness, but rather to disease-related factors, or effects of antipsychotic treatment.

Poster #T191

SOURCES OF CLINICAL DISTRESS IN YOUNG PEOPLE AT ULTRA HIGH RISK OF PSYCHOSIS

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Background: There was a recent proposal to include an “Attenuated Psychosis Syndrome”, formerly “Psychosis Risk Syndrome”, in DSM-5, based on research criteria used to identify young people at “ultra high risk” (UHR) for psychosis. The syndrome was ultimately included in the section for further research. The criteria specified that the person experienced attenuated psychotic symptoms (APS) that were sufficiently distressing or disabling to seek help. Although APS are the main means of determining whether a person meets UHR criteria, clinical experience suggests that such symptoms are often not the main source of clinical distress in this patient group. We aimed to assess the main sources of clinical distress in UHR patients at time of referral to a specialized UHR clinic.

Methods: Data on the sources and associated intensity of distress were collected from treating clinicians on 71 UHR patients. The association with transition to psychosis was explored.

Results: Of the total sample, 89.04% fulfilled the APS UHR criteria. APS symptoms were reported to be distressing for 52.1% of the sample, but social and functioning difficulties (78.1%) and depressive symptoms (58.9%) were the highest sources of distress in terms of frequency and intensity that led UHR patients to seek help.

Discussion: Higher intensity of distress associated with APS, anxiety symptoms and substance use was associated with transition to psychosis. Even though APS were reported to be distressing to only a subgroup of UHR patients, the findings suggest that the intensity of distress associated to these symptoms may be an important indicator of risk for psychotic disorder.

Poster #T192

FUNCTIONAL NEUROANATOMY OF THE "JUMPING TO CONCLUSIONS"-TASK IN PATIENTS WITH SCHIZOPHRENIA, ANOREXIA, DEPRESSION AND IN HEALTHY SUBJECTS

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Background: According to current models, "jumping to conclusions" (JTC) is a cognitive bias that may play an important role in the origin of delusions and is a possible mediator of treatment success in CBT psychotherapy. Although research on JTC in psychosis is constantly increasing, only a very limited number of studies so far investigated the underlying neurobiology using functional neuroimaging. Moreover, only limited information is available for psychiatric diseases other than psychosis.

Methods: One version of the classical "beads task", the fish task" (Moritz et al. 2007) was modified into a functional magnetic resonance imaging task. During an fMRI scan, subjects either indicated by button press with their right index finger certainty that a series of fish stemmed from one out of two lagoons ("guess" condition). During a control condition, subjects counted number of fish out a series ("count condition"). Functional imaging data were acquired using a 1.5 Tesla Siemens scanner (one run, 285 scans, TR=2250 ms, 27 slices). Data were analysed using SPM5 software. Preliminary data are available from 9 patients with schizophrenia, 7 patients with unipolar depression, 6 patients with anorexia and 17 healthy controls (11 female).

Results: Patients with schizophrenia showed earlier responses in the "guess" condition than the other groups, compatible with the assumptions of the JTC theories. Preliminary results indicate stable differences between schizophrenia and healthy controls for the guess>count contrast. Moreover, preliminary results indicate a negative correlation between performance in the guess task and BOLD response in right hemisphere temporoparietal regions across all subjects.

Discussion: Modification of the beads task into a functional magnetic resonance imaging paradigm appears successful according to preliminary data. The rather robust correlation between BOLD-response in the right temporoparietal cortex and performance is good compatible with the continuum hypothesis for psychosis in general and for jumping to conclusions.

Poster #T193

SEX-DIFFERENCES IN THE RELATIONSHIP BETWEEN CANNABIS USE AND RISK OF ADMISSION IN YOUNG SUBJECTS WITH AN EARLY PSYCHOSIS: A 1-YEAR FOLLOW-UP STUDY

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Background: A high prevalence of substance misuse is characteristic of patients with first-episode of psychosis. In early stages of psychosis, cannabis misuse has been associated with more severe psychotic symptoms, poorer treatment compliance and increased risk of relapse and hospitalisation. We

aimed to study the relationship between cannabis misuse and outcome measures in a sample of young subjects at risk for psychosis or with a first psychotic episode.

Methods: We designed a prospective, longitudinal study that included 50 young subjects (aged between 18 and 35 years old, 66% men) who attended the Early Psychosis Program from Reus (HU Institut Pere Mata, Reus, Spain). All participants met criteria for first-episode of psychosis (FEP, n=40, 80%) or at risk mental state (ARMS, n=10, 20%). All subjects were followed-up for a period of one year with assessment of psychotic symptoms (Baseline and 1 year, with the PANSS) and Cannabis use (Baseline, 6 months and 12 months, with a semistructured interview). Cannabis use during the follow-up period was recoded in three categories: 1) never used, 2) initial use and stopped, and 3) continued use. Hospital admissions (previous or during the follow-up period) were registered. Statistical analysis were conducted with SPSS v. 19.0. ANOVA (or Wilcoxon test when needed) was used to compare continuous data between cannabis groups. Chi-square was used for comparing categorical data. We conducted a sex-stratified analysis to explore whether there were sex-differences in the risk of admission by cannabis consumption. Survival analysis (Kaplan-Meier) was used to explore whether the time to admission differed between groups.

Results: Of all 50 subjects, 34% never used cannabis, 20% reported initial use and stopped and 46 had a maintained cannabis consumption. Men reported more cannabis consumption than women ($p=0.019$). We did not find statistically significant differences in cannabis consumption between diagnostic groups (FEP vs ARMS). 27 patients (54%) had a previous admission before the follow-up period. 14 patients had an admission during the follow-up period: 6 (12%) had the admission during the first 6 months and 8 (16%) had the admission between 6 and 12 months. Cannabis use was not associated with previous hospitalizations or admissions during the follow-up period. In the Kaplan-Meier analysis, we did not find differences in time to admission between cannabis groups. However, the group of patients who had an initial cannabis consumption but reached abstinence showed a lower risk of admission, comparable to those who never used cannabis. In the sex-stratified analysis, we found that maintained cannabis use was associated with a greater risk of admission during the follow-up period in men ($p=0.037$) but not women ($p=0.422$).

Discussion: In a sample of young subjects with early psychosis we found that gender plays an important role in cannabis use and increases the risk of admission, with a greater risk in men. Although we did not find statistically significant differences between cannabis use in the survival analysis, our negative findings may be also explained by a small sample size and a lack of statistical power to detect differences. In fact, from a descriptive view, survival curves for those patients without cannabis use or who stopped cannabis were similar, in contrast with those patients who reported a maintained cannabis consumption during the follow-up period. Our results are in accordance with previous studies that have also found an increased risk of admission in FEP patients with cannabis consumption. Our study suggests that there is a sex-difference in this association, being greater in men.

Poster #T194

IMPROVING FUNCTIONAL OUTCOMES FOR SCHIZOPHRENIA PATIENTS IN THE NETHERLANDS USING COGNITIVE ADAPTATION TRAINING AS A NURSING INTERVENTION – A PILOT STUDY

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Background: Cognitive Adaptation Training (CAT) has been shown to im-

prove functional outcome in schizophrenia outpatients living in the United States. The effectiveness of CAT for patients living outside the US as well as for long-term hospitalized patients remains to be determined. In addition, it has not yet been studied whether CAT can be successful if patients receive the treatment from psychiatric nurses. The aim of this pilot study was to investigate the effectiveness and feasibility of CAT as a nursing intervention for schizophrenia patients living in the Netherlands.

Methods: Thirty schizophrenia patients (long-term hospitalized patients: 63%) participated in this study. Sixteen patients received treatment as usual (TAU) plus CAT, fourteen patients only received TAU. Patients in CAT participated in the treatment for eight months, consisting of weekly home-visits by a psychiatric nurse, supervised by a psychologist. After eight months, CAT interventions were integrated in the usual treatment. Outcome measures were the Multnomah Community Ability Scale (MCAS), the Social and Occupational Functioning Scale (SOFAS), and the Negative Symptom Assessment – Motivation subscale (NSA-M). For the inpatients, participation in work-related activities was also tracked, for a duration of 16 months.

Results: Patients receiving CAT had better scores on the MCAS (trend), as compared to TAU patients. Moreover, inpatients' work-related activities increased in CAT, relative to TAU inpatients, reaching significance after ten months. Improvements on the SOFAS and NSA-M were not significant.

Discussion: These results indicate that CAT as a nursing intervention may improve outcomes in patients with schizophrenia living in the Netherlands, including long-term hospitalized patients. Larger, randomized controlled studies are needed to investigate the long-term effects of CAT as a nursing intervention systematically.

Poster #T195

PSYCHOLOGICAL MECHANISMS UNDERLYING THE ASSOCIATION BETWEEN CHILDHOOD ADVERSITY AND PSYCHOSIS: AN EXPERIENCE SAMPLING STUDY

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Background: In recent years, there has been renewed interest in the role of social adversity in the aetiology of psychosis. One hypothesized psychological mechanism through which childhood adversity may increase risk for psychosis is through elevated stress sensitivity, characterised by intense emotional reactions in response to daily hassles. Exposure to adversity and trauma may further link to formation of psychotic experiences through enhanced anticipation of threat. We sought to investigate: 1) whether there is an association between a) daily hassles and intense emotional reactions, and b) enhanced threat anticipation and increased intensity of psychotic experiences; and 2) whether these associations are stronger in individuals exposed to childhood adversity.

Methods: The Experience Sampling Method (ESM), a structured, random time-sampling diary technique, was used to assess daily hassles, anticipation of unpleasant events, negative affect, and psychotic experiences in three groups: cases with first episode psychosis, subjects with an at-risk mental state (ARMS), and population-based controls with no family history of psychosis. Data on childhood adversity was collected, including physical, sexual, and psychological abuse, peer bullying, and household discord. Linear mixed models were used to account for the multilevel structure of ESM data, treating multiple observations (level-1) as nested within subjects (level-2).

Results: The ESM was completed by 37 cases, 31 ARMS, and 47 controls, yielding a total of 4713 observations. Daily hassles (cases vs. controls, $B=0.31$, 95% CI 0.02–0.59; ARMS vs. controls, $B=0.36$, 95% CI 0.060–0.66), threat anticipation (cases vs. controls, $B=0.76$, 95% CI 0.29–1.23; ARMS vs. controls, $B=1.22$, 95% CI 0.72–1.71), negative affect (cases vs. controls, $B=1.15$, 95% CI 0.75–1.55; ARMS vs. controls, $B=1.10$, 95% CI 0.68–1.52) and psychotic experiences (cases vs. controls, $B=1.05$, 95% CI 0.64–1.46; ARMS vs. controls, $B=1.05$, 95% CI 0.63–1.48) were more common in cases and ARMS than in controls. We further found that the association between daily hassles and negative affect was strongest in ARMS subjects (cases, $B=0.25$, 95% CI 0.11–0.38; ARMS, $B=0.65$, 95% CI 0.52–0.78; controls, $B=0.29$, 95%

CI 0.19–0.39; likelihood ratio (LR) test, $\chi^2=23.95$, $P<0.001$), whereas the association between enhanced threat anticipation and increased intensity of psychotic experiences was strongest in cases (cases, $B=0.14$, 95% CI 0.11–0.17; ARMS, $B=0.10$, 95% CI 0.08–0.12; controls $B=0.11$, 95% CI 0.08–0.13; LR test, $\chi^2=5.9$, $P=0.051$). In initial analyses, there was evidence that the associations between daily hassles and negative affect (LR test, $\chi^2=0.02$, $P=0.901$) and enhanced threat anticipation and psychotic experiences (LR test, $\chi^2=2.6$, $P=0.110$) were similar in controls exposed and not exposed to any severe adversity in childhood. By contrast, negative emotional reactions in response to daily hassles were stronger in cases exposed ($B=0.49$, 95% CI 0.20 to 0.78) compared with those not exposed ($B=0.15$, 95% CI -0.08 to 0.38) (LR test, $\chi^2=3.34$, $P=0.068$). Similarly, the association between threat anticipation and psychotic experiences was stronger in cases exposed ($B=0.24$, 95% CI 0.19 to 0.30) compared with those not exposed ($B=0.09$, 95% CI 0.03 to 0.15) (LR test, $\chi^2=14.6$, $P<0.001$).

Discussion: Our findings provide initial evidence that stress sensitivity may to be an important mechanism in particular during the initial formation of psychotic experiences, whereas enhanced threat anticipation may be more relevant after transition to psychosis. Further, these findings tentatively suggest that stress sensitivity and threat anticipation may be potential mechanisms that link childhood adversity and psychosis.

Poster #T196

IMPACT OF PSYCHIATRIC COMORBIDITY IN INDIVIDUALS AT ULTRA HIGH RISK (UHR) OF PSYCHOSIS

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Background: Recent studies examining Axis-I diagnoses in individuals at ultra-high risk (UHR) of developing psychosis have found that the prodromal phase of psychosis is associated with various comorbid nonpsychotic psychiatric disorders, especially depressive and anxiety disorders. These comorbid Axis I disorders have been shown to have adverse effects on the global functioning and psychopathology, as well as contributing to help seeking behaviors and transition to psychosis, in UHR individuals. Not much published evidence on comorbidity in Asian UHR samples is currently available.

Methods: We examined the prevalence of psychiatric comorbid disorders (past and current) in 163 UHR youths recruited from the Longitudinal Youth At-Risk Study (LYRIKS), a prospective observational study initiated in Singapore in 2008. The UHR status of the participants was assessed using the Comprehensive Assessment of At-Risk Mental State (CAARMS), and the Structured Clinical Interview for DSM IV Axis I disorders (SCID-I) was used to assess the presence of any comorbid psychiatric disorder. We compared the baseline demographic, clinical and functional variables of UHR participants with and without comorbid disorders, using multivariate tests. Logistic regression was used to examine the predictors of comorbid SCID diagnoses.

Results: About 81% of the UHR sample had a comorbid psychiatric disorder, with almost equal prevalence of past and current comorbidities (50.3% and 49.7% respectively). 37.4% of the UHR individuals were assessed as having a past depressive disorder whereas only 7.9% had a past anxiety disorder. The prevalence of current depressive and anxiety disorders was 31.9% and 27.6% respectively. Major Depressive Disorder was the most common diagnosed condition in the UHR sample, whereas Obsessive Compulsive Disorder was the most commonly diagnosed anxiety disorder. The prevalence of past Alcohol and other substance use disorders was 6.7% and 5.5% respectively. Most of the UHR participants with comorbidity belonged to the CAARMS Attenuated Psychotic Symptoms group (APS) group. 81.8% of the UHR individuals with comorbidity were referred from a clinical source, and a significantly larger proportion of them (69.7%) were on psychotropic medications. Compared to those without comorbidity, those with comorbidity scored significantly higher on CAARMS Composite, Positive and Negative Syndrome Scale (PANSS) - positive and general psychopathology domains, Childhood Trauma Questionnaire (CTQ) - emotional abuse scale, Calgary Depression Scale for Schizophrenia (CDSS) and Beck Anxiety Inventory (BAI). CAARMS Composite and CTQ Emotional Abuse scores were significant predictors of comorbid SCID diagnoses. When individuals with and without current comorbidity were compared, those with current comorbidity

had significantly higher scores on CAARMS Composite, PANSS- positive and general psychopathology, CDSS and BAI, and a lower score on Global Assessment of Functioning (GAF).

Discussion: We found a high prevalence of comorbid Axis I diagnoses in our sample of UHR, which is consistent with results from other prodromal studies. These comorbid disorders might be a part of the psychosis prodrome or parallel conditions, co-existing with the prodromal symptoms. Association of these comorbidities with more severe psychopathology and functional impairments in UHR individuals has important clinical implications. Childhood emotional abuse plays a likely role in development of both UHR symptoms and other psychiatric illnesses, and warrants further research, towards prevention of these illnesses.

Poster #T197

ANTIPSYCHOTICS AND ANTIDEPRESSANTS AND THEIR ASSOCIATIONS WITH SUICIDAL IDEATION – THE NORTHERN FINLAND BIRTH COHORT 1966

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Background: It has been reported previously that antipsychotic and antidepressant drugs may increase the risk of suicidality. These drugs have many side effects which may increase the risk suicidality. We wanted to find out whether there is any association between use of these drugs and suicidal ideation in cases of psychotic and non-psychotic disorders in population based sample.

Methods: Our sample was the Northern Finland Birth Cohort 1966. Information on the use of prescribed drugs was collected in 1997 with a postal questionnaire (N=8,211). The presence of suicidal ideation was assessed using the Symptom Check List - 25 -questionnaire. We studied associations between suicidal ideation, adjusted for symptoms of depression and anxiety, and antipsychotic/antidepressant medication in different diagnostic groups (schizophrenia, other psychosis, no psychosis). We compared suicidality also by dose of medication.

Results: According to the questionnaire 69 respondents (0.9%) were on antipsychotic medication; 41 of them had schizophrenia, 10 other psychoses and 18 were non-psychotic. 111 individuals (1.4%) were on antidepressants, of them 9 had schizophrenia, 10 other psychosis, and 92 had no psychosis. Individuals receiving antipsychotics or antidepressants had in general more suicidal ideation, although the associations diminished when taking other symptoms into account. Among those non-psychotic persons who were receiving antipsychotics higher doses correlated with more suicidal ideation ($r=0.81$, $p<0.001$). Antidepressant dose did not associate with suicidal ideation.

Discussion: Higher doses of antipsychotics are associated with suicidal ideation among individuals without a diagnosis of psychosis even after adjustment for other psychiatric symptoms. However, no such association was observed in the cases of schizophrenia or other forms of psychosis. Antidepressant medication was not associated to increased suicidal ideation when other symptoms of depression and anxiety are taken into account. Our results suggest that one should take suicidal ideation into account when prescribing antipsychotic medication, especially for off-label use.

Poster #T198

THE FACTOR STRUCTURE AND ASSOCIATED CLINICAL VARIABLES OF FORMAL THOUGHT DISORDER IN FIRST EPISODE PSYCHOSIS

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Background: Up to six different factors have been identified within the construct of formal thought disorder (FTD). A variety of cognitive and linguistic abnormalities are associated with this symptom, which may also be associated with dysfunction of NMDA receptors and the anterior cingulate gyrus. There have been difficulties in identifying a definitive biological marker of FTD however and this may be partly due to the absence of a clear clinical phenotype. We aimed to test the factor structure of FTD in affective and non-affective first episode psychosis (FEP) and investigate the clinical correlates of the resulting factors.

Methods: Confirmatory factor analysis of FTD in all cases of FEP in an Irish epidemiologic catchment area between 2006 and 2013. Diagnosis was established with SCID-IV and FTD was measured with the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS). Three different models of FTD factor structure, based on literature review, were tested using the IBM Amos Software Package.

Results: A total of 558 cases of FEP were included, of which 37.5% had at least mild FTD. A four-factor solution for FTD, comprising a disorganisation factor (DF), a poverty factor (PF), a verbosity factor (VF) and a blocking factor (BF), was the best fit for the data (GFI = 0.984). DF was most severe ($\chi^2=66.28$, df=7, $P<0.001$) in those with substance induced mood disorder and mania and least severe in delusional disorder. PF was most severe ($\chi^2=40.93$, df=7, $P<0.001$) in depression and schizophrenia-spectrum disorder and least severe in mania. Shorter duration of untreated psychosis was associated with significantly more severe DF, VF and BF (all p values <0.01) but was not associated with severity of PF. Those treated as inpatients (n=329) and those treated involuntarily (n=131) had significantly more severe DF, VF and BF than outpatients and those treated voluntarily (all p values <0.001). Every factor showed significant correlations, of small magnitude, with global functioning; the Spearman's rho ranged from -0.12 (VF) to -0.17 (DF). PF and VF showed a weak correlations ($Rho=-0.13$, $P<0.01$ and $Rho=0.13$, $P<0.01$ respectively) with a proxy measure of premorbid adjustment, whilst DF and BF showed no such correlation. DF, VF and BF factors showed no significant correlations with delusions or hallucinations, and all were modestly correlated with bizarre behaviour ($Rho=0.39$, 0.38 and 0.27 respectively, $P<0.001$). VF and BF were weakly correlated with negative symptoms ($Rho=-0.18$ and $Rho=0.15$ respectively, both $P=0.01$) however DF was not significantly associated with negative symptoms. Conversely, PF factor was more strongly associated with negative symptoms ($Rho=0.64$, $P<0.001$) and not correlated with bizarre behaviour. All of the factors showed a modest correlation with inattention, except VF which showed only a weak correlation.

Discussion: Formal thought disorder was prevalent in this epidemiologic FEP sample. A complex, four-factor model provided the best fit for the data. Each of the factors can help to distinguish between diagnostic groups. The disorganisation, blocking and verbosity factors were almost completely un-related to other symptom domains. These factors may be considered measures of clinical severity as they were associated with shorter duration of untreated psychosis, inpatient treatment status and involuntary hospital treatment. The poverty factor, however, appeared to be strongly related to negative symptoms and had no such associations with markers of clinical severity. None of the factors were strongly correlated with a measure of global functioning.

Poster #T199

WORKING MEMORY AND VISUAL MEMORY DEFICIT IN CHILDREN OFFSPRING OF SCHIZOPHRENIA PATIENTS

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Background: The detection of individuals at high risk (HR) of developing a psychotic disorder has been a main objective of clinicians and researchers for a long time. Cognitive deficits (considered a feature of schizophrenia) have also been found in non-affected relatives of schizophrenia patients. Studies which lead the focus to adolescents' and early adults' offspring of schizophrenia patients have shown a significant worse performance on working memory, attention and visual memory tasks [1–4]. The goal of the

present study was to examine the neuropsychological performance on the genetically HR group of offspring children of schizophrenia and compare it with a age-matched control group, expecting less efficiency on the domains of attention, visual memory and working memory.

Methods: 35 children and adolescents offspring of patients with schizophrenia or schizoaffective disorder following DSM-IV TR criteria (32.5% female; mean age = 10.55 years, SD=3.44) and 95 offspring of healthy control subjects (55.1% female; mean age=11.70 years, SD=3.19) were evaluated in the Psychiatry Department of Hospital Clinic in Barcelona and the Hospital General Universitario Gregorio Marañón in Madrid, Spain. Based on results of previous literature c, d, every participant was assessed using Digits Forward (subtest of WISC-IV) and CPT to evaluate attention, Weschler Memory Scale and Rey-Osterreich Complex Figure to assess visual memory and Digits Backward and Number-Letter sequencing for working memory. Moreover, a IQ score was calculated through the Weschler Intelligence Scale for Children Revised (WISC-R). To analyses a general linear model was used controlling for age, sex, IQ, cannabis consume and ADHD diagnosis (according to DSM-IV-TR criteria).

Results: The general lineal model showed significant differences between both groups showing the patient's offspring group significantly worse performance in visual memory ($F_6;129=27.90$; explained variance 55.6%, $P=0.000$) and working memory ($F_6;126=14.14$; explained variance 37.9%, $P=0.000$) than the control group. However, no significant differences between groups were found in global attention ($F_6;129=1.56$; explained variance 2.6%, $P=0.163$).

Discussion: Results showed, consistently with previous studies with adolescents [3,4], that offspring of patients with schizophrenia display significantly worse performance on visual memory and working memory. Although most effect sizes are mild, the explained variance (55%) in visual memory should be highlighted, which is similar to the medium size effect that came up in other recent studiesb and sets off the difference with the control group. These results provide more evidence to conclude that visual memory and working memory can be considered as endophenotypes of the illness.

