Whole brain voxel-based analyses were performed using cluster-based non-parametric permutation testing on gFAR 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 gFAR) 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 patients 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 oligodendrocyte 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
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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 Malecha of Ludwig Maximilian University of
Munich has examined the impact of adding cognitive training to aerobic exercise in multi-episode schizophrenia patients. This combination led to increased verbal memory and improved global functioning. Increase in left temporal grey matter volume is a promising brain mechanism of action. Dr. Keith Nuechterlein from UCLA will present results from a recently completed RCT of first-episode schizophrenia patients in which aerobic exercise training was added to computerized cognitive training to determine the extent to which it could enhance the impact of cognitive training. He will show that this combination significantly enhances cognition and work/school functioning gains beyond the effect of cognitive training alone and leads to increases in prefrontal cortical thickness and functional connectivity. Furthermore, he will examine early BDNF increases in response to treatment as a predictor of later cognitive and functional improvements. Dr. Peter Falkai will lead the discussion of the promise of aerobic exercise as an intervention to improve physical health, cognition, and functional outcome in schizophrenia and consider the potential mechanisms of action.

11.1 EFFECT OF INTERVAL TRAINING ON METABOLIC RISK FACTORS IN OVERWEIGHT INDIVIDUALS WITH PSYCHOSIS: A RANDOMIZED CONTROLLED TRIAL

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Background: Among adults with psychotic disorders, negative symptoms and unhealthy lifestyle habits contribute to a high prevalence of metabolic syndrome and obesity. Lifestyle interventions, mainly physical activity (PA) has emerged as an essential component. Furthermore, interval training (IT) was found to be efficacious in other populations but poorly studied among people with psychosis.

The objective was to determine the effects of a 6-month IT program on metabolic, anthropometric, and psychiatric/functional outcomes.

Methods: Randomized controlled trial comparing the effects of a bi-weekly 30 minutes supervised IT program to a waiting list of overweight individuals with psychosis. Body composition and metabolic risk factors (blood pressure, insulin resistance, lipid profile) were measured at baseline and every 3 months. The groups were compared on an intent to treat basis with repeated-measures mixed linear models with the restricted maximum of likelihood method of estimation.

Results: Sixty-seven individuals (28 control: waiting list; 39 IT intervention) with psychosis (60.6% men, mean age: 31.0 ± 7.2 years old; BMI: 32.0 ± 6.1 kg/m²; waist circumference: 107.7 ± 13.3 cm) were included in the study, and 67.2% completed the study. Attendance for the IT sessions was 61.8% and the dropout rate was 32%. IT was associated with significant improvements on waist circumference (-2.72 cm, SE = 1.34; p = 0.04), negative symptoms (-2.93, SE = 1.34; p = 0.03), social (SOFAS) (+5.23, SE = 2.39; p = 0.03) and global functioning (+7.34, SE = 2.05; p < 0.001). The effects of exercise in the first-episode psychosis (FEP) sub-group were similar to those of the entire cohort.

Discussion: These promising results suggest that IT may be used as a treatment strategy for the management of metabolic complications and possibly improve social functioning in obese individuals with psychotic disorders. Further studies are needed to understand if IT could prevent weight gain and metabolic complications if used before these comorbidities emerge and to understand factors associated with the persistence of exercising.

11.2 THE IMPACT OF AEROBIC EXERCISE ON COGNITIVE FUNCTIONING AND BIOMARKERS OF COGNITIVE CHANGE IN INDIVIDUALS WITH SCHIZOPHRENIA

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Background: Individuals with schizophrenia (SZ) display substantial cognitive deficits across multiple domains. These deficits have been identified as major determinants of poor functioning and disability, representing a serious public health concern and an important target for interventions. At present, available treatments offer only minimal to limited benefits to ameliorate these deficits. Thus, there remains an urgent need to identify novel treatments for cognitive deficits in people with SZ. Emerging evidence from studies of animals, clinical and non-clinical populations suggest that Aerobic Exercise (AE) is efficacious in improving cognition via up-regulation of Brain-Derived Neurotrophic Factor (BDNF). Yet, the impact of AE on cognition and daily-functioning, and the role of BDNF, have not been investigated in schizophrenia. Additionally, limited information is available on the putative link between inflammation markers to cognitive functioning.

Methods: Employing a single-blind RCT design, 33 individuals with schizophrenia were randomized to receive “treatment as usual” (n=17; TAU) or attend a 12-week, 3 times-per-week, 60-minutes AE program (n=16) utilizing active-play video-games (Xbox-360 Kinect) and traditional AE equipment.

Results: At baseline, cognitive functioning was associated with serum BDNF (r=.51, p=.01), along with TNF-alpha (r=.38, p=.03), IL-12 (r=.36, p=.04) and IL-6 (r=.33, p=.06). Twenty-six participants completed the study (79%). Following the intervention, the AE participants improved their cognitive functioning (MCCB) by 15.1% (vs. -2.0% in the TAU group; p=.03). Hierarchical multiple-regression analyses indicated changes in AF and serum BDNF predicted 25.4% and 14.6% of the cognitive improvement, respectively. Additionally, changes in aerobic fitness (VO2peak ml/kg/min) correlated with informant-reported improvements in work-related daily-functioning skills (SLOF; r=.51, p=.01). Fidelity with target training intensity, was correlated with cognitive improvement (r=.70, p=.02).

Discussion: The results indicate AE is effective in enhancing cognitive and daily functioning skills in people with schizophrenia and provide support for the impact of AE-related BDNF up-regulation on cognition. Additional studies are needed to establish the link between inflammation markers and cognitive functioning and the potential impact of AE on this putative pathway. Overall, low aerobic fitness represents a modifiable risk-factor for cognitive dysfunction in schizophrenia for which AE training offer a relatively safe, non-stigmatizing, and side-effect-free intervention.

11.3 CLINICAL AND NEUROBIOLOGICAL EFFECTS OF A CONTINUOUS AEROBIC ENDURANCE TRAINING IN MULTI-EPSISDE SCHIZOPHRENIA PATIENTS

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