Neurobiological effects of physical exercise in schizophrenia: a systematic review

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Abstract

Purpose: The aim of the present systematic review was to provide a summary of neurobiological effects of physical exercise for people with schizophrenia. Methods: A systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. Searches were conducted up to April 2013 across three databases: Medline, PsycINFO, and Embase. A methodological quality assessment using the Downs and Black Quality Index was carried out with all of the included studies. Results: Of the 654 initial data search results, two studies reported in 3 articles including 48 patients (six women) with schizophrenia, met the eligibility criteria. The methodological quality of each study was high. Data on hippocampal volume changes following physical exercise were conflicting while physical exercise-induced changes in other brain areas were absent. Increases in hippocampal volume following physical exercise were correlated with improvements in aerobic fitness and short-term memory. Conclusions: Future research is needed to investigate whether brain health in people with schizophrenia is activity-dependent. Additionally, research that considers the neurobiological mechanisms and associated functional outcomes of physical exercise in individuals with schizophrenia is required.

Keywords

Physical activity, physical therapy, psychosis

Introduction

It is hypothesised that the pathophysiology of schizophrenia is associated with various neurobiological changes [1]. These neurobiological changes occur, in particular, in the monoamine system [2,3], neurogenesis system [4,5], the neuroimmune system [6] and in the hypothalamo–pituitary–adrenal (HPA) axis [7]. Genetic [8], molecular [2], and neuroimaging studies [9] continue to contribute to advances in our understanding of the neurobiological basis of schizophrenia. However, the extent to which findings from neurobiological studies can help improve the clinical and functional outcome of people with schizophrenia is uncertain [10]. The identification of single candidate genes associated with schizophrenia has been difficult because of the likelihood that schizophrenia is polygenic [11] and associated with interactions between genetic variants and environmental exposures [12,13]. Therefore, studying both the genes and environment (e.g. lifestyle factors) in schizophrenia may prove a fruitful strategy to identify variations that may give rise to both the psychotic vulnerability and the variability of its course [14,15].

In recent years, it has been demonstrated in the general population that an individual’s lifestyle and, in particular, exercise participation has important neurobiological effects [16], most prominently in the neurogenesis [17,18] and neuroimmune system [19,20] and on the HPA-axis [21]. Importantly, any observed effects are however specific to each mental health diagnosis [22]. For the purposes of this study, we will examine if neurobiological effects of physical exercise exist in individuals with schizophrenia.

Compared to the general population, individuals with schizophrenia are known to exercise less than the general population [23]. Previous reviews [24–26] concluded that physical exercise...
programmes have beneficial effects on physical and mental health parameters. Regular physical exercise is therefore an interesting complementary treatment recommended for individuals with schizophrenia provided they can overcome a lack of motivation [27]. However, a systematic review on the neurobiological effects of physical exercise in people with schizophrenia is currently lacking.

The first aim of the present systematic review therefore was to provide a summary of neurobiological effects of physical exercise for people with schizophrenia. The second aim was to explore neurological mechanisms responsible for any neurobiological effects of physical exercise and whether any neurobiological effects were related with improvements in functional outcomes.

Methods

Search strategy

Two independent reviewers (D.V. and A.H.) searched Medline, PsycINFO, and Embase from database inception to April 2013. Keywords used were [“schizophrenia” OR “psychosis”] AND [“exercise” OR “physical activity”] AND [“inflammatory” OR “neurogenesis” OR “BDNF” OR “dopamine” OR “serotonin” OR “monoamines” OR “inflammatory” OR “neurogenesis” OR “BDNF” OR “dopamine” OR “serotonin” OR “monoamines” OR “inflammatory” OR “neurogenesis” OR “BDNF” OR “dopamine” OR “serotonin” OR “monoamines” OR “inflammatory” OR “neurogenesis” OR “BDNF” OR “dopamine” OR “serotonin” OR “monoamines” OR “hypothalamic-pituitary-adrenal axis” OR “HPA” OR “cortisol” OR “oxidative stress”] in the title, abstract or index term fields. Manual searches were also conducted using the reference lists from all of the included articles.