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Poster #T200

SUBGROUP ANALYSIS IN A RANDOMIZED CLINICAL TRIAL OF LONG-ACTING INJECTABLE RISPERIDONE AND ORAL ANTIPSYCHOTICS IN UNSTABLE CHRONIC SCHIZOPHRENIA

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Background: In a long-term randomized trial of unstable schizophrenic patients, against flexibly prescribed oral treatment, a long-acting injectable (LAI) antipsychotic showed no advantage over oral treatment on the primary outcomes of preventing or delaying time to psychiatric hospitalizations or on several secondary outcome measure of symptoms, substance abuse, side effects or quality of life. We examined whether selected clinically defined subgroups showed differential benefit.

Methods: Patients with schizophrenia or schizo-affective disorder who had been hospitalized within the past 2 years or judged to be at risk of hospitalization because of increasing psychiatric service use (N=369) were randomly assigned to LAI risperidone bi-weekly 12.5-50 mg/injection or to the psychiatrist's choice of oral antipsychotics and followed for up to two years. The primary intention-to-treat endpoint was time to psychiatric re-hospitalization. Symptoms, quality of life and global functioning were assessed through blinded video-conference interviews. Substance abuse and side effects were assessed through face to face interviews. Cox proportional

hazards regression and mixed effects models were used to assess difference in treatment effect within subgroups defined by hospitalization at study entry, substance abuse, race, symptom severity, quality of life, age, race or gender, or reported medication compliance.

Results: Mixed models and Cox proportional hazards regression using up to 24 months of data showed no significant differences in treatment effect between LAI risperidone and oral risperidone across subgroups on psychiatric symptoms, quality of life, or time to hospitalization. With adjustment for multiple comparisons treatment effect differed with respect to substance use by race with whites showing more benefit from LAI than non-whites.

Discussion: Over two years, LAI risperidone showed no superiority to psychiatrist's choice of oral treatment in patients with schizophrenia at relatively high risk of hospitalization. Subgroup analyses showed these results were generally observed uniformly across clinically defined subgroups.

Poster #T201

BEHAVIOURAL AND FMRI EVIDENCE OF SEMANTIC CATEGORISATION DEFICITS IN SCHIZOPHRENIA

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Background: Abnormalities in semantic processing are commonly proposed to be central to cognitive abnormalities and thought disturbances in schizophrenia. Deficits have been reported on a range of tasks including categorisation tasks. The current investigation completed two studies: study 1 investigated behavioural categorisation ability and study 2 examined the underlying neural substrates involved during categorisation. Our aim was to confirm behavioural categorisation deficits in schizophrenia; illustrate the underlying neural correlates of these difficulties and further to extend this investigation into patients with bipolar disorder.

Methods: A revised version of Chen et al's. (1994) categorisation task was used. The task consisted of eighteen categories with five different exemplar words (i.e. high frequency, low frequency, borderline, related but outside category and unrelated) selected for each category. Participants were asked to indicate whether exemplars were or were not part of the category. Accuracy and reaction time were recorded. Study 1 included 32 schizophrenia patients, 28 bipolar disorder (Type 1) patients and 32 healthy controls and examined behavioural performance. Study 2 included 10 schizophrenia patients 10 bipolar disorder (Type 1) patients and 16 healthy controls. These participants performed that task during fMRI completed in a 1.5T MRI.

Results: Behaviourally, schizophrenia and bipolar patients had most difficulty categorising related words whilst the controls had most difficulty with borderline examples; although both patient groups had reduced accuracy and increased reaction times across all five exemplar types. There were no behavioural differences between schizophrenia and bipolar patients. Categorisation ability (main effects) in the healthy controls was related to activity in the left and right inferior frontal (BA44/45), left and right middle temporal gyrus (BA21/22), left hippocampus, left precuneus, anterior cingulate and the cerebellum; areas typically reported during semantic processing. No above threshold main effect activation was observed for patients, however at very liberal thresholds a similar network was revealed. Further examination of the interaction between task and group illustrated the patients exhibited hypo-activation within left frontal cortices, the left hippocampus and to a lesser extent posterior temporal cortex.

Discussion: Both schizophrenia and bipolar disorder patients show difficulty with categorising semantic information. The fMRI data revealed impairments in the distributed frontal-temporal network during this task. This network is known to be engaged in the representation and processing of meaning of words, text, and discourse. Significantly, these deficits crossed diagnostic boundaries. We predict that we may have started to outline the mechanisms involved in thought and communication disturbance in psychosis.

Poster #T202**SOCIAL COGNITION IN NEUROCOGNITIVE SUBTYPES OF PSYCHOTIC DISORDERS**

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Background: Schizophrenia (SZ) and psychotic affective disorders are associated with common neurocognitive impairments that are reported with greater severity in SZ. These cognitive deficits may partially underpin social cognitive deficits demonstrated in SZ. However, strong and consistent evidence for social cognitive deficits (as seen in SZ) is lacking in other psychotic disorders (e.g., bipolar disorder, psychotic depression), and it is possible that only those patients with more severe neurocognitive deficits show significant impairment in emotion recognition and Theory of Mind (ToM) capacities. In this study we investigated whether subtypes of psychotic disorder patients with more severe neurocognitive deficits showed differential social cognitive abilities to those without severe impairment.

Methods: Participants were 120 clinical cases with an established diagnosis of schizophrenia (n=39), schizoaffective disorder (SzA; n=19), bipolar-I disorder (BD; n=57), and other disorders with psychotic features (n=5; including 3 cases with psychosis NOS, 1 with delusional disorder, and 1 with psychotic depression), and 43 healthy controls (HC). A global cognitive deficit score was derived from performance across eight major neurocognitive domains, and patients were dichotomised into a clinical group of mixed diagnoses with more severe levels of cognitive deficit ("cognitive deficit" group; CD, N=62; SZ n=24; SzA n=13; BD n=23; Other n=2), compared to a clinical group with relatively spared cognitive performance ("cognitively spared" group; CS N=58; SZ n=15, SzA n=6, BD n=33, Other n=3). A sub-set of participants also completed the Ekman 60-faces test of facial emotion recognition and The Awareness of Social Inference Test (TASIT).

Results: The CD patients exhibited deficits on all neurocognitive domains relative to both CS and HC groups, while CS patients demonstrated impairments in the general verbal ability and processing speed domains only, compared to HC. The CD group further demonstrated impairments in both emotion recognition and ToM, relative to CS and HC groups. There were no differences on social cognition tasks among the CS and HC groups.

Discussion: Patients with more severe neurocognitive deficits displayed extensive social cognitive impairments compared to those with less severe cognitive impairment. These findings suggest that general neurocognitive impairments account for substantial impairments in social cognition, and demonstrate the utility of examining psychotic disorder patients according to subgroups defined by neurocognitive impairment, as a potential marker of a subtype of psychosis that spans current diagnostic categories.

Poster #T203**USING PERSONALISED COMPUTER MODELLING TO CLASSIFY PEOPLE WITH TREATMENT-RESISTANT OR ULTRA-TREATMENT-RESISTANT SCHIZOPHRENIA BASED ON COGNITIVE MEASURES**

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Background: Clozapine (CLZ) is uniquely effective for treatment-resistant schizophrenia (TRS). However, many patients still suffer from residual symptoms or do not respond at all (ultra-treatment resistant schizophrenia; UTRS). We hypothesised that a computer-based personalised model (PM) could be used to correctly classify patients as suffering from either TRS or UTRS.

Methods: This study was conducted as part of a larger cross-sectional study that aimed to discover biomarkers of TRS; only participants with TRS (n=20) or UTRS (n=16) were included in this analysis. Participants underwent a series of cognitive tasks using a touch screen computer. The tasks were

designed to measure verbal memory and working memory capacity, sustained attention, information processing speed and efficiency, sensorimotor response, time estimation, premorbid IQ, verbal fluency, executive function (maze), impulsivity (Go/No-Go), emotional identification and selective attention (auditory oddball). Missing values were replaced with the average of all values for that task measure. The data was then used to build a personalised model (PM) for each participant using weighted k-nearest neighbours and a leave-one-out cross-validation algorithm. Briefly, the computer built a PM for each person by determining the most important features specific to that person that classified them in their respective class (TRS or UTRS). The features represented individual measures for each task, such as reaction time and false misses for sustained attention.

Results: Although 100% of participants with UTRS were correctly classified, only 40% (8/20) of participants with TRS were correctly classified using personalised modelling. The features selected as important in >10 participants' PMs were completion time and path learning time in the maze, sad emotion identification, reaction time and false alarm rate in the auditory oddball task and reaction time variability during the Go/No-Go.

Discussion: Although the predictive power of the PMs was poor using outcome measures from the cognitive tasks while undergoing treatment, the features identified as important were similar to those identified using electroencephalography-based personalised modelling. Poor classification may be due to improved cognition, which has been previously attributed to treatment with CLZ, which 83% of patients were receiving at the time of testing.

Poster #T204**STUDYING RELATIONSHIP BETWEEN SCHIZOPHRENIA AND PAI-1 4G/5G POLYMORPHISM IN IRANIAN PATIENTS**

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Background: Schizophrenia is a widespread neurodegenerative disorder with disruptions in cognition abilities and emotions and behavioral abnormalities. Plasminogen activator inhibitor-1 (PAI-1) 4G/5G polymorphism has been implicated in much neurodegenerative disorder, so in current study, we investigated the possible association between schizophrenia and 4G/5G polymorphism in the PAI-1 gene promoter in Iranian patients.

Methods: In this cross-sectional study, 106 blood samples were collected from individuals suffering from schizophrenia based on DSM.IV.TR standards and 122 healthy controls have been selected based on the GHQ questionnaire. DNA was extracted from the samples and the frequency of the polymorphism was analyzed using ARMS-PCR methods. Finally, the products were detected on 2% agarose gel electrophoresis and confirmed by sequencing.

Results: The analysis of the data showed that 18% of patients and 2% of controls were mutant homozygous and 65% of patients and 56% of controls were heterozygous and finally 17% of patients and 64% of normal controls were normal homozygous.

Discussion: We observed significant susceptible effects of PAI-1 4G/5G Polymorphism among Schizophrenia cases. To our knowledge, this is first study in Iran that assessed the frequency of the polymorphism among Iranian patients. Our data support the involvement of PAI-1 in schizophrenia liability, and especially, its role as a genetic factor of the disorder features.

Poster #T205**TRAJECTORIES OF NEUROCOGNITIVE FUNCTIONING ACCORDING TO CANNABIS USE PATTERN IN CHILDREN AND ADOLESCENTS WITH FIRST EPISODE PSYCHOSIS: A 2-YEAR FOLLOW-UP STUDY**

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Background: The relationship between cannabis use and cognitive function in patients with first episode psychosis (FEP) remains controversial. Studies suggest either a decrease in attention, executive function, and working memory [1–3] or an improvement in the pattern of cannabis use [4–7]. Studies in early onset psychosis have consistently failed to report a longitudinal decrease in neurocognitive functioning [8,9]. We compared the progress of neurocognitive function in patients with early onset psychosis who used cannabis (CU) and those who did not (NCU). In a secondary analysis, we examined the progress of 3 subgroups of adolescents with FEP: 1) those who continued cannabis use (CCU), 2) those who discontinued cannabis use (DCU) and 3) those who initiated cannabis use (ICU) after their FEP compared with NCU patients.

Methods: The study sample comprised 155 adolescents with FEP (69% male, mean age 15.68±1.7 years) of whom 64 (41.3%) were CU at baseline. According to the pattern of use they were classified in three subgroups (CCU, DCU, and ICU). Supplement 5 (substance abuse disorders) of the Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL) and urine analysis were used to determine the pattern of use after 2 years of follow-up. Neurocognitive function was assessed using a comprehensive neuropsychological battery including measures of overall attention (WAIS-III [digits forward], Stroop test [words and colors], Continuous Performance Test [CPT-II], and Trail Making Test [TMT-A]), executive function (Wisconsin Card Sorting Test [WCST], subtest derived from TMT-B [TMT (B-A/A)], number of words and categories in the Verbal Fluency Test [FAS], interference with the Stroop test), learning and memory (Spanish version of the California Verbal Learning Test [TAVC]), and working memory (digits backward and letters and numbers from WAIS-III). The progress of neurocognitive function was examined at baseline and after 2 years of follow-up using mixed model analyses after controlling for the following: age; change in positive, negative, and general symptoms of the PANSS scale; use of tobacco products, alcohol, and other drugs.

Results: A longer reaction time in CPT-II was observed in CU ($F=5.68$; $p=0.021$) than in NCU after 2 years of follow-up. A time x group interaction between the 4 typologies of cannabis use was also found in the color trial of the Stroop test, with better performance in the DCU group than in the NCU, CCU, and ICU groups ($F=7.38$; $p=0.001$). Time x group interactions from baseline to follow-up were also observed between the 4 groups in the conceptual responses of the WCST ($F=4.76$; $p=0.009$; CCU>ICU>NCU>DCU), Stroop interference ($F=2.92$; $p=0.005$; NCU>DCU>ICU>CCU), and subtest of the TMT-B (TMTB-A/A) ($F=4.38$; 0.012 ; CCU>NCU>DCU>ICU).

Discussion: Continued cannabis use resulted in a reaction time that was shorter in CU adolescents with FEP than in NCU. An interaction effect was observed in specific attention and executive function tasks in CU adolescents depending on the pattern of use. Discontinuing cannabis during the first 2 years of follow-up after the FEP seems to be associated with better automation of novel inputs. Furthermore, patients who continued to use cannabis for up to 2 years obtained better results in the executive control of cognitive processes such as task switching and conceptual skills than patients with other CU typologies. Finally, NCU patients obtained better results than CU in measures to control and inhibit cognitive interference.

Poster #T206

POSSIBLE ASSOCIATION BETWEEN ITIH3 GENE POLYMORPHISM AND SCHIZOPHRENIA IN A JAPANESE POPULATION

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Background: A recently published genome-wide analysis indicated that a

polymorphism (rs2535629) of ITIH3 gene showed the strongest association signal with susceptibility to psychiatric disorders in Caucasian populations. In the present study, we attempted to replicate the association of rs2535629 with schizophrenia in a Japanese sample. We have previously shown that rs2535629 influences the ITIH4 gene expression levels. Therefore, we further investigated whether the cerebrospinal fluid level of ITIH4 is altered in patients with schizophrenia.

Methods: The polymorphism rs2535629 was genotyped in 641 patients with schizophrenia (355 men: mean age ±standard deviation 42.5 ± 13.0 years, mean age at onset 23.3 ± 7.8 years; 286 women: mean age 43.5 ± 14.9 years, mean age at onset 25.3 ± 9.9 years) and 1,249 healthy controls (421 men: mean age 45.5 ± 16.1 years; 828 women; 46.3 ± 15.4 years). All subjects were biologically unrelated Japanese individuals. The cerebrospinal fluid level of ITIH4 was examined in 30 patients with schizophrenia and sex- and age- matched 30 healthy controls. The study protocol was approved by the ethics committee at the National Center of Neurology and Psychiatry, Japan.

Results: A total of 611 patients with schizophrenia and 1,193 healthy controls were successfully genotyped for rs2535629. A significant difference in genotype and allele distribution was found between patients with schizophrenia and controls (heterozygote odds ratio [OR] = 1.26, 95% confidence interval [CI]: 1.01–1.57, $P = 0.042$; homozygote OR=1.44, 95% CI: 1.09–1.91, $P=0.011$; allelic OR=1.21, 95% CI: 1.05–1.39, $P=0.0077$). No significant difference in cerebrospinal fluid levels of ITIH4 was observed between patients with schizophrenia and controls ($P=0.29$). The cerebrospinal fluid levels of ITIH4 did not significantly correlate with the Positive and Negative Syndrome Scale scores of patients with schizophrenia ($r=-0.15$, $P=0.43$).

Discussion: Our results showed that the G allele of rs2535629 was associated with an increased risk for schizophrenia in a Japanese population. The finding is consistent with that in Caucasian populations which indicated that the G allele of rs2535629 was associated with an increased risk of psychiatric disorders. We found no evidence of involvement of ITIH4 in the pathophysiology of schizophrenia. Further studies are warranted to determine the mechanism by which rs2535629 confers susceptibility to schizophrenia.

Poster #T207

A NOVEL DIGITAL HEALTH APPROACH TO TREATING NEGATIVE SYMPTOMS USING A PERSONALIZED REAL-TIME INTERVENTION FOR MOTIVATIONAL ENHANCEMENT (PRIME)

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Background: Recent data suggests that negative symptoms, and amotivation in particular, are arguably the single most important factor that affects functional disability in schizophrenia and undermines a patient's ability to engage in and adhere to effective treatment. Prior approaches to improve motivation and engagement in schizophrenia have had mixed success and primarily relied on psychotherapy or psychosocial remediation strategies using methods derived from rehabilitation and neuropsychology. This presentation will discuss the design, development, and preliminary data of a Personalized Real-time Intervention for Motivational Enhancement (PRIME) to treat functional outcomes in recent onset schizophrenia patients using a newly developed mobile app.

Methods: Using a participatory design strategy, patients, treatment providers, and caregivers were involved in the design of PRIME. A series of focus groups, individual interviews, and a workshop were conducted. We are also currently launching a series of field tests to determine feasibility of PRIME, with the randomized clinical trial (RCT) scheduled to start February 1. Forty participants with a recent onset of schizophrenia will be randomized to either using PRIME or a wait-list control condition. Data on symptoms, functioning, and motivation will be collected in the lab as well as real-time data captured using app analytics. One of the most significant advantages of delivering PRIME via a mobile app is the potential to collect real-time data and thereby prevent recall bias. We have devised an evaluation strategy that will use app analytics to measure the following: 1) Engagement with the app; 2) Motivation (behavioral and attitudes, effort), and 3) Social functioning. One example of our approach

to evaluate motivation in the app is custom surveys to evaluate the degree of perceived vs actual difficulty of goals and we will be able to evaluate whether participants are attempting and achieving more difficult goals over time. Social functioning will be measured by the number of social connections initiated and sustained over the course of using the app. We will validate the analytics by examining the concurrent validity of these metrics with our laboratory measures of motivation and social functioning.

Results: We will present the qualitative results from the focus groups and individual interviews as well as the quantitative findings from the PRIME field tests and RCT. 100% of participants (N=10, ages 17-26 years old, 65% male) reported that PRIME would inspire them to work on goals and improve their lives. Several participants reported enhanced behavioral activation following the design process. For instance, one participant initiated a social engagement with a peer despite going months without seeing his friend. Another participant created a song from the digital recording of his individual interview, which we will share in our presentation.

Discussion: The PRIME mobile intervention encourages patients to initiate and sustain social, role, and health-promoting goals. While the randomized clinical trial we will conduct will ultimately determine the efficacy of PRIME, the initial responses have been encouraging and suggest that participants are inspired by the potential of PRIME and believe it will have a positive influence in their lives.

Poster #T208

PROACTIVE: EXPLORING LONGITUDINAL SYMPTOM COURSE TO UNDERSTAND OUTCOMES IN LAI-ORAL COMPARISONS

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Background: In the PROACTIVE study, an eight site randomized clinical trial (RCT) comparing the LAI risperidone (LAI-R) to oral second generation oral antipsychotics (ORAL) in schizophrenia and schizoaffective outpatients, we found no significant differences between treatments in time to relapse or rehospitalization during treatment exposure of up to 30 months (Schooler et al 2011). This finding is congruent with the results of the study by Rosenheck and colleagues (2011) and generalizes their findings from a very largely male Veterans Affairs (VA) sample to a broader United States context in settings that treat more women than the VA and is consistent with findings internationally. We also found that there were significant differences based on the blinded ratings favoring LAI-R in the BPRS Total Score and BPRS psychosis cluster (Schooler 2011). An important clinical question is whether the absence of statistically significant differences in relapse can be extended to make the statement that oral and injectable medications confer equal benefit in the long term treatment of schizophrenia. Data from the PROACTIVE RCT will be used to explore this question. Clinical trial characteristics that may contribute to reduced likelihood of detecting treatment effects will also be considered.

Methods: The PROACTIVE RCT included 304 schizophrenia subjects who were randomly assigned to LAI-R or oral second-generation antipsychotics and who whose psychopathology was assessed by blinded central raters every three months. Given the significant differences based on the blinded ratings favoring LAI-R in the BPRS Total Score and BPRS psychosis cluster (Schooler 2011), we examined the possible source of this difference. We used a narrow definition of psychotic symptoms and examined whether absence of psychotic symptoms accounted for the differences. Cases were dichotomously classified as having either no psychotic symptoms or any.

Results: We found that the proportion of such ratings increased over time for the RLAI group (20% to 39%) compared to the ORAL group (22% to 23%) (Treatment X Visit F=1602, df 1, 1739, p=0.0001). This difference would not be reflected in an assessment of relapse which measures increase in symptoms rather than increase in absence of symptoms.

Discussion: There are a number of characteristics of the PROACTIVE trial that may have contributed to an inability to detect a difference in time to relapse if a true difference exists. First, all subjects consented to research participation and to randomization to treatment. Following randomization, seven LAI-R subjects and two ORAL subjects never received treatment. In the LAI-R arm there was only one treatment option whereas in the ORAL

arm patients who had a sub-optimal response to the first oral antipsychotic could be offered another and still remain in the study. In order to maintain comparable clinical contact between treatment arms all subjects were seen every two weeks. This is far more frequent than clinical visit frequency for patients receiving oral prescription medication. These visits included a clinical assessment of symptoms. Oral medication was dispensed at these biweekly visits which further increased comparability to the injectable treatment arm but which further differentiated the oral condition from usual outpatient clinical care for schizophrenia. On balance, data from the PROACTIVE RCT suggest that for the population of patients included in such studies the benefits of LAI treatment may lie in increasing the likelihood of an absence of psychotic symptoms over time rather than in preventing increase of symptoms to the level of frank relapse. This may be because this population represents more adherent patients for whom oral medication prescribed and administered under optimal clinical conditions serve well to prevent relapse and rehospitalization.

Poster #T209

FLEXIBLY DOSED PALIPERIDONE PALMITATE IN NON-ACUTE BUT SYMPTOMATIC PATIENTS WITH SCHIZOPHRENIA PREVIOUSLY UNSUCCESSFULLY TREATED WITH LONG-ACTING INJECTABLE RISPERIDONE

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Background: To explore tolerability, safety and treatment response of flexibly dosed paliperidone palmitate (PP) in adult non-acute but symptomatic patients with an established diagnosis of schizophrenia previously unsuccessfully treated with long-acting injectable risperidone treatment (RLAT).

Methods: International, prospective 6-month open-label study. Major outcomes were clinical response (percentage of patients with ≥20% improvement in Positive and Negative Syndrome Scale (PANSS) total score at endpoint), functioning (Personal and Social Performance scale (PSP)), Extrapyramidal Symptom Rating Scale (ESRS), sleep quality, daytime drowsiness and treatment-emergent adverse events (TEAEs).

