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Effects of endurance training on brain structures in chronic schizophrenia patients and healthy controls ☆

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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.

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,

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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 (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_{130}), 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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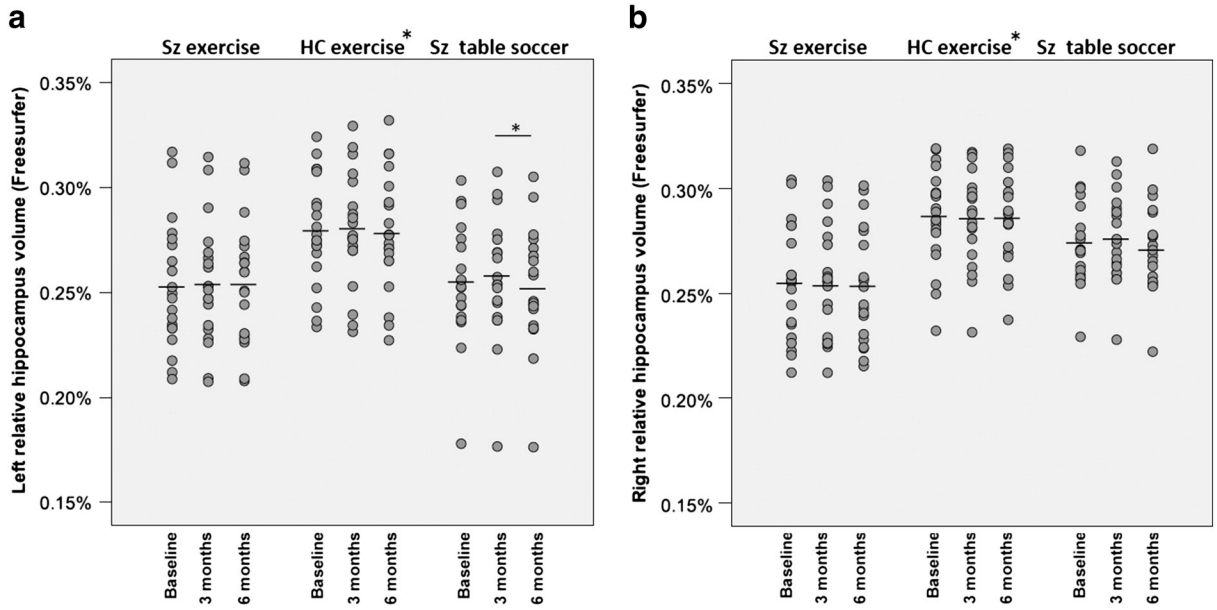

Fig. 1. Hippocampal volumes measured automatically (FreeSurfer) relative to intracranial volume at baseline, after 3 and 6 months in the schizophrenia (SZ) endurance training, healthy control (HC) endurance training and SZ table football group. Lines indicate group means. In the table soccer group, left total hippocampal volume was decreased (after 6 vs. after 3 months, $p = 0.001$). Additionally, significant group effects were observed for volumes of total hippocampus ($p = 0.002$), with higher volumes in HC endurance training and in SZ table soccer compared to the SZ endurance training group.

cogpack.de/) was added as an intervention in each group to train cognitive performance. Patients and healthy controls completed the memory and attention tasks two times per week over a period of 6 weeks subsequent to the other training sessions.

2.4. Structural imaging parameters

Structural magnetic resonance imaging (MRI) scans of the whole brain were acquired on a single 3 T Scanner (Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany) at baseline and after 6 weeks and 3 and 6 months. Images were obtained by using a standard 8-channel phased-array head coil. The head was stabilized with small cushions to minimize motion during scanning. A 3D anatomical T1-weighted dataset of the whole head was acquired (Magnetization Prepared Rapid Gradient Echo [MPRAGE]; 176 continuous sagittal slices of 1 mm thickness, echo time = 3.26 ms, repetition time = 2250 ms, inversion time = 900 ms, flip angle 9°, in-plane voxel size $1 \times 1\ mm^2$). All images were quality controlled by a board-certified radiologist and depersonalized to ensure investigator blindness to participant identity.

2.5. Voxel-based morphometry (VBM)

Individual high-resolution T1-weightened images were pre-processed (deobliquing, reorientation to FSL-friendly space, skull striping) using AFNI (Analyses of Functional Images, http:afni.nimh.nih.gov/afni). All images were visually inspected for head motion before they were further processed. Structural data analysis was performed with the VBM tool implemented in FSL 5.0.5 (www.fmrib.ox.ac.uk/fsl). Structural images were extracted with the brain extraction tool (BET) (Smith, 2002). Tissue-type segmentation was performed with FMRIB's Automated Segmentation Tool (FAST) (Zhang et al., 2001). The resulting grey matter partial volume images were normalized to MNI152 standard space (Montreal Neurological Institute, Montreal, Canada) by an initial affine (FMRIBs Linear Image Registration Tool, FLIRT) (Jenkinson et al., 2002) and a subsequent nonlinear registration (FMRIBs Non-Linear Image Registration Tool, FNIRT) (Andersson et al., 2007a, b). The resulting warped grey matter images were averaged to create a study-specific template and the native grey matter images were then non-linearly re-registered to this template. To correct for local expansion or contraction the registered partial volume images were divided into the Jacobian of the warp field (modulation). The modulated normalized grey matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 4 mm. The grey matter of each individual's total was used as a covariate. Group differences in grey matter volume were determined with Randomise version 2.9 (permutation-based nonparametric testing, 5000 permutations) (Nichols and Holmes, 2002). A repeated measures design for three measurements was chosen for longitudinal intra-group effects. The measurements after 6 weeks were excluded from further analysis, because for logistical reasons not all participants underwent these measurements. We applied a statistical threshold with family-wise error rate (threshold-free cluster enhancement) corrected for multiple comparisons (Smith and Nichols, 2009). Significance-corrected effects were then correlated with age, gender, PANSS general, positive and negative values and stable medication doses to exclude any unspecific effects. Workbench version 0.85 was used for surface reconstructions (www.humanconnectome.org).