Eligibility criteria

Studies were included if they met the following criteria: (a) studies in people with a Diagnostic and Statistical Manual of Mental Disorders – Fourth Text Revision (DSM-IV) [28] or International Classification of Diseases – Tenth Revision (ICD-10) [29] diagnosis of schizophrenia on stable medication following an exercise programme; (b) if studies were randomised controlled trials, placebo conditions, any control interventions with a similar duration, or standard care were allowed as control interventions. Standard care was defined as care that people would normally receive had they not been included in the research trial. Such care would include medication, hospitalization, community psychiatric nursing support, and outpatient care; and (c) at least one relevant biomarker related to brain health, inflammation, neurotransmitters, oxidative stress or the hypothalamic–pituitary–adrenal axis was measured. Studies were excluded if: (a) they reported non-exercise intervention components (i.e. hypocaloric diet); (b) it were abstracts from conferences and review papers. If there was any overlap in data (e.g. neurobiological outcomes) only the most recent study was included. There were no limitations regarding study design or language.

Data extraction

Two reviewers (A.D.H./D.V.) independently extracted data from the included studies using a predetermined form. The form captured data in five domains including (a) characteristics of the sample, (b) study designs, (c) exercise protocols performed, (d) neurobiological assessment tools/outcomes, (e) chosen biomarkers, (f) underlying mechanisms for neurobiological effects, and (g) associated functional outcomes. Overlap in data was only allowed if other neurobiological outcomes, underlying mechanisms or associated functional outcomes were investigated.

Data synthesis

On the basis of the first full-text screening, we identified that the data available was limited. Further to this, there was too much heterogeneity in protocols, outcomes investigated and assessment tools to apply a formal meta-analysis. Findings are presented as a narrative synthesis.

Methodological quality assessment

Two reviewers (D.V. and A.H.) independently assessed the methodological quality of included articles using the Downs and Black Quality Index [30]. The Downs and Black Quality Index has 27 questions grouped into five sections: (a) reporting, (b) external validity, (c) internal validity, bias, (d) internal validity, confounding, and (e) power. The aggregated maximum possible score is 32, with higher scores indicating greater methodological quality. When rating discrepancies occurred, the two reviewers resolved differences by consensus with a third reviewer to achieve a single score. Inter-rater reliability of the methodological assessment of the ratings in this study, using the intraclass correlation coefficient (ICC), was 0.95 (95% confidence interval = 0.92–0.96) for the Downs and Black score.

Results

Search results

The initial electronic database search resulted in a total of 654 studies. Through an additional hand search of reference lists three other potentially eligible articles were identified. Of the 14 potentially eligible articles, 2 studies reported in 3 articles [31–33] were finally included in this review. Full details of the search and reasons for exclusion of studies are shown in Figure 1.

Included participants with schizophrenia

The number of included participants with schizophrenia ranged from 16 to 32 in each study providing an overall number of 48 unique patients, of which 6 were women. All studies included relatively young but multi-episode patients with schizophrenia with the mean age ranging from 28.4 to 32.9 years. There were no studies available in drugs-naive or first-episode patients. The mean total Positive and Negative Symptoms Scale score [34] ranged from 59 to 74. The characteristics of the included studies are presented in Table 1.

Interventions in the included studies

All the interventions consisted of well-defined physical exercise. In the study of Scheewe et al. [33] aerobic exercise was combined with strength training in the studies of Pajonk et al. [31] and Falkai et al. [32] the intervention consisted of cycling on an ergometer. The durations of the interventions ranged from 3 to 6 months. The frequency of the included physical exercise programmes ranged from 2 to 3 times a week while the intensity was defined by either heart rate (±10 beats/min) corresponding to a blood lactate concentration of about 1.5 to 2 mmol/L or a stepwise increase from 45 to 75% of heart rate reserve.