Results: The intent-to-treat population comprised 56 patients previously treated with RLAT (64.3% male, mean age 39.9±11.0 years, 71.4% paranoid schizophrenia, mean BMI 28.5±5.8 kg/m². 71.4% of patients completed the 6-month study. Withdrawal of consent (8.9%) and adverse events (10.7%) were the most frequent reasons for early discontinuation. The median mode maintenance dose of PP was 100 mg eq. Mean PANSS baseline total score was 67.5±20.7 and decreased by -9.2 points on average at endpoint (95% confidence interval -15.0; -3.5, p<0.0001). At endpoint, 61.1% of patients had improved as measured by ≥20% in PANSS total score compared to baseline. Patient functioning in PSP increased by 5.2±15.3 points (p=0.0163). Sleep quality and daytime drowsiness improved significantly (both p<0.0292). Extrapyramidal symptoms in ESRS significantly improved from 3.5±7.1 at baseline to 2.5±6.4 at endpoint (p=0.0038). Concomitant use of anticholinergic medications decreased from 7.1% at baseline to 5.4% at endpoint. TEAEs reported in ≥5% of patients were psychotic disorder (10.7%), injection site pain, headache, schizophrenia, anxiety (7.1% each), constipation and somnolence (5.4% each). Mean body weight decreased by 0.9±4.5 kg from baseline to endpoint.

Discussion: These data suggest that paliperidone palmitate is associated with a meaningful clinical response and functional improvement and is well tolerated with less EPS in non-acute, symptomatic schizophrenia patients previously unsuccessfully treated with RLAT.

Poster #T210**PALIPERIDONE PALMITATE IN ACUTE PATIENTS WITH SCHIZOPHRENIA – TREATMENT RESPONSE, SAFETY AND TOLERABILITY: A PROSPECTIVE FLEXIBLE DOSE STUDY IN PATIENTS PREVIOUSLY UNSUCCESSFULLY TREATED WITH ORAL ANTIPSYCHOTICS**

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Background: Exploring treatment outcomes with once-monthly paliperidone palmitate (PP) in more representative patients with schizophrenia may guide recommendations for use of and transition to PP. This study explores tolerability, safety and treatment response of flexible doses of PP in adult patients with an acute exacerbation of schizophrenia previously unsuccessfully treated with oral antipsychotics.

Methods: International prospective 6-month, open-label study. Outcome parameters were change in Positive and Negative Syndrome Scale (PANSS) total score, Clinical Global Impression-Severity Scale (CGI-S), adverse events (AEs), and weight change.

Results: 212 acute patients (ITT, intent-to-treat population): 59.0% male, mean age 36.4±12.1 years, 85.4% paranoid schizophrenia were enrolled. Main reason for transition from prior oral antipsychotic treatment was lack of efficacy in 45.8% of patients. 70.3% of patients completed the 6-month study. Most frequent reasons for early discontinuation were subject choice (9.4%), AE (9.0%), loss to follow-up (4.7%) and lack of efficacy (2.8%). Recommended initiation regimen of PP (150 mg eq on day 1 and 100 mg eq on day 8) was administered in 92.9% of subjects. Mean baseline PANSS total score decreased from 98.5±20.1 as of day 8 of treatment to 67.4±24.0 at endpoint (mean change -31.0±28.97; 95% confidence interval [CI] -35.0; -27.1; p<0.0001). 66.7% of patients improved ≥30% in PANSS total score and percentage of patients rated markedly ill or worse in CGI-S decreased from 75.1% at baseline to 20.5% at endpoint. AEs reported in ≥5% were injection site pain (13.7%), insomnia (10.8%), psychotic disorder (10.4%), headache (6.1%) and anxiety (6.1%). Mean weight change at endpoint was 2.6±5.6 kg (95%CI 1.8; 3.4).

Discussion: These data support results from previous randomized controlled studies that flexibly dosed paliperidone palmitate is well tolerated and associated with an early and clinically relevant treatment response in acute schizophrenia patients previously unsuccessfully treated with oral antipsychotics.

Poster #T211**GLUTAMATERGIC DYSFUNCTION ASSOCIATED WITH FOCAL BRAIN CORTICAL THICKNESS IN ANTIPSYCHOTIC-NAÏVE PATIENTS WITH SCHIZOPHRENIA**

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Background: Altered prefrontal glutamatergic neurotransmission is of critical relevance for major aspects of the so called “hypofrontality” and associated negative symptoms and cognitive deficits. Hence, exploring the interrelation between disturbed prefrontal glutamatergic neurotransmission and focal brain structural abnormalities might further elucidate the neuronal foundations of altered prefrontal circuitry in schizophrenia. In this multimodal study, we thus focused on associations between dorsolateral

prefrontal glutamate metabolism and cortical structure in first episode antipsychotic-naïve schizophrenia patients.

Methods: Dorsolateral prefrontal cortex (DLPFC) glutamate was measured by proton MR spectroscopy (1H-MRS). Cortical thickness was computed with an automated surface based technique (FreeSurfer). 28 antipsychotic-naïve first episode patients and 27 matched healthy controls were integrated in this study. DLPFC glutamate values were correlated with node-by-node cortical thickness covering the entire cortex in patients and controls.

Results: Patients demonstrated significantly reduced DLPFC glutamate levels and cortical thinning in prefrontal and temporal regions. In patients, decreased DLPFC glutamate was associated with reduced cortical thickness in the DLPFC and the dorsal anterior cingulate cortex (dACC). This association was not observed in healthy controls with a significant difference at a whole brain level.

Discussion: In conclusion, we provide first evidence for a direct linkage of prefrontal glutamatergic dysregulation and cortical thinning in early acute schizophrenia observed in neuroanatomical key regions including the DLPFC and the dACC. This co-occurrence of prefrontal glutamatergic hypo-function and cortical abnormalities may be a correlate of focally disturbed neuronal/synaptic plasticity in the early course of schizophrenia.

Reference:

[1] Schultz, CC. et al., submitted.

Poster #T212**MENTAL HEALTH LITERACY ON PSYCHOSIS AND DEPRESSION: DO LABELING AND CAUSAL ATTRIBUTION AFFECT TREATMENT RECOMMENDATIONS?**

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Background: Good mental health literacy is thought to improve help-seeking and treatment compliance. Therefore, we investigated the treatment recommendations for psychosis and depression in a general population sample in relation to the recognition and causal attribution.

Methods: 1'184 German-speaking participants of a telephone survey (age 16 to 40) were asked to answer a questionnaire on mental health literacy and attitudes whose two versions vary in their diagnostically unlabeled case vignette (schizophrenia or depression). 1'061 (89.6%) agreed to participate, 645 (60.8%) questionnaires were returned: 331 with a schizophrenia case vignette, 314 with a depression case vignette.

Results: Type of the vignette had a near moderate effect on the main treatment recommendation that could be chosen from 7 categories: Psychotherapy received the highest degree of recommendation throughout – though even slightly more for the schizophrenia vignette (Cramer's V=0.165), while “electro-convulsive therapy” (ECT) was hardly ever recommended for both vignettes. At a moderate effect size (Cramer's V=0.292), the type of the depicted mental problem had the largest effect on the recommendation of a psychopharmacological treatment: it was recommended for psychosis by 68.9%, and for depression by just 39.8% of the respective vignette responders. Thus, for the depression vignette, all treatment options but ECT were more frequently recommended than medication. For the schizophrenia vignette, medication was the second most recommended treatment option. The effect of the type of vignette was even more pronounced when correct or incorrect labeling of the vignette was taken into account (Cramer's V= 0.367 and 0.354): While correct labeling decreased the recommendation of both psychotherapy and alternative treatments in favor of medication in schizophrenia, it only decreased recommendation of alternative treatments in favor of medication in depression. Similar to the effect of correct labeling, the adoption of a biological or non-biological causal model had an additional, yet smaller increasing effect on the effect of the type of vignette (Cramer's V= 0.320 and 0.195) that was similar in its direction.

Discussion: In schizophrenia and severe depression, psychopharmacological treatment is considered indispensable by professionals, yet its acceptance in the young adult general population is very low. Surprisingly, the adoption of a biological causal model had only a limited positive effect on the recommendation of medication. The main positive effect on recommendation of medication was exerted by a correct recognition of the disorder. Other

than psychopharmacotherapy, psychotherapy was highly recommended, although in depression, esp. when not correctly recognized as such, alternative treatments played a similarly important role in recommendations. The high acceptance of psychotherapy encourages early intervention. While the bad reputation of pharmacological medication might have a negative effect on compliance and should be targeted in awareness campaigns.

Poster #T213

THE COURSE OF AT-RISK SYMPTOMS FOR PSYCHOSIS IN THE GENERAL POPULATION: 2-YEAR FOLLOW-UP OF THE BERN EPIDEMIOLOGICAL AT-RISK (BEAR) STUDY

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Background: In clinical samples recruited in specialized early detection and intervention services, both ultra-high risk (UHR) criteria, mainly attenuated psychotic symptoms (APS), and basic symptom criteria, i.e., cognitive disturbances (COGDIS) and cognitive-perceptive basic symptoms (COPER), are not only associated with a 1-year conversion rate of roughly 20% but also with various other impairments, e.g., in neurocognitive performances, quality of life or functioning, and increased rates of other mental disorders. Their prevalence and psychopathological significance outside help-seeking samples, however, had been largely unknown and, starting in 2011, was studied in 1,229 16- to 40-year olds of the general population in the BEAR study. In the first interview, 25.2% of the young adults acknowledged the presence of any lifetime at-risk phenomenon, but only 2.8% met criteria for any at-risk criterion (incl. frequency and onset requirements) within the last 3 months. Of interviewees, 97.4% agreed to being re-contacted for a similar interview in future.

Methods: In a 2-year follow-up study that started in September 2013, those with any lifetime at-risk phenomenon and a control group are being re-interviewed for at-risk phenomena and criteria, the development of psychosis and other axis-I disorders as well as help-seeking. At the time of writing, 53 follow-up interviews had been conducted: in 23 persons who had acknowledged at least any 1 lifetime risk phenomenon in the first interview (RISK, 30% male, mean age at first interview: 36±4 years) and in 30 who had not (CONTROL, 43% male, mean age at first interview: 36±2 years). So far, none of the recontacted persons refused to participate in the second interview.

Results: One of the RISK, but none of CONTROL group reported the meanwhile development of a first-episode psychosis (major depression with psychotic features that was treated with antidepressants and antipsychotics by a psychiatrist). Furthermore, interviewees of the RISK group were significantly more likely than those of CONTROL to report presence of any at-risk phenomenon within the follow-up period (36% vs. 7%; $\chi^2(1)=7.206$, $p=0.012$, Cramer's $V=0.372$). Thus, the relative risk to still report at-risk phenomena when these had already been reported before was 5.455 (95% CI: 1.281; 23.219). Altogether 13% met criteria for a non-psychotic current or within-follow-up axis-I disorder according to DSM-IV whose presence was unrelated to presence of at-risk phenomena at first or second interview (13% in both RISK and CONTROL).

Discussion: These first results indicate that at-risk phenomena are frequently not just fleeting experiences but tend to persist. Thereby, they do not seem to generally increase the likelihood of developing any mental disorder but might indeed predispose to the development of psychotic symptoms. However, at the time of writing, only a small number of interviews had been conducted, and mainly persons of the upper age range had been reinterviewed who can be assumed to be at a slightly lesser risk for developing a first-episode psychosis than younger adults.

Poster #T214

A SYSTEMATIC REVIEW OF FACTORS INFLUENCING ANTIPSYCHOTIC MEDICATION ADHERENCE IN SCHIZOPHRENIA

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Background: Despite the variety and reasonable efficacy of antipsychotic agents available for the treatment of schizophrenia, a large proportion of patients do not adequately adhere to their prescribed regimen. Suboptimal adherence in this patient population is associated with significant costs to patients and society. Partly due to methodological heterogeneity, there is a widespread lack of consensus in the current literature on which factors influence adherence behaviour. The more robust identification of correlates of medication adherence in schizophrenia is required for providing stronger empirical support to existing and future adherence-enhancing interventions.

Methods: A systematic review of studies investigating factors influencing medication adherence in schizophrenia was conducted. Medline and Embase databases were searched using the following terms in various combinations: "schizophrenia", "antipsychotic*", "neuroleptic*", "adherence", "nonadherence", "non-adherence", "compliance", "noncompliance", and "non-compliance". Articles published between 1980 and 2013 were included and the last searched was conducted on 23 June 2013. The application of a quantitative, meta-analytic approach was deemed inappropriate due to highly heterogeneous study designs, and a qualitative synthesis of studies was therefore undertaken.

Results: A sample of 13 observational studies (total N=6235) meeting selection criteria was critically appraised. Reported adherence rates ranged from 47.2 - 95%, depending on definition and measurement of adherence. A more positive attitude to psychotropic medication and insight into illness were the only consistently identified predictors of good adherence, while contradictory results were found for the majority of factors examined. Neither socio-demographic characteristics, nor symptom severity or antipsychotic-induced side effects were consistently associated with medication adherence. Only distinct aspects of the therapeutic relationship and social support in younger patients were demonstrated to be predictive of good adherence. Antipsychotic type or formulation as well as neurocognitive functioning did not appear to impact medication adherence.

Discussion: There is an evident lack of consistently identified factors influencing antipsychotic medication adherence in schizophrenia, mirroring inconclusive findings of previous reviews and highlighting the need for further clarification in order to contribute to the improvement of non-adherence management strategies. Recommendations for more targeted and methodologically refined future research are provided.

Poster #T215

ASSOCIATION BETWEEN STRESSFUL LIFE EVENTS AND PSYCHOTIC EXPERIENCES IN ADOLESCENCE: EVIDENCE FOR GENE-ENVIRONMENT CORRELATIONS

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Background: Exposure to stressful life events is associated with psychotic experiences and an increased risk of developing psychosis. It is however unknown to what degree this is explained by genes or environmental influences. Stressful life events might act as environmental agitators, but in addition there may be a shared genetic propensity for stressful life events and psychotic experiences. This study aimed to estimate the extent to which genetic and environmental factors influence the relationship between stressful life events and psychotic experiences.

Methods: Participants included 4,830 16-year-old twin pairs from the Twins Early Development Study, a large community-based sample. Stressful life events and psychotic experiences were assessed using self and parent report. Structural equation model fitting was employed.

Results: Stressful life events were correlated with positive psychotic experiences ($r=0.12$ – 0.14 , all $p<0.001$). Modest heritability was shown for psychotic experiences (25–57%) and dependent stressful life events (32%). Genetic influences explained some of the covariation between positive psy-

chotic experiences and dependent stressful life events (bivariate heritabilities = 42–86%). Analyses indicated familial influences with hallucinations, and grandiosity and delusion, as it was not possible to differentiate between genetic and common environmental effects.

Discussion: Further to stressful life events being an environmental risk, individuals may have a genetic propensity for dependent stressful life events and positive psychotic experiences via a gene-environment correlation.

Poster #T216

ASSOCIATION OF VITAMIN-D WITH HIPPOCAMPAL GRAY MATTER VOLUME IN ANTIPSYCHOTIC - NAIVE SCHIZOPHRENIA PATIENTS

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Background: Converging evidences from epidemiological studies in schizophrenia have implicated the role of vitamin D in schizophrenia pathogenesis. Various animal studies suggest a possible role of vitamin D in maintaining the volume of grey matter of hippocampus, one of the most important brain regions implicated in schizophrenia. The objective of the present study was to evaluate evidence for relationship between serum vitamin-D level and hippocampal gray matter volume in schizophrenia patients

Methods: 36 antipsychotic-naïve/free schizophrenia patients were recruited. Fasting level of serum vitamin-D was measured using Enzyme-Linked Immunosorbent Assay. To test the correlation between serum vitamin D levels and hippocampal grey matter volume, we used optimized voxel-based morphometry of 1-mm MRI acquired in a 3-Tesla scanner

Results: Serum levels of vitamin D showed a significant positive correlation with right hippocampal gray matter volume (x, y, z MNI coordinates: 35 -18 -8, $p_{FWE} = 0.02$ at an uncorrected threshold of $p = 0.001$). The results were significant even after controlling for several possible confounding factors like age, sex, years of education and total intracranial volume

Discussion: To the best of our knowledge, this is the first study reporting the relationship between serum vitamin D levels and hippocampal gray matter volume in schizophrenia patients. This further strengthens the vitamin D deficiency hypothesis in the pathogenesis of schizophrenia warranting further systematic studies

on the incidence and course of psychotic disorders, especially in low- and middle-income countries. We present a partial description of the sample of a population-based study currently in course in the region of Ribeirão Preto, a large Brazilian catchment area. Our center is part of the international consortium “European Network of National Networks Studying Schizophrenia Gene-Environment Interactions” (EU-GEI; <http://www.eu-gei.eu/>), and data collection is scheduled for a three-year period. The study also aims to investigate social and biological factors associated to first episode psychosis (FEP), using a case-control design.

Methods: The international consortium has an uniform research protocol with a battery of socio-demographic, environmental, clinical, neuropsychological and family history assessments, as well as genetic evaluations. The inclusion criteria are a diagnosis of FEP in individuals aged between 16 to 64 years old seeking mental health treatment for the first time in their lives. We planned a final sample of 300 FEP, 150 siblings and 300 population-based controls for the case-control study. The cases are recruited in a region with a population at risk of 941,459 person-years. Diagnosis is established with the Structured Clinical Interview for DSM-IV applied by trained mental health professionals. If a face to face interview is not possible, the SCID is applied based on information from medical records and mental health professionals involved in the care of the patient. We describe demographic and clinical characteristics of a preliminary sample from 18 months of recruitment. Ethical consent was obtained from all participants.

Results: Two hundred and sixty-six patients were screened as possible FEP and 163 met the inclusion criteria. From these, 90 were males (55.2%). Their age ranged from 16 to 61 years (mean = 30.5, SD = 12.0). Males (mean = 27.7, SD = 11.4) were significantly younger than females (mean = 33.9, SD = 12.0) ($t=3.31$, $df=157$, $p=0.001$). Almost half of the sample (48.5%) lived in the larger city of the catchment area. The first contact with a mental health service for the majority of the patients ($n=104$, 63.8%) was through emergency settings. The diagnoses of non-affective and affective psychosis correspond respectively to 44.8% and 55.2%. The period between the beginning of the psychotic symptoms and the first contact with a mental health service ranged from 0 to 1292 weeks (median = 6.5 weeks) and the median time for starting effective treatment was 8 weeks after the beginning of the psychotic symptoms.

Discussion: Preliminary data suggest similar demographic and clinical profiles to those observed in a previous study in Brazil. The novelty of this study is based on this broad and integrated approach of the different components of the etiology and mechanisms involved in schizophrenia and the other psychotic disorders. Moreover, this international multicenter consortium, with specific, consistent and uniform protocols, is a pioneering strategy that will enable greater integration and cooperation among diverse groups of researchers involved in this research network.

Poster #T217

PRELIMINARY SAMPLE DESCRIPTION OF FIRST EPISODE PSYCHOSIS IN A BRAZILIAN LARGE CATCHMENT AREA

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Background: Severe mental disorders, such as schizophrenia and other psychotic disorders, are associated with significant social and psychological impact to both patients and families. However, scarce data are available

Poster #T218

THE THIRD NATIONAL SURVEY ABOUT PRESCRIPTION PATTERNS OF PSYCHOTROPIC DRUG FOR THREE MENTAL DISORDERS IN CHINA

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Background: Prescription pattern of mental disorders is increasingly becoming the focus of attention. For past ten years, pharmacotherapy for the mental disorders develops quickly. The debates related the prescription pattern are going on, for example monopharmacy vs polypharmacy, cost vs benefits, evidence based vs experience based. Based on the protocols and results from the previous two national surveys, the third national survey about prescription patterns of psychotropic drug for three mental disorders in China was performed. After sampling all outpatients and inpatients in the study sites, the distribution of three psychiatric diseases in the Chinese clinical setting was obtained. And based on the survey, we analyzed the prescription patterns of psychotropic drugs for schizophrenia, depression and bipolar disorder. This report is aimed to present the protocol implementation and basic results from the third investigation.

Methods: This was a cross-sectional study which was conducted in 45 typical medical institutions in 10 provinces from 6 regions of China from 9 July 2012 to 23 July 2012. Inpatients and outpatients visited each study site at seven working days were sampled to receive investigation. Double

entry and validation of data was conducted using Epidata3.1 software. And statistical analysis was carried out using SPSS18.0 software.

Results: A total of 7070 patients in 45 medical institutions were recruited into the study. After double entry and validation of data, 7022 effective CRFs were entered into statistical analysis. In outpatient settings, patients with schizophrenia, depression and bipolar disorder accounted for 55.7%, 28.5% and 15.6%, respectively. In inpatient settings, the percentages were 66.8%, 15.9% and 17.2%, respectively. Of all outpatient and inpatients, monopharmacy covered 67.9% and 63.9% of patients with schizophrenia, 87.7% and 86.1% of patients with depression. For patients with bipolar disorder, rate of polypharmacy is higher than the patients with schizophrenia and depression, most of patients were treated with combination of mood stabilizers and antipsychotic drugs, accounted for 58.2% and 70.5% for outpatient and inpatient, respectively.

Discussion: Schizophrenics accounted for more than half of all patients in Chinese psychiatric institutions. Compared with previous study, the ratio of patients with depression and bipolar disorder were increased in recent years. Patients with bipolar disorder used combination of drugs commonly. Single antidepressant treatment still was the main strategy for patients with depression. For schizophrenics and depression, there were minor differences in drug combination prescription between inpatients and outpatients.

Poster #T219

PITFALL OF USING ABSOLUTE RISK SCORE FOR RISK ASSESSMENT AND PREVENTION

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Background: Absolute risk estimation, a cornerstone for the primary prevention of cardiovascular disease strategy, has been incorporated in Framingham Heart Study (FHS) and recommendations from the US Preventive Services Task Force, NHLBI's Adult Treatment Panel III (ATP III) to European and Canadian guidelines for lifestyle and pharmacological preventive interventions. The Framingham Risk Score is an important and well-established risk prevention tool for guiding the assessment and management of risk for coronary heart disease (CHD). Previous studies applying FRS have been all focused on "absolute risk" (Goff et al., 2005; Daumit et al., 2008), i.e. the probability of developing CHD over a given period of time. This might not be most appropriate for the individuals in schizophrenia population, since the original Framingham Cox Survival model (Wilson et al., 1998) was developed based on a white middle-class population from the Framingham Heart Study.

Methods: The objective of this paper was to examine the recalibration procedure for absolute risk survival model, using the FRS risk estimate as an example, evaluate the validity of using these absolute risk estimates in populations in which no baseline risk has been established, and investigate whether risk ratio (relative to an optimal risk profile as the reference risk state) can provide more accurate risk estimate than the usual absolute risk score for individuals with serious mental illness. We calculated estimates for FHS optimal risk based on optimal blood pressure (systolic <120 mm Hg and diastolic <80 mm Hg), TC 160 to 199 mg/dL (or LDL 100 to 129 mg/dL), HDL-C of 45 mg/dL in men, no diabetes, and no smoking (Wilson et al., 1998). To recalibrate the FRS risk estimates for a new study population, we need to replace 1) the Framingham baseline survival rate for CHD risk (RISKO) and 2) the overall mean of risk factors in the FRS prevention algorithm (GMEAN for age, proportion of smoker, proportion of subjects in each lipid and hypertension risk categories) with values from this new study population.