2.6. Longitudinal subcortical segmentation with FreeSurfer

The FreeSurfer version 5.3.0 software package (http://surfer.nmr.mgh.harvard.edu) longitudinal stream was used for automatic subcortical segmentation and volume estimates of the T1-weighted images (Reuter et al., 2012). An unbiased within-subject template space and image (Reuter and Fischl, 2011) was created by robust, inverse consistent registration (Reuter et al., 2010). Several processing steps, such as skull stripping, Talairach transforms, atlas registration and spherical surface maps and parcellations were initialized with common information from the within-subject template, which significantly increased reliability and statistical power (Reuter et al., 2012). On the basis of the longitudinal processed images the hippocampal subfield volumes were computed from each individual participant's structural images (Van Leemput et al., 2009).

2.7. Manual segmentation of the hippocampus

The manual volumetric measurements were performed by editing the region of interest (ROI) segmentation obtained by the longitudinal

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pipeline of the FreeSurfer software, as described above. The manual editing was carried out with 3DSlicer Version 4.3.1 (http://www.slicer.org, (Fedorov et al., 2012)). The label maps were edited in all slices first in the sagittal view, then in the coronal view and finally in the axial view. During this process the manual editing was performed in one direction only, e.g. from lateral to medial, and controlled and corrected in the other direction, e.g. from medial to lateral. The whole procedure was conducted by one rater (KK), who was blinded to group membership, diagnosis and date of acquisition; the intra-rater reliability intra-class correlation coefficient (ICC) was 0.924 for a period of 6 weeks, with no significant correlations between time of editing and volume. In addition, interrater reliability was calculated considering measurements by an independent rater (HK, n = 10, ICC = 0.927). The rater (KK) was trained beforehand by an experienced neuroradiologist (BEW). We included the subiculum and the white matter of alveus and fimbria in our ROI. The protocol for the delineation procedure was based on the borders recommended in the literature (Konrad et al., 2009). Duvernoy et al. (2013) were consulted for anatomical validation. The following landmarks were used: the alveus as the superior border, white matter of the parahippocampal gyrus as the inferior border, the cerebrospinal fluid of the lateral ventricle as the lateral border, the crus of fornix as the posterior border and cerebrospinal fluid of the ambient cistern in superior parts, an arbitrary line from inferior to superior medial in the inferior parts of the medial border. Ambiguous boundaries were discussed with an experienced rater and board-certified neuroradiologist (BEW), both of whom were also fully blinded. The final calculations of the ROI volumes were also performed with 3DSlicer (Fedorov et al., 2012).

2.8. Power analysis

Assuming a type I error of $\alpha = 0.025$, a power of $1 - ß = 0.8$, a medium effect size of $f = 0.36$, three groups (schizophrenia endurance training, schizophrenia table soccer, healthy controls endurance training), three measurement time points and a correlation between the measurements of $r = 0.4$, for all effects (within-subject factor time, between-subject factor group and interactions between time and group) a sample size of $n = 19$ per group was required to show differences in outcomes. The effects that were observed in the published exercise study described above (Pajonk et al., 2010) were larger than the effects assumed for this study (e.g. hippocampus volume: $f = 1.27$, PANSS negative score: $f = 0.37$). Power analyses were conducted with G*Power 3.1.3 (Faul et al., 2007).

2.9. Statistical analysis

All tests were two-tailed. Statistical calculations were performed with SPSS statistics 21. Per protocol analysis was applied, i.e. all valid data were included in the analyses. The primary dependent variable was total manual hippocampal volume relative to intracranial volume at baseline and after 3 months. Because the hippocampal volume was measured manually and automatically with Freesurfer, the significance level for primary analyses was adjusted to $\alpha = 0.05/2 = 0.025$. Because three subgroup analyses each were performed for the manual and the automatic approaches, significance level for subordinate analyses was $\alpha = 0.05/6 = 0.0083$. Secondary variables were hippocampal volumes (total and subregions CA 1, CA 2/3 CA 4/dentate gyrus, subiculum and fimbria) and subcortical volumes (amygdala, thalamus, caudate, putamen, accumbens, cerebellum white matter, cerebellum cortex, brain stem) relative to intracranial volume (Reuter et al., 2012) at baseline and after 3 and 6 months. Further secondary variables were psychopathology measured by the PANSS total score and respective subscores and sport performance data relative to body weight. For secondary analyses, the significance level was adjusted for the number of variables in each field.

As preliminary analyses, for all dependent variables Kolmogorov–Smirnov tests were used to analyse whether there were significant deviations from the normality assumption, which was not the case. Pearson correlations were performed between dependent variables and age and duration of school education. The influence of gender was evaluated for all dependent variables by one-way analysis of variance. If age, gender or education showed a significant effect, the further analyses were adjusted for these intervening variables.

