

## 11.3 Clinical and neurobiological effects of a continuous aerobic endurance training in multi-episode schizophrenia patients

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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 as 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/m<sup>2</sup>, 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-EPISEODE SCHIZOPHRENIA PATIENTS

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**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 distinct 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

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**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 Posit 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

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**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 PFK1 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.