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Exercise therapy, cardiorespiratory fitness and their effect on brain volumes: A randomised controlled trial in patients with schizophrenia and healthy controls

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Abstract
The objective of this study was to examine exercise effects on global brain volume, hippocampal volume, and cortical thickness in schizophrenia patients and healthy controls. Irrespective of diagnosis and intervention, associations between brain changes and cardiorespiratory fitness improvement were examined. Sixty-three schizophrenia patients and fifty-five healthy controls participated in this randomised controlled trial. Global brain volumes, hippocampal volume, and cortical thickness were estimated from 3-Tesla MRI scans. Cardiorespiratory fitness was assessed with a cardiopulmonary ergometer test. Subjects were assigned exercise therapy or occupational therapy (patients) and exercise therapy or life-as-usual (healthy controls) for six months 2 h weekly. Exercise therapy effects were analysed for subjects who were compliant at least 50% of sessions offered. Significantly smaller baseline cerebral (grey) matter, and larger third ventricle volumes, and thinner cortex in most areas of the brain were found in patients versus controls. Exercise therapy did not affect global brain and hippocampal volume or cortical thickness in patients and controls. Cardiorespiratory fitness improvement was related to increased cerebral matter volume and lateral and third ventricle volume decrease in patients and to thickening in the left hemisphere in large areas of the frontal, temporal and cingulate cortex irrespective of diagnosis. One to 2 h of exercise therapy did not elicit significant brain volume changes in patients or controls. However, cardiorespiratory fitness improvement attenuated brain volume changes in schizophrenia patients

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and increased thickness in large areas of the left cortex in both schizophrenia patients and healthy controls.

1. Introduction

In schizophrenia, structural brain abnormalities, in particular smaller grey matter volume, enlargement of lateral and third ventricles, decreased hippocampal volume, and cortical thinning have consistently been demonstrated (Hulshoff Pol et al., 2002; Shenton et al., 2001; Wright et al., 2000). Longitudinal studies have shown that these brain volume abnormalities are progressive in nature (Olabi et al., 2011), not only in the early phases of the illness (Pantelis et al., 2005) but also in chronic stages (Hulshoff Pol and Kahn, 2008; Kempton et al., 2010). These changes are related to the clinical course as several studies have shown that patients with poorest outcome have most pronounced brain loss over time (Cahn et al., 2009; Hulshoff Pol and Kahn, 2008; Pantelis et al., 2005; van Haren et al., 2008a). To explain these progressive brain volume reductions in schizophrenia, researchers have suggested that these reductions are core to the illness and could be due to the so-called "toxic" effects of the psychotic state of the brain (Lieberman et al., 2001; McGlashan, 2006; Seok et al., 2005). Some evidence has been provided by the findings of a five year follow-up MRI study which found longer duration of psychosis during follow-up was associated with more pronounced grey matter volume reductions and increases of ventricular volume (Cahn et al., 2009). In addition, it has been shown that genetic factors play a role in the progressive brain volume reductions in schizophrenia patients (Brans et al., 2008; Gogtay et al., 2007). Nevertheless, others have argued that volume decrease over time originates from (unhealthy) environmental factors patients with schizophrenia are frequently exposed to (Mathalon et al., 2003; Moncrieff and Leo, 2010; Navari and Dazzan, 2009; Rais et al., 2008, 2010; van Haren et al., 2011).

Indeed, alcohol abuse (Mathalon et al., 2003), cannabis use (Rais et al., 2008, 2010), and antipsychotic treatment (Moncrieff and Leo, 2010; Navari and Dazzan, 2009; van Haren et al., 2011) have been found to influence brain changes over time in schizophrenia. Furthermore, physical inactivity (Lindamer et al., 2008) and poor cardiorespiratory fitness (Strassnig et al., 2011) could also explain brain volume reductions seen in schizophrenia. If physical inactivity and poor cardiorespiratory fitness explain the brain volume reductions in schizophrenia, one would expect that the brain volume decreases will diminish when cardiorespiratory fitness increases. Interestingly, animal studies have unequivocally shown that physical exercise positively affects brain morphology, especially in the hippocampus, and brain functioning (van Praag, 2008, 2009). In healthy elderly, studies have shown that exercise increases cerebral grey and white matter (Colcombe et al., 2006) and hippocampal volumes (Erickson et al., 2011). As far as we know only one neuroimaging study has been performed examining the effects of exercise in schizophrenia (Pajonk et al., 2010). They examined the hippocampal volume and found hippocampus volume enlargement after three months of exercise in male patients ($n=8$). Moreover, this increase was related to

cardiorespiratory fitness improvement (Pajonk et al., 2010). They did not examine the effects on global brain volume nor on cortical thickness.

This study examines the effect of exercise therapy on global brain volume, hippocampus, and cortical thickness in schizophrenia patients and healthy controls. Since we recently showed that exercise therapy in schizophrenia improves cardiorespiratory fitness, in particular peak workload (measured as W_{peak}) (Scheewe et al., 2012) we also investigated the association between changes in global brain volumes, hippocampus and cortical thickness and change in cardiorespiratory fitness.