Multivariate repeated measures analyses of covariance (RM MANCOVA) were conducted as the main analyses, with the within-subject factors time of measurement and hemisphere, the between-subject factor group and intervening variables identified from the initial analyses. RM MANCOVAs were performed separately for manual hippocampal volumes, automatic total hippocampal volumes and hippocampal subregions and subcortical volumes; in case of significance, subsequent Bonferroni corrected analyses were performed between time points and groups. For PANSS and sport performance variables, the same RM MANCOVA design was used without the factor hemisphere.

We calculated the differences between baseline and 3 months in the measurements of dependent variables and analysed if the change in volume correlated with age, gender, education or medication or with the changes in psychopathology and sport performance.

The influence of antipsychotic medication on the results was examined by Spearman correlations between dependent variables and chlorpromazine equivalents (CPE), because medication showed significant deviations from normal distribution (Rey et al., 1989; Woods, 2003).

In order to replicate the findings of an increase of hippocampal volume after endurance training, we used the same statistical methods described above to analyse the subsample of male right-handed schizophrenia endurance training patients, in line with the population of our previous exercise study (Pajonk et al., 2010).

3. Results

3.1. Study participants

In total, 22 schizophrenia patients completed the endurance training, 21 the control intervention and 23 age- and gender-matched healthy controls completed the endurance training. MRI was available for 20 schizophrenia endurance sport patients, 19 schizophrenia table soccer patients and 21 healthy controls (see Supplementary Fig. 1). Sociodemographic and clinical characteristics are presented in Table 1.

A significant change in symptom severity was not observed in either the schizophrenia exercise group or the schizophrenia control group.

3.2. Hippocampal volumes

Relative hippocampal volumes measured manually and automatically at baseline differed significantly between each schizophrenia patient group and the healthy controls (group effect $p = 0.013$ manually and $p = 0.002$ automatically). At baseline, the schizophrenia exercise group showed significantly smaller relative hippocampal volumes than healthy controls for automatic measurements ($p = 0.001$). After three months, hippocampal volumes in the schizophrenia exercise group were smaller than in healthy controls (automatic: $p = 0.001$, manual: $p = 0.006$). The schizophrenia table soccer group showed no significant differences in hippocampal volumes compared to healthy controls at baseline. The hippocampal volumes obtained by both manual tracing and the FreeSurfer software revealed no significant impact of a 3-month period of continuous endurance training on bilateral hippocampal volumes in either the schizophrenia patients or the healthy controls. We did not find an effect of the intervention on hippocampal volumes in the schizophrenia table soccer group, but after the 3-month training-free period we found a significant volume decrease of the left hippocampus ($p = 0.001$, Bonferroni corrected) (see Fig. 1). Because manually outlined hippocampal volumes and FreeSurfer-based

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Table 1
Sociodemographic and clinical variables and endurance capacity.

	Schizophrenia exercise			Healthy controls exercise			Schizophrenia table soccer			Group comparison ANOVA*		
	n	m	sd	n	m	sd	n	m	sd	F	df	p
Age (years)	20	36.3	11.7	21	37.4	11.5	19	35.3	14.5	0.1	2, 57	0.87
Height baseline (cm)	20	178.8	10.4	21	175.5	9.9	19	176.2	8.6	0.6	2, 57	0.53
Weight baseline (kg)	20	93.1	17.0	21	79.5	14.6	19	86.8	16.6	3.7	2, 57	0.032
Waist (cm)	20	101.1	12.4	21	89.1	12.8	19	92.4	18.7	3.6	2, 57	0.035
Duration of school education (years)	20	11.8	1.6	21	11.9	1.4	19	11.4	1.9	0.6	2, 57	0.57
Total duration of education (years)	20	15.2	3.9	21	16.2	3.8	18	14.8	3.5	0.7	2, 56	0.50
Smoking (cigarettes/day) baseline	20	7.7	10.7	21	2.5	6.5	19	4.1	6.6	$Chi^2 = 3.2$	2	0.20
Blood pressure (sys) baseline	20	124.0	19.1	21	133.5	14.6	19	133.2	14.4	2.2	2, 57	0.12
Blood pressure (dia) baseline	20	74.1	12.9	21	76.9	10.4	19	80.6	10.4	1.6	2, 57	0.20
Pulse baseline	20	84.5	15.4	21	73.3	13.3	19	84.7	14.4	4.2	2, 57	0.020
Disease duration (years)	20	9.3	7.9				19	11.1	10.8	0.4	1, 37	0.54
Number of hospitalizations	20	4.2	3.4				19	4.9	6.7	0.2	1, 37	0.64
PANSS positive score baseline	20	13.8	7.6				19	13.8	4.9	0.0	1, 37	0.99
PANSS positive score 3 months	20	12.6	5.6				19	12.5	4.2	0.0	1, 37	0.96
PANSS negative score baseline	20	19.3	8.8				19	19.6	8.8	0.0	1, 37	0.89
PANSS negative score 3 months	20	16.2	6.3				19	18.3	8.5	0.8	1, 37	0.38
PANSS general score baseline	20	31.8	18.8				19	40.4	14.6	2.6	1, 37	0.12
PANSS general score 3 months	20	29.8	14.3				19	37.0	13.6	2.6	1, 37	0.11
PANSS total score baseline	20	64.8	32.9				19	73.8	26.6	0.9	1, 37	0.35
PANSS total score 3 months	20	58.5	24.6				19	67.8	25.1	1.4	1, 37	0.25
PWC 130 per kg baseline	18	1.1	0.3	21	1.3	0.4	18	1.1	0.3	3.4	2, 54	0.040
PWC 130 per kg 3 months	18	1.2	0.4	21	1.5	0.4	17	1.1	0.3	4.9	2, 53	0.011
PWC 130 per kg 6 months	19	1.1	0.4	21	1.4	0.3	19	1.0	0.4	6.6	2, 56	0.003
CPE daily dosage baseline	20	794	703				19	337	309	$Z = -2.5$	1	0.011
CPE daily dosage 3 months	20	799	764				19	311	322	$Z = -2.5$	1	0.012
CPE daily dosage 6 months	19	615	647				19	281	307	$Z = -2.4$	1	0.015
CPE cumulative dosage (baseline − 6 months)	20	134762	118816				19	53,824	53,404	$Z = -2.8$	1	0.005