Results: We compared the mean (or proportion) for each of the categories of the FRS risk factors in CATIE and FHS studies: mean age 40 in CATIE versus 49 in FHS, total cholesterol \geq 240 mg/dL is 20% in CATIE versus 26% in FHS, HDL<35 mg/dL is 25% in CATIE versus 11% in FHS, Stage I-IV hypertension 28% in CATIE versus 32% in FHS, Diabetes mellitus (women 16% and men 11%) in CATIE versus (women 4% and men 5%) in FHS, and smoker (women 56% versus men 73%) in CATIE versus (women 38% and men 40%) in FHS. It follows that GMEAN is 2.8 for men in the CATIE study and 3.0975 in the FHS. Specifically, the low 10-year absolute risk (reference risk state) was 7% for both men and women of age 55-59 years based on

the FHS. Replacing the FHS RISKO (=0.1) and GMEAN (=3.0975) with new hypothetical recalibrated values (RISKO = 0.125 and GMEAN = 2.8), the low 10-year CHD risk was 12% (vs. 7% FHS value) and the absolute risk 26% (vs. 16% FHS value) for men aged 55-59. In contrast, risk ratio was virtually the same (=2.2) for both the FHS and the new recalibrated models. We developed a simple proof to show that risk ratio (relative to the low risk state) does not depend on baseline risk (RISKO) and mean risk factors GMEAN when the cumulative hazard is small, and hence more useful to be compared across populations.

Discussion: Our findings suggest that risk ratio (relative to low risk state based on an optimal risk profile) instead of absolute risk might be more appropriate for prediction of cardiovascular risk in schizophrenia patients using risk prevention algorithms such as the Framingham Scoring Model.

Poster #T220

TRANSITION AND PSYCHOSIS RELATED HEMODYNAMIC CORRELATES OF MOTIVATIONAL SALIENCE PROCESSING

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Background: Motivational salience processing deficits were related to the psychotic symptoms and to the dopamine (DA) transmission alterations. We focused on salience processing hemodynamic changes during the development of psychosis i.e. in the individuals with an at-risk mental state (ARMS) and first-episode of psychosis (FEP), especially without confounding effect of antipsychotic medication (in FEP unmedicated; FEP-UM) compared to healthy controls (HC). Additionally, we wanted to examine the effect of acute medication in FEP patients.

Methods: We used functional magnetic resonance imaging during the Salience Attribution Task [1,2] in 19 HC, 34 ARMS and 29 FEP individuals, which included a subgroup of 17 FEP without antipsychotic medication (FEP-UM). To investigate the effect of transition, we compared ARMS who transited (ARMS-T) subsequently with ARMS without transition (ARMS-NT) to psychosis. The groups were compared with respect to high-relative-to-low probability reward (relevant) cues = adaptive salience contrast and with respect to subjectively-high-relative-to-low probability reward (irrelevant) cues = aberrant salience contrast.

Results: The groups were well matched for gender, age, handedness, and verbal IQ. FEP-UM, FEP-M and ARMS groups had more positive, negative psychotic symptoms and worse global functioning compared with HC ($P < 0.005$). There were no significant behavioral differences between groups in motivational salience. The ARMS-T group showed higher hemodynamic responses during adaptive salience in the right putamen and thalamus compared to the ARMS-NT and the FEP group. The FEP-UM group had lower response in the left anterior cingulate and middle frontal gyri compared to the HC group. The FEP-M group had lower responses in the right precentral gyrus and insula compared to the HC group. We found neither effect of medication nor transition-to-psychosis associated differences in aberrant salience processing.

Discussion: The ARMS-NT showed lower dorsal striatal and thalamic adaptive salience-related response than ARMS-T. This appears to be contradictory to the expected hyperdopaminergia underlying the onset of psychosis [3] and the elevated striatal DA synthesis capacity in ARMS-T compared to the ARMS-NT and HC [4]. The adaptive salience contrast was previously related to the phasic increase of DA firing [5] in the ventral striatum. We speculate that during prodromal psychosis additionally to the known phasic- also chaotic- DA firing increases and contributes to the 'noise' in neural response measured with fMRI. It was postulated that unmedicated schizophrenia patients should show reduced brain activation following the adaptive salience stimuli [5]. Our FEP showed reduced neural responses in the dorsal striatum than the ARMS-T, but not than the HC group contrary to the previous results [6,7]. We found no effect of antipsychotics on the

motivational salience processing. Antipsychotic drugs may block post- as well as pre-synaptic D2-DA receptors and result in a compensatory increase in DA synthesis [3]. Additionally, the extracellular DA levels can be elevated in striatum [8] and decreased in the prefrontal cortex [9] in unmedicated schizophrenia patients. Antipsychotic medication may interfere with salience attribution [10] and DA dysfunction may be particularly prominent during very early stages of psychosis [5]. Thus, FEP-UM as well as FEP-M, could have dysregulated striatal DA levels. Overall, antipsychotics target brain areas related to pathophysiology in early psychosis, but do not cause these alterations [11].

References: 1, 2. Roiser 2009 & 2010; 3, 4. Howes 2009 & 2011; 5. Heinz 2010; 6. Gradin 2013; 7. Grimm O 2012; 8, 9. Abi-Dargham 2000 & 2012; 10. Schlagenhauf 2008; 11. Radua 2012.

Poster #T221

MECHANISM OF ACTION OF ITI-007: A NOVEL THERAPY FOR THE TREATMENT OF SCHIZOPHRENIA AND RELATED PSYCHOSES

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Background: ITI-007 is an investigational new drug with a unique pharmacological profile currently in development for the treatment of schizophrenia and other psychiatric and neurological indications. ITI-007 combines potent 5-HT2A receptor antagonism ($K_i=0.54$ nM) with lesser affinity for dopamine D2 receptors ($K_i=31.9$ nM), D1 receptors ($K_i=52$ nM), and the serotonin transporter (SERT, $K_i=52$ nM). This presentation summarizes the preclinical pharmacology supporting the mechanism of action of ITI-007.

Methods: Behavioral Pharmacology: 5-HT2A antagonism in vivo by ITI-007 was measured by blockade of head-twitch behavior induced by the 5-HT receptor agonist, DOI. Catalepsy was assessed in mice after ITI-007 administration using the bar-grip test. Inhibition of locomotor hyperactivity by ITI-007 was measured as distance travelled (cm) after amphetamine treatment in rats. Social approach behavior was measured in mice treated for 28d with ITI-007 using the chronic resident intruder model. In vivo microdialysis: The effects of ITI-007 on extracellular concentrations of dopamine and DOPAC were measured in the prefrontal cortex and striatum of freely moving rats using in vivo microdialysis. In vivo dopamine metabolism: Striatal levels of dopamine and DOPAC were measured by HPLC in mice after chronic oral dosing with ITI-007. In vivo phosphoprotein analysis: Brain levels of phospho-Y1472 GluN2B, phospho-S40 tyrosine hydroxylase (TH), and phospho-S9 GSK3 were measured by western blotting in mice treated with ITI-007.

Results: ITI-007 potently inhibited DOI-induced head twitch ($ED_{50}<0.1$ mg/kg PO) and did not induce cataleptic behavior at doses <30 mg/kg (PO). ITI-007 blocked amphetamine hyperactivity ($IC_{50}=1$ mg/kg, PO) and reversed social avoidance behavior in mice (1 mg/kg, IP) repeatedly exposed to an aggressive resident intruder. Biochemically, ITI-007 significantly increased extracellular dopamine concentrations in prefrontal cortex, but not in striatum. ITI-007 did not increase striatal dopamine metabolism, as measured by DOPAC/DA ratio, or levels of phospho-S40 TH, a marker for enhanced striatal neurotransmission. Phosphoprotein analysis also revealed that doses of ITI-007 relevant for antipsychotic activity in animals significantly increased phosphorylation of the glutamate receptor, GluN2B, and GSK3, a target for known antipsychotic drugs through the dopamine D2 receptor, in mesolimbic/mesocortical regions of mouse brain.

Discussion: ITI-007 displays potent functional 5-HT2A receptor antagonism with cell type-specific modulation of phosphoprotein cascades downstream of dopamine receptors and serotonin reuptake inhibition suggesting a compound with actions on dopaminergic and glutamatergic systems in brain regions key for antipsychotic efficacy. ITI-007 acted as a pre-synaptic partial agonist and a post-synaptic antagonist at dopamine D2 receptors in vivo, exhibiting mesocortical selective increases in dopamine release, predicting antipsychotic efficacy, and no disruption of striatal dopamine neurotransmission, predicting a low liability for motor side effects. ITI-007 reversed social defeat behavior in mice in a model that predicts antidepressant activity. ITI-007 also engaged glutamate neurotransmission by promoting phosphorylation of glutamatergic NMDA NR2B receptors downstream of D1 receptor activation. The unique pharmacological profile of ITI-007 – including significant SERT activity and activation of mesolimbic/mesocortical

glutamate receptors – is predicted to translate into improved antipsychotic efficacy for the treatment of positive, negative, and cognitive symptoms in addition to anticipated antidepressant efficacy.

Poster #T222

ABNORMAL HYPERACTIVE SELF-AWARENESS PROCESSING IN SCHIZOPHRENIA

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Background: Schizophrenia have defects in emotion processing, which is a complex social cognition process requiring participation by multiple brain regions. Dysfunctional emotion processing is demonstrated to be affected by disturbance of self-awareness. This study aimed to investigate the neural correlates of emotional self-awareness in patients with schizophrenia using functional magnetic resonance imaging.

Methods: Twenty schizophrenia patients and twenty-five healthy controls performed a face-matching task during functional magnetic resonance imaging. During the task, a stimulus consisted of a face (self, famous or unfamiliar other) and a word (positive, negative or neutral noun) and subjects were asked to determine relevance score of them (1; no relevance, 2; moderate relevance, 3; strong relevance).

Results: Schizophrenia reported significantly higher rating of relevance for negative words than controls. Compared with controls, patients with schizophrenia significantly increased activities in the right dorsomedial prefrontal cortex during self-awareness in fMRI data.

Discussion: The findings of this study suggest that schizophrenia may have a more negative view of self than healthy controls. This study also suggest that hyperactivity of right dorsomedial prefrontal cortex is related to self-awareness schizophrenia.

Poster #T223

AXIS I AND AXIS II DISORDERS IN YOUNG PEOPLE AT ULTRA-HIGH RISK OF DEVELOPING A PSYCHOTIC DISORDER: A LONG-TERM FOLLOW UP STUDY

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Background: There has been little research into the longer-term pattern of onset and persistence of non-psychotic Axis I disorders in the ultra high risk (UHR) for psychosis population (Yung & McGorry, 1996). Most research thus far has been cross-sectional. In addition, scarcely any literature addresses the prevalence of Axis II disorders in this population and their impact on functional outcomes. The current study investigated the comorbidity of non-psychotic Axis I disorders over the long-term (5–8 years since baseline) and Axis II disorders (at follow-up) in the UHR population. We further examined the association of these disorders on functioning in social and occupational domains. This research will have bearing on the issue of whether the UHR phenotype is a pluripotential syndrome (ie. might evolve into various different disorders) or is more specific to psychosis outcomes.

Objective: To investigate whether UHR status is a specific risk state for psychosis or for a range of Axis I and Axis II disorders.

Methods: The sample comprised 172 UHR individuals who were previously recruited to research studies at the PACE Clinic, Orygen Youth Health, between 2002 and 2006. Axis I and II disorders were assessed using the Structured Clinical Interview for DSM-IV (SCID). UHR status was determined using the Comprehensive Assessment of At Risk Mental States (CAARMS).

Results: This study is currently in the recruitment phase. This presentation will address study rationale, objectives, and preliminary follow-up data. Currently, 118 (68%) participants have been followed up.

Discussion: We anticipate that this study will validate previous findings that Axis I comorbidity poses an ongoing problem for those identified as being at UHR for psychosis (Lin et al., 2012). However, in contrast to the limited research on Axis II disorders in this population, our preliminary findings indicate a lower prevalence of Axis II disorders than previously reported. Improved understanding of the relationship of Axis I and II disorders to functional outcomes will inform treatment options and facilitate management of illness in the UHR population.

Acknowledgement: This research project is supported by a National Health and Medical Research Council Project Grant (APP1027741).

Poster #T224

TACKLING STIGMA: DEVELOPING NEIGHBOURHOOD INTERVENTIONS BY MEANS OF FOCUS GROUPS

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Background: People with psychiatric problems are often confronted with stigmatisation. This can take place at home or in their neighbourhood, with friends or family, at the gym or at work. Stigma is characterised by limited knowledge, prejudice, and discrimination. To effectively change stigma contact with the stigmatised group is essential, as well as increasing the current knowledge concerning mental health problems. Given the trend of clients living in residential areas in the Netherlands, it seems essential to tackle stigma concerning mental health right now. Especially since in general residents associate psychiatric problems with violence, irresponsible behaviours and think they should be “kept in hospitals”.

Methods: Focus groups will be formed in Assen to investigate the role of stigmatisation in neighbourhoods, both mental health care clients and residents will be invited to participate in separate groups. Each group will consist of 5-15 participants and a moderator. Within these groups a structured discussion will be held concerning the following topics: For clients: 1. experience of stigmatisation, 2. most affected parts of life, 3. possible solutions; for residents the following topics will be addressed: 1. experience of stigmatisation, 2. most stigmatised groups, 3. possible solutions. Neighbourhoods have been selected based on: 1. number of mental health service clients, 2. comparable demographic characteristics, 3. overall satisfaction of residents regarding their living environment. Clients will be invited in the mental health facility to participate if they live in one of the selected residential neighbourhoods in Assen, residents will be invited to participate from the same residential neighbourhoods, and they will be invited through community workers. Based on the results of the focus groups interventions will be developed aiming at a reduction of stigmatisation and an improvement of quality of life the neighbourhood. Two areas will be compared, one neighbourhood will be in the active condition and receive interventions, the other will serve as control neighbourhood.

Results: Results of the focus groups will be presented on the poster. Outcomes will be presented of the neighbourhood focus group and the client focus group.

Discussion: Results of the focus groups will be discussed on the poster. This will include recommendations with regard to interventions on a local level.

Poster #T225

FAILURE TO FIND ADDITIVE INTERACTION BETWEEN SOCIAL ADVERSITY IN CHILDHOOD AND FAMILY RISK OF PSYCHOSIS

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Background: There is robust evidence that early adversities are associated

with an increased risk of psychosis (Fisher et al. 2010). However, no etiological theory for psychosis may hope to be comprehensive without taking in consideration genetic factors. We hypothesized that early social adversities (defined as presence of separation and/or loss from one or both parents before age of 17) interact with psychosis family history as proxy of genetic risk in increasing the risk of psychosis.

Methods: As part of the GAP, CAPsy, and EU-GEI studies, we collected information on social adversity from a sample of first episode psychosis patients (n=507) and in a control sample (n=425) recruited from the areas in South-East London covered by the South London and Maudsley NHS Foundation Trust. To assess the additive interaction we constructed a logistic model that took into consideration 3 variables, each taking on two values: social adversity in childhood (no/yes) psychosis family history in first relatives (no/yes), and outcome status (case/control). Confidence intervals and p-values for the Interaction Contrast Ratio [ICR] were calculated using the nlcom procedure in STATA 12.

Results: Compared to controls, cases were 2.3 times (95% CI 1.6–3.2) more likely to report only adversity in childhood, 5.2 times (95% CI 2.3–11.7) more likely to report only psychosis family history, 4 times (95% CI 2–7.7) more likely to report both. However, our preliminary data do not support a synergistic relationship between early adversities and genetic risk. The combined effect was lower than the sum of the individual effects (Interaction Contrast Ratio [ICR] -2.56, 95%CI -7.3–2.2).

Discussion: In contrast with our hypothesis, there was no evidence that early adversities and psychosis family history combined synergistically to increase odds of psychotic disorder beyond the effect of each individually. Further analyses need to be conducted to understand if and how early adversities and psychosis genetic risk combine to create vulnerability for psychosis.

Poster #T226

SOCIAL ANXIETY DISORDER IN RECENT-ONSET SCHIZOPHRENIA SPECTRUM DISORDERS: THE RELATION WITH SYMPTOMOLOGY, ANXIETY, AND SOCIAL RANK

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Background: Social anxiety disorder (SAD) represents a common comorbidity in schizophrenia. However, to date few studies have focused on the specific ways that individuals with schizophrenia and a comorbid diagnosis of SAD are affected in distinct psychotic symptoms, as well as how such symptoms relate to social rank, a key concept of social anxiety.

Methods: Forty-two patients with recent-onset schizophrenia were evaluated for SAD comorbidity using a comprehensive clinical interview which included the Structured Clinical Interview for the DSM-IV (SCID) and the Liebowitz Social Anxiety Scale (LSAS). All participants were also assessed with the Positive and Negative Syndrome Scale (PANSS) and the Social Comparison Scale (SCS).

Results: Eighteen patients met the full criteria for comorbid diagnosis of SAD (SZ+), and 24 patients did not meet all criteria for such comorbidity (SZ-). The SZ- group showed more severe impairments in cognitive symptoms on the PANSS as compared to SZ+, including conceptual disorganization ($t(40)=2.11$, $p=0.041$), difficulty in abstract thinking ($t(40)=2.51$, $p=0.016$), and poor attention ($t(40)=2.18$, $p=0.007$); conversely, the SZ+ group showed higher levels of suspiciousness/persecution ($t(40)=-2.92$, $p=0.006$), active social avoidance ($t(40)=-2.62$, $p=0.012$), and anxiety ($t(40)=-3.23$, $p=0.001$). Patients with SZ+ showed higher scores of social anxiety on the LSAS ($t(40)=-2.88$, $p=0.006$), but social anxiety only correlated with specific psychotic symptoms in the SZ- group. The SZ+ group demonstrated reduced social rank compared to SZ- ($t(40)=2.90$, $p=0.006$). The two groups also displayed differing patterns of correlations between social rank and psychotic symptoms: in patients with SZ+, a negative correlation between social rank and delusions was present ($r=-0.505$, $p=0.033$), whereas in the SZ- group, a positive correlation between the two was present ($r=0.432$, $p=0.035$). The SZ- group also had a positive correlation of social rank with grandiosity ($r=0.484$, $p=0.016$) and passive/apathetic social

withdrawal ($r=0.501$, $p=0.013$), while no such associations were observed in the SZ+ group.

Discussion: There are distinct differences in the severity of psychotic symptoms between patients with SZ+ and SZ-, as well as differing patterns of correlations between psychotic symptoms and social rank; moreover, an association between psychotic symptoms and social anxiety is only present in the SZ- group. Together, these results support the notion that these populations represent two unique subgroups. Finally, the dissimilarities in perceived social rank and the differing relation between social rank and symptomatology suggests that social rank is also an important factor which is related to the presentation of the disorder in both patient groups.

Poster #T227

TRANSDIAGNOSTIC EXPLORATION OF THE ASSOCIATION OF TOXOPLASMA GONDII WITH PSYCHIATRIC DISORDERS. A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Many studies have investigated the association of Toxoplasma gondii (T. gondii) and schizophrenia. A meta-analysis in 2007 of Torrey and Yolken showed a significant Odds Ratio (OR) of 2.7, which was replicated in an updated review in 2012 and by an independent meta-analysis (Torrey 2007, Torrey 2012, Arias 2012). However, other studies have looked at the association between T. gondii and other psychiatric disorders such as major depression, obsessive compulsive disorder (OCD) and bipolar disorder (Pearce 2012, Miman 2010, Hamdani 2013), raising the question whether T. gondii is specifically associated with schizophrenia or with other psychiatric disorders as well. Furthermore, questions remain as to the timing of the infection, whether gender specific effects are present, whether general prevalence of T. gondii in the population is relevant and whether schizophrenia is associated with a new, latent or reactivated T. gondii infection.

Methods: Pubmed, MEDLINE, Psychinfo were systematically searched by two reviewers to identify relevant studies that met the prespecified inclusion criteria. We also reviewed reference lists from the retrieved articles and approached authors to request for other (un)published studies. Odds Ratios (ORs) were extracted and pooled using the random effects models. All major psychiatric disorders in relation to T. gondii were searched. To explore possible moderators of the association between T. gondii and psychiatric disorders, additional data was derived from the articles and the authors on timing of analyses (before onset, recent onset, chronic population), gender specific rates, IgM and IgG specific rates and high versus low positive antibody titers in cases and controls.

Results: 44 studies were included in our meta-analysis with a total of 9782 patients and 67502 healthy controls. Most studies had investigated schizophrenia and T. gondii (30). Schizophrenia (OR 2.1, $p<0.000$) and Bipolar Disorder (OR 1.6, $p=0.002$) were significantly associated with T. gondii, whereas major depression had a non-significant association (OR 1.3, $p=0.097$) and addiction had a few low quality studies yielding no significant association (OR 1.8, $p=0.22$). OCD was studied just once. No studies on T. gondii and other psychiatric disorders (anxiety disorder/eating disorder/autism/adhd) were found. Further exploration of the association between T. gondii and schizophrenia, yielded a significant association of the presence of T. gondii infection before onset of schizophrenia (OR 1.5, $p<0.000$). When baseline exposure in the healthy control population was analysed as a moderator a trend significant decline of the association was found if the seroprevalence of the healthy control population exceeded 20% (OR 2.5 versus OR 1.9, $Q=2.742$, $p=0.098$). Gender specific analyses yielded no significant differences. When distinguishing high versus low positive antibody titers a remarkably high OR was found (OR 2.9, $p<0.000$). Finally, separate analysis of IgM against T. gondii showed a modest but significant association with schizophrenia (OR 1.3, $p<0.05$).

Discussion: Our meta-analysis showed that T. gondii is associated with schizophrenia and bipolar disorder, but not with depression. Addiction yielded interesting, albeit non significant findings. The implications of the analysis of several aspects of the association between T. gondii and schizophrenia will be discussed.

Poster #T228

REDUCED ANTERIOR CINGULATE GRAY MATTER VOLUME AND THICKNESS IN SUBJECTS WITH DEFICIT SCHIZOPHRENIA

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Background: Patients with deficit schizophrenia (D-SZ) differ from patients with the non-deficit form of schizophrenia (ND-SZ) in several aspects such as risk factors, neurobiological correlates, treatment response and clinical outcome. It has been debated if brain morphology could differentiate D-SZ from ND-SZ. Anterior cingulate gyrus (ACG) region regulates cognitive and emotional processing and past studies reported structural changes in this region in patients with SZ.

Methods: 1.5-T 3D MRI scans were obtained from 18 D-SZ patients, 30 ND-SZ patients and 82 healthy controls (HCs). We used FreeSurfer-initialized labeled cortical distance mapping (FSLCDM) to measure ACG gray matter volume, cortical thickness, and area of the gray/white interface. Furthermore, cortical thickness was compared among the 3 groups using the pooled labeled cortical distance mapping (LCDM) method.

Results: The right ACG gray matter volume was significantly reduced in D-SZ patients as compared with healthy controls ($p = 0.005$). Pooled LCDM demonstrated that the ACG cortex was bilaterally thinner in both the ND-SZ group and the D-SZ group compared with the control group. The ACG cortex of the D-SZ group was thinner than the ND-SZ group.

Discussion: Our data suggest that qualitative, categorical differences in neuroanatomy may distinguish between deficit and non-deficit subtypes of schizophrenia.