2. Experimental procedures

2.1. Sample and setting

This multicentre study included 63 patients with a schizophrenia spectrum disorder and 55 healthy controls, matched for gender, age, and socioeconomic status of their parents (expressed as highest educational level of one of the parents). Patients were recruited at the University Medical Center Utrecht (The Netherlands), the Institute for Mental Health Care Altrecht (Utrecht, The Netherlands), GGZ Duin- en Bollenstreek (Voorhout, The Netherlands), and GGZ Friesland (Heerenveen, The Netherlands). Participants were enroled in the study between May 2007 and May 2010 and written informed consent was obtained after the procedures and possible side effects were explained. After baseline measurement, a computer-generated randomisation procedure, incorporating concealed allocation (ratio 1:1), was performed with stratification for gender, recruitment site and Body Mass Index (BMI; below or above critical 25). Patients were assigned to exercise therapy or occupational therapy whereas controls were assigned to exercise therapy or life as usual for six months. Patients had a diagnosis of schizophrenia ($n=45$), schizoaffective ($n=15$) or schizophreniform disorder ($n=3$) according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatri Association, 2000). Diagnosis was confirmed by psychiatrists using the Comprehensive Assessment of Schizophrenia and History (CASH) (Andreasen et al., 1992). Patients were stable on antipsychotic medication, i.e. using the same dosage for at least four weeks prior to inclusion. They showed no evidence for significant cardiovascular, neuromuscular, endocrine or other somatic disorders that prevented safe participation in the study (IOC Medical Commission, 2004). Patients did not have a primary diagnosis of alcohol or substance abuse and had an IQ$\geq$70, as measured with the Wechsler Adult Intelligence Scale Short Form (WAIS-III SF) (Christensen et al., 2007).

Healthy participants were recruited via advertisements from the local population. The inclusion criteria for the healthy controls were an age between 18 and 48 years, no diagnosis of psychiatric disorders according to DSM-IV lifetime (American Psychiatric Association, 2000), no first-degree relative with a psychotic or depressive disorder, and being physically inactive before inclusion (i.e., undertaking less than 1 h of moderate physical activity weekly).

The study was approved by the Human Ethics Committee of the University Medical Center Utrecht and research committees of participating centres.

2.2. Assessments

All subjects underwent a six months intervention. Demographic and clinical baseline and follow-up measurements were assessed by a research assistant and sports physician blind to randomisation. All assessments at baseline and follow-up were acquired within a time frame of 14 days.

2.2.1. Cardiorespiratory fitness testing

Cardiorespiratory fitness (CRF) was assessed with a cardiopulmonary exercise test (CPET), performed using a 20 W per minute (W/min) stepwise incremental protocol to exhaustion on a cycle ergometer (Lode Excalibur, Lode BV, Groningen, the Netherlands) (Godfrey, 1974). CRF was defined as the peak work rate at the moment of exhaustion (W_{peak} in wattage (W)) (Astorino, 2009). Heart rate (twelve led ECG) and oxygen uptake were measured continuously during the CPET (MetaLyzer® 3B, Cortex Medical GmbH, Leipzig, Germany). Maximal efforts were assumed when the respiratory exchange rate (RER) equalled or exceeded 1.1 (Doherty et al., 2003).

2.2.2. Symptom severity and medication

To evaluate severity of symptoms, the Positive and Negative Syndrome Scale (PANSS) total score was assessed in patients (Kay et al., 1988). Information on amount, type and compliance of prescribed antipsychotic and other medication was gathered for lifetime, at baseline and monthly between baseline and six months. Antipsychotics are described in cumulative dosage (up to baseline and baseline to follow-up) and converted into haloperidol equivalents (clozapine, 40:1; olanzapine, 2.5:1; risperidone, 1:1; aripiprazole, 3.75:1; quetiapine, 50:1; pimozide, 0.85:1; pipamperon, 50:1; penfluridol, 1:1; broomperidol, 1:1; zuclopentixol, 5:1; haloperidol, 1:1 in conformance with a table from the Dutch National Health Service) (Commissie Farmaceutische Hulp, 2002). Detailed information on medication prescription and compliance was assessed monthly by the research assistant.

2.2.3. Imaging and preprocessing

Structural MRI scans of the whole brain were acquired on a single 3 T Achieva medical scanner (Philips, Best, The Netherlands). A three dimensional (3D) anatomical T_1-weighted image of the whole head was acquired (Fast Field Echo (FFE) using parallel imaging; 180 0.8-mm contiguous sagittal slices, echo time [TE]=4.6 ms, repetition time [TR]=10 ms, flip angle=90°, Field of View (FOV)=240 mm/100%, in-plane voxel size 0.75×0.75 mm², reconstruction matrix=$200 \times 320 \times 320$). Volumetric processing was performed on the computer network of the Department of Psychiatry of the Brain Division, University Medical Center Utrecht, The Netherlands. All brain images were coded to ensure investigator blindness to subject identification.

2.2.4. Volumetric processing

The T1-weighted images were automatically placed in Talairach orientation (Talairach and Tournoux, 1988) without scaling, by registering them to a model brain. Intracranial masks were created by registration from the T1-weighted image to a model brain using an iterative process of non-linear transformations with increasing precision up to voxel resolution. This model brain was created from an independent group of schizophrenia patients, their siblings and healthy controls (Boos et al., 2011) following a similar procedure as described previously (Peper et al., 2008). Intracranial masks were manually edited, where necessary. The intracranial segment served as a mask for all further segmentation steps. The T1-weighted images were corrected for field inhomogeneities using the N3 algorithm (Sled et al., 1998). An automatic image-processing pipeline was used to define the volume of the cerebrum, cerebral grey matter and white matter (Brouwer et al., 2010). In short, pure grey and white matter intensities were directly estimated from the image. The amounts of pure and partial volume voxels were modelled in a non-uniform partial volume density, which is fitted to the intensity histogram. Expected tissue fractions, based on the pure intensities and the partial volume density, were subsequently computed in each voxel within the cerebrum. Total brain volume was calculated by adding the grey and white matter volumes. Lateral and third ventricle volumes were also assessed. The software included histogram analysis, mathematical morphology operations, and anatomical knowledge-based rule to connect all voxels of interest, as was validated before (Schnack et al., 2001). The segments for lateral and third ventricles were visually checked and edited to ensure an accurate segmentation.

