Overall Abstract: This symposium has a translational approach. First, we present human post-mortem and in-vivo imaging studies on the pivotal role of oligodendrocyte loss and dysfunction with consequent impairments of brain connectivity in schizophrenia. Natalya Uranova will show morphometric data on ultrastructural alterations of oligodendrocytes, myelin damage and degeneration and disturbed oligodendrocyte-axon interactions in post-mortem prefrontal white matter in schizophrenia. Adrienne Lahti will report diffusion tensor imaging data suggesting impaired axonal and myelin integrity. Because, MR Spectroscopy permits the non-invasive measurement of metabolites, such as N-acetylaspartate, a marker of neuronal integrity, and glutamate, which can be neurotoxic when overproduced, this technique provides further understanding of the relationship between white matter microstructure and neuronal function.

Second, we present data from cell culture and animal models suggesting that restoration of oligodendrocyte function (in terms of energy metabolism, maturation and myelin production) is a promising target for the development of novel treatment strategies in schizophrenia. Proteomic studies in postmortem brain by Daniel Martins-de-Souza have suggested a schizophrenia-related energy metabolism dysfunction in oligodendrocytes. These findings have been followed up using oligodendroglia cell lines and induced pluripotent stem cell-derived cerebral organoids, supporting the notion that alterations in glycolysis in oligodendrocytes are pivotal to the overall energy dysfunction in schizophrenia brains. Lan Xiao’s lab has shown that oligodendrocyte dysfunction and impaired myelination in the prefrontal cortex is correlated with schizophrenia-like behavior in mice undergoing prolonged social isolation. Enhancing oligodendrocyte generation and myelin repair by FDA-approved compounds, like quetiapine (an APD) or clemastine (a histamine antagonist) successfully reversed the above phenotype.

25.1 OLIGODENDROCYTE PATHOLOGY IN PREFRONTAL WHITE MATTER IN SCHIZOPHRENIA

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Background: Recent neuroimaging studies have shown altered brain connectivity in patients with schizophrenia, associated with disturbed myelination in different fiber tracts and disruptions of white matter (WM) integrity, including prefrontal WM. We aimed to perform a qualitative and morphometric study of the ultrastructure of oligodendrocytes, myelin-forming cells, in prefrontal WM in schizophrenia and normal controls.

Methods: WM of the prefrontal cortex (Brodman’s area 10) was studied by transmission electron microscopy and morphometry. Size, volume density (Vv) and the number (N) of organelles in oligodendrocytes were estimated in 21 patients with schizophrenia and 20 normal matched controls. Pearson correlation analysis was performed to assess possible correlations between the parameters measured and age, post-mortem interval, neuroleptic treatment and duration of the disease. ANCOVA tests were used for group comparisons.

Results: Qualitative study showed swelling, vacuolation, pauciety of ribosomes and mitochondria and accumulation of lipofuscin granules in oligodendrocytes in schizophrenia as compared to controls. Morphometry detected lowered Vv and N of mitochondria and higher Vv and N of lipofuscin granules and vacuoles in oligodendrocytes in the schizophrenic group as compared to the control group (all p<0.01).

Discussion: Altered metabolism of oligodendrocytes, previously reported reduced number of oligodendrocytes, disrupted myelin/axon integrity, damage and progressive degeneration of myelin sheaths in prefrontal WM in schizophrenia may lead to disturbances in myelination, deficiency of nerve impulses propagation and contribute to network dysfunctions in schizophrenia. Oligodendrocyte and myelin abnormalities may be a target to prevent or restore WM abnormalities and dysfunction of neuronal connectivity in schizophrenia.

25.2 UNDERSTANDING WHITE MATTER PATHOLOGY IN SCHIZOPHRENIA USING DIFFUSION TENSOR IMAGING AND MAGNETIC RESONANCE SPECTROSCOPY

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Background: Diffusion tensor imaging (DTI) studies in schizophrenia consistently show global reductions in fractional anisotropy (FA), a putative marker of white matter integrity. Because magnetic resonance spectroscopy (MRS) studies permit for the non-invasive measurements of neurometabolites, such as N-acetylaspartate (NAA), a marker of neuronal integrity, and glutamate, which can be neurotoxic when over-released, this technique provides further understanding of the relationship between white matter microstructure and neuronal function.