Methodological quality assessment

Scores on the Downs and Black Quality Index [30] ranged from 28 [32] to 29 [31,33]. Significant limitations for each study are summarised in Table 2. Most common limitations were lack of intention-to-treat, the limited sample sizes and the questionable external validity due to potential selection biases.

Exercise and its effect on brain health and associated functional outcomes

All studies investigated the effect of physical exercise on brain health. As can be noticed in Table 1, Pajonk et al. [31] found...
significant increases in hippocampal volume in patients with schizophrenia after 12 weeks, 3 times a week, 30 min cycling at moderate intensity corresponding to a blood lactate concentration of about 1.5 to 2 mmol/L (14–18 mg/dL) derived from the results of the maximal incremental ergometer cycle test at baseline. However, Scheewe et al. [33] observed no significant changes in hippocampal volume following 6 months twice a week aerobic and strength training at an intensity of 45 to 75% of the heart rate reserve based on a baseline maximal incremental ergometer cycle test (see Table 1). Falkai et al. [32] did not show any changes in cortical volume in patients with schizophrenia after 12 weeks, 3 times a week, 30 min cycling at moderate intensity (see Table 1).

As can be noticed in Table 1, in the study of Pajonk et al. [31], a significant positive correlation was found between the change in relative hippocampal volume and the change in maximal oxygen uptake. Aerobic exercise also led to a 34% improvement in the short-term memory of persons with schizophrenia, as measured with the Rey Auditory Verbal Learning Test (RAVLT). No improvement of memory scores were found in healthy controls. In persons with schizophrenia, however, the long-term memory score as measured with the RAVLT and visuospatial short-term memory as measured with the Corsi Block Span Score did not change significantly (data not reported in Table 1). For the total schizophrenia group in the Pajonk study [31], the change in hippocampal volume correlated with the change in short-term memory ($r = 0.51; p < 0.05$).

Exercise and its effect on inflammation
No study investigated the effects of physical exercise on inflammatory markers in patients with schizophrenia.

Exercise and its effect on monoamines
No study investigated the effects of physical exercise on monoamines in patients with schizophrenia.

Exercise and its effect on the HPA-axis
No study investigated the effects of physical exercise on the HPA-axis in patients with schizophrenia.

Discussion
General findings
To the best of our knowledge the present systematic review is the first to investigate neurobiological effects of physical exercise in patients with schizophrenia. Research has only very recently started to explore neurobiological mechanisms related to physical exercise in people with schizophrenia. The available evidence therefore is limited to only 2 studies reported in 3 articles. Data considering the effects of physical exercise on inflammatory markers, monoamines or the HPA-axis was not considered within any of the studies.

While Pajonk et al. [31] were able to demonstrate volume expansion in the hippocampus of multi-episode schizophrenia patients after physical exercise, Falkai et al. [32] did not find physical exercise-induced changes in the cortical areas in the same sample. As sample sizes in the physical exercise conditions were small, it is possible that effects in favour of cortical gray matter increasing could be detected with larger patient samples. It might however also be the case that antipsychotic medication use is an important confounding variable. Antipsychotic medication is known to have some influence on cortical volume while influencing hippocampal volumes to a lesser extent [35], and regeneration capacity may therefore be attenuated in the cortical areas.

Similar significant increases in the size of hippocampal brain areas following physical exercise have been reported previously as well in elderly [36] and in patients with Alzheimer Disease [37].

However, there was conflicting data from the included studies that considered the effects of physical exercise on hippocampal volume in patients with schizophrenia. While Pajonk et al. [32] found hippocampal volume increased after 30 min of physical exercise 3 times weekly for 3 months (12%), Scheewe et al. [33] did not find any changes in patients randomised to 60 min of aerobic and strength training twice a week for 6 months. However, it is important to recognise factors that can be used to explain such difference. For example there was a lower average weekly exercise frequency performed by patients in the study undertaken by Scheewe et al. [34] (1.5 exercise sessions/week) compared to the study undertaken by Pajonk et al. [31] (2.6 exercise sessions/week). Differences in results may also have resulted from differences in assessment procedures, and in particular the brain segmentation or the delineation of neuroanatomical structures in magnetic resonance images. Incorporation of manual segmentation of hippocampal volumes, as used by Pajonk et al. [31], has shown to have higher reliability [38] compared to automated segmentation as used in the study of Scheewe et al. [33].
SMRI was carried out using a 1.5-T scanner (Sonata; Siemens, Erlangen, Germany). A T1-weighted MPRAGE sequence (echo time = 1900 ms, inversion time = 700 ms, flip angle = 15°, field of view, 256 x 256 mm) of 176 consecutive slices was acquired with a voxel size of 1 x 1 x 1 mm.