2.2.5. Hippocampus volume

Measurement of hippocampal volume was done using automated hippocampal volume methodology (FMRIB software library, FSL 4.1). Hippocampi were automatically labelled using the subcortical segmentation routines "FIRST," provided as part of the FSL software distribution (version 4.1.2, http://www.fmrib.ox.ac.uk/fsl/). Before starting the FSL-FIRST-based segmentation the T1-weighted images were automatically placed in Talairach orientation as described earlier. The initial step for FSL-FIRST was an affine registration of each brain to MNI-152 space (Mazziotta et al., 2001). The correct affine registration was visually confirmed in all cases. The number of modes of variation for the hippocampal template to be warped to fit the individual hippocampi was set to 300. Each automatically segmented hippocampus was saved as an inclusive binary mask in the same space as the original image. The volumes of right and left hippocampi were extracted. See also ENIGMA Consortium protocols, http://enigma.loni.ucla.edu/protocols/.

2.2.6. Cortical thickness

To estimate cortical thickness, we used the CLASP (Constrained Laplacian Anatomic Segmentation Using Proximity) algorithm designed at the McConnell Brain Imaging Centre of the Montreal Neurological Institute (Kabani et al., 2001; Kim et al., 2005; MacDonald et al., 2000). A 3-dimensional surface consisting of 81,920 polygons was fitted to the white matter-grey matter interface. This defined the inner surface of the cortex, which was then expanded to fit the grey matter-cerebrospinal fluid interface, thereby creating the outer cortical surface (Kim et al., 2005; MacDonald et al., 2000). Cortical thickness was estimated by taking the distance between the two surfaces; thus, each polygon vertex on the outer surface had a counterpart vertex on the inner surface. The surfaces of both measurements for each participant were registered to an average surface created from 152 individuals (Lyttelton et al., 2007), allowing comparison of cortical thickness locally between participants at baseline and the follow-up measurement. Region-of-Interests (ROIs) were automatically segmented using the automated anatomical labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002), resulting in 78 ROIs (39 for both left and right hemispheres). For each person, the change in cortical thickness was calculated for each of the AAL areas.

2.3. Intervention

The exercise therapy intervention was designed to improve CRF and primarily incorporated cardiorespiratory exercises. Cardiorespiratory exercises were performed using the following exercise equipment: upright bicycle ergometer, recumbent bicycle ergometer, rowing machine, cross-trainer, and treadmill. In addition, muscle strength exercises (six exercises per week; three times 10-15 repetitions maximum for biceps, triceps, abdominal, quadriceps, pectoral, deltoid muscles) were included to provide variation. The programme followed the recommendations of the American College of Sports Medicine (American College of Sports Medicine, 1998;

Kraemer et al., 2002). Exercise therapy was supervised by a psychomotor therapist specialised in psychiatry. Information on amount of training and compliance was registered in a logbook. Exercise therapy subjects were prescribed an hour of exercise, consisting of both cardiovascular exercises (40 min) and muscle strength exercises (20 min) twice weekly for six months. To prevent dropout of patients due to injury and exhaustion, exercise intensity was increased stepwise (week 1-3: 45%; week 4-12: 65%; week 13-26: 75% of heart rate reserve based on baseline CPET) (American College of Sports Medicine, 1998).

Patients not randomised to physical therapy were offered occupational therapy by an occupational therapist 1 h twice weekly for six months. Occupational therapy comprised creative and recreational activities. Compared to exercise therapy, occupational therapy provided a similar amount of structure and attention, but no physical activation.

2.4. Statistical analysis

SPSS 18.0.1 was used to analyse the demographic and brain volume data. All statistical tests were performed two-tailed and a p-value of <0.05 was considered significant. Data were examined for outliers. Analyses were performed with and without outliers to examine their impact on the results. In case of non-normal distribution logarithmic transformation was applied, or non-parametric testing was performed.

Previously, exercise therapy was found to reduce symptom severity (Marzolini et al., 2009) and increase hippocampal volume in schizophrenia patients (Pajonk et al., 2010). Moreover, parahippocampal gyrus growth was only seen in schizophrenia patients with a higher intelligence (Brans et al., 2010). In case of significant brain volume change results, PANSS total change, antipsychotic medication used between baseline and follow-up (in haloperidol equivalent), and intelligence were added to analyses to investigate whether these factors explain results.

All analyses were performed in those subjects who were compliant at least 50% of 52 sessions, unless stated otherwise. The minimal compliance demand is chosen since a minimal workload of at least 1 h weekly is needed to be able to expect any effect in untrained subjects (Kraemer et al., 2002)

2.4.1. Baseline comparisons

Multiple analyses of variance for non-categorical variables and χ^2 analyses for categorical variables were used to examine differences between groups in demographics and clinical characteristics. Univariate analyses were used to examine baseline brain volume differences between patients and controls and between exercise therapy and occupational therapy/life-as-usual. For measures of cortical thickness, regression analyses were used, with gender, age and handedness as covariates to investigate main effects for group, intervention and the interaction between group and intervention.

