Background: Structural and functional brain alterations as well as cognitive deficits are well-documented findings in schizophrenia patients. Cognitive impairments affect the long-term outcome of schizophrenia and are the main contributors to disability. Aerobic endurance training has been shown to have effects on brain plasticity, gray and white matter volume as well as functional connectivity measures and on cognitive functioning in animal models and healthy humans. However, effects of physical exercise in combination in combination with cognitive remediation (CR) are unknown in schizophrenia.

Methods: 21 chronic schizophrenia patients and 21 age- and gender-matched healthy controls underwent 3 months of aerobic exercise (endurance training, 30 min, 3 times per week). 21 additionally recruited schizophrenia patients played table soccer (known as “foosball” in the USA) over the same period. After 6 weeks of endurance training or table soccer, all participants commenced standardized cognitive training with a computer-assisted training program. Clinical symptoms, thorough neuropsychological testing and multimodal neuroimaging with 3D-volumetric T1-weighted sequences, DTI and magnetic resonance spectroscopy (MRS) were performed on a 3T MR scanner at baseline and after the 3-month intervention and 3 additional training-free months. DNA from all subjects was genotyped with the Infinium PsychArray Chip (Illumina, San Diego, CA, USA). Polygenic risk scores were calculated and associated with hippocampal subfield volume change.

Results: In summary, a 3-month endurance training program combined with CR therapy for the last 6 weeks of the intervention period was feasible (Keller-Varady et al. 2016) and had positive effects on everyday functioning in multi-episode schizophrenia patients. Deficits improved from medium to mild as assessed with the GAF. Negative symptoms, short- and long-term verbal memory and cognitive flexibility also improved with endurance and cognitive training (Malchow et al. 2015). We could demonstrate grey matter volume increase in the left temporal lobe in schizophrenia patients undergoing endurance training. A non-endurance and coordinative training stimulus like playing table soccer led to a clearly distinctive pattern of grey matter alterations in schizophrenia patients (Malchow et al. 2016). There were no effects of the intervention on structural and functional brain networks in schizophrenia patients as well as MRS measures (in preparation). No effects of PRSs were found on total hippocampal volume change. Subfield analyses showed that the volume changes between baseline and 3 months in the left CA4/DG were significantly influenced by PRSs in schizophrenia patients performing aerobic exercise. A larger genetic risk burden was associated with a less pronounced volume increase or a decrease in volume over the course of the exercise intervention. Results of exploratory enrichment analyses reinforced the notion of genetic risk factors modulating biological processes tightly related to synaptic ion channel activity, calcium signaling, glutamate signaling and regulation of cell morphogenesis (Papiol et al. 2017).

Discussion: Exercise interventions are feasible and effective interventions for people with schizophrenia and might also help to disentangle the underlying brain pathology of the disorder.

11.4 AEROBIC EXERCISE ENHANCES COGNITIVE TRAINING EFFECTS IN FIRST EPISODE SCHIZOPHRENIA: COGNITIVE AND FUNCTIONAL GAINS AND PROMISING BIOLOGICAL MECHANISMS OF ACTION

Keith Nuechterlein*,1, Sarah McEwen1, Joseph Ventura1, Kenneth Subotnik1, Luana Turner1, Michael Boucher1, Laurie Casaus1, Jacqueline Hayata1

1University of California, Los Angeles

Background: The search for treatments to remediate cognitive deficits and their functional outcome consequences remains a critical frontier in schizophrenia. Cognitive training and aerobic exercise both show promising moderate impact on cognition and everyday functioning. Aerobic exercise is hypothesized to increase brain-derived neurotrophic factor (BDNF) and thereby stimulate neurogenesis and synaptic plasticity, leading to increased learning capacity. Systematic cognitive training should take advantage of increased learning capacity and be more effective when combined with aerobic exercise.

Methods: In a recently completed randomized controlled trial, we examined the impact of a 6-month program of Cognitive Training & Exercise (CT&E) compared to Cognitive Training alone (CT) in 47 first-episode schizophrenia outpatients. All participants were provided the same Positive Science computerized cognitive training, four hours/week, using BrainHQ and SocialVille programs. The CT&E group also participated in total body circuit training exercises to enhance aerobic conditioning. The exercise intensity was in the 60–80% of aerobic capacity range, combining clinic and home-based exercise for a target of 150 minutes per week.

Results: Mixed model analyses demonstrate that the MATRICS Consensus Cognitive Battery Overall Composite improves significantly more by 3 months with CT&E than with CT alone (6.6 vs. 2.2 T-score points, p<.02). Work/school functioning improves substantially more with CT&E than with CT alone by 6 months (p=.001). BDNF is a promising mechanism of action, improving even after 2 weeks and predicting the amount of cognitive gain at 3 months. The magnitude of cognitive gain by 3 months predicts the amount of work/school functioning improvement at 6 months, suggesting a cascade of effects. Analyses by Dr. McEwen show differential increases in cortical thickness in the left dorsal lateral prefrontal gyrus (p=.02) and right superior frontal gyrus (p=.02) over 6 months and increased functional connectivity in the central executive network (p=.04) with CT&E compared to CT alone and correlations of these increases with cognitive and functional outcome gains.