Methods: Twenty-nine schizophrenia patients and twenty controls participated in this 3T imaging study where we used DTI and tract-based spatial statistics (TBSS) to assess white matter integrity of the cingulum bundle and MRS to quantify NAA and glutamate in the anterior cingulate cortex (ACC) and hippocampus, i.e. in cortico-limbic regions connected by the cingulum bundle.

Results: We found FA reductions with overlapping radial diffusivity (RD) elevations in patients in multiple tracts, suggesting white matter abnormalities in schizophrenia are driven by loss of myelin integrity. In controls, but not in patients, high hippocampal NAA levels were significantly associated with low RD in the hippocampal part of the cingulum, and low ACC glutamate levels were significantly associated with high FA in the hippocampus part of the cingulum.

Discussion: In conclusion, we demonstrate the potential utility of a multimodal neuroimaging approach to help further our understanding of the relationship between white matter microstructure and neurochemistry in distinct cortical regions connected by white matter tracts.

25.3 OLIGODENDROCYTES MEDIATE ENERGY METABOLISM ALTERATIONS IN SCHIZOPHRENIA: A PROTEOMIC STUDY

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Background: While comparing the proteomes and subproteomes of 8 post-mortem brain regions and cerebrospinal fluid from schizophrenia patients to controls, we consistently observed alterations in energy metabolism, cell growth and maintenance, synaptic function, and myelination processes. Considering the nature of these analyses, it was not possible to reveal which particular cell types display such alterations. This is essential information given increasing evidence of glia cells as pivotal players in schizophrenia. With this in mind, we analyzed the proteomes and phosphoproteomes of cultured astrocytes, oligodendrocytes and neurons treated with MK-801, a NMDA-receptor antagonist which impairs glutamatergic transmission as postulated in schizophrenia. We also analyzed biochemical pathways modulated by typical and atypical antipsychotics in human oligodendrocytes. Results led us to employ induced pluripotent stem cell-derived cerebral organoids to deepen our understanding of the data. The central aim of this study is to depict which cell type(s) present proteome changes similarly to those we found in our earlier analysis of human brain tissue as well as identify key pathways for an effective antipsychotic response.

Methods: Cell line cultures (astrocytes, oligodendrocytes and neurons) were treated with MK-801 and oligodendrocytes were also treated with a range of typical and atypical antipsychotics. In addition, human embryonic stem cells reprogrammed from schizophrenia patients and controls fibroblasts were cultured in mTeSR1 media on Matrigel coated surface and then differentiated into cerebral organoids. All pre-clinical models here employed...
were submitted to state-of-the-art large-scale proteomic analyses. In silico systems biology was employed to identify key pathways in the studied processes.

**Results:** MK-801-treated astrocytes, and especially MK-801-treated oligodendrocytes displayed several proteins differentially expressed which overlapped with previous findings of schizophrenia human brains. On the other hand, MK801-treated neurons displayed very few differences in their proteome, an overlap with previous findings in human brain tissue below 10%. More interestingly, the dysregulation of glycolytic enzymes in MK801-treated oligodendrocytes are very similar to our observations in schizophrenic brain tissue, corroborating with recent findings about of the importance of oligodendrocytes in the energy status of the brain. In oligodendrocytes, antipsychotics displayed differences in translational machinery and eIF2 signaling. Findings on cerebral organoids also showed overlaps with previous postmortem data, mainly on synaptic proteins and specially energy metabolism-associated pathways.

**Discussion:** These findings hold potential for the investigation of developmental and evolutionary features of schizophrenia brains and provides targets to be drug-screened as well as leads to the schizophrenia pathobiology.

25.4 PROMOTING MYELIN REPAIR RESCUES MICE FROM SCHIZOPHRENIA-LIKE BEHAVIOR INDUCED BY SOCIAL ISOLATION

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**Background:** Although pathological and genetic evidence suggest that oligodendrocyte (OL) or myelin deficits are associated with schizophrenia, the contribution of OL/myelin deficits to its etiology has not been clearly dissected, because OL/myelin abnormalities may be a concomitant phenomenon during the pathogenesis of schizophrenia.

**Methods:** Using olig2 ablation specifically in OLs (olig2 CKO) mice, we detected myelin development status and animal behaviors under normal condition or subjected to social isolation. We also examined the therapeutic effect of FDA-approved compounds, like quetiapine (an APD) or clemastine (a histamine antagonist) on animal behaviors.