2.4.2. Brain volume change

Brain volume change was calculated by subtracting baseline volume from follow-up volume. To assess the differential effect of intervention (exercise therapy versus occupational therapy/life-as-usual) on brain volume (change) between the groups multiple linear regression analyses were performed. For cerebrum, cerebral grey and white matter, lateral and third ventricles, and hippocampal volume, change was added as the dependent variable in analyses. Group (patient or control), intervention (exercise therapy or occupational therapy/life-as-usual), and the group × intervention interaction were the independent variables. Intracranial volume, gender, and age were included as covariates.

For cortical thickness, regression analyses were used with age, gender, and handedness as covariates, to examine change in thickness per AAL region. This produced F statistics at each AAL region for the effect of group (patient versus controls), intervention

(exercise therapy versus occupational therapy/life-as-usual), and group × intervention. We adjusted for multiple comparisons using a False Discovery Rate (FDR=0.05, two-tailed) (Genovese et al., 2002). In addition, mean cortical thickness change in each hemisphere was investigated using regression analyses, using the same covariates.

2.4.3. Effect CRF change on brain volume

Previously, we showed that W_{peak} improved after exercise therapy compared to occupational therapy in patients with schizophrenia (Scheewe et al., 2012). We therefore performed further analyses to examine whether an increased CRF ameliorated brain volume deterioration in patients with schizophrenia and investigated whether this effect is seen in healthy controls, independent of intervention. To assess the effect of CRF change on brain volume (change) multiple linear regression analyses were performed on all included subjects with two successful scans (so not using the 50% compliance criterium). For cerebrum, cerebral grey and white matter, lateral and third ventricles, hippocampal volume, and cortical thickness, change was the dependent variable in analyses. Group (patient or control), CRF-change, measured as W_{peak}-change, and an interaction group × W_{peak}-change were the independent variables. Intracranial volume, gender and age were included as covariates when investigating brain volume change. Handedness, gender and age were included as covariates when investigating cortical thickness change.

3. Results

In total, 31 patients were randomised to exercise therapy and 32 patients to occupational therapy, whereas 27 healthy controls were randomised to exercise therapy and 28 to life-as-usual (see study diagram in Figure 1). Diagnostic subgroups were equally distributed between exercise therapy (schizophrenia: n=24; schizoaffective disorder: n=6; schizophreniform disorder: n=1) and occupational therapy patients (schizophrenia: n=21; schizoaffective disorder: n=9; schizophreniform disorder: n=2; $\chi^2(4)$=1.67, p= 0.80). Drop-out of patients was significantly higher in the occupational therapy (n=7) compared to the exercise therapy group (n=2, $\chi^2(2)$=8.33, p=0.02).

Mean number of attended sessions did not differ significantly between exercise therapy patients (mean ± SD; 41 ± 8), exercise therapy controls (44 ± 7), and occupational therapy patients (43 ± 7; $F(2,58)$=1,37, p=0.26). Detailed baseline demographic and clinical data are depicted in Table 1.

3.1. Baseline volumes

After controlling for age, gender, and intracranial volume, patients had significantly lower baseline volumes of the cerebrum ($F(1,77)$=0.763, p=0.007), cerebral grey matter ($F(1,77)$=10.95, p=0.001), and higher baseline volumes of the third ventricle ($F(1,77)$=8.14, p=0.006). In addition, the mean cortical thickness in each hemisphere was significantly smaller in patients as compared with controls (left: $F(1,77)$=17.69, $p<0.001$; right: $F(1,77)$=12.64, p=0.001) (see Table 2). Locally, the cortex was thinner in almost all parts of the brain in patients relative to controls, reaching significance (FDR corrected: right $p<0.030$ and left $p<0.036$) in 26 out of 39 ROIs in the right hemisphere and 33 out of 39 ROIs in the left hemisphere. No significant
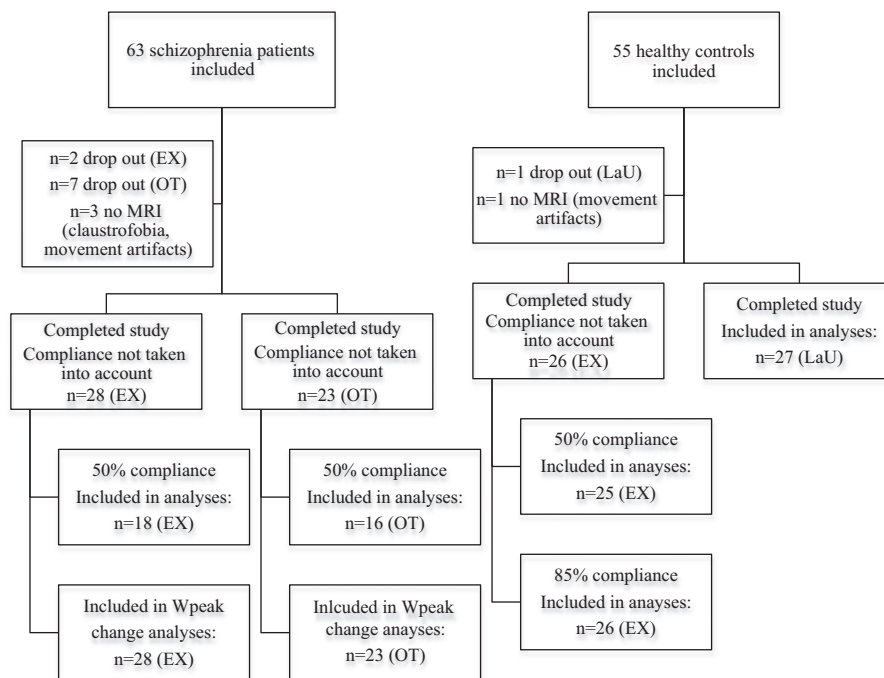
Figure 1 Study diagram for exercise therapy (EX) and occupational therapy (OT) patients, EX and life as usual (LaU) controls.

