10. THE MOLECULAR MECHANISMS OF SCHIZOPHRENIA FROM GLIAL CELLS PERSPECTIVE

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9.3 PSYCHOsis BIOTYPES VERSUS CLINICAL SYNDROMES THROUGH THE PRISM OF INTRINSIC NEURAL ACTIVITY

Brett Clementz*1, Godfrey Pearlson2, Carol Tamminga3, John Sweeney1, Matcheri Keshavan4
1University of Georgia; 2Olin Neuropsychiatry Research Center; 3University of Texas Southwestern Medical Center; 4Beth Israel Deaconess Medical Center & Harvard Medical School

Background: Deviation in level of intrinsic neural activity (ongoing brain signals recorded with EEG/MEG) is observed in psychosis. Neurophysiological models have proposed this physiological indicator as a genetically mediated core deviation in psychosis. Translational models of intrinsic activity deviations promise to identifying multiple distinct physiological mechanisms for psychosis manifestation. Intrinsic activity deviations may masquerade as higher levels of neural response in sensory cortices, but ultimately may lead to poor signal-to-noise ratios, particularly when psychosis cases are required to identify stimulus salience.

Why do we not hear more about intrinsic activity as a core biomarker for any psychosis variation? An explanation is provided by the current project. The Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) published a means for categorizing psychoses by neurophysiological homology via use of multiple biomarkers (psychosis Biotypes) rather than by clinical features. B-SNIP demonstrated the superiority of Biotypes versus DSM diagnoses for capturing neurobiological similarity through multiple external validating measures (social functioning, measures of brain volume from structural magnetic resonance images, clinical diagnoses and biomarker features among first-degree relatives). Independent analyses since the initial publication have provided additional support for the usefulness of psychosis Biotypes.

Methods: For this project, we analyzed ongoing neural activity from 64 EEG sensors during 150 intervals of 10 sec duration from over 1450 B-SNIP subjects. These data (never before published) were from the inter-trial interval (ITI) of an auditory paired-stimuli task used in Biotypes construction (these ITI data themselves were not used). Although the subjects were engaged in a task (counting the number of stimulus pairs), the data used here were not part of the task itself. Data were evaluated for single trial power (estimate of neural response strength on individual trials) as a function of frequency of neural oscillations (from 2–50 Hz) over the whole head. Data were then averaged over single trials to yield an estimate of the overall strength of nonspecific (unrelated to sensory processing) neural activity.

Results: When evaluated by DSM diagnoses (schizophrenia, schizoaffective disorder, bipolar disorder), the 95% confidence intervals for all groups overlapped the healthy group means across all frequencies. When considered by psychosis Biotypes, differences were obvious and statistically significant. In the past decade, rapid advances in the field of neuroscience resulted in a dramatic paradigm shift in the way we understand the role...
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. Building 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 glial 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 lines and 3D cultures as neurospheres and cerebral organoids. Results from these studies point to the central role of glycolysis, EIF2 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 fronto-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

Juliana Nascimento1,2, Daniel Martins-De-Souza1, Veronica M. Saia-Cereda1, Flavia C. A. Gomes1, Stevens K. Rehen3

1University of Campinas; 2Federal University of Rio de Janeiro; 3Instituto D’Or de Pesquisa e Ensino (IDOR) and Federal University of Rio de Janeiro

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

Paul Klauser1, Philipp S. Baumann1, Margot Fournier2, Lijing Xin1, Alessandra Griffia1, Martine Cleusix1, Raoul Jenni1, Michel Cuenod2, Patric Hagmann4, Philippe Conus1, Kim Q. Do4

1Lausanne University Hospital; 2Center for Psychiatric Neuroscience, Lausanne University Hospital; 3Animal Imaging and Technology Core (AIT), Center for Biomedical Imaging (CIBM), École Polytechnique Fédérale de Lausanne; 4Signal Processing Laboratory, École Polytechnique Fédérale de Lausanne, Lausanne University Hospital

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 (Cocoboa 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 ratio-limiting precursor of GSH, was measured by high performance liquid chromatography from plasma samples collected at the same time-point as MRI brain scans.