				Likelihood ratio test		
	No. 1. item/no. 2. item	No. 1. item/no. 2. item	No. 1. item/no. 2. item	Chi^2	df	p
Gender (no. male/no. female)	14/6	14/7	13/6	0.1	2	0.97
Hand preference (no. right/no. left)	16/4	17/4	18/1	2.4	2	0.30
Marital status (no. in partnership/no. single)	1/18	9/12	5/14	8.5	2	0.014
Occupational status (no. employed/no. unemployed)	7/13	18/3	8/11	13.6	2	0.001
Living status (no. own apartment/no. other)	15/5	19/2	13/6	3.3	2	0.19
Antidepressants (yes/no)	6/14		3/16	1.1	2	0.29

hippocampal volumes correlated at both baseline and the 3-month measurement (baseline left hippocampus: r = .874, baseline right hippocampus: r = .884; left hippocampus after 3 months: r = .854, right hippocampus after 3 months: r = .891, all correlations significant at the 0.01 level [2-tailed]; see Fig. 2), we decided to discontinue the time-consuming and rater-dependent approach of manual hippocampal outlining for the follow-up measurement and relied on the FreeSurfer volumes alone. Longitudinal analysis of the volumes of other subcortical structures segmented by the FreeSurfer software revealed no significant changes.

3.3. Hippocampal subfield volumes

A 3-month period of regular endurance training had no effect on hippocampal subfield volumes in schizophrenia patients. At the 6-month follow-up, healthy controls showed an increased volume of the right cornu ammonis 1 region (CA1) of the hippocampus ($p < 0.007$) compared to 3-month follow-up.

3.4. Longitudinal VBM analysis

T1-weighted scans were obtained at baseline and after 3 and 6 months in a total of 20 schizophrenia exercise patients, 21 healthy controls and 19 schizophrenia patients playing table soccer. Hypothesis-free VBM revealed a corrected trend for a voxel cluster in the left anterior temporal lobe ($p < 0.1$, corrected; see Figs. 3A, 4A, Table 2). Further VBM analysis with an 'anterior medial temporal gyrus mask' as provided by the Harvard–Oxford Cortical Structural Atlas revealed a significant cluster of 462 voxels of increased grey matter volume in the left anterior temporal lobe in schizophrenia patients after 3 months of exercise compared to baseline ($x = -48$, $y = 0$, $z = -26$; $p < 0.05$ corrected; see Fig. 3B, Table 2). The effect did not correlate with the demographic variables age or gender, with PANSS scores or medication doses. The increased structural VBM effect vanished after an additional 3 months without exercising (see Fig. 4A *lower rows*, Table 2). Compared to baseline, we found no effects on brain structure in healthy controls after 6 weeks (supplementary information) and 3 months of regular endurance training and 6 months' follow-up. In the schizophrenia table soccer group, changes in grey matter volume were found in the anterior cingulate cortex (ACC) and the motor cortex areas bilaterally ($p < 0.05$, corrected) (see Supplementary Figs. 2, 3). These effects did not correlate with age, gender, medication or PANSS scores and also disappeared after an additional 3 months without playing table soccer (see Fig. 4C *lower rows*, Table 2).

3.5. Clinical symptoms

At baseline, there were no significant group differences between the schizophrenia table soccer and endurance sports groups in any PANSS scores. An analysis of the two schizophrenia groups separately found no significant time effects. Moreover, we did not find effects of groups.

3.6. Correlation with medication

Besides significant correlations of absolute and relative caudate volumes with CPE at baseline and with CPE cumulative dosage (rho > 0.41,