difference in volumes of cerebral white matter ($F(1,77)=$ 0.11, $p=0.74$), hippocampus ($F(1,76)=0.67$, $p=0.42$), and lateral ventricles ($F(1,77)=1.97$, $p=0.17$) were found (see Table 2). No differences were found in brain volumes and cortical thickness at baseline between those patients assigned to exercise versus occupational therapy or in controls assigned to exercise therapy versus life-as-usual.

3.2. Brain volume change

No significant main effect for group or intervention nor interaction effects between the two were found for change in cerebral, cerebral grey and white matter, lateral and third ventricle volume (see Table 2). For change in hippocampal volume, group or intervention effects were not significant, the interaction effect reached trend level significance ($p=0.05$). In schizophrenia patients, hippocampal volume decreased slightly after exercise therapy with no change after occupational therapy; the opposite effect was observed in healthy controls. No significant main effect for group or intervention nor an interaction effect was found for change in cortical thickness. Thus, exercise therapy, once to twice a week for 1 h during six months did not increase global brain volume, hippocampal volume, or cortical thickness in schizophrenia patients or healthy controls.

3.3. Effect CRF change on brain volume

For this analysis all individuals who had two MRI scans and two CRF measures were included. Interaction effects between CRF improvement and group were found. CRF improvement was significantly related to cerebral matter volume increase (0.164 ml/W; $p=0.045$), lateral ventricle (-0.018 ml/W; $p=0.035$) and third ventricle volume decrease (-0.0018 ml/W; $p=0.013$) in patients but not in

healthy controls (cerebral matter: -0.001 ml/W; $p=0.990$; lateral ventricle volume: 0.002 ml/W; $p=0.745$; third ventricle volume: 0.0003 ml/W; $p=0.510$; see Table 3 and Figure 2). CRF improvement was, at trend-level significance, related to increase in cerebral grey matter (0.159 ml/W; $p=0.059$) in patients but not in healthy controls (cerebral grey matter: -0.019 ml/W; $p=0.763$; see Table 3). Exclusion of outliers did not change findings except for lateral ventricle volume where exclusion of one outlier led to a trend-level significant effect of CRF improvement (-0.013 ml/W; $p=0.078$). Addition of symptom severity (PANSS total) change, antipsychotic medication use, and intelligence as covariates in the analyses had no influence on these results. In addition, CRF improvement was significantly associated with thickening (or less thinning) in the left hemisphere only ($t>2.29$, $p<0.024$ after FDR correction), in large parts of the frontal, temporal and cingulate cortex (see Figure 3). In the right hemisphere all but four t-values were positive as well, indicating a thickening of the cortex (or less thinning) being associated with an increase in CRF, but none of the areas reached significance. For cortical thickness change, no significant interaction between Group and CRF change was found.

4. Discussion

This six-month randomised controlled trial investigated the effect of exercise therapy on global brain volumes, hippocampal volume and cortical thickness in patients with schizophrenia and healthy volunteers. In addition, cardiorespiratory fitness improvement achieved after six-months of exercise was related to the brain changes. At baseline, in line with a large body of evidence (Hulshoff Pol et al., 2002; Shenton et al., 2001; Wright et al., 2000), we found smaller cerebral and grey matter volumes, larger third ventricle

Table 1 Demographic and clinical characteristics of all exercise therapy (EX) and occupational therapy (OT) patients, EX and life as usual (LaU) controls with baseline and follow-up MRI and compliance of at least 50% of 52 sessions.