Table 1. Overview of the included articles in patients with schizophrenia.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Participants</th>
<th>Intervention</th>
<th>Neurobiological assessment tools</th>
<th>Neurobiological outcomes and underlying mechanisms</th>
<th>Associated functional outcomes</th>
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<tbody>
<tr>
<td>Pajonk et al. [31]</td>
<td>RCT</td>
<td>16 male patients with a ICD-10 and DSM-IV-I diagnosis of schizophrenia; 8 exercisers (mean age = 32.9 ± 10.6 yrs; mean illness duration = 9.8 ± 1.4 yrs; total PANSS = 68.1 ± 17.6) and 8 non-exercisers (mean age = 37.4 ± 8.1 yrs; mean illness duration = 12.5 ± 4.5; total PANSS = 65.9 ± 13.4).</td>
<td>Experimental: 12 weeks, 3 x week, 30 min cycling a heart rate (±10 beats/min) corresponding to a blood lactate concentration of 1.5 to 2 mmol/L, derived from the results of the maximal incremental ergometer cycle test at baseline (average of sessions attended = 2.6 per week). Control: 12 weeks, 3 x week, 30 min table top football with comparable levels of stimulation to that provided for aerobic exercise.</td>
<td>SMRI was carried out using a 1.5-T scanner (Sonata; Siemens, Erlangen, Germany). A T1-weighted MPRAGE sequence (echo time = 4.42 ms, repetition time = 1900 ms, inversion time = 700 ms, flip angle = 15°, field of view, 256 x 256 mm) of 176 consecutive slices was acquired with a voxel size of 1 x 1 x 1 mm.</td>
<td>Hippocampal volume increased by 12% in the exercisers versus −1% in the controls, F (1,14) = 13.8; p = 0.002. Changes in hippocampal volume were correlated with aerobic fitness measured by change in maximum oxygen consumption (r = 0.71; p = 0.003) and with a 35% increase in the N-acetylaspartate to creatine ratio (F1,13 = 8.13; p = 0.01). Improved short-term memory (Rey Auditory Verbal Learning Test) in the combined exercise and non-exercise group was correlated with change in hippocampal volume (r = 0.51; p &lt; 0.05).</td>
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<tr>
<td>Falkai et al. [32]</td>
<td>RCT</td>
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<td>No exercise-related changes in cortical regions.</td>
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<tr>
<td>Scheewe et al. [33]</td>
<td>RCT</td>
<td>32 (26.7%) patients with a DSM-IV diagnosis of schizophrenia with at least 50% adherence to the protocol; 18 exercisers (mean age = 28.5 ± 7.3 yrs; total PANSS = 61.4 ± 11.2) and 14 non-exercisers (mean age = 31.1 ± 8.0 yrs; total PANSS = 59.0 ± 10.2).</td>
<td>Experimental: 2 x week, 6 months cardiorespiratory fitness including exercises (40 min) on upright bicycle ergometer, recumbent bicycle ergometer, rowing machine, cross-trainer, and treadmill + muscle strength exercises (20 min; 6 exercises per week; three times 10–15 repetitions maximum for biceps, triceps, abdominal, quadriceps, pectoral, deltoid muscles). The exercise intensity was increased stepwise (week 1–3: 45%; week 4–12: 65%; week 13–26: 75% of heart rate reserve based on a baseline maximal incremental ergometer cycle test. The average of sessions attended = 1.5 per week. Control: Occupational therapy, 2 x week for 6 months.</td>
<td>SMRI on a single 3-T Achieva medical scanner (Philips, Best, The Netherlands). A 3D anatomical T1-weighted image of the whole head was acquired (Fast Field Echo using parallel imaging: 1800-8-mm contiguous sagittal slices, echo time = 4.6 ms, repetition time = 10 ms, flip angle = 90°, Field of View = 240 mm/100%, in-plane voxel size = 0.75 x 0.75 mm², reconstruction matrix = 200 x 320 x 320).</td>
<td>Exercise therapy did not increase global brain volume, hippocampal volume, or cortical thickness in schizophrenia. Cardio-respiratory fitness 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) and at trend level for cerebral gray matter (0.159 ml/W; p = 0.059).</td>
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RCT, randomized controlled trials; PANSS, positive and negative syndrome scale; SMRI, structural magnetic resonance imaging.
Quality of the evidence