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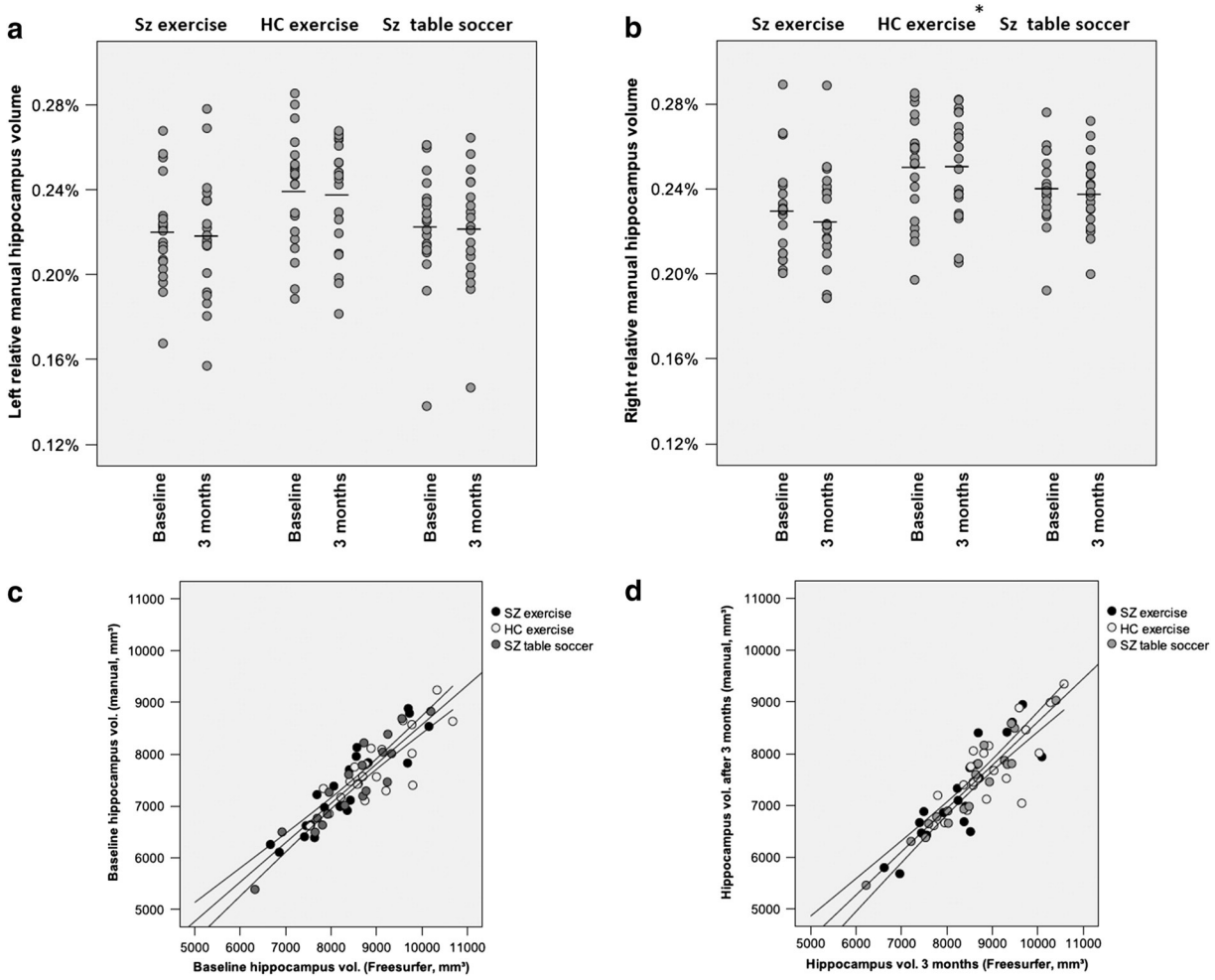

Fig. 2. Hippocampal volumes measured manually relative to intracranial volume at baseline and after 3 months in the SZ exercise, HC exercise and SZ table football group. (a) Total relative manual hippocampus volume, (b) scatterplot of automatic and manual total hippocampus volume at baseline, (c) scatterplot of automatic and manual total hippocampus volume after 3 months. Lines indicate group means. Significant group effects were observed for total hippocampal volume ($p = 0.013$, higher volumes in the HC exercise compared to the SZ exercise group).

$p < 0.01$), antipsychotic medication had no significant influence on the outcome variables.

3.7. Endurance capacity

At baseline, PWC_{130} did not differ between the three groups. After 3 months of endurance training, both the schizophrenia patient cohort ($p = 0.009$) and the healthy control cohort ($p = 0.003$) showed a significant improvement in PWC_{130}. This effect was no longer significant after the 3-month, training-free follow-up period. In both endurance-training groups, leisure time physical activity was significantly reduced during the intervention period and increased again after completion of the intervention programme but did not reach statistical significance. In the schizophrenia table soccer group, no difference was detected during follow-up (see Supplementary Fig. 4). Mean attendance was 92% for both schizophrenia and healthy controls endurance training and 93% in the table soccer group, respectively.

4. Discussion

In our study we found no effects of endurance training on hippocampal volume or hippocampal subfield volume in schizophrenia patients and healthy controls. Because our sample consisted of male and female schizophrenia patients, we subsequently conducted a subgroup analysis in a right-handed, male-only subsample, similar to the sample of Pajonk et al. (2010). In this subgroup, endurance training also had no significant effects on hippocampal volume or hippocampal subfield volume. This finding is contradictory to our previous study (Pajonk et al., 2010), but in line with a recent report (Scheewe et al., 2013b). We also found no effect of endurance training in healthy controls. In the study by Scheewe et al. (2013a,b), the intervention period lasted 6 months and endurance training was performed only twice a week but for slightly longer period (40 min) and was accompanied by 20 min of resistance training. It could be argued that not the total amount of endurance training but the frequency and intensity of the training stimulus could play a crucial role in altering hippocampal structure. Thus, these differences might account for varying results between studies, but other factors like the variability of plasticity responses and the different sample sizes need to be taken into account.

