of glia in normal brain functions and brain disorder pathology. A growing body of evidence shows that diversified populations of astrocytes, microglia, oligodendrocyte precursors and mature oligodendrocytes play a critical role in the regulation of synaptic functions, blood-brain barrier, immune response regulation, myelination and axonal conduction, and in the synthesis of the extracellular matrix, a key regulator of neural plasticity. Based on this evidence, exciting new findings are beginning to emerge, shedding light on glia abnormalities in schizophrenia and their impact on these functions. This symposium aims to discuss and integrate the current state of knowledge on direct evidence for glia abnormalities in schizophrenia and their underlying mechanisms.

Dr. Juliana Nascimento will present novel findings on the effects of NMDAr antagonists and antipsychotics influence glial cell line and 3D cultures as neurosphere and cerebral organoids. Results from these studies point to the central role of glycolysis, EGF2 signaling and translational machinery in oligodendrocytes and astrocytes. Dr. Paul Klauser will report on elegant investigations on the implication of developmental redox imbalance inducing oxidative stress leading to impairments of oligodendrocytes, myelin formation and eventually to the disruption of white fibers integrity and conductivity, especially in brain regions where the metabolic demand is high. In patients, alterations of white matter were found to be inversely correlated with blood levels of GSH precursor cysteine and could be prevented by the early administration of the antioxidant N-acetyl cysteine. Dr. Sabina Berretta will discuss recent findings on novel modalities of interaction between glial cells, extracellular matrix and neurons, postulated to affect synaptic structural plasticity and axonal conductance. A growing body of evidence from her group shows disruption of such interactions in schizophrenia, potentially contributing to synaptic pathology and impacting neural connectivity. Dr. Dost Ongur will build on previous work showing abnormal diffusion of neuron-specific metabolite NAA in frontal white matter in patients with chronic schizophrenia in the absence of abnormalities in the diffusion of non-specific metabolites Cr and Cho. State-of-the-art recent studies on first episode psychosis patients and matched healthy controls show that NAA diffusion is normal in first episode patients but Cr and Cho diffusion is abnormal, suggesting that white matter abnormalities in non-neuronal elements in early phases of schizophrenia which are followed by neuronal damage in chronic disease.

10.1 STEM CELL- DERIVED IN VITRO MODELS FOR DEPICTING THE ROLE OF GLIA IN SCHIZOPHRENIA FROM A PROTEOMIC PERSPECTIVE

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Background: A number of basic and translational studies have clearly indicated the vital role of glia in brain function and the pathophysiological mechanisms of neuropsychiatric disorders, including schizophrenia. The difficulty on studying the molecular basis of glial cells in vivo, led to the development of animal models, which are considered the gold standard to this type of understanding. However, the inherent difficulties in establishing these models for psychiatric disorders and the simplicity of in vitro models, especially given the recent advances in stem cell-based technologies have driven the development of sophisticated in vitro models, which may be attractive for studying the molecular basis of schizophrenia.

Methods: Here, we report our investigations in terms of proteome while establishing protocols to generate human pluripotent stem cells-derived cerebral organoids as well as human cerebral organoids-derived astrocytes and oligodendrocytes.

Results: The proteome of cerebral organoids show major proteins from neuronal cells as expected, but also several glial markers, supporting the notion that glial cells may be obtained out of these organoids. Besides, the proteome of three schizophrenia and three control organoids have been investigated. Proteins found are broadly distributed on functional activities such as cell growth and maintenance, energy metabolism and cell communication and signaling, and are correlated to cortical brain tissue. We also succeeded in isolating astrocytes out of cerebral organoids. These cells are under investigation in terms of molecular differences associated to schizophrenia.

Discussion: The generation of brain organoids and isolation of astrocytes and eventually oligodendrocytes hold great potential for the investigation of the role of glia in schizophrenia, providing an useful approach to drug screening and disease modeling, as our results showed in schizophrenia- and control-derived cells. Additionally, proteomics adds knowledge about information and connections being formed into these models.