Characteristic	Treatment				Statistic	p
	Patients (n=32)		Controls (n=52)			
	EX (n=18) N	OT (n=14) N	EX (n=25) N	LaU (n=27) N		
Gender (male/female)[a]	14/4	12/2	18/7	18/9	1.93	0.59
CASH (schizophrenia/295.7/295.4)[a]	14/3/1	10/4/0			1.33	0.51
Parental education level (number of subjects (educational level: 2,3,4,5,6,7))[b, a]	0,1,5,6,4,2	0,0,2,5,4,3	0,0,1,8,8,8	1,0,4, 8,10,4	13.70	0.55
	Mean **SD**	**Mean** **SD**	**Mean** **SD**	**Mean** **SD**		
Age (year)[c]	28.5 7.3	31.1 8.0	29.5 8.3	28.4 7.0	0.44	0.72
Length (cm)[c]	178.9 10.9	178.6 5.6	180.5 10.6	176.6 9.8	0.71	0.55
Baseline weight (kg)[c]	85.8 18.8	85.2 20.1	78.2 16.6	74.6 12.4	2.28	0.09
Follow-up weight (kg)[c]	84.6 16.2	87.6 21.6	78.0 16.0	74.7 12.6	2.61	0.06
Baseline BMI (kg/m^2)[c]	27.2 7.5	26.6 5.7	23.8 3.4	23.9 3.1	2.67	0.05
Follow-up BMI (kg/m^2)[c]	26.7 6.2	27.4 6.3	23.8 3.3	23.9 3.0	3.23	**0.03**
Baseline VO$_{2peak}$ (ml/min/kg)[c]	32.0 9.1	34.8 12.5	36.7 5.7	35.6 5.4	1.33	0.27
Follow-up VO$_{2peak}$ (ml/min/kg)[c]	32.6 9.4	31.5 9.6	39.2 7.8	36.2 7.0	3.50	**0.02**
Baseline W_{peak} (W)[c]	221.6 43.5	247.9 57.9	265.6 54.3	247.4 54.9	2.41	0.07
Follow-up W_{peak} (W)[c]	247.6 40.9	236.1 52.6	275.2 68.3	243.7 57.9	1.94	0.13
Baseline WAIS Total IQ[c]	84.8 12.0	99.1 22.1	111.8 13.2	105.8 14.0	12.10	**<0.001**
Baseline PANSS total score[d, c]	61.4 11.2	59.0 10.2			0.35	0.56
Follow-up PANSS total score[d, c]	54.8 12.1	58.9 9.8			1.05	0.31
Duration of illness (years)[c]	6.0 5.7	7.9 5.0			0.93	0.34
Hospitalisation until baseline (days)[e]	109.9 107.0	268.0 398.4			105.000	0.43
Baseline HEQ dose (mg/day)[f, c]	7.3 6.2	9.2 4.5			0.847	0.37
HEQ baseline to follow-up (mg)[g, c]	1489.1 1331.7	1821.2 975.9			0.61	0.44

Significant differences at <0.05 level are presented in bold.
EX, OT, and LaU were compared (at baseline) on relevant demographic and clinical characteristics.
[a]Chi-square were used.
[b]Psychosocial status, expressed as highest level of education of one of both parents according to Verhage, 1983.
[c]ANOVA was used.
[d]PANSS total score: Positive and Negative Syndrome Scale assesses severity of psychosis.
[e]Mann–Whitney U-tests was used.
[f]Baseline antipsychotic medication used in haloperidol equivalent in milligrams per day.
[g]Antipsychotic medication used between baseline and follow-up MRI-scans in haloperidol equivalent in milligrams.

volume and thinning of most areas of the cortex in patients with schizophrenia as compared to healthy controls. There was no global brain volume, hippocampal volume and cortical thickness change over time in patients and healthy controls, who were randomised to the exercise therapy group, as compared to those subjects who were randomised to the occupational therapy or/life as usual groups. Nevertheless, overall improvement in cardiorespiratory fitness in the patients was associated with an increase in total cerebral matter volume (or less volume decrease) and attenuated increase (or even decrease) in lateral and third ventricle volumes.

In addition, improvement in cardiorespiratory fitness was associated with cortical thickening (or less thinning) in the left hemisphere in patients with schizophrenia as well as in

healthy controls. This suggests that moderate exercise induces subtle changes in cerebral (grey matter) volume most clearly (at least measurably) expressed in changes in cortical thickness. The underlying mechanisms of brain volume increases as a result of improved fitness are still unknown, but increased production of neurotrophic growth factors, improved vascularisation, and improved energy metabolism, all of which are of central importance in neurogenesis (Cotman and Berchtold, 2002; van Praag, 2008, 2009) seem to play a role. Given the crucial role exercise plays in neuronal plasticity, exercise therapy may ameliorate brain abnormalities in schizophrenia.

Failing to find an association between global brain volumes and cardiorespiratory fitness in healthy controls could be related to the young mean age of the subjects

Table 2 Raw baseline and follow-up brain volumes in subjects with a minimal compliance of 50% of 52 sessions. In column I, unstandardised regression coefficients b indicate the brain volume change in patients relative to controls (i.e. main effect of group). Columns II and III provide the results from the interaction between group and intervention. Column II shows the effect of exercise in controls only, and column III shows the additive effect of exercise in patients, corrected for sex, age and intracranial volume, in which b represents the corrected volume difference in millilitres.

