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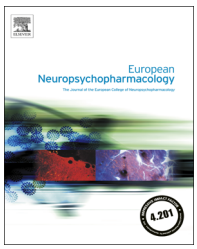

Exercise therapy, cardiorespiratory fitness and their effect on brain volumes: A randomised controlled trial in patients with schizophrenia and healthy controls

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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.