10.2 REDOX DYSREGULATION, OLIGODENDROCYTES AND WHITE MATTER ALTERATIONS IN SCHIZOPHRENIA

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Background: Widespread (Klauser et al., 2016) and progressive (Cropley et al., 2017) cerebral anomalies of white matter diffusion properties (i.e. fractional anisotropy, FA) have been observed in the Australian Schizophrenia Research Bank (ASRB), one of the largest samples of patients with schizophrenia. From a topological perspective, widespread alterations of white matter tend to concentrate into hub regions that interconnect brain areas over long-distances in a so-called “rich-club” (van den Heuvel et al., 2013; Klauser et al., 2016) in which the metabolic demand is high and thus are most likely to suffer from oxidative stress. Evidence from human and animal models suggests that redox dysregulation leading to oxidative stress during neurodevelopment is implicated in schizophrenia pathogenesis (Steullet et al., 2017). At the cellular level, the triad composed of NMDAR hypofunction, neuroinflammation and dopamine dysregulation interacts with redox imbalance and leads to oxidative stress, affecting oligodendrocytes precursor cells (OPC) and parvalbumine interneurons (Steullet et al., 2016). However, the links between redox imbalance, oligodendrocytes and gross alterations of white matter integrity are largely unexplored. Under oxidative stress induced in vitro by impairing the synthesis of glutathione (GSH), the key player in antioxidant defense, OPC showed a decreased proliferation mediated by an upregulation of Fyn kinase activity. In the prefrontal cortex of a mouse model with impaired GSH synthesis, mature oligodendrocyte numbers as well as myelin markers were decreased at peripuberty (Monin et al., 2014). FA was also reduced in fornix-dimbria and anterior commissure, a change accompanied by a reduced conduction velocity (Corcoba et al., 2015).

Methods: 49 patients with psychosis and 64 healthy controls were scanned with the same 3-Tesla scanner. The diffusion spectrum imaging (DSI) sequence included 128 diffusion-weighted images with a maximum b-value of 8000 s mm−2. White matter diffusion properties were estimated using generalized fractional anisotropy (gFA). Total blood cysteine (Cys, protein-bound form, free reduced and free oxidized form), the rate-limiting precursor of GSH, was measured by high performance liquid chromatography from plasma samples collected at the same time-point as MRI brain scans.

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Whole brain voxel-based analyses were performed using cluster-based non-parametric permutation testing on gFA maps. Cerebral levels of GSH were assessed by localized 1H-MRS measurements from a volume of interest in medial prefrontal cortex.

**Results:** As previously described in ASRB, we observed widespread abnormalities of white matter in patients. Interestingly, the degree of white matter alterations (i.e. decreased gFA) patients could be predicted by the levels of blood cysteine, a precursor of GSH, strongly suggesting the important role played by oxidative stress in the pathophysiological mechanism. Also, we found that white matter alterations could be reversed by 6 months of add-on treatment with the antioxidant and GSH precursor N-acetylcysteine (NAC). Most importantly, this improvement was positively correlated with an increase in prefrontal GSH levels.

**Discussion:** We propose that developmental redox imbalance inducing oxidative stress may lead to impairments of oligodendrocytes, myelin formation and eventually to the disruption of fibers integrity and conductivity, especially in brain regions having high metabolic demand. In patients, alterations of white matter are inversely correlated with blood levels of GSH precursor cysteine and could be prevented by the early administration of the antioxidant NAC.

**10.4 DIFFUSION WEIGHTED SPECTROSCOPY STUDIES OF CELL-TYPE SPECIFIC ABNORMALITIES IN SCHIZOPHRENIA**

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**Background:** In previous work we used diffusion tensor spectroscopy (DTS) to identify abnormal diffusion of the neuron-specific metabolite NAA in frontal white matter in patients with chronic schizophrenia in the absence of abnormalities in the diffusion of cell-type non-specific metabolites Cr and Cho.

**Methods:** DTS relies on the same principles as DTI, but the diffusion characteristics of metabolites are probed, instead of those of water. Since brain metabolites are concentrated in specific cellular and sub-cellular compartments, their diffusion reflects the local geometry of these compartments. We have implemented a DTS approach at a 4 Tesla Varian MRI scanner (described in Du et al 2013).

**Results:** We have now collected similar data from first episode psychosis patients and matched healthy controls. We find that NAA diffusion is normal in the frontal PFC in first episode patients, but Cr and Cho diffusion is abnormal.

**Discussion:** Taken together, our studies suggest white matter abnormalities in non-neuronal elements in early phases of schizophrenia which are followed by neuronal damage in chronic disease.

**11. AEROBIC EXERCISE TRAINING FOR INDIVIDUALS WITH SCHIZOPHRENIA: THE BROAD BENEFITS ACROSS PHYSICAL HEALTH, COGNITION, AND EVERYDAY FUNCTIONING AND PROMISING MECHANISMS OF ACTION**

Keith Nuechterlein
University of California, Los Angeles

**Overall Abstract:** Recently aerobic exercise training has begun to be systematically examined in randomized controlled trials (RCTs) in schizophrenia. This symposium will report and discuss the results of RCTs that examined the impact of aerobic exercise on physical health, cognition, and everyday functioning across first-episode and established illness phases of schizophrenia. In addition, data on neurotrophic and brain structural changes will be examined as promising mechanisms of action.

Dr. Amal Abdel-Baki of the University of Montreal has focused on the physical health benefits of interval training in her RCT with first episode and multi-episode schizophrenia. This symposium will report and discuss the results of RCTs that examined the impact of aerobic exercise on physical health, cognition, and everyday functioning across first-episode and established illness phases of schizophrenia. In addition, data on neurotrophic and brain structural changes will be examined as promising mechanisms of action.