Outcome variables	Patients (n = 32)				Controls (n = 52)				I			II			III		
	EX (n = 18)		OT (n = 14)		EX (n = 25)		LaU (n = 27)		Changes in patients compared to controls			Effect of exercise in controls only			Additive effect of exercise in patients		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	b	t	p	b	t	p	b	t	p
Intracranial volume																	
Baseline	1520.8	139.4	1526.1	130.4	1506.8	135.6	1535.8	132.5									
Follow-up	1519.4	139.8	1524.6	131.2	1507.4	135.9	1535.1	132.1	−1.51	−1.28	0.21	1.36	1.3	0.2	−0.55	−0.33	0.74
Total cerebrum																	
Baseline	1100.4	111.5	1104.7	96.9	1113.5	103	1134.8	99.4									
Follow-up	1098.3	110.6	1102.1	100.1	1110.2	102	1134.3	97.1	−1.18	−0.33	0.74	−2.72	−0.89	0.37	2.62	0.53	0.6
Gray matter																	
Baseline	590.5	54.8	601	53.4	606.9	55.9	623.8	51.4									
Follow-up	589.2	52.3	596.6	58.4	602.1	56.8	622.3	50	−1.19	−0.34	0.74	−2.36	−0.8	0.43	4.68	0.98	0.33
White matter																	
Baseline	509.8	66.5	503.8	60	506.6	52.7	511	56									
Follow-up	509.1	67.3	505.6	59.1	508.1	52.2	512	55.9	0.01	0.004	1	−0.36	−0.2	0.84	−2.07	−0.71	0.48
Lateral ventricle																	
Baseline	16.89	7.92	17.88	9.9	14.39	8.1	14.64	9.04									
Follow-up	17.09	7.96	18.21	10.42	14.77	8.32	14.43	8.91	0.47	1.25	0.22	0.57	1.79	0.08	−0.68	−1.3	0.2
Third ventricle																	
Baseline	0.84	0.42	0.93	0.49	0.58	0.28	0.7	0.28									
Follow-up	0.84	0.39	0.96	0.56	0.59	0.29	0.67	0.27	0.05	1.47	0.15	0.03	1.05	0.3	−0.05	−1.16	0.25
Hippocampal volume																	
Baseline	8.01	0.8	7.99	0.7	8.07	0.66	8.13	0.87									
Follow-up	7.93	0.82	8	0.64	8.06	0.64	8.06	0.85	0.07	1.28	0.2	0.06	1.26	0.21	−0.14	−2	0.05

All global brain volume measurements are expressed in mean and SD millilitres (ml). The real effect of exercise in patients (in ml) is calculated by adding b in column II (effect in controls) to b in column III (additive effect in patients), significant differences at <0.05 level are presented in bold.

Table 3 The association between global brain volume change and CRF change (W_{peak}), expressed as the unstandardised b (in ml change/W change in W_{peak}) for healthy controls, and the additive effects in patients.

Outcome variables	All subject with two MRI-scans					
	W_{peak} Change			W_{peak} Change		
	In healthy controls only			Additive in patients		
	b	t	p	b	t	p
Cerebral volume change	−0.001	−0.012	0.99	0.164	2.03	**0.045**
Gray matter change	−0.019	−0.302	0.763	0.159	1.911	0.059
White matter change	0.018	0.346	0.73	0.005	0.077	0.939
Lateral ventricle change	0.002	0.327	0.745	−0.018	−2.138	**0.035**
Third ventricle change	0.0003	0.661	0.51	−0.0018	−2.539	**0.013**
Hippocampal volume	0.0004	0.473	0.637	0.0005	0.443	0.659

Results expressed as b which represents the corrected brain volume difference in millilitres, corrected for gender, age, and intracranial volume, significant differences at <0.05 level are presented in bold.
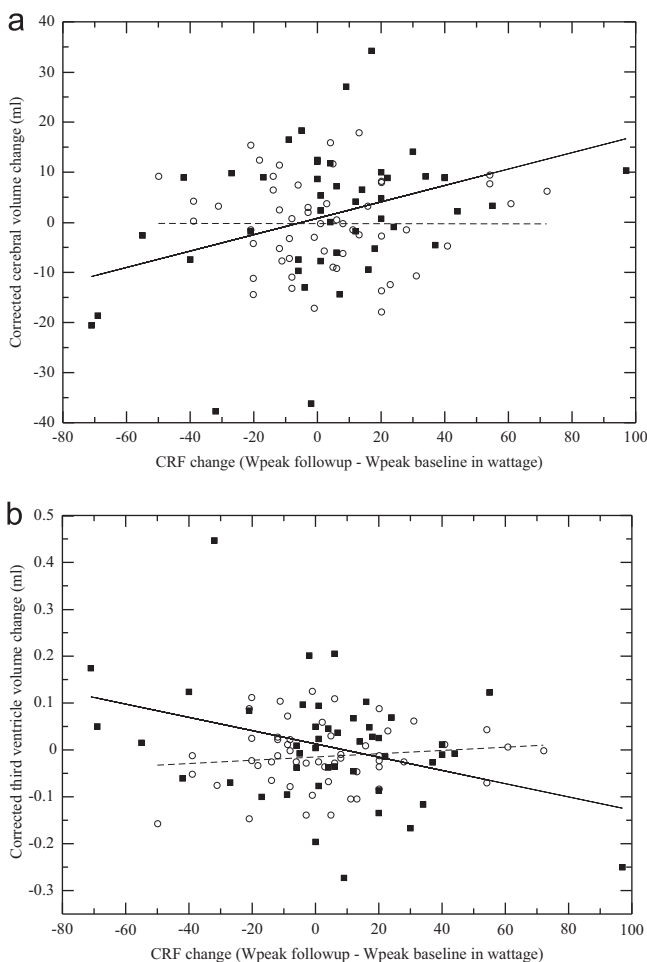

Figure 2 Scatterplot of relationship between cerebral (a) change (gray matter change looks similar) and third (b) ventricle volume change (lateral ventricle volume change looks similar) (in ml, corrected for gender, age, IC-volume) and CRF change in W_{peak} for patients (squares) and healthy controls (circles) with successful MRI-scans at baseline and follow-up.

since not many brain changes occur in this age span (van Haren et al., 2008b). In line with this explanation, a randomised trial showed exercise to increase both cerebral grey and white matter in sedentary older adults (Colcombe et al., 2006) whereas exercise was only found to attenuate the grey matter insula volume loss in young and mid-aged adults (Gondoh et al., 2009).