Discussion: We conclude that aerobic exercise significantly enhances the impact of cognitive training on cognition, functional outcome, and frontal cortical thickness in first-episode schizophrenia and that BDNF is a promising mechanism of action for these effects.

12. SYNAPTIC DYSFUNCTION IN SCHIZOPHRENIA: EXPLORATION OF NOVEL HYPOTHESES AND PROMISING NEW LEADS

Laura Rowland

University of Maryland School of Medicine

Overall Abstract: Accumulating evidence suggests that bioenergetic function is impaired in the brain in schizophrenia. In normal brain, glucose is metabolized to lactate and pyruvate, which are monocarboxylate intermediates that serve as the primary energy source for neurons. Working memory and other cognitive domains are dependent on the shuttling of lactate from astrocytes to neurons. Defects in this complex pathway may underlie cognitive dysfunction in schizophrenia. The focus of this symposium is to present evidence of such defects, and to identify substrates that may be targeted for the development of new treatment strategies. Dr. Laura Rowland (University of Maryland, Baltimore, Maryland, USA) will present evidence of bioenergetic dysfunction in living subjects with schizophrenia. Increased levels of lactate (P < 0.05) were present in the ACC in schizophrenia (n = 27) compared to controls (n = 29). Higher lactate levels were associated with lower scores on the MATRICS Consensus Cognitive Battery. These data establish a direct link between cognition and bioenergetic function in vivo in schizophrenia. Dr. Robert McCullumsmith (University of Cincinnati, Cincinnati, Ohio, USA) will present evidence of alterations in the lactate shuttle and glycolytic enzymes in postmortem samples from schizophrenia (n = 20) and control subjects (n = 20). Cell-subtype specific changes (P < 0.05) in transcripts include increased levels of the lactate transporter MCT4, decreased levels of the glycolytic enzymes PKF1 and hexokinase, and decreased levels of the glucose transporters Glut1 and Glut3. These data suggest attenuated glycolysis in pyramidal neurons, with a shift towards pathways that boost protection from oxidative stress.

Abstracts for the Sixth Biennial SIRS Conference
The last two speakers will present data that address mechanisms related to these findings, using animal models with behavioral endophenotypes of schizophrenia. Dr. Eduard Bentea (Free University of Brussels (VUB), Brussels, Belgium) will present data from the xCT knockout mouse showing that disruption of system xc−, which supports oxidative stress buffering mechanisms, leads to synaptic dysfunction. Specifically, electron microscopy studies indicate depletion of both pre-and post-synaptic glutamate, while electrophysiological studies show diminished excitatory postsynaptic potentials. These findings directly connect oxidative balance and extracellular glutamate levels with development of “broken” synapses, highlighting a potential mechanism for perturbation of bioenergetic coupling between astrocytes and neurons. Dr. Amy Ramsey (University of Toronto, Toronto, Canada) will present evidence from an animal model of synaptic dysfunction, the GluN1 knockout mouse. These mice show a bioenergetic defect similar to schizophrenia, with decreased expression of glycolytic enzymes and glucose transporters. These translational findings indicate that genetic risk for schizophrenia may lead to an intermediate bioenergetic phenotype, where diminished supply of lactate and other energetic molecules to neurons could contribute to cognitive dysfunction. Taken together, the work presented by these speakers will provide a fresh look at the bioenergetic defects in schizophrenia, establishing that 1) metabolic perturbations in the brain are prominent and not just an effect antipsychotic treatment, 2) altered neuron-astrocyte coupling leads to synaptic dysfunction, and 3) genetic risk for “broken” synapses disrupts metabolic function.

12.1 CELL-SUBTYPE SPECIFIC BIOENERGETIC DEFECTS IN SCHIZOPHRENIA

Courtney Sullivan¹, Robert McCullumsmith*¹

¹University of Cincinnati

Background: Novel insights into the pathophysiology of schizophrenia are needed to move the field forward by providing the conceptual framework to facilitate development of new treatment strategies. It is well established that glutamatergic systems are disrupted in schizophrenia, which are intimately linked to metabolic function. While there are many promising new directions, accumulating evidence suggests that bioenergetic function is impaired in the brain in schizophrenia. There are multiple mechanisms in the brain to meet neuronal energy demands, including glycolysis, lactate uptake, and oxidative phosphorylation. In normal brain, neurons and astrocytes are coupled through the astrocyte-neuron lactate shuttle, where astrocytes metabolize glucose to lactate and pyruvate, primary energy substrates that are transported to neurons via monocarboxylate transporters (MCTs). Lactate generated by glycolysis in glial cells constitutively supports synaptic transmission even under conditions in which a sufficient supply of glucose and intracellular adenosine triphosphate (ATP) are present. Interestingly, working memory and other cognitive domains are dependent on the shuttling of lactate from astrocytes to neurons. This process highlights the bioenergetic coupling between astrocytes and neurons that develop as the brain matures, forming a critical biological process in the mature adult brain. We assessed elements of these systems in postmortem brain, testing the hypothesis that there are cell-subtype defects in bioenergetics function in the frontal cortex in schizophrenia.