The methodological quality of the included papers was high, especially in comparison with previous studies on physical exercise in patients with schizophrenia. In the present review, the minimum score on Downs and Black Quality Index [30] was 28. In a previous review [23], the mean score using the same methodological quality assessment tool was 25 with scores ranging from 20 to 31. All included studies had a randomised controlled design. Nevertheless, methodological weaknesses still remain present within the included studies. Sample sizes were limited and an intention-to-treat analysis was only performed in one study [33].

Underlying mechanisms for the neurobiological effects

Mechanisms explaining the brain adaptations summarised in this review are not yet understood, but cardio-metabolic and neurochemical pathways between skeletal muscle, the spinal cord, and the brain offer plausible, testable mechanisms that might help explain the effects of physical exercise on brain health [17,18]. For example, changes in hippocampal volume in the exercise group of Pajonk et al. [31] were correlated with improvements in aerobic fitness measured by change in maximum oxygen consumption. Further to this, Scheewe and colleagues [33] noted that improvement in cardio-respiratory fitness was associated with cortical thickening (or less thinning) in the left hemisphere. Underlying mechanisms of brain volume increases as a result of improved fitness are also still unknown, but it might be hypothesised that increased production of neurotrophic growth factors, improved vascularisation, and improved energy metabolism have a role to play, as all of these factors are of importance in neurogenesis [17,18,39]. More research is needed and schizophrenia-like animal models might assist researchers in exploring the underlying mechanisms for brain health improvements in patients with schizophrenia following a physical exercise programme.

Functional outcomes associated with the neurobiological effects

Increases in the hippocampal volume following physical exercise were found to be associated with improvements in short-term memory. These improvements in short-term memory are clinically relevant. Cognitive deficits occur already at an early stage in patients with schizophrenia and mainly affect memory and executive functioning [40]. These deficits do not only represent a core feature of the disease, but are the main predictor for poor social-functioning [41].

Limitations of the current systematic review

The findings of the present study need to be interpreted with caution because of some methodological limitations. Firstly, the small number of eligible trials and the small sample sizes of the included studies reduce the generalisability of our findings. Secondly, absence of data from unpublished studies is a potential weakness, since effects estimated from published studies may be inflated because of bias towards the non-publication of small studies with null effects. However, null effects on the outcome of interest in two of three included trials in patients with schizophrenia mitigates concerns about publication bias, since decisions to publish appear independent of the observed effect.

Conclusions

Our systematic review indicates that future research is needed to investigate whether brain health in people with schizophrenia is activity-dependent. Further research needs to explore in more detail which regions of the brain might benefit from physical exercise and what the dose–response relationship is. Also, further research that considers the neurobiological mechanisms and associated functional outcomes of physical exercise in individuals with schizophrenia is required.

Declaration of interest

The authors report no conflicts of interest. Davy Vancampfort is granted by the Research Foundation – Flanders (FWO – Vlaanderen).

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Disabil Rehabil, Early Online: 1–6

6. Vancampfort et al.


