with methylphenidate (MPH). The control group consisted of 21 healthy subjects. The PERGs were recorded in a steady state mode in response to checkerboard stimuli of 12 reversals/s. Data collection with people with schizophrenia is ongoing, and results will be reported at SIRS. Results: Before treatment, the patients with ADHD presented with elevated background noise (higher by 127%) in comparison to the control group. After treatment, noise level did not differ from what was observed in the control group. Retinal background noise was found to be highly correlated with the severity of the ADHD symptoms. The results will be discussed in relationship to our findings in patients with schizophrenia. Discussion: These data provide further evidence for the hypothesis that elevated background noise is linked to ADHD and cognitive deficits. The findings are of special relevance because ADHD is a disorder with a dedicated treatment option for cognitive symptoms. Interestingly, a similar pathophysiological mechanism for cognitive dysfunction has been proposed for both schizophrenia and ADHD. However, because ADHD medications, such as MPH, typically elevate dopamine levels, potentially leading to exacerbation of psychotic symptoms, different approaches for treating cognitive symptoms in schizophrenia need to be explored. On this basis, current approaches used to target neuronal noise and cognitive symptoms in patients with schizophrenia will be discussed and their relevance for future research will be addressed.

7.4 PHENOTYPIC AND GENETIC ASSOCIATIONS BETWEEN SCHIZOPHRENIA AND RETINAL VESSEL DIAMETER

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Background: Individuals with schizophrenia are at increased risk for cardiovascular diseases, and this risk cannot be fully explained by antipsychotic medications or lifestyle factors. Retinal imaging offers a non-invasive means of visualizing the microvasculature in living individuals with schizophrenia. Here we test whether individuals with schizophrenia exhibit retinal microvascular abnormality (Meier et al., AJP, 2013), and test for overlap in the genetic variants associated with schizophrenia and retinal microvascular abnormality.

Methods: To test whether individuals diagnosed with schizophrenia showed microvascular abnormality, we used data from the Dunedin Study, a representative cohort of 1,000 New Zealanders followed from birth to age 38. The cohort underwent retinal imaging at age 38, and retinal venular (small veins) and arteriolar (small arteries) diameters were obtained. Analyses compared individuals with schizophrenia (n=27), healthy individuals (n=412), and individuals with medical or psychiatric conditions (n=110–210) on retinal vessel diameter. To test for overlap in the genetic variants associated with schizophrenia and retinal microvascular abnormality.

Results: Adults diagnosed with schizophrenia had wider retinal venules (standardized mean=0.59) compared with same-age healthy adults (standardized mean=-0.20) and compared with individuals diagnosed with hypertension, diabetes, and tobacco dependence. Findings could not be explained by antipsychotic medication, as venular diameter was similar in the subset of individuals diagnosed with schizophrenia who had not taken antipsychotic medication in the year prior to retinal imaging (n=22: standardized mean=-0.69). There were no differences in arteriolar diameter between individuals diagnosed with schizophrenia and all other groups. Results from LD regression showed a small genetic correlation between schizophrenia and venular diameter (r=-0.05, p=.31) and a slightly larger genetic correlation between schizophrenia and arteriolar diameter (r=0.17, p=.02).

Discussion: Wider venular diameter is a distinguishing feature of schizophrenia, but genetic variants associated with schizophrenia overlap more strongly with variants associated with arteriolar diameter. It is possible that environmental influences associated with schizophrenia tend to narrow arterioles, obscuring a phenotypic link between schizophrenia and wider arterioles. Pathophysiological mechanisms underlying vessel diameter, including inflammation and endothelial dysfunction, might be related to the development of schizophrenia, and particular genes might contribute to both schizophrenia and arteriolar diameter. Findings will be discussed in relation to links between retinal vessel diameter and IQ (Shaley, Meier et al., Psychol Sci, 2013) and depression (Meier et al., Psychosom Med, 2014).