**Results:** Our results demonstrated that deleting of olig2 led to impaired development of OLs and myelin deficit from postnatal day14 (P14) to P56, preferentially in cerebral cortex, and these young adult Olig2 KO mice showed anxiety-like behavior, motor skill learning deficit and cognitive deficit. Moreover, Olig2 CKO mice exhibited earlier social avoidance behavior than the WT littermates under prolonged social isolation, indicating that myelin deficit may enhance risk of schizophrenia upon environmental stress attacking. Interestingly, enhancing oligodendrocyte generation and myelin repair by quetiapine or clemastine successfully reversed the above phenotype.

**Discussion:** Taking together, promoting myelin repair may present a new therapeutic strategy against schizophrenia.

26. NOVEL APPROACHES TO PSYCHOSIS RISK: MOVEMENT, STRESS MODULATION, REWARD AND LANGUAGE

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**Overall Abstract:** Research on psychosis risk now encompasses novel and innovative approaches for understanding not only positive symptoms, but also impairment in sensorimotor function, stress regulation, reward learning, and language. These include the use of machine learning and cluster analysis with resting state functional connectivity analyses, in vivo measures of dopamine function in response to stress, computational modeling, and automated natural language processing analyses in collaboration with IBM.

First, Vijay Mittal will describe subtypes of clinical risk, identifying a group with aggregated measures of sensorimotor dysfunction, developmental markers, negative symptoms and cognitive deficits, who have a discrete pattern of corticostriatal connectivity.

Second, Romina Mizrahi will present her results from a study of dopamine response to stress in prefrontal cortex, using positron emission tomography, and correlations with cortisol release, across stages of illness, including schizophrenia and clinical risk, with healthy volunteers for comparison.

Third, James Waltz will present data on the computational processes that may underlie both positive and negative symptoms, in respect to dopamine-based signals of salience. These include aberrant or erratic salience signaling, as well as a decreased ability to identify relevant salient stimuli, which could impair reward learning and motivation. His cohort includes individuals with psychosis, and those at clinical risk for it, as well as non-psychosis patient controls.

Fourth, Cheryl Corcoran will describe the use of automated natural language processing (NLP), with machine learning (ML) to identify semantic and syntactic features that predict psychosis onset. She will show data on cross-validation of the classifier in a second risk cohort, and its correlation with demographics and manual linguistic features. Overall, there is an apparent norm of semantic coherence and syntactic complexity from which individuals with psychosis deviate, even prior to its onset.

Finally, the discussant will review these data in the context of his experience and ongoing leadership in the field of psychosis risk research, leading audience discussion, and outlining a roadmap for future research in the field.

26.1 MOTOR SUBTYPES AND PREDICTION OF COURSE IN PSYCHOSIS RISK YOUTH

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**Background:** Prominent etiological conceptions of psychosis implicate abnormal cortico-striatal circuits. Dysfunction in these critical systems, responsible for filtering information and modulating higher-order function, may account for heterogeneous presentations of symptoms and characteristics of psychosis. Collectively, a body of work from our group and from other teams indicates that evaluating select motor behaviors and abnormalities, which directly reflect function of these circuits, may be a useful method for understanding and predicting the neural underpinnings of psychosis. In the context of the psychosis risk period, partitioning clinical high-risk (CHR) youth based on objective behavior may help guide early detection and intervention efforts, and provide a novel perspective on different etiological pathways or patient subtypes.

**Methods:** Using an unsupervised machine learning approach, 69 CHR young adults were included in a K-means cluster analysis based on their performance on instrumental measures of psychomotor slowing, dyskinesia, and neurological soft signs (NSS)—distinct motor domains affected across the psychosis spectrum. We also recruited a group of 70 matched healthy controls (HC) for comparison. All participants were also assessed with a resting-state functional connectivity analysis (rfMRI). The resulting CHR group clusters and HCs were then compared on positive and negative symptoms, multiple cognitive domains, and cortical-striatal seed based resting state analysis.

**Results:** Results of a 3-cluster solution suggest that there are subtypes of CHR individuals who show psychomotor slowing, average motor performance, and impairment on measures of dyskinesia as well as NSS domains for motor coordination, sequencing and sensory integration. The cluster of individuals showing dyskinesia and abnormal NSS also have more severe negative symptoms and impairment on a number of cognitive domains. Furthermore, the clusters of CHR individuals who show psychomotor...