Exercise therapy did not cause hippocampal volume to increase in patients with schizophrenia nor in healthy controls. Furthermore, hippocampal volume change was not related to cardiorespiratory fitness improvement. As far as we know, only one MRI study examined the effects of exercise on brain volumes in schizophrenia. Pajonk et al. (2010) found hippocampal volume increased in schizophrenia patients randomised to 30 min of exercise three times weekly for three months (12%) as well as in exercising healthy controls (16% increase). In healthy elderly, after one year of exercise, the anterior hippocampal volume was increased but the posterior hippocampal volume was not affected by exercise (Erickson et al., 2011). Thus, failing to find an effect of exercise on hippocampal volume in our study is unexpected, as there is also robust evidence from animal studies that hippocampal neurogenesis occurs as a result of exercise (van Praag, 2008). The failure to find a relationship between exercise/cardiorespiratory fitness improvement and hippocampal volume possibly resulted from a low average weekly exercise frequency performed by patients in our study compared to Pajonk et al. (2010) (1.5 versus 2.6 exercise sessions weekly). Differences in results may also have resulted from the segmentation procedure which was used. Incorporation of manual segmentation of hippocampal volumes, as used by Pajonk et al. (2010), has shown to have higher reliability compared to automated segmentation (Morey et al., 2009) as used in the present study whereas automated procedures are less time consuming, less costly, and have no inter-rater and possibly lower intersession variability in a longitudinal design (Niemann et al., 2000).

Some limitations should be considered when interpreting the present results. First, due to drop out, poor quality MRI-scans,
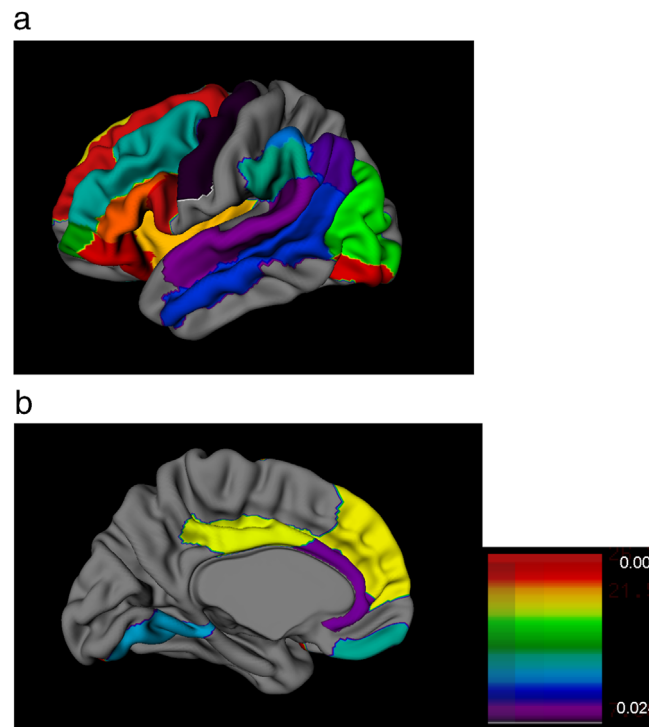
a

b

Figure 3 Lateral (a) and medial (b) view depicting significant association s between CRF improvement (W_{peak} change in W) and thickening (or less thinning) in the left hemisphere ,in large parts of the frontal, temporal and cingulate cortex.

and limited compliance, the final sample size for exercise therapy analyses was relatively small. The longitudinal exercise therapy analyses were performed on 62% of the initial number of included patients. Therapy adherence in schizophrenia patients is problematic and needs to be improved. As shown by two recent studies adherence to exercise regiments in schizophrenia can be increased by incorporation of motivational techniques (Beebe et al., 2011, 2012). Second, exercise frequency in the present study was limited namely one to two 1-h sessions weekly. This is lower than was previously incorporated by Pajonk et al. (2010). We suggest future studies incorporate a higher, for example three sessions weekly, exercise frequency. Third, this trial did not include a 'treatment as usual' and therefore we were unable to examine the differential effect of exercise therapy, occupational therapy versus treatment as usual. No follow-up measurements were performed in our study. Therefore, it remains unknown whether patients continued to exercise after trial cessation and whether improvement of cardiorespiratory fitness and associated global brain volumes and cortical thickness changes lasted.

In summary, our study shows that improvement in cardiorespiratory fitness is associated with cortical thickening in most areas of the left frontal, temporal, and cingulate cortices in schizophrenia patients and healthy controls. Fitness improvement is also associated with an increase in total cerebral matter volume increase (or attenuated volume decrease) and a decrease in lateral and third ventricle volume (or less increase) in the patients (not in the healthy controls). However, exercise therapy, at least when limited to 1–2 h weekly for six months as was the case in our study, did not elicit significant brain volume changes. Further research is warranted to examine whether exercise

therapy can ameliorate brain abnormalities in schizophrenia patients.

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Contributors

Scheewe, Cahn, Backx, and Kahn conceived, designed, and amended the original protocol. Kahn, Backx, and Cahn coordinated the study throughout. Scheewe, Cahn, and de Glint implemented and monitored data collections for the whole trial. Data cleaning and analyses were performed by Scheewe, van Haren, Sarkisyan, Schnack, and Cahn. Scheewe, van Haren, and Cahn wrote the first draft. Sarkisyan, Schnack, Brouwer, de Glint, Hulshoff Pol, Backx, and Kahn revised the paper. All authors contributed to and approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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