Poster #T229

SEXUAL SIDE EFFECTS IN PATIENTS USING LONG-ACTING DEPOT ANTIPSYCHOTICS

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Background: Sexual dysfunction in patients with schizophrenia may be related to the disease itself, as well as to psychosocial factors, physical health and the use of psychotropic medications. Sexual side effects have a considerable impact on quality of life and are a major factor in non-adherence to prescribed antipsychotic drugs. Most studies investigated patients using oral antipsychotics with a short duration of treatment whereas depot antipsychotics and sexual functioning during maintenance treatment are infrequently studied. The aim of this study is to investigate the frequency of sexual dysfunction in patients using depot antipsychotics.

Methods: In a cross-sectional study, 53 outpatients using depot antipsychotics were included. At the day of a new depot injection, three questionnaires evaluating sexual side effects were administered: the Antipsychotics and Sexual Functioning Questionnaire (ASFQ), the Subjects' Reaction to Antipsychotics (SRA) and a new questionnaire, the Response to AntiPsychotics (RAP), the latter takes the full dose interval with bloodlevel fluctuations of the medications into account.

Results: Most patients were male ($n=37$; 70%). The mean age was 44.0 years (± 10.0) and ranged from 25 to 66. 79% of the patients were diagnosed with schizophrenia. Other diagnoses were schizoaffective disorder (13%), psychotic disorder NOS (4%) and bipolar disorder (4%). Most patients (60%)

have been using the current antipsychotic for more than 2 years, while 89% of patients have been using any antipsychotic for more than 2 years. 66% of the patients reported at least one sexual dysfunction in one or more of the three questionnaires. Depending on the instrument between 43-55% of the patients reported at least one sexual dysfunction (ASFQ: 47%; SRA 55%; RAP 47%).

Discussion: Sexual dysfunction is frequently occurring in patients using long-acting depot antipsychotics. This result is consistent with previously reported sexual side effects of the oral equivalents of the used depot antipsychotics. In contrast to most studies on oral antipsychotics, in the present study the fast majority of patients have been taking antipsychotics for many years and we are confident about the dose of the antipsychotic and the compliance. The current results indicate that sexual dysfunction is a persistent problem in patients using antipsychotics.

Poster #T230

EFFECTS ON COGNITION OF CLOZAPINE IN TREATMENT-NAÏVE FIRST-EPIISODE SCHIZOPHRENIA (FES): PRELIMINARY RESULTS

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Background: The mechanism of action of clozapine, the unique treatment with a demonstrated advantage in resistant schizophrenia is markedly different as compared to other typical and atypical antipsychotics. Restrictions on clozapine use leave open the question of its potential utility in the earliest stages of the disease, as a first option, when the deterioration rate may be more pronounced. In the context of a clinical trial, our group has developed a 2-year longitudinal study to test the hypothesis that the use of clozapine in Treatment-Naïve FES may limit the degree of prefrontal gray matter loss and, consequently, it can attenuate the cognitive and functional early impairment better than risperidone.

Methods: Up to date, 34 Treatment-Naïve FES patients were included in the trial. They were randomly assigned to clozapine or risperidone as drug treatment. 52.9% of the sample have completed the trial, 12 patients in the clozapine group and 6 patients in the risperidone group. 23 healthy controls matched for age, sex and educational level were recruited. Patients were evaluated twice by a neuropsychological battery related to prefrontal functions: in the first week after attending mental health services and 2 years later. For statistical analysis of related samples Wilcoxon non-parametric test was used.

Results: At baseline, FES patients (n:18) yield significantly below controls on all neuropsychological variables assessed, except in immediate verbal recall. The analysis of the treatment groups did not describe differences between them at baseline. At 2 years follow-up evaluation, the healthy controls still show better performance compared to patients. Patients group (n=18) showed significance improvement on their performance at 2 year follow-up on sustained attention - CPT-Hits ($M=11.05$ (9.04); $Z=-3.59$; $p<0.001$), shifting attention -TMTB-A ($M=28.0$ (40.87); $Z=-2.35$; $p=0.018$), working memory - WAIS III inverse-digits ($M=-1.87$ (2.98); $Z=-2.20$; $p=0.022$), processing speed-TMTA ($M=9.61$ (18.52); $Z=-2.14$; $p=0.032$), semantic fluency ($M=-5.33$ (7.92); $Z=-2.46$; $p=0.014$), Visuospatial ability -ROCF Copy ($M=-1.36$ (3.53); $Z=-1.97$; $p=0.048$) and Verbal Memory - RAVLT ($M=-1.94$ (3.38) $Z=-2.23$; $p=0.025$). Health-control group improved on fonologic fluency ($M=-4.00$ (4.47); $Z=-2.39$; $p=0.016$) and semantic fluency (-3.83 (5.73); $Z=-1.97$; $p=0.049$). Risperidone group (n:6) significantly improved their performance on visuospatial ability - ROCF Copy - ($M=-3.08$ (3.04); $Z=-2.21$; $p=0.027$). Clozapine group (n:12) significantly improved their performance on Sustained attention-CPT-Hits ($M=-13.91$ (8.80); $Z=-3.61$; $p=0.002$), processing speed- TMTA ($M=13.08$ (21.44); $Z=-2.00$; $p=0.045$), working memory-WAIS-III Inverse digits ($M=-0.75$ (0.86); $Z=-2.31$; $p=0.021$), cognitive flexibility -WSCT Perseverative Errors % ($M=7.16$ (12.54); $Z=-2.08$; $p=0.037$) and resistance to retroactive interference RAVLT ($M=1.42$ (1.97); $Z=-2.04$; $p=0.041$)

Discussion: These preliminary results suggest a better cognitive response in patients treated with clozapine on several neuropsychological variables related to prefrontal cortex processes. They describe significance improvement on processing speed, sustained and shifting attention, and working

memory processes (manipulation and effective retrieval of information). However, at this time, the hypothesis that clozapine can attenuate cognitive decline associated with the early stages of schizophrenia cannot be firmly supported due to the small sample size.

Poster #T231

ANTI-PSYCHOTIC TREATMENT DECREASED PLA2 ACTIVITY IN FIRST-EPIISODE DRUG NAÏVE PATIENTS

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Background: One consistent biochemical finding in schizophrenia is an increased activity of the enzymes phospholipases A2 (PLA2). Whereas treatment with anti-psychotic drugs was found to reduce the enzyme activity to levels similar to those observed in control subjects. However the mechanisms underlying this reduction are not yet understood. This family of enzymes is responsible for the metabolism of membrane phospholipids and is composed by three main groups: calcium-dependent cytosolic PLA2 (cPLA2), calcium-dependent secretory PLA2 (sPLA2) and calcium-independent intra-cellular PLA2 (iPLA2). There are so far no investigations of PLA2 groups' activity in first episode drug naïve patients

Methods: Twelve first episode drug naïve patients with schizophrenia (DSM-IV, American Psychiatric Association) were recruited to this study. The control group comprised 17 age-matched, healthy individuals. Patients and controls were assessed at baseline. Patients were also assessed after remission with antipsychotic treatment. PLA2 activity was determined in platelets by a radio-enzymatic assay addressing PLA2 groups, ie., cPLA2, sPLA2 and iPLA2. We used a parametric T-test to access significant differences between first episode patients and healthy controls. To test variations of PLA2 activities we used Paired Samples Correlations tests. All statistical analyses were done with the software Statistical Package for Social Science (SPSS, Chicago, USA), version 14.0 and significance level was set at $p<0.05$

Results: Our results showed an increased totalPLA2 activity in patients with schizophrenia as compared to controls ($p=0.01$) but no difference regards isolated groups (iPLA2, cPLA2 and sPLA2). After remission we found an increased cPLA2 ($p=0.006$), sPLA2 ($p=0.006$) and totalPLA2 ($p=0.001$) activity as compared to controls. The effect of anti-psychotic treatment in patients with schizophrenia showed a significant reduction in iPLA2 activity ($p=0.005$). No differences were observed in cPLA2, sPLA2 and total PLA2 activity.

Discussion: Our results confirm the increased totalPLA2 activity in patients with schizophrenia so far reported. The reduction of PLA2 activity with anti-psychotic treatment is regard to iPLA2 group that are the most abundant in neurons and confirm the involvement of this group of enzyme in psychoses. The increased cPLA2 and sPLA2 group activity after anti-psychotic treatment could be explained by their capacity in activate PKC and inflammation process.

Poster #T232

ASSESSING THEORIES OF SEMANTIC MEMORY FUNCTION IN SCHIZOPHRENIA THOUGHT DISORDER AT TWO LEVELS

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Background: Aberrant semantic processing has been linked to the aetiology of formal thought disorder (TD) symptoms in schizophrenia. Two prominent theories, overactivation and disorganized structure of semantic memory, were examined in relation to TD using both implicit (priming) and explicit (fluency) semantic tasks. This study aimed to examine if both theories operated independently or in tandem; and if this differed at the implicit and explicit levels. Greater direct and indirect priming, fluency productivity

and category errors were expected for the overactivation theory. Reduced direct priming, fluency productivity and increased category errors would be characteristic of disorganized storage.

Methods: 57 schizophrenia/schizoaffective disorder patients and 48 controls completed a clinical assessment (PANSS, TLC), WTAR for premorbid intelligence and the two semantic tasks. Groups were matched for age and gender. Analyses were co-varied for WTAR due to significantly lower estimated premorbid intelligence in patients.

Results: Results showed significantly reduced direct priming in patients compared to controls ($p < 0.05$), while the greater indirect priming was not significant. There was no association between TD and degree of priming. Patients were less likely to recognize a non-word in a task with more related pairs ($p < 0.05$), degrading with severity of positive TD ($r = 0.30$, $p < 0.001$). Although patients produced more category inappropriate words ($p < 0.005$), TD overall did not influence fluency error rates, although negative TD was associated with reduced category and letter productivity ($p < 0.001$).

Discussion: Misattribution, but not semantic overactivation, at the implicit level appears related to TD. At the explicit level, negative TD appears more associated with slower processing than inaccuracy. Overall, the findings support semantic disorganization as a more trait-type impairment contributing to TD symptoms, with overactivation perhaps more characteristic of the acute TD state. It is plausible that a combination of these two aspects is responsible for the increased severity of acute TD symptoms. Executive dysfunction may combine with semantic dysfunction in the presentation of TD symptomatology.

Poster #T233

A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL STUDY OF LURASIDONE FOR THE MAINTENANCE OF EFFICACY IN PATIENTS WITH SCHIZOPHRENIA

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Background: Schizophrenia is a serious illness requiring chronic, often life-long treatment to prevent psychotic relapse. Thus, evidence for long-term maintenance of efficacy is important clinically, in addition to demonstration of efficacy for acute exacerbations of the illness. The objective of this study was to evaluate the efficacy of lurasidone for maintenance treatment in patients with schizophrenia.

Methods: Patients aged 18–75 years diagnosed with schizophrenia and experiencing an acute exacerbation were enrolled in the 12- to 24-week open-label stabilization phase of the trial, during which they received lurasidone (40 or 80 mg/d, flexibly dosed). Those who maintained clinical stability for ≥12 weeks entered the 28-week, double-blind withdrawal phase and were randomized to receive either lurasidone, at the same dose they were receiving at completion of the stabilization phase, or placebo. Weekly dose adjustments within the range of lurasidone 40–80 mg/d were permitted during the double-blind phase. Due to prespecified unblinded interim analyses, the nominal p value for statistical significance was adjusted from 0.05 to 0.042. The primary efficacy endpoint was time to relapse, analyzed using log-rank test and Cox proportional hazards models. Secondary efficacy measures included change from baseline in Positive and Negative Syndrome Scale (PANSS) total score and Clinical Global Impression–Severity (CGI-S) score, evaluated using analysis of covariance with the last observation carried forward (LOCF). Safety assessments included treatment-emergent adverse events (TEAEs), discontinuations due to AEs, and laboratory measures.

Results: A total of 676 patients enrolled in the open-label stabilization phase; 285 met protocol-specified stabilization criteria and were randomized to lurasidone (N=144) or placebo (N=141). Among the patients who completed the open-label phase and were randomized into the double-blind phase, mean (SD) lurasidone dose during the open-label stabilization phase was 67.7 mg/d (14.8 mg/d). Relapse occurred in a greater proportion of patients receiving placebo (58/141 [41.1%]) compared with the rate for lurasidone-treated patients (43/144 [29.9%]). Time to relapse based on Kaplan-Meier survival analysis was significantly longer for lurasidone compared with placebo (log-rank test, $p = 0.039$). Lurasidone was associated with a 33.7% reduction in risk of relapse versus placebo (Cox model hazard ratio [95% confidence interval], 0.663 [0.447, 0.983]; $p = 0.041$). Patients

receiving placebo demonstrated a worsening in PANSS and CGI-S scores over the double-blind period compared with scores for lurasidone-treated patients (PANSS mean change, +12.4 vs +8.3, $p = 0.029$; CGI-S mean change, +0.7 vs +0.4, $p = 0.015$; LOCF). The percentage of patients reporting any TEAE was similar in the lurasidone (53.5%) and placebo (54.6%) groups. The most commonly reported AEs for lurasidone (with incidence > placebo) during the double-blind phase were anxiety (4.2% vs 2.8%) and back pain (4.2% vs 2.1%). The discontinuation rate due to AEs was 13.9% for lurasidone and 15.6% for placebo. Minimal changes in weight, as well as prolactin, lipid, and glucose parameters were observed in either group.

Discussion: This placebo-controlled, randomized, withdrawal study demonstrated the efficacy of lurasidone maintenance treatment for patients with schizophrenia. Lurasidone was generally well tolerated, with minimal effects on weight and other metabolic parameters.

This study was sponsored by Sunovion Pharmaceuticals Inc. ClinicalTrials.gov identifier: NCT01435928.

Poster #T234

SLEEP DISRUPTION IN CHILDREN AND ADOLESCENTS AT-RISK FOR PSYCHOSIS: A PRELIMINARY STUDY

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Background: Many psychiatric disorders have their onset during childhood and adolescence. These disorders are often accompanied by sleep disruption. We examined the prevalence of self-rated sleep disturbances in three groups of children and adolescent: 1) help-seeking children and adolescents at risk for psychosis (AtRisk), 2) inpatients not assumed to be at risk for psychosis (ClinS), and 3) controls from the general population (GPS).

Methods: We analyzed data of 66 children and adolescents between the ages of 8 and 18 years (mean = 13.96, SD = 2.9) who were recruited from an outpatient early detection service, inpatient wards and the general population: 8 AtRisk, 26 ClinS and 32 GPS. AtRisk status was assessed using the Structured Interview for Prodromal Syndromes (SIPS) and Schizophrenia Prediction Instrument, Child and Youth version (SPI-CY). In addition the presence of a psychiatric disorder was assessed in all participants using the Mini-International Neuropsychiatric Interview (M.I.N.I.). Sleep disturbances were defined using the SIPS seven point scale which ranged from absent to extreme (i.e., unable to sleep at all for over 48 hours). The analysis was conducted in three steps: (1) A Chi-squared test was used to test whether the presence of sleep disturbances (yes/no) was different between the three groups, (2) A Mann-Whitney test to determine if symptom severity (based on the SPI-CY) differed between the three groups, and (3) A Spearman correlation measuring the association between the severity of sleep disturbances and severity of AtRisk symptoms, as identified by the SPI-CY, in the entire sample.

Results: The three groups varied with respect to the prevalence of sleep disturbances ($\chi^2 = 10.38$, $p = 0.006$; moderate effect size, $\Phi = 0.40$). Sleep disturbances were more severe in the AtRisk ($U = 38$, $p = 0.001$) and ClinS ($U = 278$, $p = 0.017$) compared to the GPS group. Furthermore, sleep disturbances were more severe in the AtRisk compared to the ClinS group ($U = 57$, $p = 0.046$). AtRisk symptoms were significantly correlated with sleep disturbances ($rs = 0.34$, $p = 0.005$).

Discussion: Our findings of disrupted sleep in our clinical samples are in line with previous studies showing associations between sleep and psychiatric disorders. Interestingly, sleep disruption was slightly more severe in children and adolescents symptomatically at risk for psychosis than the clinical sample not at risk for psychosis. This finding suggests that youth at risk for psychosis may be particularly susceptible to sleep problems. Associations between sleep and at-risk status should be explored in future studies with larger sample sizes and may inform clinical interventions.

Poster #T235**DEFICIENT CORTICAL ACTIVITY DURING MOTOR INHIBITION IN SCHIZOPHRENIA**

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Background: Deficient inhibition is one key mechanism in schizophrenia as evidenced by numerous behavioural and imaging studies. Functional MRI (fMRI) has shown altered activation patterns during inhibition tasks in patients with schizophrenia (e.g., Kaladjanian et al, 2007; Criaud and Boulinguez, 2013). However, findings across studies are not consistent. The aim of this study was to investigate cortical activation during motor inhibition in patients with schizophrenia.

Methods: 19 stabilized patients with schizophrenia (mean age: 32, 18 males) treated with atypical antipsychotic medication were compared with 19 siblings (mean age: 32, 8 males) and 23 healthy subjects (mean age: 30, 12 males). Subjects underwent a single 3T-MRI session including event-related fMRI (EPI BOLD sequence, 4 runs). Participants performed a volitional inhibition task consisting in a fingertip Go-NoGo task, with 30% randomized NoGo events. Preprocessing and analysis was performed using spm5 (www.fil.ion.ucl.ac.uk/spm/). Two analyses were performed: (i) whole brain statistical maps of Prep (preparation), NoGo>baseline (activation) and baseline>NoGo (deactivation) with age, gender and years of study as covariates; (ii) extraction of NoGo contrast values using Marsbar toolbox in 12 cortical regions of interest (ROIs) involved in NoGo inhibition (Criaud and Boulinguez, 2013). Results were compared between the three groups.

Results: The three groups suppressed finger movements similarly during NoGo trials. For whole brain analysis and ROI analysis, controls activated SMA and M1 during preparation and deactivated these areas during motor inhibition. Both activation during preparation and deactivation during inhibition were reduced in patients and siblings compared to controls. No difference was found between patients and siblings.

Discussion: The deficient brain processing during successful motor inhibition suggests that patients with schizophrenia may use alternative inhibition strategies to achieve similar performance levels to controls. The similarity between schizophrenia patients and siblings suggests that the altered brain activity patterns found during motor inhibition could reflect a genetically predetermined vulnerability trait linked to the neurodevelopmental compound of schizophrenia.

Poster #T236**ENVIRONMENTAL INFLUENCES ON SYMPTOMATOLOGY OF A FIRST EPISODE PSYCHOSIS**

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Background: Some studies have shown an effect of environment on symptomatology of adults' diagnosed with Schizophrenia (Jiang et al., 2013; Ruggeri et al., 2005). For example, patterns of correlations between symptoms' dimensions could vary between different social contexts. However, such literature is very sparse in young adults' populations with first episode psychosis (FEP). The main objective of this study is to investigate whether there are differences in underlying symptoms' dimensions in a population of FEP across different environments and trajectories of care.

Methods: Brief Psychiatric Rating Scale (BPRS 24; Ventura & al., 1993) data were collected from 243 young adults (17-31 years old) within the JADE unit (i.e. specialized unit for early recognition and treatment of mental disorders) at their entry in two different care structures (i.e. Outpatients (n= 79) or Inpatients (n=164)) after a FEP. Measures of Global functioning (Cornblatt et al., 2007) and sociodemographical data were also obtained. Exploratory (with SPSS 19) and confirmatory factor analyses (with AMOS 19) of the BPRS 24 were computed.

Results: A five-factor solution was obtained (i.e. manic/excitement, negative symptoms, depression/anxiety, positive symptoms and disorganisation), explaining almost 60% of the variance for both Outpatients and Inpatients. However, results of confirmatory analyses indicate a poor fit of our model (χ^2 (df=220, N=299) = 737.844, p<0.001, CFI = 0.83; RMSEA = 0.09) when applied on the whole sample. Further analyses showed that this could be explained by notable differences in factorial structure of BPRS across the two groups. More specifically, BPRS 24 results between care structures differed in the factor that explained the greatest proportion of variance: Manic/excitement for Inpatients (i.e. 24% vs. 9% for Outpatients) and negative dimension for Outpatients (i.e. 31% vs. 17% for Inpatients). Moreover, important differences emerged in latent correlations between structures of care. We found especially significant negative correlations between manic/excitement and depression/anxiety for Inpatient structure (-0.26; p<0.001) but a positive correlation in the Inpatient one (0.59; p<0.001). Finally, symptom severity (i.e. mean score) for Inpatients was significantly higher than for Outpatients for all dimensions (p<0.001), excepted for negative symptoms.

Discussion: Notable differences in symptoms' dimensions and patterns of correlations appear across the two care structures. Our results suggest that, despite BPRS 24 being especially suited for evaluating symptom dimensions for FEP, clinicians have to be attentive to environmental influences on expression of symptomatology (see also Ruggeri et al., 2005). We suggest a symptom-oriented approach (cf. Bentall, 2006) to be more useful compared to a broad diagnostic classification.

Poster #T237**USING STRUCTURAL NEUROIMAGING TO MAKE QUANTITATIVE PREDICTIONS OF SYMPTOM PROGRESSION IN INDIVIDUALS AT ULTRA-HIGH RISK FOR PSYCHOSIS**

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Background: Neuroimaging holds the promise that it may one day aid the clinical assessment of individual psychiatric patients. However, the vast majority of studies published so far have been based on average differences between groups, which do not permit accurate inferences at the level of the individual. We examined the potential of structural Magnetic Resonance Imaging (MRI) data for making accurate quantitative predictions about symptoms progression in individuals at ultra-high risk for developing psychosis.

Methods: Forty people at ultra-high risk for psychosis were scanned using structural MRI at first clinical presentation and assessed over a period of two years using the Positive and Negative Syndrome Scale (PANSS). Using a multivariate machine learning method known as relevance vector regression (RVR), we examined the relationship between brain structure at first clinical presentation, characterized in terms of gray matter volume and cortical thickness, and symptom progression at 2 year follow-up.

Results: The application of RVR to whole-brain cortical thickness MRI data allowed quantitative prediction of clinical scores with statistically significant accuracy (correlation = 0.34, p=0.026; Mean Squared-Error = 249.63, p=0.024). This prediction was informed by regions traditionally associated with schizophrenia, namely the right lateral and medial temporal cortex and the left insular cortex. In contrast, the application of RVR to gray matter volume did not allow prediction of symptom progression with statistically significant accuracy.

Discussion: These results provide proof-of-concept that it could be possible to use structural MRI to inform quantitative prediction of symptom progression in individuals at ultra-high risk of developing psychosis. This would enable clinicians to target those individuals at greatest need of preventative interventions thereby resulting in a more efficient use of health care resources.

Poster #T238**RELATION BETWEEN PSYCHOTIC-LIKE EXPERIENCES AND MAJOR DEPRESSION IN THE COMMUNITY BASED SAMPLE**

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Background: Psychotic-like experiences (PLEs) increase the risk of schizophrenia and other psychotic disorders in the community. There may be a relation between some PLEs and depression which may increase risk for developing both depression and psychosis. The aim of this study was to determine the prevalence of PLEs in a community based sample and to investigate whether any PLEs are associated with the depression diagnosis.

