Background: The vast majority of studies of neuropsychological (NP) functioning in Clinical High Risk (CHR) cohorts have examined group averages, possibly concealing a range of subgroups ranging from very impaired to high functioning. Our objective was to assess NP profiles and to explore associations with conversion to psychosis, functional and diagnostic outcome.

Methods: Data were acquired from 324 participants (mean age 18.4) in the first phase of the North American Prodrome Longitudinal Study (NAPLS-1), a multi-site consortium following individuals for up to 2½ years. We applied Ward's method for hierarchical clustering data to 8 baseline neuropsychological measures, in 166 CHR individuals, 49 non-CHR youth with a family history of psychosis, and 109 healthy controls. We tested whether cluster membership was associated with conversion to psychosis, social and role functioning, and follow-up diagnosis. Analyses were repeated after data were clustered based on independently developed clinical decision rules.

Results: Four neurocognitive clusters were identified: Significantly Impaired (n=33); Mildly Impaired (n=82); Normal (n=145) and High (n=64). The Significantly Impaired subgroup demonstrated the largest deviations on processing speed and memory tasks and had a conversion rate of 58%, a 40% chance of developing a schizophrenia spectrum diagnosis (compared to 24.4% in the Mildly Impaired, and 10.3% in the other two groups combined), and significantly worse functioning at baseline and 12-months. Data clustered using clinical decision rules yielded similar results, pointing to high convergent validity.

Discussion: Despite extensive neuropsychological investigations within CHR cohorts, this is one of the first studies to investigate NP clustering profiles as a contributor to heterogeneity in outcome. Our results indicate that the four NP profiles vary substantially in their outcome, underscoring the relevance of cognitive functioning in the prediction of illness progression. Our findings tentatively suggest that individualized cognitive profiling should be explored in clinical settings.

24.4 COGNITION AND COMMUNICATION AS DETERMINANTS OF ADAPTIVE DEFICITS IN LATE LIFE SCHIZOPHRENIA

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Background: Older adults with schizophrenia experience poor community integration and social functioning. These individuals are at elevated risk for functional decline and early institutionalization in long-term care facilities. Deficits in thought, language, and communication are core features of schizophrenia and may worsen with age; however, little research focuses on the functional sequelae of these impairments among older adults with schizophrenia.

Methods: The present study examined the relationships among age, TLC deficits, and functional outcomes in a sample of community-dwelling middle-aged and older adults with schizophrenia (N=245; ages 40–85). Participants completed assessments of symptoms, neurocognition, TLC deficits, and functional outcomes. Two different categories of TLC deficits were examined: verbal underproductivity (i.e., alogia) and disconnected speech.

Results: Regression analyses found that disconnected speech predicted impaired occupational functioning, while verbal underproductivity predicted capacity to communicate skillfully in semi-structured social situations, as well as community functioning across interpersonal, occupational, and everyday living domains. Exploratory mediation analyses found that cognitive impairments were mediated by disconnected speed but not under productivity on certain functional outcomes.

Discussion: Targeted training to improve TLC deficits, especially verbal underproductivity, among older adults with schizophrenia could have downstream effects on community functioning, improving outcomes for a vulnerable group. It is likely that cognitive training interventions would also facilitate these interventions.

25. OLIGODENDROCYTE-BASED IMPAIRMENT OF BRAIN CONNECTIVITY AS TARGET FOR NEW TREATMENT STRATEGIES IN SCHIZOPHRENIA

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Abstracts for the Sixth Biennial SIRS Conference
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 neurometabolites, 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 (Brodmann’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, paucity 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 dysfunction 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 TENOR 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 hippocampal 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 to 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