In our study, we applied both manual and automated approaches to hippocampal volume estimation. These two measures were strongly correlated and therefore should not account for the negative results. In the schizophrenia table soccer group the left hippocampus showed a significant volume decline after 6 months compared to 3 months and baseline, which has not been detected in the schizophrenia endurance-training group. Therefore, a potential protective effect of endurance training for hippocampal volume decline over time could be hypothesized, but this effect should be replicated after longer follow-up periods. Furthermore,

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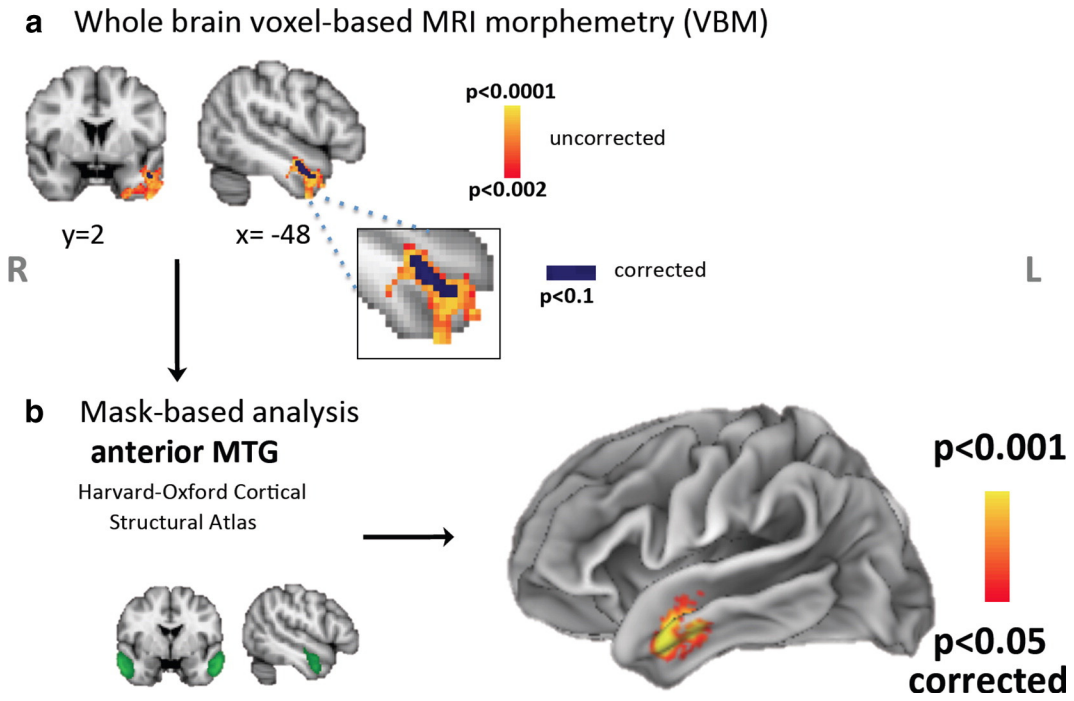

Fig. 3. Cluster of difference in grey matter volume in the temporal lobe in exercising schizophrenia patients after 3 months compared to baseline. (A) shows a corrected trend ($p < 0.1$) and (B) the masked-based approach with the anterior medial temporal gyrus mask. The 462 voxel cluster ($p < 0.05$, corrected) covers Brodmann areas (BA) 20, 21, 22 and 38 (anterior STG, medial temporal gyrus, inferior temporal gyrus and parts of the fusiform gyrus) and is shown in the surface view.