Methods: Addresses were contacted in a multistage clustered area probability sampling frame of administrative neighborhoods and households, covering 9 districts and 302 neighborhoods in the Izmir metropolitan area between November 2007 and October 2008. One household member aged between 15 and 64 years and available to complete the interview was randomly selected using a within-household sampling method. 4011 (female: 57.3%) respondents were successfully interviewed with a response rate of 75.8%. The primary screening instrument was the Composite International Diagnostic Interview (CIDI) 2.1. The prevalence of MDD was based on diagnosed depression by physician, psychotic like experiences responses to systematic screening questions of the relevant questions (CIDI 2.1, G_16; assessment delusional PLE, G_23; assessment hallucinational PLE).

Results: The prevalence of diagnosed MDD was 11.9%. Delusional and hallucinational PLEs prevalences were 20.2% and 11.9% respectively. Delusional PLEs and hallucinational PLEs associated with major depression respectively OR: 3.7 (95% C.I.; 3.1-4.4) and OR:5.5 (95% C.I.;4.5-6.8).

Discussion: Delusional and hallucinational PLEs were strongly related to depression in the community sample. Both PLEs and depression in the community sample may play an important role in developing psychosis and probably depression.

Poster #T239**DIMENSIONAL EXPLORATION OF PERSONALITY DISORDERS IN SCHIZOPHRENIC PATIENTS AND THEIR FIRST-DEGREE RELATIVES USING THE SHEDLER-WESTEN ASSESSMENT PROCEDURE**

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Background: Epidemiological studies have shown that Cluster A, Avoidant, Dependent and Borderline Personality Disorders are associated with schizophrenia and psychotic episodes. In light of these data, it becomes important to identify maladaptive personality traits of psychotic patients and their relatives to detect the predisposing and protective factors. This study examined personality dimensions and identified personality subtypes of adults with DSM IV schizophrenia and their first-degree relatives. Previous work evaluating schizotypy in siblings of schizophrenic patients suggests that the Shedler-Westen Assessment Procedure (SWAP-200) is a useful diagnostic instrument not only to detect schizotypal traits but also for a global evaluation of the personality profiles.

Methods: Trained and clinically experienced interviewers provided data on a sample of 144 subjects including 59 schizophrenic patients, 43 first-degree relatives (parents and siblings) of these patients and 42 age-matched healthy controls. To verify the hypothesis of the difference between the profiles of the Personality Disorders we used two MANOVA (for Personality Disorders [PD T] and for Q Factors [Q T] scales) and subsequent planned comparisons for the three groups.

Results: MANOVA are statistically significant (PD T Wilk's Lambda(11, 131) <0.001; Q T Wilk's Lambda(12, 130) <0.001 p<0.001). The multivariate tests of the planned comparisons are statistically significant for PD T scales (Patients vs Relatives, Wilk's Lambda(11, 131) = 0.304 p<0.001; Patients vs Controls, Wilk's Lambda(11, 131) = 0.253 p<0.001; Relatives vs Controls, Wilk's Lambda(11, 131) = 0.712 p<0.001), as well as for Q T scales (Patients

vs Relatives, Wilk's Lambda(12, 130) = 0.297 p<0.001; Patients vs Controls, Wilk's Lambda(12, 130) = 0.233 p<0.001; Relatives vs Controls, Wilk's Lambda(12, 130) = 0.652 p<0.001). In the univariate tests, for both the PD T and Q T scores, the three groups showed statistical significant differences not only, as expected, for Cluster A and High Functioning, but also for specific traits of Cluster B and C. On average, patients with schizophrenia scored higher than both their relatives and the controls on all SWAP-200 scales, with a few exceptions including the High Functioning scale. The PD T scores of the relatives of schizophrenic patients were higher than those of healthy controls for Cluster A scales, but lower for High Functioning scale. Moreover, relatives of schizophrenic patients showed statistical significant differences when compared with controls, reporting lower Q T scores on the dysphoric, obsessive and high functioning depressive dimensions, and higher Q T scores on the schizoid dimension.

Discussion: Borderline, Dependent and Avoidant Personality Disorders, comorbid with Cluster A Personality Disorders, may have a specific relevance in the psychotic transition within the schizophrenia spectrum disorders. In our sample, patients scored statistically higher than both their relatives and the control group in all these scales, while the scores of their first-degree relatives compared to the control group were statistically higher for the Cluster A, but not for the other Personality Disorders. These results may indicate the features of the Cluster A as common phenotypes and traits of other Personality Disorders as predisposing to overt psychosis.

Poster #T240**CAN CHILDHOOD ADVERSITY PREDICT ONSET AND CLINICAL OUTCOMES OF PSYCHOTIC DISORDERS?**

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Background: Over the past decade, increasing interest has been shown in the relationship between childhood adversity and risk of psychosis in adulthood. However, it is not clear what the potential long-lasting impact of traumatic early experiences is on the clinical course of psychotic disorders. The aim of this study is thus to analyse the impact of childhood adversity on 1 year clinical outcomes in first-presentation psychosis patients.

Methods: Data on exposure to childhood adversity prior to 17 years of age (separation from a parent for at least 6 months, death of a parent, taken into local authority care, physical and sexual abuse) was collected using the Childhood Experience of Care and Abuse Questionnaire from 319 psychosis patients at first presentation to mental health services and 254 healthy controls who participated in the Genetics and Psychosis study. Data on illness course (complete recovery, relapsing episodes, chronic illness), number of days on a psychiatric ward (median split of <48 and ≥48 days) and compliance with medication was collected for the year following first contact with mental health services for psychosis from clinical records using the Personal and Psychiatric History Schedule. Binary logistic regression models were used to investigate associations between baseline predictors and 1 year outcome variables. Statistical interactions were assessed using likelihood ratio tests. Analyses were conducted using SPSS version 21 and STATA version 10.1.

Results: Over three-quarters of patients (69.9%) and around half of the controls (49.2%) reported at least one experience of childhood adversity before age 17. The odds of being a psychosis patient increased more than two times with the experience of at least one adversity during childhood (odds ratio [OR]=2.40, 95% CI 1.70–3.37, p<0.001) and the association held after adjusting for age, ethnicity and gender (adj. OR=2.44, 95% CI 1.72–3.45, p<0.001). Follow-up data have so far been collected at 1 year for 208 first-presentation psychosis patients. No significant differences in illness course were observed between those who reported at least one experience of childhood adversity compared to those who did not. Patients with a lifetime history of childhood adversity tended to have longer psychiatric hospital stays (≥48 days) compared to those who did not (OR 1.79, 95% CI 0.93–3.45, p=0.082) and to be less compliant with medication at 1 year (OR 0.52, 95% CI 0.24–1.11, p=0.090), though these associations failed to reach conventional levels of significance. More specifically, history of separation from either parent was significantly associated with a higher number of

hospital admission days (OR 2.00, 95% CI 1.08–3.69, p=0.027) and lower compliance with pharmacological treatment throughout the year (OR 0.51, 95% CI 0.27–0.94, p=0.032). Stratifying by gender, a stronger association between history of parental separation and hospital admission days was observed for women (OR 2.50, 95% CI 0.91–6.86, p=0.075) compared to men (OR 1.61, 95% CI 0.72–3.57, p=0.243) but no statistical interaction by gender was found (Likelihood ratio $\chi^2 = 0.45$, p=0.501). No associations were found for other types of adversity.

Discussion: Our data reveal a higher prevalence of childhood adversity in FEP patients and further extend previous research by suggesting that a history of parental separation during childhood is associated with longer hospitalisations and poorer medication compliance over the first year of treatment. More research is warranted to better understand mechanisms involved between adversity and clinical outcomes in psychosis.

Poster #T241

DOSE AND DOSING FREQUENCY OF LONG-ACTING INJECTABLE ANTIPSYCHOTICS: A SYSTEMATIC REVIEW OF PET AND SPECT DATA AND CLINICAL IMPLICATIONS

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Background: Brain imaging data of antipsychotics have mainly been derived from oral antipsychotic drugs, which hampers our understanding of the requirement of dose/dosing frequency of long-acting injectable (LAI) antipsychotics for the maintenance treatment of schizophrenia. The objectives of this systematic review are two-fold: (1) to characterize dopamine D₂ receptor occupancy with LAI antipsychotics and (2) to examine the requirement of dose/dosing frequency of this formulation for the maintenance treatment of schizophrenia.

Methods: A systematic literature search was performed to identify positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies that assessed dopamine D₂ receptor occupancy levels with LAI antipsychotic drugs in humans, using PubMed, EMBASE, and PsycINFO (last search: September 2013).

Results: An initial search identified 472 articles; of these 452 reports were excluded because of a lack of relevant data (e.g. review article, animal experiment, duplicate publication, lack of brain imaging data or antipsychotic treatment). Thus, 20 (15 PET and 5 SPECT studies) were found to be eligible and critically appraised in this review. The most investigated drug in these PET and SPECT studies was haloperidol decanoate (44 subjects; 11 studies), followed by risperidone LAI (24 subjects; 3 studies), olanzapine pamoate (14 subject; 1 study), and fluphenazine decanoate (12 subjects; 3 studies). The data have demonstrated high and continuous D₂ receptor blockade with LAIs; effects of LAI first generation antipsychotics on the central nervous system may persist for several months. The prospective and cross-sectional studies showed that continuous dopamine D₂ receptor blockade above 65% (i.e. lower end of the established "therapeutic window" for acute phase treatment) was not always necessary for maintenance treatment for at least some of the patients.

Discussion: Because of the limited brain imaging data on LAI antipsychotics, we still do not know the best way to dose them. Still, the currently available brain imaging data raises a possibility that the dosing interval of LAI antipsychotics may be extended beyond the currently indicated range in some patients. Even though this tentative conclusion has to be confirmed in future well-designed trials, this notion could provide important clinical implications to optimize efficacy and to reduce side effects as we consider LAI antipsychotic dose/dosing frequency as well as future antipsychotic development.

Poster #T242

EXCEPTIONAL EXPERIENCES IN HEALTHY PEOPLE – EARLY WARNING SIGNALS OF PSYCHOSIS?

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Background: Exceptional experiences (EE) are widespread in the general population and comprise a whole set of different phenomena that deviate from the normal perceptual experiences in everyday life and are often interpreted as "paranormal". From a psychiatric point of view such experiences can be described as "psychotic-like" since they overlap with, and exhibit parallels to positive symptoms observed in schizophrenia patients. However, most of the surveys assessing exceptional experiences are mainly aimed at quantifying beliefs or do not explicitly differentiate between beliefs and experiences. Therefore, we employed a survey that assesses the bare phenomenology of EE entailing a classification into four categories. We intended to elucidate the relationships of these categories with established measures of schizotypy and psychological distress. In terms of early detection and prevention of mental disorders, a phenomenological approach to EE might reveal more information about the exact relationships between mental disorders and EE.

Methods: In this on-going study a population of 90 healthy subjects, representing a cross section of ordinary Swiss-German population with respect to age (20–60 years), gender and level of education, has been acquired from the population of a precedent study and through online advertisements. Participants with a past psychiatric treatment or a first-degree family history of mental illness were excluded from the study. The participants completed a survey assessing the phenomenology of past EE (Fragebogen zur Erfassung der Phänomenologie außergewöhnlicher Erfahrungen), which incorporates a classification of EE according to four different possibilities (external, internal, dissociative and coincidental phenomena). Furthermore, the study subjects completed questionnaires assessing schizotypy (Schizotypal Personality Questionnaire, SPQ) and psychological distress (Symptom Checklist 90 revised, SCL).

Results: An exploratory data analysis (Spearman's rho, Bonferroni corrected) revealed that all of the four types of EE correlate positively with the SPQ sum score ($\rho = 0.553$ –0.677, $p < 0.01$), the global severity index ($\rho = 0.444$ –0.620, $p < 0.01$) and the positive symptom total ($\rho = 0.467$ –0.623, $p < 0.01$) of the SCL. Concerning the subscales of the SPQ, all EE correlate positively with scores for ideas of reference (0.409–0.543, $p < 0.01$), odd beliefs (0.528–0.655, $p < 0.01$), unusual perceptual experiences (0.578–0.689, $p < 0.01$) and odd speech (0.372–0.453, $p < 0.05$). Furthermore, with the SCL subscales somatisation (0.512–0.551, $p < 0.01$), depression (0.373–0.534, $p < 0.05$) and phobia (0.403–0.461, $p < 0.01$). Correlations not including all types of EE are not listed for brevity. No significant correlations were found with the SPQ scales excessive social anxiety, no close friends, constricted affect and the SCL scales for aggression and unspecified complaints.

Discussion: As expected, all four types of EE are positively linked to scales with similar content such as ideas of reference, odd beliefs or unusual perceptual experiences. More importantly, EE are also correlated with general psychological distress and the number of distressful symptoms. Hence, our data support the notion of a continuous distribution of psychotic experiences and their accompanying psychological features from mentally healthy to mentally ill with a purely phenomenological approach to EE in healthy people. Additional data and further analyses will shed more light onto the ambiguous relations between the four categories of EE and single subscales of the SPQ and SCL, respectively.

Poster #T243

[¹¹C]GMOM AS NEW POTENTIAL PET RADIOTRACER TO IMAGE THE NMDA RECEPTOR IN VIVO

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Background: Accumulating evidence shows that NMDA receptor hypo-

function is involved in the pathophysiology in schizophrenia. The glutamate hypothesis helps to provide a better view of the negative and cognitive symptoms of schizophrenia. In vivo imaging of the NMDA receptor would be a valuable tool to assess the NMDA receptor in patients with schizophrenia. [¹¹C]N-(2-chloro-5-thiomethylphenyl)-N'-(3-methoxy-phenyl)-N'-methylguanidine ([¹¹C]GMOM) has excellent preclinical characteristics for this purpose and is suitable for evaluation in human subjects. The aim of this study is to assess the applicability of [¹¹C]GMOM for in vivo imaging of the NMDA receptor in humans.

Methods: This was a phase I study. Dynamic [¹¹C]GMOM 90 minute scans were obtained on a Philips PET-CT scanner. Ten healthy volunteers were included in the study. Four subjects (mean age= 24±5, 4 men) received a dose of 370 MBq [¹¹C]GMOM and six subjects (mean age= 22±2, 5 men) were scanned twice with a dose of 370 MBq of [¹¹C]GMOM before and after administration of S-ketamine (0.3 mg/kg). Input functions were obtained using on-line arterial blood sampling. Pharmacokinetic modeling was performed to find the best model for data analysis. S-ketamine displacement was assessed in various brain regions.

Results: [¹¹C]GMOM entered the brain. Kinetic analyses revealed the irreversible two tissue compartment model as the optimal model. In most brain regions there was a small decrease in net influx rate (Ki) values after administration of S-ketamine. This decrease was most prominent in brain regions with high NMDA receptor density, such as the hippocampus and thalamus.

Discussion: This study demonstrated [¹¹C]GMOM brain uptake. The decrease in Ki after the challenge suggest some specific binding of this radiotracer. Further studies should test more methylguanidine compounds in order to find the best NMDA receptor radiotracer for PET. In vivo imaging of the NMDA receptor can play a significant role in the understanding of the mechanism of action of pharmaceuticals, which is of high interest for the development of novel compounds acting on the negative and cognitive symptoms of schizophrenia.

Poster #T244

TESTING THE ESTROGEN HYPOTHESIS OF SCHIZOPHRENIA: ASSOCIATIONS BETWEEN CUMULATIVE ESTROGEN EXPOSURE AND CEREBRAL STRUCTURAL MEASURES

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Background: Reduced bone mineral density (BMD) in patients with psychotic disorder may be secondary to disease-related factors and/or treatment with prolactin-raising antipsychotics. Alternatively, loss of BMD (as a marker of cumulative estrogen exposure) may reflect risk of psychotic disorder, due to diminished cerebral exposure to estrogen and its neuroprotective effects. The aim of the present study was to investigate: i) BMD as a marker of risk of psychotic disorder in genetically vulnerable individuals, and ii) the association between estrogen (indexed by BMD) and cerebral structural measures.

Methods: Dual X-ray absorptiometry (DEXA) scans were acquired in 62 patients with psychotic disorder, their unaffected siblings (n=67) and 48 healthy controls. Total BMD (g/cm²), Z- and T-scores were assessed in the lumbar spine and femur. Magnetic resonance imaging (MRI) scans were performed in the same sample. Cerebral cortical thickness (CT) (indicating grey matter status) and fractional anisotropy (FA) (indicating white matter integrity) were measured. Multilevel random regression models were used to examine associations between group and BMD (primary analysis) and BMD and CT/FA (secondary to findings primary analysis).

Results: BMD loss was specific to the femur in female patients (patients versus controls: total BMD B=-0.100 and p=0.010; Z-score: -0.884 and p=0.009; T-score: -0.851 and p=0.012). BMD was not reduced in male patients or siblings of either sex. In the female patient group (n=14), femoral BMD measures were positively associated with CT at trend-level significance (total BMD: B=0.266 and p=0.067; Z-score: B=0.034 and p=0.046; T-score: B=0.034 and p=0.052). There were no significant associations between femoral BMD measures and FA.

Discussion: Familial risk of psychotic disorder was not associated with

BMD. Instead, decreased BMD in the femur may reflect treatment effects or non-familial risk associated with low cumulative estrogen levels in female patients. The data tentatively suggest that in women with psychotic disorder, alterations in the neuroprotective effect of estrogen impact cortical grey matter, but not white matter integrity. These findings merit further investigation and, if replicated, would lend support to the estrogen hypothesis of schizophrenia.

Poster #T245

COGNITIVE FUNCTIONING ASSOCIATED WITH STIMULANT USE IN PATIENTS WITH NON-AFFECTIVE PSYCHOSIS, THEIR UNAFFECTED SIBLINGS AND HEALTHY CONTROLS

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Background: Little is known about the effect of stimulant use (amphetamines, cocaine, ecstasy) on cognitive functioning in schizophrenia patients. The current study examined (1) whether recency and frequency of stimulant use is associated with cognitive functioning and (2) whether these associations differ between psychotic patients, their unaffected siblings and controls.

Methods: Participants completed a comprehensive cognitive test battery. Stimulant use was assessed by urinalysis and by the Composite International Diagnostic Interview (CIDI). Using random effects regression models, the main effects of Stimulant Use and the interaction with Diagnostic Status on cognitive functioning were assessed.

Results: The interaction term between Stimulant Use and Diagnostic Status was not significant for any of the cognitive outcome variables, indicating similar effects of stimulant use in all three groups. Recent stimulant users showed more errors deficit in verbal learning in comparison to never users (Cohen's d=-0.60, p<0.005). Lifetime frequent stimulant use was significantly associated with worse immediate and delayed verbal recall, working memory and acquired knowledge (Cohen's d=-0.22 to -0.29, p<0.005). Lifetime infrequent stimulant use was not associated with significant cognitive alterations in comparison to never use.

Discussion: The presence of cognitive deficits associated with lifetime stimulant use is dependent on the frequency of use, with no observed deficits in infrequent users and modest negative effects in frequent users.

Poster #T246

PLASMA OXYTOCIN AND TESTOSTERONE LEVELS IN PATIENTS WITH PSYCHOTIC DISORDER, THEIR UNAFFECTED SIBLINGS AND HEALTHY CONTROLS: RESULTS FROM THE EU-GEI PROJECT

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Background: Oxytocin and testosterone are biological markers of social interaction. Decreased testosterone levels are associated with the experience of defeat, whereas oxytocin promotes social behaviour and interpersonal trust. The aim of our study was to investigate differences in peripheral oxytocin and testosterone plasma levels in patients with a first psychotic episode, their unaffected siblings and healthy controls. We expected decreased levels of these hormones.

Methods: Plasma hormone assays of oxytocin and testosterone were obtained from 85 patients with a psychotic disorder, 27 of their unaffected siblings and 59 healthy controls. Sex-hormone binding globulin (SHBG) was collected to calculate the free androgen index (FAI; testosterone/SHBG), a broad indicator of androgen status. We analyzed group differences in hormone levels, as well as associations with demographic and illness parameters.

Results: There were no significant differences in plasma oxytocin levels

or FAI across groups. In fact, 80% of oxytocin measures were below the detection limit of 1.5 pmol/l. Adjusted for age, smoking, time of blood draw and BMI, we found a significant group difference in plasma testosterone levels in males ($F(6,72)=2.8$; $p<0.05$), not in females. This effect was primarily driven by significantly higher mean plasma testosterone levels in antipsychotic-naïve men ($n=15$) compared to their unaffected brothers ($p<0.01$) and healthy controls ($p<0.05$).

Discussion: This study indicates that plasma-oxytocine should probably be measured using a vigorous stimulus. The results contradict previous findings of decreased testosterone in patients with a psychotic disorder. Increased plasma testosterone in antipsychotic-naïve male patients may reflect social distrust and paranoid thinking. It further underlines a potential mechanism of antipsychotic medication of normalizing androgen activity.

Poster #T247

SUBTLE MOVEMENT DISORDERS IN INDIVIDUALS AT RISK OF SCHIZOPHRENIA

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Background: Accurate prediction of psychosis development in high-risk populations is of the utmost importance as indicated prevention is currently regarded as the most promising strategy to attenuate, delay, or even avert psychosis [1]. However, prodromal signs and symptoms have a low predictive power, with conversion rates in high-risk populations between 10 and 40%, partly by not being specific and based on subjective (culture-dependent) symptoms [1]. Hence, there is a need for objective prodromal signs with strong predictive power. We hypothesize that movement Disorders (MD) can be measured with a mechanical or electronic device, which makes the assessment objective and reliable, and that MD may predict the development of psychotic disorder.

Methods: Literature search combined with the results of our own studies. **Results:** Several groups at risk for psychosis were studied. Children (mean age 14 yrs.) with an schizotypal personality disorder showed more abnormal movements compared to patients with other psychiatric diagnoses and healthy controls and the severity of the abnormal movements was related to the severity of prodromal signs. After one year, the symptoms were more severe in those children with abnormal movements at baseline than those without [3]. In a four-year follow-up of adolescents with a higher risk to develop a psychotic disorder, 25% converted to a psychotic syndrome and those with more (and more severe) movement abnormalities had a higher risk [4]. Sibs of patients with schizophrenia had an increased risk on psychotic disorders, and the metaanalysis showed also a small, but significant higher prevalence for MD [5]. In the Genetic Risk and Outcome of Psychosis (GROUP) study sibs of patients had more MD than controls and sibs with MD had more schizotypal symptoms compared to sibs without MD [6]. The frequency of MD in sibs vs. healthy controls was significantly higher in the sibs when measured with a mechanical device [7].

Discussion: Data from several groups of individuals at risk for psychosis show an interrelationship between MD and psychosis, and suggest that MD have a predictive value for psychotic symptoms and may therefore be useful in screening programs for individuals at risk for psychosis. Subtle MD can be measured objectively, culturally free, and reliably with a mechanical device, and probably also with an electronic device, which is currently validated in our research centre.

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Poster #T248

NEGATIVE SYMPTOMS, SOCIAL SELF-EFFICACY AND SOCIAL FUNCTION IN SCHIZOPHRENIA: WHAT IS THE PATHWAY?