Plenary

8. DECREASING CARDIOVASCULAR RISK IN PERSONS WITH SCHIZOPHRENIA: INTERVENTIONS AND FUTURE DIRECTIONS

Gail Daumit
Johns Hopkins Medical Institutions

Overall Abstract: Persons with schizophrenia experience two to three times higher mortality than the overall population. This premature death is due in large part to cardiovascular disease and is potentially preventable. All cardiovascular risk factors are elevated in persons with schizophrenia. This presentation will describe the evidence for interventions to reduce cardiovascular risk factors in this vulnerable population, including obesity and tobacco smoking, and will describe models of integrated physical and mental health care. Ongoing research on interventions to decrease cardiovascular risk in schizophrenia will be presented, and future research needs will be discussed including implementation strategies to scale-up interventions to reduce cardiovascular disease risk in community settings.

Concurrent Symposia

9. DOES BIOLOGY READ THE DSM? TRANSDIAGNOSTIC FINDINGS IN PSYCHOSIS AND IMPLICATIONS FOR TREATMENT

Michael Owen
Cardiff University

Overall Abstract: A major emerging issue in schizophrenia research is the degree to which the mechanisms underlying the disorder are specific to schizophrenia or are common to a number of disorders, potentially indicating common and distinct pathways to illness. Understanding this is important for diagnosis, biomarkers and the development of new treatments. This symposium will bring together new data to consider the latest findings from different genetic, imaging and clinical approaches.

Dr. Owen, Wales, will present the latest genetic data from the largest genome-wide genetic analyses to date in psychotic disorders (schizophrenia and bipolar disorder) and neurodevelopmental disorders (autism, intellectual disability and ADHD), comprising samples from over 100,000 patients and controls. These data identify novel shared pathways involving neurodevelopmental genes, synaptic function and histone modification that are common across these disorders, but also identify differences in the degree of involvement of particular pathways.

Dr. Howes, England, will present new data from neurochemical and structural imaging studies comparing patients across psychotic and neurodevelopmental disorders (including schizophrenia, bipolar disorder people...
at risk of autism), showing that there are common dopaminergic alterations linked to psychosis across disorders, as well as showing that structural and neurochemical brain heterogeneity is increased in most brain regions, but also identifying key cortical and sub-cortical regions with increased homogeneity.

Dr. Clementz, USA, will present new EEG and cognitive data from over 400 patients with schizophrenia, and bipolar disorder. This shows differences in intrinsic neural activity that cuts across diagnoses, identifying sub-types that were linked to differences in cognitive functioning.

Dr. Wichers, Netherlands, will present new data from a longitudinal study of adolescents using in-depth real-time phenotyping using experience sampling to investigate the relationship between the coherence of responses and the subsequent development of psychotic and other symptom domains one year later. Her novel application of complex systems theory identifies suspiciousness as a common predictor of the later development of a number of symptoms, but also that other responses, such as low mood, determine the specificity of later outcomes to psychosis.

Overall this symposium will bring together researchers using different, complementary approaches to provide a comprehensive and multi-disciplinary analysis. By bringing researchers from different disciplines together it will enable common mechanisms to be considered, and new insights to be developed. Finally, Dr. Delisi’s wide-reaching experience means she is well placed to lead the discussion of the implications of these findings for understanding the neurobiology of schizophrenia, and for biomarker development as well as considering their implications for the developing new treatments.

The symposium includes gender diversity in presenters and chairs, speakers from multiple institutions across continents, and diversity in career levels with speakers from early, mid and established positions.

9.1 GENOMICS AND PSYCHIATRIC DIAGNOSIS

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**Background:** Recent genomic studies have begun to reveal the genetic architecture of psychiatric disorder and to give important insights into the relationship between the psychiatric syndromes that form the basis of current taxonomy. These studies have demonstrated the highly polygenic nature of psychiatric disorders, and have indicated that many individual genetic associations are shared across multiple disorders in a way that points to extensive biological pleiotropy and challenges the biological validity of existing diagnostic approaches.

