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## Effects of endurance training on brain structures in chronic schizophrenia patients and healthy controls<sup>☆</sup>

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### ABSTRACT

The objective of this longitudinal magnetic resonance (MR) imaging study was to examine the effects of endurance training on hippocampal and grey matter volumes in schizophrenia patients and healthy controls. 20 chronic schizophrenia patients and 21 age- and gender-matched healthy controls underwent 3 months of endurance training (30 min, 3 times per week). 19 additionally recruited schizophrenia patients played table soccer (“foosball” in the USA) over the same period.

MR imaging with 3D-volumetric T1-weighted sequences was performed on a 3 T MR scanner at baseline, after 6 weeks and after the 3-month intervention and 3 additional training-free months. In addition to voxel-based morphometry (VBM), we performed manual and automatic delineation of the hippocampus and its substructures. Endurance capacity and psychopathological symptoms were measured as secondary endpoints.

No significant increases in the volumes of the hippocampus or hippocampal substructures were observed in schizophrenia patients or healthy controls. However, VBM analyses displayed an increased volume of the left superior, middle and inferior anterior temporal gyri compared to baseline in schizophrenia patients after the endurance training, whereas patients playing table soccer showed increased volumes in the motor and anterior cingulate cortices. After the additional training-free period, the differences were no longer present. While endurance capacity improved in exercising patients and healthy controls, psychopathological symptoms did not significantly change.

The subtle changes in the left temporal cortex indicate an impact of exercise on brain volumes in schizophrenia. Subsequent studies in larger cohorts are warranted to address the question of response variability of endurance training.

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### 1. Introduction

Structural brain alterations with local and overall volume reductions are well-documented findings in multi- and first-episode schizophrenia patients (Honea et al., 2005; Ellison-Wright and Bullmore, 2010; Leung et al., 2011; Cooper et al., 2014). In addition to global atrophy and larger ventricles, the most pronounced reduction of grey matter volume has been observed in the heteromodal association cortices of the left hemisphere, especially in the superior temporal gyrus (STG). More specifically,

hippocampal volumes have been found to be smaller in schizophrenia (DeLisi et al., 2004; Honea et al., 2005; Steen et al., 2006; Velakoulis et al., 2006; Vita et al., 2006; Vita and de Peri, 2007). Reductions of hippocampal volumes have been linked to impaired declarative memory function, which is considered a core clinical feature of schizophrenia (Tamminga et al., 2010; Hasan et al., 2013). Changes in STG volume are discussed to be related to general symptom severity (Mitelman et al., 2007) and auditory verbal hallucinations (Palaniyappan et al., 2012; Modinos et al., 2013; van Tol et al., 2014). Furthermore, a growing body of evidence documents that these structural brain changes and especially the cortical grey matter deficits are progressive over the course of the illness and are regionally distinct (Hulshoff Pol et al., 2002; Mane et al., 2009; Kempton et al., 2010; Ho et al., 2011b; Olabi et al., 2011; Vita et al., 2012). However, the underlying pathophysiology of these changes is still unclear and may be related to antipsychotic medications (Lieberman et al., 2005), alcohol and drug use (Van Haren et al., 2012) and differences in activity levels (Vancampfort et al., 2012).

Endurance training is known to induce both structural and functional brain changes, but these changes do not necessarily reflect reversibility of changes that are directly related to the disease process underlying schizophrenia. In animal models, exercise-induced neurogenesis and angiogenesis in the hippocampus in adult and ageing mice led to long-term potentiation and production of neurotrophic factors like BDNF and improved cognitive functioning (Voss et al., 2013). In healthy humans, cross-sectional and longitudinal studies underpin these observations and point to preserved grey matter and hippocampal volumes and cognitive functioning in higher age due to endurance training (Erickson and Kramer, 2009; Honea et al., 2009; Erickson et al., 2010; Erickson et al., 2011). Pereira et al. (2007) showed that endurance training increased cerebral blood volume (CBV) in the dentate gyrus of the hippocampus in healthy humans and mice. The elevated CBV was also correlated with increased aerobic fitness and cognitive function. The first proof-of-concept study investigating the efficacy of 3 months of endurance training in addition to standard antipsychotic treatment in eight chronic schizophrenia patients reported increased hippocampal volumes and elevated hippocampal N-acetylaspartate to creatine ratios (Pajonk et al., 2010). These changes correlated with improved aerobic fitness, indicating that the hippocampus of schizophrenia patients is responsive to a plasticity-inducing stimulus. Subsequent analysis of cortical surface expansion of the same cohort did not reveal any significant changes in the schizophrenia exercise group (Falkai et al., 2013). A randomised controlled trial (RCT) with 63 probands comparing 6 months of endurance training to occupational therapy in schizophrenia could not replicate these initial findings (Scheewe et al., 2013b), but showed improved cardiovascular fitness following the intervention. Until now, only these two neuroimaging studies with contradictory results have reported the impact of endurance training on brain structure and function in schizophrenia (Malchow et al., 2013). Furthermore, it is unknown whether the pattern of brain structure changes outlasts the intervention period in terms of a consolidation process of whether endurance-induced brain volume changes represent only short-term effects. In addition, a combination of aerobic exercise with targeted cognitive remediation in terms of an enriched environment intervention may increase the beneficial effect of the exercise interventions.