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Background: Negative symptoms are one of several important predictors of functioning in schizophrenia and can be conceived of in two different ways. Either as a defining feature and primary symptom of the disorder, or as a secondary psychological reaction that develops from defeatist or self-deprecating beliefs, such as low self-efficacy. In this study we test two different models for the association between negative symptoms, beliefs and functioning. In Model I (negative symptoms as a primary symptom) the association between negative symptoms and social functioning is mediated by social self-efficacy, whereas in Model II (negative symptoms as a secondary reaction) negative symptoms mediate between social self-efficacy and social functioning.

Methods: Fifty-one individuals (32 males/19 females; mean age 27.9, SD=7.9) diagnosed with schizophrenia ($n=38$) or schizoaffective disorder ($n=13$) underwent assessment with a comprehensive neuropsychological test battery and clinical protocol as part of the TOP study in Oslo, Norway. Negative symptoms were indexed by the PANSS negative subscale, social self-efficacy was assessed with the 19 social items of the Revised Self-efficacy Scale (RSES), and social functioning with the 6 social subscales of the Social Function Scale (SFS). The models were tested using a series of stepwise hierarchical regression analyses as proposed by Baron & Kenny.

Results: Negative symptoms were significantly associated with social self-efficacy ($r=-0.34$, $p=0.02$) and social functioning ($r=-0.40$, $p<0.01$). Social self-efficacy was strongly related to social function ($r=0.65$, $p<0.01$). In Model I the significant association between negative symptoms and social functioning was reduced to a non-significant level ($r=-0.20$, $p=0.08$) when controlling for social self-efficacy. In Model II, controlling for negative symptoms did little to change the strong and statistically significant association between social self-efficacy and social functioning ($r=0.59$, $p<0.01$).

Discussion: We found that social self-efficacy mediated between negative symptoms and social functioning. Our findings are in line with an understanding of negative symptoms as a primary symptom of schizophrenia where the pathway seems to go from negative symptoms through reduced beliefs in one's ability to master social situations to reduced social functioning.

Poster #T249

PSYCHOSIS LIABILITY, PARANOIA AND DISTRESS IN EXPERIMENTAL VIRTUAL REALITY SOCIAL ENVIRONMENTS

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Background: Psychotic syndromes can be understood as disorders of adaptation to social context. It is not clear, however, how symptoms of psychosis develop in the daily social environment, in interaction with individual liability. Virtual Reality (VR) technology may help to investigate relationships between environment and psychosis, as it allows controlled exposure to various social risk environments.

Methods: Four groups (total $N=54$) with different liability to psychosis (patients with first episode psychosis (FEP), siblings, ultra high risk individuals (UHR) and healthy controls) were exposed to virtual social environments. Psychological and physiological responses were measured repeatedly. The virtual environment was varied with regard to social stressors (population density, ethnic density and hostility of avatars).

Results: Paranoid thoughts and social anxiety in real life correlated significantly with paranoid thoughts about avatars and subjective distress in virtual social stress environments (Spearman's correlation coefficients 0.4–0.5, $p<0.01$). FEP and UHR experienced higher levels of subjective distress in VR than siblings and healthy controls (Mann-Whitney U test, $p=0.04$).

Physiological arousal was more pronounced in FEP, and habituation was slower in FEP than in controls. Increase in virtual social stressors was associated with higher degree of paranoid thoughts about avatars in all groups. This increase was accompanied by an increase in subjective distress only in FEP and UHR.

Discussion: VR is a promising method to explore dynamic relationships between liability to psychosis and daily social environments. In social stress situations, everyone may have paranoid thoughts to some degree, but high liability to psychosis may lead to more subjective and physiological distress in combination with these paranoid thoughts.

Poster #T250

THEORY OF MIND IN FIRST EPISODE SCHIZOPHRENIA: CLINICAL AND NEUROCOGNITIVE CORRELATES, STATE VS TRAIT, RELATIONSHIP TO DAILY FUNCTIONING

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Background: The Theory of Mind (ToM) deficit has been clearly documented in recent-onset patients. Strong correlations have been found consistently linking neurocognition, ToM, and negative symptoms with functional outcome in chronic schizophrenia patients. However, fewer studies have addressed whether these associations exist in first-episode schizophrenia, before patterns of chronic functional disability have become entrenched. The question of whether ToM is a state-related domain that is subject to symptom fluctuations or a stable trait also needs further exploration.

Methods: First-episode schizophrenia patients (n=68) were assessed within a few weeks of starting outpatient treatment with risperidone and again at 6 months. Healthy controls (n=21) were matched on age and parental education to the patients. The assessment battery consisted of standard tests of neurocognition, MATRICS Comprehensive Consensus Battery (MCCB), Theory of Mind (ToM; Social Animations Task), symptoms (SANS/SAPS), and domains of functioning which included Family and Social Relationships, Independent Living, and Work Productivity (Role Functioning Scale). Patients who met an operational definition of remission were compared to controls on ToM performance.

Results: Recent-onset patients had at baseline significantly lower levels of ToM abilities compared to controls for both Intentionality (2.92, 3.87, t=-4.78, p<0.01) and Appropriateness (1.83, 2.36, t=-4.49, p<0.01), and at 6 months when the patients were in remission. Analyses at baseline indicated that, for patients, ToM Intentionality and Appropriateness were significantly correlated with negative symptoms ($r=-0.36$, $p<0.01$; $r=-0.33$, $p<0.01$), neurocognition ($r=0.47$, $p<0.01$; $r=0.45$, $p<0.01$), and with daily functioning ($r=0.37$, $p<0.01$; $r=0.33$, $p<0.01$). This pattern of correlations was similar in direction and magnitude at the 6 month follow-up point and included disorganization ($r=-0.39$, $p<0.01$). There was a significant improvement in ToM over the 6 month period ($p=0.05$) that was associated with an improvement in disorganization ($r=0.30$, $p<0.05$), and a trend toward an improvement in functioning ($r=0.25$, $p<0.10$). Further, there is evidence indicating that TOM is moderately stable for Intentionality ($r=0.57$, $p<0.01$) and for Appropriateness ($r=0.41$, $p<0.01$).

Discussion: We confirm the existence of ToM deficits even in recent-onset schizophrenia patients, and that the deficit is correlated cross-sectionally with neurocognition, negative symptoms, and disorganization. Interestingly, ToM abilities were also significantly associated with several domains of functioning: work/school performance, independent living skills, family relationships, and social functioning. Consistent with research on chronic patients, the ToM deficit appears to be a vulnerability indicator that, although correlated with symptoms, is present even during periods of symptom remission. These patterns are present early in the illness, even before patterns of chronicity are established. Improvements in ToM might be rate-limited by symptoms of disorganization.

Poster #T251

INTERACTION BETWEEN GSK-3 β RS12630592 AND HTR2A RS6314 POLYMORPHISMS ON CEREBRAL ACTIVITY AND BEHAVIOR DURING ATTENTION

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Background: Glycogen synthase kinase 3 β (GSK-3 β) is highly expressed in the brain and plays a key role in neurodevelopmental processes. A functional SNP within the GSK-3 β gene (GSK3B rs12630592, G>T) has been associated with GSK-3 β expression, altered fMRI prefrontal activity and diagnosis of schizophrenia. Serotonin receptors 2a (5-HT2AR) are disseminated in prefrontal cortex and modulate prefrontal activity during cognition. Furthermore, previous findings suggest that 5-HT2AR stimulation also affects GSK-3 β activity possibly through a molecular cascade including Akt1. The T allele of a functional SNP within the 5-HT2A gene (HTR2A rs6314,C>T) has been associated with reduced expression and attenuated response to treatment with olanzapine in patients with schizophrenia. The rs6314 T allele has also been associated with inefficient prefrontal activity and behavior during working memory and attention, which are phenotypes crucially related to schizophrenia. Aim of this study is to investigate with fMRI if the interaction between GSK-3 β rs12630592 and HTR2A rs6314 polymorphisms modulates prefrontal activity and behavior during attentional processes in healthy humans.

Methods: 180 healthy subjects were genotyped for GSK-3 β rs12630592 and HTR2A rs6314, resulting in 47 GSK-3 β GG/HTR2A CC, 11 GG/T-carriers, 100 T-carriers/CC and 22 T-carriers/T-carriers. Groups were matched for a series of demographic and neuropsychological variables (gender, Hollingshead, Handedness, IQ), but not for age. All subjects performed the Variable Attentional Control (VAC) task during event-related fMRI at 3 Tesla, allowing investigation of brain activity during increasing demands of attentional control (low, intermediate, high levels). ANOVA in SPM8 was performed, using as threshold a FWE small volume corrected $p<0.05$ (K=20). Age was used as a covariate of no interest. Furthermore, 365 healthy subjects (90 GG/CC, 20 GG/T-carriers, 209 T-carriers/CC and 46 T-carriers/T-carriers), matched for a series of demographics, performed the Continuous Performance Test (CPT), which is a measure of selective attention. ANOVA was used to investigate genotype-genotype interaction on % of correct response during the task.

Results: SPM8 analysis on imaging data indicated an interaction between GSK-3 β rs12630592 and HTR2A rs6314 in the IFG (BA 9), with greater DLPFC activity in GSK-3 β GG/HTR2A T-carriers subjects than in the other genotype groups ($F(1,176)=10,173$, $p=0.00169$). Furthermore, ANOVA on CPT data revealed an rs12630592 by rs6314 interaction on accuracy, which was lower in GSK-3 β GG/HTR2A T-carrier individuals.

Discussion: These findings suggest an epistatic interaction between HTR2A and GSK-3B variation in modulating attentional processing. Further studies are needed to investigate relevance of this genetic interaction for schizophrenia.

Poster #T252

IS AEROBIC EXERCISE EFFECTIVE IN IMPROVING NEGATIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA? THE RESULTS OF A META-ANALYSIS

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Background: Negative symptoms comprise a great deal of the disease burden in schizophrenia. Till now, no satisfactory pharmacological treatment is found. Research on psychosocial interventions as well as Transcranial Magnetic Resonance (TMS) show moderate effect sizes. Aerobic exercise

has positive effects on psychopathology of depression and anxiety disorders. This meta-analysis aims to evaluate the effect of aerobic exercise on negative symptoms in schizophrenia.

Methods: The Cochrane Library, Medline, Embase, PsycINFO and CINAHL were searched from their inception. All randomised controlled trials (RCT's) comparing aerobic exercise with any other treatment in patients with schizophrenia were included if negative symptoms were assessed. Studies were screened on methodological quality using the Clinical Trials Assessment Measure (CTAM, range 0-100) (Tarrer and Wykes, 2004). Data extraction consisted of population characteristics, intervention characteristics, outcome measures and analysis. A meta-analysis (random effects) was conducted according to the PRISMA guideline.

Results: Seven studies were included with in total 376 patients. Six out of seven studies had poor quality (score <65) as measured with the CTAM. Three RCT's compared exercise with treatment as usual (TAU); two studies compared exercise to yoga and TAU; one RCT compared exercise with token reinforcement and TAU; one RCT compared exercise with occupational therapy. All, except for one study, showed a within group reduction in negative symptoms. In three studies this effect was significant compared to TAU. Two studies reported a significant effect of yoga compared to exercise and one study reported a significant effect of token reinforcement compared to exercise. Data of two studies were not available for analysis (not reported nor provided on request). The meta-analysis on five studies showed a non-significant result in favour of exercise compared to any control group (Hedges' $g=0.07$, 95% CI = -0.571-0.704). There was substantial heterogeneity between the studied interventions.

Discussion: This meta-analysis detected no effect of aerobic therapy on negative symptoms. The methodological quality was poor in almost all studies. More RCT's, having negative symptoms as primary outcome and sufficient power, will provide evidence whether aerobic exercise can be successful in reducing negative symptoms.

Poster #T253

DIFFERENTIAL DIAGNOSIS OF SCHIZOPHRENIA VS. BORDERLINE PERSONALITY DISORDER USING PATTERN CLASSIFICATION METHODS IN STRUCTURAL MRI IMAGES

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Background: Everyday clinical routine is frequently challenged by difficulty to choose among differential diagnostic options, especially since many psychiatric disorders share similar phenotypes. E.g., borderline personality disorder (BPD) can be associated with psychotic syndromes, making it hard to delineate these symptoms from schizophrenia (SZ). Thus, psychiatric diagnoses strongly rely on the correct contextual interpretation of symptoms, which in turn is highly dependent on clinical training and experience. Hence, introducing objective diagnostic measures (such as MRI) could improve the reliability of clinical evaluations.

Methods: For this study structural MRI data of 114 female patients (57 SZ, mean age: 34±10 years; 57 BPD, mean age 26±7 years) were used to train a multivariate disease classifier. Patients were enrolled at the Department of Psychiatry and Psychotherapy, Ludwig-Maximilian University, Munich. A consensus diagnosis was achieved by two experienced psychiatrists at study inclusion and after 1 year using the DSM-IV. All MR images were processed using voxel-based morphometry and high-dimensional registration to the MNI template. The resulting grey matter volume maps were fed into a machine learning pipeline consisting of (1) adjustment for possible age effects using the data of 432 healthy controls, (2) principal component analysis for dimensionality reduction followed by (3) linear v-support vector classification. The diagnostic performance of the classifier was determined by repeated nested 10-fold cross-validation.

Results: Using the methods described above we were able to correctly classify unseen test subjects' diagnosis with 74% accuracy. Classification sensitivity and specificity was 74%. Closer inspection of the most predictive voxels revealed that following pattern was involved in the decision function: Volume reductions in SZ vs. BPD were predominantly located in the left peri- and intrasylvian regions (inf-, mid- and sup.-temporal gyrus, insula, rolandic operculum extending to inf.- frontal operculum

and the inf. frontal gyrus (triangular part)), orbitofrontal regions (frontal mid. orbital gyrus, gyrus rectus and frontal sup. orbital gyrus), as well as the nucleus caudatus bilaterally and the right cerebellum. Volume reductions in BPD compared to SZ were found predominantly in the left cerebellum (Crus I and II, Vermis), in limbic areas (anterior cingulate gyrus bilaterally, left amygdala and olfactory gyrus, right hippocampus) and the left inferior occipital gyrus.

Discussion: Our results suggest that patients with schizophrenia can be differentiated from patients with borderline personality disorder at the single-subject level by means of sMRI and pattern classification methods. In the future, this method might enhance clinical evaluations of patients and improve the accuracy and reliability of differential diagnosis, especially in a context where sufficient psychiatric expertise might not be available.

Poster #T254

DYNAMIC CAUSAL MODELING OF FMRI DATA REVEALS DISORDERED FRONTAL-HIPPOCAMPAL-STRIATAL INTERACTIONS DURING ASSOCIATIVE LEARNING IN SCHIZOPHRENIA PATIENTS

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Background: Associative learning is an ideal cognitive domain in which to study schizophrenia-related pathophysiology, disordered activation, and functional disconnection. In a recent study, we applied GLM analyses to an fMRI paired associative learning paradigm, demonstrating increased activation within the fronto-hippocampal-striatal circuit and decreased modulation by the hippocampus of all regions except the basal ganglia (Wadehra et al, 2013). However, conventional approaches to fMRI data are inadequate in characterizing disordered effective connectivity between brain sub-circuits. Here, we report an extended analysis of this group of subjects, using Dynamic Causal Modeling (DCM; Friston et al., 2003) to investigate frontal-striatal-hippocampal dysfunction. DCM permits evaluation of competing models of network architecture distinguished at a second stage using a Bayesian selection framework. Coupling estimates between regions provide evidence of effective connectivity (Friston, 2005) related to endogenous connections and the modulatory effects of a task on these connections.

Methods: fMRI (4.0T) was collected in SCZ (n=12) and controls (n=10; 18≤age≤35yrs). Because DCM relies on Bayesian model selection (BMS) to identify the most appropriate generative model for the data relative to neurobiologically-plausible competitors, 144 models were constructed by permuting connections between 6 brain regions. In addition to three primary regions, the supra-network included visual, inferior temporal, and parietal cortices. This set of 2,736 models (144 models 19 subjects) was submitted to a second-level Random Effects Analyses for BMS. Inter-group inferences were based on Bayesian averages of estimated network coupling (Penny et al., 2010). All analyses were conducted in SPM8.

Results: BMS identified one winning model with an exceedance probability 60% greater than its closest competitor. In this model, patients evidenced inhibitory fronto-hippocampal coupling, but hyper-excitatory striatal-hippocampal coupling.

Discussion: These results demonstrate that DCM is sensitive to identifying reduced fronto-hippocampal coupling and compensatory increases in fronto-striatal coupling during associative learning in schizophrenia. Impaired fronto-hippocampal-striatal function is a hallmark of schizophrenia-related pathophysiology. Therefore, the application of DCM to *in vivo* fMRI data constitutes a substantive new advance in the application and ability of fMRI to identify possible correlates of schizophrenia-related pathophysiology (Wadehra et al, 2012).

Poster #T255**TISSUE-SPECIFIC DNA METHYLATION ACROSS BLOOD AND BRAIN AND ITS APPLICATION TO SCHIZOPHRENIA**

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Background: Schizophrenia and other psychiatric illnesses are influenced by complex gene - environment interactions, but little is known about how precisely environmental factors contribute to disease risk. Epigenetic processes such as DNA methylation have been put forward as the molecular code of environmental influences. However, it is unclear to what extent methylation measured from peripheral tissues such as blood or saliva (which are both commonly used in epigenetic studies due to easy access) relate to changes in brain tissue. In this study, we aimed to investigate 1) how DNA methylation signatures in blood relate to those in brain tissue and 2) which brain-related (epi-)genetic pathways are impaired in schizophrenia.

Methods: To analyze how DNA methylation patterns in blood relate to those in brain tissue, we obtained twelve pairs of blood and brain biopsy samples from twelve patients with pharmacotherapy-resistant temporal lobe epilepsy during neurosurgical treatment of cortical dysplasia (dataset 1). Blood and brain tissue samples were then analysed using the Illumina Infinium HumanMethylation450 BeadChip (Illumina Inc, CA, USA). Subsequently quality control and further analysis was performed in R using various Bioconductor packages, leaving a total of 440,518 probes for subsequent analyses. We calculated similarity of blood and brain methylation profiles in a within-subject design based on spearman correlation coefficients and p-values. Furthermore, we created subsets containing only variable probes (defined as variable across subjects in blood only) or probes for which there is evidence that the associated genes are expressed in the human brain. To apply this new knowledge to clinical research in schizophrenia, we studied DNA methylation assessed using the Illumina Infinium HumanMethylation27 BeadChip in blood samples of 111 patients with DSM-IV schizophrenia and 122 healthy controls from the Mind Clinical Imaging Consortium study of schizophrenia (Gollub et al. 2013) (dataset 2). We then performed gene-set enrichment analyses (Subramanian et al. 2005) using only variable, brain-associated and highly correlated markers from dataset 1 to identify gene sets with altered methylation profiles associated with schizophrenia in dataset 2.

Results: 74.5% of all probes in dataset 1 passing quality control were variable. For 72.3% of all probes there was evidence that the associated gene is expressed in the human brain. Only 7.9% of these 227,428 variable, brain-associated probes showed a significant correlation ($\rho \geq 0.59$, $p < 0.05$) of moderate size between blood and brain tissue. GSEA analysis for diagnosis using all variable, brain-associated, highly correlated markers also present in dataset 2 ($N=1221$) showed that altered methylation profiles associated with schizophrenia are mainly found in gene sets related to neurodevelopmental processes.

Discussion: Using a set of markers collected invasively from both brain and blood, we characterized epigenetic risk mechanisms of schizophrenia assessed via easily accessible markers taken from blood samples, for which there is evidence for a high correlation with brain DNA methylation markers. Our results using blood-based markers are therefore also applicable to brain-related biological pathways and processes. Furthermore, analyzing the epigenetic alterations in schizophrenia may shed light on the influence of non-genetic risk factors and thus provide an advantage over studying only gene effects.

Poster #T256**AGE OF ONSET AND PREVALENCE OF SUBSTANCE USE IN HELP-SEEKING ULTRA-HIGH RISK YOUTH ARE LINKED TO CURRENT PSYCHOPATHOLOGY**

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Background: There is a well-established connection between psychosis and substance use. The Mind in Transition (MinT) project prospectively recorded substance use and psychological symptom severity (both self-report and interview-observed mental state) in a population identified as being at ultra high-risk (UHR) for psychosis. The study aimed to assess whether drug use within a UHR sample was significantly elevated relative to the general population, and secondly to explore the relationship between drug use and symptom severity.

Methods: We report preliminary data from 59 participants (37 female) mean age 19.1 years (range 14-24 years) attending the Sydney site of the MinT project. Participants were assessed using measures of substance use; the Opiate Treatment Index (OTI), Alcohol Use Disorders Identification Test (AUDIT) and Cannabis Use Disorder Identification Test (CUDIT), and symptom severity; the Brief Psychiatric Rating Scale (BPRS) and Comprehensive Assessment of At Risk Mental State (CAARMS). Australian National Bureau of Statistics information will be used to compare the prevalence of drug use in the UHR sample relative to a similar age range within the same geographical region within the general population.

Results: We recorded tobacco, alcohol or cannabis use in greater than 69% of our UHR sample. Rates of stimulant (i.e. cocaine and amphetamines) and hallucinogens ranged between 37 and 50%. When examining recent use (i.e. in the past month), 55% had used tobacco, 65% alcohol, 34% cannabis, 11% hallucinogens, and 8% amphetamines. Correlational analyses revealed significant associations between both earlier age of first drug use and greater recent drug use with higher ratings of current symptomatology.

Discussion: Our data confirm high prevalence of substance use in a UHR sample. Those UHR participants who used substances more recently or commenced at a younger age were more likely to report current psychiatric symptoms.

Poster #T257**PERCEPTIONS OF PARTICIPATING IN A LIFESTYLE INTERVENTION – FROM THE PERSPECTIVE OF PATIENTS WITH PSYCHOSIS**

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Background: The concept of physical activity is rarely found in psychiatric literature, and there is not a strong tradition of viewing the body and mind as connected. This problem area has begun to come into focus now as it appears that the lifespan of persons with psychotic disorders can be shortened by up to 25 years, in large part due to preventable metabolic diseases. To prevent this a range of different lifestyle interventions have been offered. However, these lifestyle interventions have been criticized for not taking the patient's perspective into account, which may be one reason why they have sometimes had difficulties showing improvements in long term outcomes. There is limited knowledge about how patients with psychosis experience lifestyle intervention. The aim of the study was therefore to enhance understanding of the perception of participation in lifestyle interventions by patients with psychosis.

Methods: The sampling for the study was purposeful. Forty interviews were conducted with patients with a psychotic disorder. Prior to the interviews the participants had undergone a lifestyle intervention in groups, focusing on physical activities and lifestyle education, under the guidance of health coordinators. These health coordinators were trained in motivational interviewing and had significant experience of working with this patient group through their jobs in outpatient psychiatry. Phenomenographic analysis was performed.

Results: The participants describe the importance of the intervention program, as a whole, being at a moderate level. A moderate level creates not only the conditions to continue the intervention in the short term, but also the potential to maintain a healthy lifestyle after the intervention has ended. Belonging to a group and sharing experiences with each other emerged as important components that create contacts and opportunities outside the mental health services. These were perceived as success factors to bring into the future.

Discussion: It seems essential to find a sufficiently challenging level that does not underestimate the participant's ability. A challenge is to find a solution that does not exclude participants by placing the bar too high, while at the same time meeting the desire to do whatever "common people" do.

Poster #T258

METABOLIC SYNDROME IN PEOPLE WITH PSYCHOSIS: IS CANNABIS PROTECTIVE?