Methods: Well-validated assays were used to assess the activity of three glycolytic enzymes in postmortem dorsolateral prefrontal cortex (DLPFC) samples (n=16/group): lactate dehydrogenase (LDH), hexokinase (HXK), and phosphofructokinase (PFK). Each sample was assayed with and without a specific inhibitor (in duplicate) and normalized to protein loaded into the assay. We also probed for differences in protein expression using western blot analysis. Western blot analyses were run in duplicate using the following antibodies optimized for postmortem brain: MCT1, LDH, LDHA, LDHB, HXK1, glucose transporter 3 (GLUT3). We performed real time quantitative polymerase chain reaction (RT-qPCR) using TaqMan PCR assays (MCT1, MCT4, HXK1, HXK2, LDHA, LDHB, PFK1, GLUT1, and GLUT3) in duplicate on cDNA samples in 96-well optical plates on a Stratagene MX3000P (Stratagene, La Jolla, California). We also coupled laser capture microdissection (LCM) with RT-qPCR from superficial and deep layers of DLPFC using the Veritas Microdissection instrument and CapSure Macro LCM caps (Life Technologies, formerly Arcturus, Mountain View, CA, USA). Similar studies were performed in haloperidol-decanoate or vehicle (sesame oil) treated rats (intramuscular injection every 3 weeks for 9 months).

Results: We found a 24% decrease in PFK1 mRNA expression in the dorsolateral prefrontal cortex in schizophrenia (p=0.039). We also found decreases in HXK (26%, p=0.002) and PFK (16%, p<0.001) activity in the dorsolateral prefrontal cortex. These changes were not present in haloperidol treated rats. At the cell-level, in pyramidal neurons we found an increase in MCT1 mRNA expression (22%, p=0.038), and decreases in HXK1 (19%, p=0.023), PFK1 (22%, p=0.003), GLUT1 (20%, p=0.008), and GLUT3 (20%, p=0.023) mRNA expression. We found increases in MCT1 (17%, p<0.05) and GLUT3 (20%, p<0.05), but not HXK1, PFK1, or GLUT1, mRNA expression in enriched pyramidal neuron samples of antipsychotic treated rats.

Discussion: As the brain develops, bioenergetic organization and the formation of synapses occur simultaneously, creating a fundamentally interdependent system. There is accumulating evidence of implicating a number of abnormalities associated with glucose metabolism, the lactate shuttle, and bioenergetic coupling in schizophrenia, suggesting energy storage and usage deficits in the brain. Bioenergetic deficits and genetic risk for synaptic dysfunction in schizophrenia could contribute to the pathophysiology of this illness. In normal brain, glucose enters cells through GLUTs and is processed by glycolytic enzymes resulting in bioenergetic substrates such as pyruvate. Pyruvate can then be converted to lactate and transported between cells or intracellularly by MCTs to be oxidized in the TCA cycle when neuronal energy demand is high. Our findings of decreased glycolytic enzyme and lactate transporter mRNA expression suggests a decrease in the capacity of pyramidal neurons to generate bioenergetic substrates from glucose via glycolytic pathways. Additionally, if neurons were unable to take up adequate amounts of glucose for glycolysis, the intracellular pool of available pyruvate/lactate for transport into mitochondria may be diminished, ultimately impacting energy supply. It is also possible that there is attenuated glycolysis in pyramidal neurons, with a shift towards pathways that boost protection from oxidative stress (pentose phosphate pathway). Other studies also report region and cell-subtype specific changes in the expression of genes encoding proteins involved in metabolism in this illness. Importantly, the above changes were not attributable to antipsychotic treatment. Both synaptic function and meeting of energetic demands are essential for cognition, and failure of either could contribute to the cognitive symptoms seen in schizophrenia. Augmenting affected systems such as glucose utilization pathways could offer a novel approach to restoring cognitive function in schizophrenia. This could include targeting pro-metabolic substrates pharmacologically.

12.2 METABOLIC CONSEQUENCES OF DEVELOPMENTAL NMDA RECEPTOR HYPOFUNCTION

Adam Funk¹, Catharine Mielnik², Sinead O’Donovan¹, Courtney Sullivan¹, Yuxiao Chen², Robert McCullumsmith¹, Amy Ramsey*²

¹University of Cincinnati; ²University of Toronto

Background: Several imaging and postmortem studies provide evidence that, in the brains of people with schizophrenia, there are alterations in glucose metabolism and energy utilization. However, it is difficult to determine whether altered excitatory transmission alters bioenergetics that then contributes to symptoms of the disorder. We have used a mouse model to begin to address these questions. GluN1 knockdown mice have a mutation that reduces NMDA receptor levels throughout development and maturity.