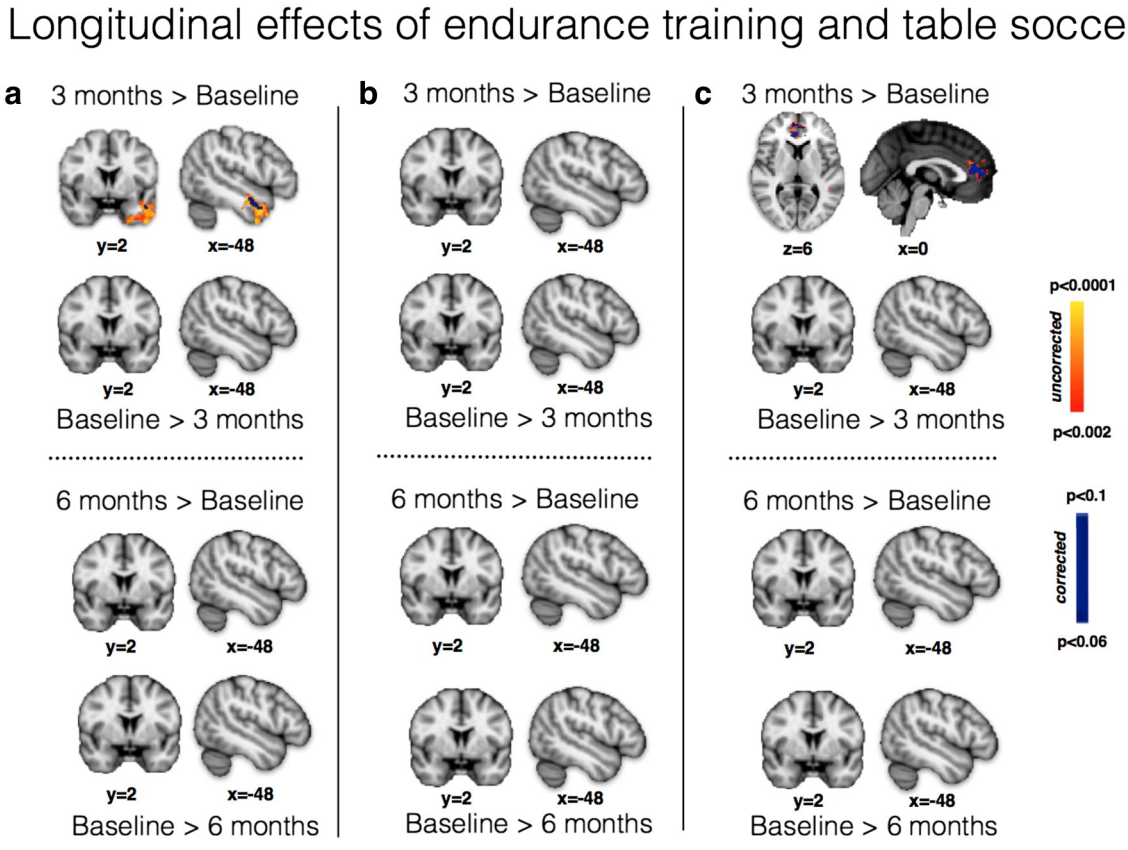

Fig. 4. Clusters of difference for all groups after the 3-month intervention are shown in the upper rows and at follow-up after 6 months (after a 3-month training-free period) are shown in the lower rows ($p < 0.1$, corrected). The uncorrected effects ($p < 0.002$) are shown for visual purposes only. A) Intra-group comparisons for the exercising schizophrenia patients, B) Intra-group comparisons for the exercising healthy controls, C) Intra-group comparisons for the schizophrenia patients playing table soccer. The pattern of structural differences in both the schizophrenia exercising group and schizophrenia table soccer group reversed after the 3-month training-free period. There was no significant effect on grey matter volume in the group of healthy controls.

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Table 2
Structural group differences in grey matter volume (also see Fig. 4) derived from VBM analysis. Note: Only significant corrected trends ($p < 0.1$) and corrected effects ($p < 0.05$) are reported for the different repeated measures contrasts of the experimental groups.

Cluster	Region	Hemisphere	No. of voxels	p-value	Coordinates[a] (x y z)		
Whole brain approach 3 months endurance training > baseline $p_{corr} \leq 0.1$							
1	MTG, STG (BA 21, 38)	L	54	0.083	−48	6	−30
Mask-based analysis 3 months endurance training > baseline $p_{corr} \leq 0.05$							
1	ITG, MTG, STG, FG (BA 20,21,22,38)	L	462	0.003	−50	6	−30
3 months table soccer > baseline $p_{corr} \leq 0.1$							
1	ACC, MFG (BA 9, 24, 32)	L,R	364	0.052	−6	48	10

Abbreviations: ACC = anterior cingulate cortex, BA = Brodmann Area, ITG = inferior temporal gyrus, FG = Fusiform Gyrus, MFG = medial frontal gyrus, MTG = middle temporal gyrus, STG = superior temporal gyrus, MTG = medial temporal gyrus, STG = superior temporal gyrus.
[a] Coordinates are given in MNI152 standard space.

endurance training had no significant impact on subcortical brain structures in schizophrenia patients and healthy controls, suggesting that effects of endurance training might be region specific.

With a hypothesis-free longitudinal VBM approach, we were able to show increase in grey matter volume of the left anterior temporal lobe after 3 months of endurance training in schizophrenia patients, whereas no such effect was observed in healthy controls. However, the relationship between the observed changes in grey matter volume and the underlying alterations on the cellular or molecular level in schizophrenia patients remains unclear. The reported changes in grey matter volume do not necessarily relate to the tissue changes related to schizophrenia and, at a microscopic level, they may not reflect the changes that underlie schizophrenia. Possible mechanisms, which can only be investigated in animal models, include increased neurogenesis, synaptogenesis, prolonged cell survival, and changes in vascularization, all of which may influence activity-dependent structural brain plasticity (May, 2011; Johansen-Berg, 2012).

The left temporal lobe is commonly considered a key region for the pathophysiology of schizophrenia and regional grey matter volume is decreased already in early stages of the disease and in people at high risk of developing schizophrenia (Honea et al., 2005; Cooper et al., 2014). Moreover, longitudinal studies in chronic schizophrenia patients have found pronounced volume loss over time in the left STG (Mane et al., 2009; Vita et al., 2012), while others have found no alterations in temporal lobe grey matter, but only in white matter (Olabi et al., 2011). In contrast to our results, Scheewe et al. found no alterations in cortical thickness after endurance training, but an association between improvement in cardiorespiratory fitness and less cortical thinning in the left hemisphere in both schizophrenia patients and healthy controls (Scheewe et al., 2013a).

Areas associated with motor learning showed a volume increase after 3 months of repetitive table soccer play. In detail, schizophrenia patients showed a significant increase in grey matter volume in the motor cortex after 6 weeks and in the bilateral ACC after 3 months. However, this effect was not consolidated and could not be displayed 3 months after the end of intervention. An increase in the ACC was found that might be associated with cognitive control of a complex and demanding task (table soccer) that is more challenging after basic skills have been acquired. Recently, structural changes in the brain were observed after only two hours of playing a complex video game (Sagi et al., 2012). In our study the effects lasted only during the specific intervention period and were no longer visible 3 months after cessation of the respective exercise.

Despite our negative finding regarding hippocampal volumes, on the basis of the results of our VBM analysis one could still assume that exercise-dependent interventions have the potential to reverse volume deficits in schizophrenia patients. However, different moderating factors like the amount of endurance training or the individual capacity to respond to a plastic stimulus need to be considered when discussing plasticity effects after endurance training. Studies using non-invasive brain stimulation to induce plasticity have clearly shown that the individual interneuron architecture, the age of participants, the timing of the intervention, concomitant drug treatment and the genetic background can affect the development of neural plasticity (Ridding and Ziemann, 2010; Hamada et al., 2013). One could assume that less than 50% of subjects will show the expected effect after a plastic stimulus (Hamada et al., 2013). Thus, the composition of the respective sample is of critical importance. Either studies with large sample sizes or the development of a factor to identify those participants who will respond to the plastic stimulus will help to clarify the impact of endurance training on plasticity in schizophrenia patients and in healthy controls.