**Methods:** I will present genomic data, predominantly from the study of rare variants, that support the idea of a neurodevelopmental continuum, in which schizophrenia and bipolar disorder, together with childhood neurodevelopmental disorders, such as ID, ASD and ADHD represent the diverse range of outcomes that follow from disrupted or deviant brain development and furthermore that, within the neurodevelopmental continuum, severe mental illnesses occupy a gradient of decreasing neurodevelopmental impairment as follows: ID, ASD, schizophrenia and bipolar disorder. I will also present findings indicating that common genetic variation modifies the outcome of neurodevelopmental impairment explaining in part the diversity of psychiatric outcomes. Finally, I will explore how genetic data might be used to inform novel approaches to patient stratification which will be informative for prognosis and treatment response and facilitate the identification of novel drug targets.

**Results:** Finally, despite the undoubted complexity and the fact that much of the genetic risk remains unaccounted for at the DNA level, there are encouraging signs that the genes implicated in schizophrenia converge onto sets of plausible biological processes. In particular, the data point to synaptic function and histone modification and implicate mechanisms involved in brain plasticity that are important in development and in learning and cognition. While these are almost certainly not the only processes involved, they provide robust entry points for clinical and basic neuroscience research.

**Discussion:** N/A

9.2 BRAIN STRUCTURAL AND NEUROCHEMICAL HETEROGENEITY AND HOMOGENEITY IN PSYCHOTIC DISORDERS: TRANSDIAGNOSTIC PET AND MRI IMAGING FINDINGS IN SCHIZOPHRENIA AND BIPOLAR AFFECTIVE DISORDER

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**Background:** Psychosis is seen in a number of disorders and treated with the same drugs. However, there is considerable variability in response to treatment and clinical course. Understanding the neurobiology underlying psychosis across diagnoses and in treatment response is important to help guide the development of new treatments and biomarkers for treatment response. Elevated dopamine synthesis and release capacity and structural brain changes have been consistently associated with schizophrenia, but it remains unknown how variable these are, or how they compare across psychotic disorders.

**Methods:** Two cohorts of first episode patients, one with a diagnosis of schizophrenia (n=16) and another with a diagnosis of bipolar affective disorder (n=22) received 18F-DOPA PET and [1H]-MR spectroscopy imaging and clinical measures. All patients had experienced a psychotic episode and received clinical follow-up over 18 months to determine diagnostic stability. We then conducted a meta-analysis using a novel meta-analytic approach to quantify variability in measures to investigate structural and neurochemical heterogeneity in schizophrenia and bipolar affective disorder. The entire PubMed, EMBase and PsychInfo databases were searched from inception to identify relevant studies and the natural log of the measures of dispersion and the coefficient of variance.

**Results:** Striatal dopamine synthesis capacity (Kicer) was significantly elevated in both bipolar (effect size=1.02; p<0.003) and schizophrenia (effect size=0.9; p<0.05) groups, compared to controls. There was no significant difference in dopamine synthesis capacity between bipolar and schizophrenia groups (p>0.4). Kicer was significantly positively correlated with positive psychotic symptom severity in the transdiagnostic group of people with psychosis (r=0.52, p<0.004), and in the bipolar group after adjusting for manic symptom severity (r=0.6, p=0.01). There were no differences in glutamate levels in the anterior cingulate cortex.

In the meta-analyses a total of 128 studies were identified including >4000 patients and >4000 controls. Variability ratio was significantly increased in patients relative to controls in gray matter volumes in temporal lobe (VR=1.1, p=0.004) and thalamus (VR=1.6, p<0.001), and in striatal dopamine receptor density (p<0.05) but unaltered in frontal cortex and significantly reduced in the anterior cingulate cortex (VR=0.9, p=0.02).

**Discussion:** Elevated dopamine synthesis capacity is associated with psychosis across diagnostic boundaries and linked to the severity of psychotic symptoms, even after adjusting for manic symptom severity. Striatal dopamine receptor density and structural gray matter volumes in a number of cortical and sub-cortical regions show heterogeneity in psychotic disorders, but frontal cortical regions show unaltered and, in the case of the anterior cingulate cortex, reduced heterogeneity, suggesting alterations are homogenous across patients. Taken together these findings striatal dopamine synthesis and structural changes in frontal cortex are common mechanisms linked to psychosis across disorders.

**Abstracts for the Sixth Biennial SIRS Conference**