10.3 GLIA-EXTRACELLULAR MATRIX INTERACTIONS IN THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA AND BIPOLAR DISORDER

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-acetyl-cysteine (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.

10.3 GLIA-EXTRACELLULAR MATRIX INTERACTIONS IN THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Growing evidence from our group and others indicates that key neural functions, including regulation of synaptic plasticity and axonal guidance and connectivity, arise from interactions between glial cells, neurons, and the extracellular matrix. Several distinct populations of glial cells critically contribute to the composition of main components of the extracellular matrix (ECM), synthesizing them and secreting them into the extracellular space, where they become incorporated in organized ECM structures. The brain ECM, and chondroitin sulfate proteoglycans (CSPGs) in particular, play a key role in brain development and adult life, in turn regulating glial functions as well as synaptic plasticity and neural connectivity. We have previously shown that glial cells expressing CSPGs are altered in the amygdala and entorhinal cortex of people with schizophrenia (SZ) and bipolar disorder (BD). These changes are accompanied by marked decreases of perineuronal nets (PNNs), organized ECM structures unsheathing distinct neuronal populations. Recent and ongoing studies are focused on novel CSPG-enriched ECM structures, related to synaptic complexes and myelinated axons, their relationship to glial populations and their involvement in the pathophysiology of SZ and BD.
Methods: Postmortem tissue samples from the amygdala, entorhinal cortex and thalamus from a well characterized cohort of healthy control, SZ and BD subjects were included in these studies. Multiplex immunofluorescence combined with quantitative microscopy was used to quantify glial cells and CSPGs, while electron microscopy on human and mouse tissue were used to investigate ultrastructural morphology. Step-wise ANOVA analyses included several potential confounds such as exposure to pharmacological agents and substance abuse.
Results: Our results show that at least two novel ECM structures are present in the human brain. The first, enriched in CSPGs bearing chondroitin sulfation in position 6 (CS-6), and named here 'CS-6 clusters' was found to be markedly decreased in the amygdala of people with SZ and BD. Electron microscopy studies show that CS-6 clusters are composed of astrocytes synthesizing and secreting CS-6 CSPGs in the vicinity of adjacent groups of dendrites, where it is incorporated into postsynaptic densities of dendritic spines. The second CSPG-enriched ECM structure, i.e. axonal coats, has been observed in the human thalamus to envelope distinct populations of axons, interweaving with myelin sheets. Its main CSPG components appear to be synthesized and secreted by oligodendrocytes precursor cells located in the vicinity of axon bundles. Preliminary results show abnormalities affecting both oligodendrocyte precursors and axonal coats in SZ.
Discussion: In summary, our results show complex interactions between glial cells, neurons and ECM, potentially affecting synaptic functions and axonal conductance. Results in SZ and BD point to a profound disruption of these interactions in several brain regions.

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
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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 outpatients. She is demonstrating improved waist circumference, diastolic blood pressure, HDL cholesterol, and social functioning in first episode and multi-episode patients. Dr. David Kimhy of Icahn School of Medicine at Mount Sinai in New York has focused on the impact of aerobic exercise training on cardiovascular fitness, Brain-Derived Neurotrophic Factor (BDNF), cognition, and functional outcome in individuals with an established schizophrenic illness. He has demonstrated beneficial effects at each of these levels. Furthermore, relationships between fitness improvements and BDNF increases and the cognitive and functional gains suggest potential mechanisms of action. Dr. Berend Malchow of Ludwig Maximilian University of