Endurance training significantly improved the endurance capacity of schizophrenia patients and healthy controls. At follow-up after a 3-month training-free period, endurance capacity did not differ compared to baseline, suggesting short-lived effects of endurance training on endurance capacity. The schizophrenia patient cohort who played table soccer did not improve in terms of endurance capacity. Schizophrenia symptoms did not significantly improve or worsen during either the potentially stressful training settings or the training-free period. However, we did not detect an effect of endurance training in symptom severity. This is in contrast to previous findings (Pajonk et al., 2010; Scheewe et al., 2013a) and may be based on our heterogeneous sample.

There are several limitations that need to be considered when interpreting our results. First, throughout our study the schizophrenia endurance-training patients were taking higher doses of antipsychotic medication than the schizophrenia table soccer group. Medication was held stable over the period of the trial. The difference in medication doses may indicate that the patients in the exercise group were more severely ill, even though symptom severity did not differ. Antipsychotic medication is known to affect brain structure in schizophrenia patients, e.g. (Lieberman et al., 2005; Ho et al., 2011a). Although we did not observe correlations between CPE and regional brain volumes, we cannot rule out that some of the observed effects on grey matter volume may be due to antipsychotic medication, despite the relatively short observation period of 6 months. Second, the frequency and duration of the endurance training sessions were possibly too low, although we used the same training intensity as in our previous study (Pajonk et al., 2010). Furthermore, we cannot clearly distinguish between effects of endurance training and cognitive remediation during the second part of the intervention, since we did not include a group of patients with cognitive training alone. The total amount of endurance training may play a crucial role. For example, the American College of Sports Medicine recommends a training period of 150 min per week to develop cardiorespiratory fitness, a period that was not reached in our study (Garber et al., 2011). The frequency and intensity of the training stimulus may also play a crucial role when trying to induce structural changes. In future studies, we recommend a more intense training stimulus. Third, because of the additional cognitive training in the second half of the intervention period (after week 6), we cannot prove that the grey matter alterations are solely caused by endurance training or playing table soccer, even though the patterns of the respective alterations are distinct between both schizophrenia patients groups. Furthermore, larger

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samples and gender heterogeneity seem to be prerequisites for further research in this field.

In summary, we were not able to replicate our initial findings of increased hippocampal volumes after endurance training in schizophrenia. However, our study demonstrates a grey matter volume increase in the left temporal lobe (superior, middle and inferior anterior temporal gyrus) in schizophrenia patients undergoing endurance training, which may correspond to an ameliorated grey matter volume loss over time. A non-endurance and more coordinative training stimulus like playing table soccer led to a clearly distinct pattern of grey matter alterations in schizophrenia patients. Both effects did not last beyond the intervention period.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2015.01.005.

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Contributors

B. Malchow, T. Wobrock, T. Schneider-Axmann, W.G. Honer and P. Falkai designed the study and wrote the protocol. B. Malchow, K. Keller, A. Hasan, T. Wobrock, P. Falkai, U. Hillmer-Vogel, P. Dechent and O. Gruber acquired the data. B. Malchow, D. Keeser, K. Keller and A. Schmitt managed the literature searches. B. Malchow, K. Keller, H. Kimura, B.S. Rauchmann, A. Hasan, T. Schneider-Axmann, B. Ertl-Wagner, W.G. Honer and P. Falkai undertook the statistical analysis and interpretation of the data. B. Malchow wrote the first draft of the manuscript. B. Malchow, D. Keeser, K. Keller, A. Hasan, T. Schneider Axmann, A. Schmitt, W.G. Honer and P. Falkai prepared the manuscript. All authors contributed to and have approved the final manuscript and undertook it a critical revision for important intellectual content.

Conflict of interest

B. Malchow, D. Keeser, K. Keller, B. Rauchmann, H. Kimura, T. Schneider-Axmann, P. Dechent, O. Gruber, U. Hillmer-Vogel and A. Niklas have no conflict of interest. A. Hasan has been invited to scientific meetings by Lundbeck, Janssen-Cilag and Pfizer and he received a paid speakership from Desitin. He is a member of the advisory board of Roche. B. Ertl-Wagner has received paid speakerships and/or honoraria for manuscript preparations from Siemens, Philips, Bracco, Roche, Novartis and Bayer Vital; she has been a member of advisory boards for Philips and Bracco. W.G. Honer is an unpaid member of the advisory board of In Silico Biosciences and a paid consultant to Otsuka/Lundbeck, Roche, Novartis, MDH Consulting and the Canadian Agency on Drugs and Technology in Health. A. Schmitt was a honorary speaker for TAD Pharma and Roche and has been a member of advisory boards for Roche. T. Wobrock has received paid speakerships from Alpine Biomed, AstraZeneca, Bristol Myers Squibb, Eli Lilly, I3G, Janssen Cilag, Novartis, Lundbeck, Roche, Sanofi-Aventis and Pfizer, has accepted travel or hospitality not related to a speaking engagement from AstraZeneca, Bristol-Myers-Squibb, Eli Lilly, Janssen Cilag and Sanofi-Synthelabo and has received research grants from AstraZeneca, I3G and AOK (a health insurance company). P. Falkai has been honorary speaker for Janssen-Cilag, AstraZeneca, Eli Lilly, Bristol Myers-Squibb, Lundbeck, Pfizer, Bayer Vital, SmithKline Beecham, Wyeth and Essex. During the past 5 years, but not presently, Peter Falkai was a member of the advisory boards of Janssen-Cilag, AstraZeneca, Eli Lilly and Lundbeck.

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