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Background: The relationship between psychotic illness and metabolic dysregulation is a complex one. There is evidence that people with psychosis are at increased risk of metabolic syndrome (Galletly 2012, McEvoy et al., 2005). A number of factors including poor diet, physical inactivity, weight gain associated with antipsychotic medication, and smoking may all be contributing factors. Of interest, several recently published studies have shown that the use of cannabis in general population samples has been associated with a lower prevalence of diabetes, smaller waist circumferences and reduced body mass index (Penner, 2013, Rajavashisth, 2012, Le Strat 2011). The aim of this presentation is to examine whether cannabis use plays a role in reducing the risk for metabolic syndrome among people with psychosis.

Methods: The second Australian national survey of psychosis was conducted in 2010, covering a population of some 1.5 million people aged 18–64 years, approximately 10% of the Australian population in this age group. A two-phase design was used. From 7955 people who were screen positive for psychosis in Phase 1, a random sample of 1825 was interviewed in Phase 2. Interviews were conducted by the interviewers who had mental health backgrounds. Data collected covered: symptomatology, substance use, physical health profile, medication use, and health service utilisation. Waist circumference and blood pressure were measured. A fasting blood sample was taken to determine levels of glucose, triglycerides, and HDL cholesterol.

Results: A third (32.8%) of the participants had used cannabis in the past 12 months (current users). The mean age of current users was 34.4 years (range 18–64 years). A quarter (24.3%) of females and 38.5% of males were current users. More than half (58.5%) were using cannabis at least weekly, with daily use very common (38.1%). Three quarters (74.0%) of participants had sufficient measures to assess the presence of metabolic syndrome. More than half of these participants (57.9%) met the harmonized criteria for metabolic syndrome. Using unadjusted logistic regression, compared to participants not using cannabis, current users were at significantly reduced risk of metabolic syndrome (OR 0.517 95% CI 0.41–0.65). This reduction in risk remained significant even after adjustment for age, sex and use of atypical antipsychotic medication (OR 0.62 95% CI 0.49–0.79).

Discussion: Our finding that cannabis users are less likely to have metabolic syndrome requires further investigation, while the potential mechanisms underlying this paradoxical action of cannabis on the endocannabinoid system remain to be understood. Alternatively, cannabis may be a proxy for some as yet unidentified factor. In ongoing work, we will examine possible confounders of the relationship between cannabis use and metabolic syndrome, including diet, level of physical activity and smoking.

Poster #T259

HIGH FALSE POSITIVE RATE OF A PUTATIVE BIOMARKER TEST TO AID IN THE DIAGNOSIS OF SCHIZOPHRENIA

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Background: Quantifiable biological measures that directly correlate with the presence of a particular pathological process (i.e., a disease) have been used in general medicine for years. Such molecular biomarkers are used to diagnose disease, assess risk, guide treatment decisions and measure efficacy. While attempts to develop such tests for psychiatric disorders have been ongoing for a number of years, minimal progress has been made to date. The need for biomarkers in psychiatry is especially important for serious and persistent mental illnesses such as schizophrenia. In 2010, a 51-analyte blood-based signature of schizophrenia was marketed to aid in the confirmation of the diagnosis of schizophrenia in individuals with a first- or recent-onset psychotic episode. The initial development work was done using a population of individuals who had a first or recent onset of schizophrenia paranoid-type, were predominantly antipsychotic naïve and were evaluated at one of 4 European Universities. Controls were matched for age, gender and social demographics. This yielded a cross-validation classification accuracy of 83% (sensitivity 83%, specificity 83%). Initially, the goal of the current study was to determine whether individuals with long-standing schizophrenia continued to have the same results on this 51-plex biomarker test as did individuals with first or recent onset schizophrenia. Originally, healthy control subjects were included only for assay validity but subsequently became the focus of the results. The current study measured the ability of a 51-analyte immunoassay panel to discriminate between subjects with chronic schizophrenia and healthy control subjects in an American population.

Methods: Subjects with a prior clinical diagnosis of schizophrenia were recruited from local community mental health center and private psychiatric clinic populations. Healthy, ambulatory volunteers with no personal or family history of schizophrenia were recruited as control subjects. Controls were over-enrolled to bridge the age range from the individuals with first onset schizophrenia for whom the test was developed and individuals with chronic schizophrenia who were initially the focus of this study. No matching other than for age was done in the current study. Blinded blood samples were sent to the RBM lab for analysis using the 51-analyte biomarker test.

Results: As indicated by the high sensitivity (89%) in our sample, the current study confirms that the 51-plex test performs in individuals with chronic schizophrenia comparably to its performance in studies of subjects with first-onset of the psychotic phase of the syndrome, indicating that the abnormalities in this multiple biomarker test persist and are not affected by the number of years this illness has been present and/or by its treatment. However, there was a high false positive rate in healthy control subjects in our sample leading to a low specificity rate of 34%.

Discussion: Due to the high false positive rate in our normal controls, this biomarker test was not able to discriminate between healthy control subjects and subjects with chronic schizophrenia in our sample. The development of this 51-plex immunoassay is an example of the continued effort to develop a clinically usable biological diagnostic test for schizophrenia. While this specific test is no longer available commercially, there is a growing interest in such tests, whether biomarkers or genetic, in psychiatry. Hence, it behoves psychiatrists to increase their familiarity with the appropriate application of such tests in clinical practice and understand the limitations of these tools.

Poster #T260

OBJECT PATTERN SEPARATION PERFORMANCE IN SCHIZOPHRENICS IS CONSISTENT WITH DISRUPTED HIPPOCAMPAL DENTATE GYRUS ACTIVITY AND COMPROMISED NEUROGENESIS

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Background: Eriksson et al. [1] demonstrated that neurogenesis occurred in the dentate gyrus (DG) of the adult human brain throughout the lifespan. The field became of interest to human cognitive neuroscience following

fMRI findings demonstrating that DG activity increased when volunteers performed a task involving difficult object pattern separations, but not with simpler pattern separations. Object pattern separation tests could therefore reflect the quality of DG activity, and by implication provide an index of neurogenesis in man. Recent evidence indicates that the G-protein coupled receptor, SREB2/GPR85, a known schizophrenia risk factor, negatively regulates hippocampal dentate gyrus neurogenesis-dependent spatial pattern separation in mice [2]. Post-mortem evidence of compromised hippocampal dentate gyrus (DG) neurogenesis in schizophrenics has also just appeared [3]. The CDR System automated picture recognition task yields an object pattern separation (OPS) measure, sensitive to DG activity, which in man selectively declines in aging and mild cognitive impairment; and has recently been found to be impaired in several other conditions in which neurogenesis is disrupted. The object of this study was to determine if DG-sensitive OPS is selectively compromised in schizophrenia.

Methods: The CDR System OPS task was administered to 91 stably medicated schizophrenic patients aged 22 to 63 years and the results contrasted to 2,330 age-matched healthy controls. Performance on the OPS task was also assessed according to Clinical Global Impression Severity (CGI-S) scores.

Results: 2-factor ANCOVA, with Normal v Schizophrenic as one factor and DG v non-DG OPS measures as the other, yielded a significant interaction between the two factors ($p=0.0005$). The difference in % accuracy scores between the populations in the DG sensitive measure was 12.8 (Effect size 1.01), compared with 5.3 (Effect size 0.42) for the non-DG sensitive measure. No such interaction was seen in a comparable forced choice non-DG differentially sensitive verbal recognition task ($p=0.57$), indicating that the OPS effect was not due to response style on such tasks. Importantly, within the 91 patients, CGI-S was significantly associated with the DG sensitive score ($p<0.05$; CGI-S 2=74%; CGI-S 3=66%; CGI-S 2=49%), but not the non-DG sensitive score ($p=0.91$).

Discussion: This is to our knowledge the first robust cognitive data from an OPS task with established DG sensitivity to show a selective deficit in schizophrenics compared to normals; further supported by statistically reliable disease severity deficits. The implications are that part of the memory deficit in schizophrenia is related to compromised DG neurogenesis and that this deficit may respond to medications which influence neurogenesis; a mechanism possessed by many second generation antipsychotics including olanzapine, risperidone, paliperidone, aripiprazole and possibly quetiapine [4]. This OPS task can serve as both a proof of principle that a compound has neurogenesis activity while also serving as a measure of efficacy.

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Poster #T261

SCHIZOPHRENIA: BILIRUBIN LEVELS CORRELATE WITH POSITIVE SYMPTOMS

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Background: There have been contradictory reports on hyper- and hypobilirubinemia in schizophrenia patients. Furthermore, it has been stipulated, that a decrease in bilirubin levels is associated with successful antipsychotic treatment. Bilirubin, besides its toxic effects, has been demonstrated to have antioxidant properties as well to counteract stress, which has been suggested to play a role in the pathophysiology of schizophrenia.

Methods: In this retrospective analysis of a prospectively studied

schizophrenia patient sample data were analysed in order to investigate a potential association between changes in psychopathology measured by the Lindenmayer 5 factor model of the Positive and Negative Syndrome Scale (PANSS) and changes in total bilirubin plasma levels.

Results: Data of 52 patients were collected at baseline as well as 2, 4, and 12 weeks after the initiation of antipsychotic monotherapy. The PANSS total score decreased significantly from baseline to weeks 2, 4, and 12 of treatment. Total bilirubin plasma concentrations also dropped significantly from baseline to week 2 and decreased further until week 4. No significant decrease was observed between baseline and week 12. Spearman's rank correlation revealed a significant association of the PANSS positive and excitement factors with bilirubin levels at baseline. No further correlations were found. Changes in total bilirubin plasma concentration from baseline to weeks 2, 4, and 12 correlated significantly with changes in the PANSS positive factor but not with other PANSS factors. They showed correlations only at varying time points.

Discussion: The consistent correlation of changes in the PANSS positive component with changes in bilirubin plasma levels expand the evidence in potential antioxidant properties of bilirubin in schizophrenia patients, particularly caused by the stress of positive symptoms.

Poster #T262

THE EFFECTS OF DOPAMINERGIC MANIPULATION IN HEALTHY CONTROLS COMPARED TO PATIENTS WITH SCHIZOPHRENIA DURING SOCIAL DECISION-MAKING

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Background: Schizophrenia is an illness characterised by perceptual abnormalities, such as auditory hallucinations and abnormal beliefs such as delusions. These difficulties in perceptual processing and abnormal interpretation are thought to be mediated by dopaminergic overactivity. We assessed decision-making, using a stochastically rewarded social task, using fMRI - while manipulating dopaminergic function in healthy subjects and comparing this with patients with schizophrenia.

Methods: We imaged 20 healthy controls under a dopamine agonist, ropinirole (0.25mg), dopamine antagonist, amisulpride (400mg), and placebo and 36 medicated patients with schizophrenia. During each scan, participants performed a social decision-making task which incorporated faces of varying social valence which were stochastically rewarded. Participants were presented with two faces, either a happy and a sad face or two neutral faces of different identities and were asked to identify which face they thought was more likely to be rewarded.

Results: Patients with schizophrenia exhibited significantly higher left Insula activity than healthy controls ($p<0.05$, family wise error corrected), when processing reward in response to emotional faces over neutral faces. However, when given a dopamine agonist, healthy controls show elevated caudate activity. Furthermore, both ropinirole and amisulpride increased the likelihood that subjects would preferentially select one of the neutral faces, in comparison with the placebo condition ($t(38)=2.08$, $p=0.04$ and $t(38)=2.23$, $p=0.03$, respectively).

Discussion: Elevated levels of dopamine caused aberrant reward processing in healthy controls in the striatum which correlates with a heightened reward sensitivity to selected neutral faces. This elevation coincides with a misattribution of value to specific faces with no emotional valence suggesting heightened sensitivity to other social stimuli. In contrast, the patients' activity in the striatum during reward is driven by the choice in the emotional condition.

Poster #T263

OTX2 EXPRESSION IN HUMAN PREFRONTAL CORTEX DEVELOPMENT AND IN SUBJECTS WITH SCHIZOPHRENIA

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Background: OTX2 is a homeoprotein that is involved in the regulation of many aspects of brain development. More recently, studies in rodents have shown that OTX2 regulates the postnatal maturation of parvalbumin

(PV)-expressing interneurons and also drives the developmental formation of perineuronal nets (PNNs), which are extracellular matrix structures that encapsulate many neurons, including PV neurons. Of interest, PV neurons and PNNs are known to be compromised in schizophrenia (SZ).

Methods: We immunohistochemically visualize OTX2-immunoreactive elements (IR) in postmortem tissue of Brodmann's area 9 in the prefrontal cortex (PFC) in a cohort of normal control human subjects (N=16), ages ranging from 2 days to 20 years old, and in a cohort of 15 SZ subjects demographically matched with 15 normal control subjects.

Results: Qualitative examination reveals that OTX2-IR elements are comprised of pyramidal cells, interneurons, glias and spherical-like shaped structures that are believed to represent transport vesicles. We found that OTX2-IR cells were present throughout postnatal development into early adulthood with no significant changes in densities. Confocal microscopic quantification of possible cell type-related changes in OTX2 immunoreactivity suggests that OTX2 in PV neurons may be decreased in SZ.

Discussion: Findings of this study will provide insight into the possible role of OTX2 in mediating the disturbances of PFC circuitry by compromising the integrity of PNNs and PV neuronal functions and may shed light onto the possible mechanism that underlie the onset of SZ.

Poster #T264

INCREASED PATTERN DETECTION IN MEANINGLESS NOISE OF HEALTHY PEOPLE WITH EXCEPTIONAL EXPERIENCES

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Background: Exceptional experiences (EE) are commonly reported within the healthy population. Their phenomenology is broad and very heterogeneous. Nevertheless, they all share a common aspect; they violate the basic cause-and-effect principles of science. Although the creative aspects of paranormal or schizotypal thoughts have been emphasized by some authors, others have equally stressed its conceptual similarity to psychotic symptoms. Furthermore, individuals with a paranormal belief exhibit a marked willingness to perceive "patterns in noise", and are more inclined to attribute meaning to random associations than skeptical persons.

Methods: In this on-going study a population of 86 healthy subjects, representing a cross section of ordinary Swiss-German population with respect to age (20-45), gender and level of education, has been recruited. Past EE and magical thinking were assessed using a questionnaire for measuring the phenomenological aspects of EE (Fragebogen zur Erfassung der Phänomenologie aussergewöhnlicher Erfahrungen, PAGE-R) and the Magical Ideation Scale (MI). The former classifies the experiences into four possible categories, i.e., internal, external, coincidence, and dissociation phenomena. In order to assess the participants inclination to perceive "patterns in noise", two visual computer tasks were deployed: the Mooney Faces Task (MFT) and a modified version thereof, the Mooney Objects Task (MOT). Compared to the former, the MOT contains images of man-made objects, e.g., tools, instead of faces. In both tasks, half of the stimuli, i.e., 15, consisted of laterally arranged pairs of a face/object with a meaningless pattern while the other comprised two meaningless patterns. Each stimulus was presented a second time as a mirror image (60 stimuli in total). After each stimulus-presentation of 150 ms, participants had to indicate via keyboard whether they saw a pair of patterns or a face/object in the left or right visual field, respectively, for a response time of one second.

Results: Concerning the relation between MI and EE, a high correlation was found (Spearman's rho=0.83, p<0.0001). The number of false positives, i.e., reporting a face, when two meaningless patterns were presented ("signals in noise") in the MFT correlated significantly and positively with the sum score of the PAGE-R (rho=0.23, p=0.033), but not with the MI score (rho=0.18, p=0.098). This score in the MOT correlated only in a trend towards significance with the PAGE-R (rho=0.19, p=0.064) and not with the MI (rho=0.093, p=0.39). Concerning the subscales of the PAGE-R, "signals in noise" showed

the strongest correlations with coincidence phenomena in both the MFT (rho=0.27, p=0.014) and MOT (rho=0.25, p=0.020) and a weaker correlation with internal phenomena (rho=0.21, p=0.050) in the MFT.

Discussion: Our results show a high correlation between the MI and the PAGE-R, where the MI measures the belief, in contrast to the experience level of the PAGE-R. Interestingly, a significant correlation of "signals in noise" detection was found only with EE (PAGE-R) but not with belief (MI); this stands at odds with former studies. Furthermore, the "signal in noise"-parameter correlates the most with experienced coincidence phenomena, i.e., déjà-vu or getting a call from a person one just thought of. These phenomena imply a perceived similarity in unrelated events. These two effects can be observed with either faces or objects as stimuli. Our result suggests therefore, that pattern detection in meaningless stimuli, as a possible source of illusions or hallucinations, could be explained as a perceptive trait, rather than a willingness to perceive "signals in noise" as would be assumed by a correlation with MI.

Poster #T265

A TREATABLE CAUSE OF CATATONIA: ANTI-NMDA RECEPTOR ENCEPHALITIS IN A YOUNG WOMAN

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Background: So far, there is no stable concept and definition about catatonia. Therefore it is very difficult to diagnose catatonia and differentiate its etiology. Although the most familial diagnosis is schizophrenia or mood disorder when psychiatrists meet catatonic patients, but we also have to consider other various organic diseases. Anti-N-methyl-D-aspartate receptor (anti-NMDA) encephalitis is a recently characterized form of autoimmune encephalitis associated with prominent psychiatric symptoms at onset. Most patients initially develop prominent psychiatric symptoms and then progress to complex symptoms such as memory impairment, seizures, dyskinesia, and catatonia. Early recognition of the symptom complex is the key to diagnosis of this fatal but potentially treatable disease.

Methods: We report a case of patient presenting with persecutory idea and catatonic feature whose symptoms were fully recovered not by benzodiazepine nor ECT but steroid pulse therapy.

Results: A 20-year-old woman presented with irrelevant speech and agitation was admitted to psychiatric unit. Because psychiatric symptoms were progressed despite of sufficient use of antipsychotics and benzodiazepines, complete workup to figure out other organic causes were done, including EEG, brain MR, CSF tapping and laboratory test. Accompanied cognitive fluctuation and subtle neurological deficits were clues to suspect organic problems. But all other results showed negative findings except vague slow wave on EEG. Additional results of Brain PET and SPECT implied that there's inflammation on focal lesions of brain. After empirical steroid pulse therapy, all of the symptoms were subsided gradually for 2 months. By detecting antibody on the patient's serum, anti-NMDA receptor antibody encephalitis is diagnosed later.

Discussion: In this case, we emphasize that psychiatrists must not overlook cognitive deficit and subtle abnormalities in functional brain work up like EEG, PET or SPECT when they meet catatonic patients. Prompt diagnosis can lead to lifesaving treatment.

Poster #T266

TARDIVE DYSKINESIA IN RELATION TO ESTIMATED DOPAMINE D2 RECEPTOR OCCUPANCY IN PATIENTS WITH SCHIZOPHRENIA: ANALYSIS OF THE CATIE DATA

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Background: The objective of this study was to evaluate the relationship between antipsychotic-induced tardive dyskinesia (TD) and estimated dopamine D2 receptor occupancy levels in patients with schizophrenia, using the dataset from the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE).

Methods: The dataset from 235 subjects (risperidone, N=88; olanzapine, N=106; ziprasidone, N=41) who presented with a score of zero on the Abnormal Involuntary Movement Scale (AIMS) at baseline in Phase 1 of the CATIE study, and remained for ≥ 6 months, was used. Peak and trough dopamine D2 receptor occupancy levels on the day of the AIMS assessment at the endpoint were estimated from plasma antipsychotic concentrations, using population pharmacokinetic analysis and our D2 prediction model. The estimated dopamine D2 receptor occupancy levels were compared between patients who presented an AIMS score of ≥ 1 at endpoint and those who did not, using the independent t-test.

Results: Estimated dopamine D2 receptor occupancy levels at trough were significantly higher in subjects who developed involuntary movements (N=40) than those who did not (N=195) ($71.5 \pm 12.4\%$ vs. $64.3 \pm 19.3\%$, $p < 0.05$) while no significant difference was found in the estimated peak D2 receptor occupancy between them ($75.1 \pm 8.0\%$ vs. $72.1 \pm 9.9\%$, $p = 0.07$). When the analyses were separately conducted for the three drugs, there were no significant differences in estimated peak or trough D2 occupancy although the values were consistently numerically higher among those developing involuntary movements.

Discussion: Greater dopamine D2 receptor blockade with antipsychotics at trough may increase the risk of tardive involuntary movements.

Poster #T267

PREFRONTAL CORTEX THICKNESS IN PTSD AND SCHIZOPHRENIA AND THE ROLE OF CHILDHOOD TRAUMA

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Background: Psychosis develops as a result of numerous interacting factors (van Os and McGuffin, 2003). However a number of features link traumatic

events to psychosis. A history of trauma is more common in subjects with psychotic disorders (Bebbington et al., 2004). Traumatic experience during childhood increases the risk of psychosis with cumulative effect (Shevlin et al., 2008) and a history of trauma is associated with psychotic symptoms in the general population (Freeman and Fowler, 2009). Additionally, psychotic symptoms appear to be related to a worse prognosis in post-traumatic stress disorder (PTSD) patients and PTSD co-morbidity is related to a worse prognosis in first episode psychosis (Mueser et al., 2010). Although it has been hypothesized that both PTSD and psychosis are related to a pathological response to traumatic experience (Morrison et al., 2003) there are few studies comparing biological features of both disorders.

Methods: 24 subjects with schizophrenia (SCZ) and 29 PTSD subjects were recruited from psychiatric outpatients clinics. Clinical interviews were carried out by trained psychiatrists and diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID-IV). Early Trauma was assessed using the Childhood Trauma Questionnaire (CTQ) (Bernstein, 2003). The CTQ contains five subscales, three assessing abuse (physical, emotional and sexual) and two assessing neglect (physical and emotional). All subjects were receiving treatment as usual at the time of scan. Brain MR images were acquired on a 1.5T Siemens Sonata scanner (TE= 3.4; TR= 2000 ms; FoV= 256; Flip Angle: 15; Slice Thickness 1mm). Images were processed and analysed using freesurfer (<http://surfer.nmr.mgh.harvard.edu/>). Between group whole cortex vertex-wise thickness analysis was carried out with a threshold of $p=0.05$ corrected for multiple comparison using a Monte-Carlo simulation. Correlation between early trauma scores and cortical thickness in SCZ and PTSD group was also investigated.

Results: SCZ group had a mean age of 35.3 (SD: 10.1 y/o) and mean CTQ score of 42.9 (SD: 13.9). PTSD group had a mean age of 45.7 (SD: 8.6 y/o) and mean CTQ of 50.4 (SD: 21.9). The total CTQ score was not significantly different between both groups (t : 1.4; p : 0.15). A significant thinning of the left anterior cingulate and orbitofrontal cortices were observed in PTSD group when compared to SCZ subjects. The total CTQ score and thickness correlation did not remain significant after correction for multiple comparisons in both groups. There was a significant association between CTQ emotional neglect subscale and the left prefrontal cortex thickness in SCZ group. No other correlation was found between CTQ subscales scores and cortical thickness.

Discussion: The prefrontal cortex is a region thought to be involved in reward guided learning and decision making (Rushworth et al., 2011). This region has been previously linked to anhedonia (Frewen et al., 2012) which is a characteristic of both disorders. Our findings may indicate that this region response to trauma in different stage during life may lead to different psychopathology.



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