The primary objective of this study was to investigate the effects of 3 months' endurance training combined with cognitive stimulation with add-on computer assisted cognitive remediation (CACR) training from week six to three months on cortical and subcortical brain structures in schizophrenia patients. We also intended to assess whether the effects remained after a subsequent 3 months' resting period with no endurance training or cognitive remediation. Further objectives were to investigate the impact of exercise on hippocampal subfields, psychopathology and endurance capacity.

## 2. Methods

### 2.1. Participants

Sixty-four patients from the Department of Psychiatry and Psychotherapy of the University Medical Center Goettingen were included in this single-centre trial between 2010 and 2013 (see Supplementary Fig. 1). The inclusion criteria were a diagnosis of schizophrenia according to the ICD-10 criteria (WHO, 2010) confirmed by the MINI-Plus interview (Sheehan et al., 1998), age between 18 and 60 years and a history of at least two confirmed psychotic episodes. Symptom severity was measured by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Antipsychotic medication had to be kept stable for 2 weeks prior to inclusion in the study and during the study period. Patients with clinically relevant psychiatric comorbidity (including current abuse of or dependence on illicit drugs or alcohol assessed by the MINI-Plus interview (Sheehan et al., 1998) and additional drug urine testing), verbal IQ < 85 as tested by the multiple-choice vocabulary test (Lehrl et al., 1995), clinically relevant unstable medical conditions, and involuntary hospitalization or pregnancy were excluded. We also enrolled 36 healthy controls matched for age, gender and handedness with no current or past mental illness (see Supplementary Fig. 1).

The local ethics committee of the University Medical Center Goettingen approved the study protocol, which was in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to inclusion in the study. The trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT01776112).

### 2.2. Exercise testing

Endurance capacity was tested before and after the full endurance training or table soccer (commonly known as “foosball” in the USA) interventions and at follow-up after a 3-month training-free period. We measured endurance performance with an incremental maximal exercise test on a bicycle ergometer (Ergoselect 200 K, ergoline GmbH, Bitz, Germany). The test started at 25, 50 or 75 W, depending on the individual's starting fitness level. During the test the resistance was increased every 3 min by a fixed increment of 25 W. Gas exchange, heart rate, blood lactate and perceived exertion were measured at each incremental stage. The test ended at volitional exhaustion or the occurrence of termination criteria (Steinacker et al., 2002). Physical activity during leisure time and at work was monitored throughout the study. Endurance was expressed as the Physical Working Capacity 130 (PWC<sub>130</sub>), i.e. the power in watts reached at a heart rate of 130 beats per minute per kg bodyweight, calculated by means of linear inter- and extrapolation.

### 2.3. Endurance training and table soccer

We used the same intervention protocol as published previously (Pajonk et al., 2010). Briefly, the intervention lasted 3 months for all three groups and consisted of three sessions per week of 30 min duration each. The endurance training was conducted on bicycle ergometers (Ergobike Premium 8, Daum electronic GmbH, Fürth, Germany) at an individually defined intensity that was gradually increased according to blood lactate concentrations of approximately 2 mmol/l, following the continuous training method (e.g. Kenney et al. (2011)). The training parameters were blood lactate concentration, heart rate and exhaustion according to the Borg scale (Borg, 1970).

The schizophrenia patients allocated to the non-endurance intervention played table soccer in groups of two to four players for the same amount of time. Blood lactate concentrations, heart rate and exhaustion were monitored in the same way as for the exercise intervention. The same sports scientist supervised both the intervention and control groups. After 6 weeks of the intervention period, the computer-assisted training programme COGPACK (software version 8.19 D/8.30 DE; Marker Software, Ladenburg, Germany, <http://www.>

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