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The Pro-Cognitive Mechanisms of Physical Exercise in People with Schizophrenia

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Abstract

Schizophrenia is associated with pervasive cognitive deficits which are unresponsive to antipsychotic medications. Physical exercise has been shown to improve cognitive functioning in people with schizophrenia, although the mechanisms for this are unclear. We conducted a systematic review of all exercise intervention studies which reported changes in either brain structure, connectivity or peripheral biomarkers which could underlie cognitive improvements from exercise in schizophrenia. An electronic database search was conducted on 22nd September 2016 using keywords relevant to exercise and neurocognition in schizophrenia. The search returned 2342 articles.Sixteen were eligible for inclusion, reporting data from 14 independent trials of 423 patients with schizophrenia. Seven studies used neuroimaging to examine the impact of exercise on brain structure and connectivity in schizophrenia, whereas seven other studies examined peripheral biomarkers to assess effects of exercise. Imaging studies collectively indicated that exercise can increase brain volume in people with schizophrenia, although the regions which responded to exercise varied across studies. Most biomarker studies assessed the effects of exercise on serum levels of BDNF. Several studies found significant increases from exercise along with positive correlations between BDNF and cognitive-enhancements (indicating a mechanistic link), althoughother studies did not observe this relationship. In conclusion, the cognitive benefits of exercise in schizophrenia may be due to exercise stimulating neurogenesis, perhaps by upregulating BDNF, although current evidence is insufficient to draw definitive conclusions. Further exploration of the pro-cognitive mechanisms of exercise in schizophrenia would inform the development of optimal interventions for reducing cognitive impairments in this population.

TARGETS	
Other protein targets[a]	**Enzymes**[e]
TNF-α	

LIGANDS	
BDNF	IGF-1
IL-6	

Abbreviations: BDNF, brain derived neurotrophic factor; CCT, controlled clinical; CRP, c-reactive protein; IGF-1, insulin-like growth factor 1; IL-6, interleukin-6; TNF-a, tumor necrosis factor alpha; HIIT, high-intensity interval training; RCT, randomized controlled trial.

Introduction

Schizophrenia is a serious mental disorder which has severe personal, social and economic impact (Vos *et al.*, 2015). The disorder affects around 1% of the population and causes a financial burden of £11.8 billion per annum in the UK alone (Schizophrenia Commission, 2012). Schizophrenia is characterized by both 'positive symptoms' (such as delusions and hallucinations) and 'negative symptoms' (e.g. low motivation and social withdrawal).

In addition to these aspects of the illness, schizophrenia is associated with pervasive cognitive deficits, including reduced short-term memory, slow processing speed and poor comprehension of social situations (Green *et al.*, 2000; Green *et al.*, 2012). These deficits are present from the onset of illness, and persist overtime to cause much of the socio-occupational disability associated with the disorder, while also impairing functional recovery (Green *et al.*, 2000). Furthermore, the cognitive symptoms of schizophrenia are unresponsive to antipsychotic medications, and other pharmacological approaches towards resolving these deficits have had little success to date (Keefe *et al.*, 2013).

Nonetheless, physical exercise is one intervention which could treat cognitive deficits of schizophrenia, and thus facilitate functional recovery. A recent meta-analysis of 10 controlled trials with 385 patients found that aerobic exercise significantly improves overall cognition in schizophrenia, with particularly large effects on working memory, attentional processes and social cognition (Firth *et al.*, 2016a). This corresponds with previous research demonstrating benefits from exercise for cognitive functioning in aging populations, healthy

adults and those with dementia (Smith *et al.*, 2010; Erickson *et al.*, 2011; Hötting *et al.*, 2013).

Despite these promising findings, there is little understanding of the neurobiological mechanisms through which exercise may exert these effects. Previous research has suggested that the cognitive benefits of exercise are a result of upregulating neurotrophic factors which stimulate neurogenesis (such as 'brain-derived neurotrophic factor'; BDNF) (Vaynman *et al.*, 2004; Huang *et al.*, 2014), reducing neuroinflammation which can impair neuronal signalling and neuronal growth (Cotman *et al.*, 2007), increasing the size of grey and white matter structures in the brain or improving the connectivity between brain areas (Colcombe *et al.*, 2006; Voss *et al.*, 2013; Best *et al.*, 2015; Svatkova *et al.*, 2015). Understanding the processes through which increasing physical activity might improve cognition is important for designing optimal exercise interventions, and for developing new treatments that can target these same pathways. However, the mechanisms which underlie cognitive improvements from exercise in schizophrenia are under-researched. Although individual studies have examined individual mechanistic factors which could be attributable for the cognitive enhancements observed following exercise interventions in schizophrenia (Pajonk *et al.*, 2010; Kimhy*et al.,* 2015), there has been no systematic review of the evidence in this area to date.

Therefore, the purpose of this review was to identify all exercise intervention studies in schizophrenia which have examined neurobiological variables that may underlie the

cognitive effects, evaluate their findings, and compare the results. In this way, we aimed to provide further insight into the mechanisms through which exercise can reduce cognitive deficits in schizophrenia, along with examining the relative effects of different types of exercise on the neurobiological factors which may underlie cognitive enhancement

Methods

Search strategy

We conducted an electronic database search of Ovid MEDLINE, PsycINFO, Embase, the Cochrane Central Register of Controlled Trials, the Health Technology Assessment Database, AMED (Allied and Complementary Medicine) and HMIC Health Management Information Consortium from inception to 22nd September 2016. The keyword search terms used were: "schizo*" or "psychosis" or "psychotic" and "exercise" or "physical activity" or "fitness" or "aerobic" or "resistance training" and "neuro*" or "cogniti*". Google Scholar and the reference lists of retrieved articles were also searched in order to identify any additional relevant publications.

Eligibility criteria

Articles were independently screened against eligibility criteria by two independent authors (JF and JC). Any disagreements were resolved through discussion. Eligible articles were exercise intervention studies published in peer-reviewed journals that were conducted in

patient samples of which at least 80% had received a clinical diagnosis of a non-affective psychotic disorder (such as schizophrenia) or were being treated for first-episode psychosis. In order to be included, studies must have examined neurobiological mechanisms pre- and post-intervention that could theoretically account for exercise-induced changes in cognitive functioning among people with psychotic disorders. This included (i) blood measures of neurotrophins, inflammatory cytokines or oxidative stress markers which could influence brain structure and functioning among patients, (ii) structural imaging data on global and region-specific brain volume and white matter integrity, and (iii) functional neuroimaging studies examining the impact of exercise on the neural circuitry which may underlie cognitive functions.

For the purpose of this review, exercise was defined as structured and repetitive physical activity that has an objective of improving or maintaining physical fitness (Caspersen *et al.*, 1985). Studies which incorporated exercise within a broader multi-aspect intervention were also eligible for inclusion provided that the exercise component was clearly defined and consisted of structured physical activity provided on at least a weekly basis (rather than just exercise advice). Interventions using only yoga or tai-chi were excluded from the analyses, as these may produce improvements in cognition through mechanisms which are independent from physical activity (Behere *et al.*, 2011). Case studies, review articles and non-english language articles were also excluded.

Data extraction and synthesis

A systematic data extraction form was developed and used to extract the following from each study:

(i) Study details – including; sample size, mean age of participants, patient diagnosis/classification (i.e. long-term or first-episode), and trial design.

(ii) Exercise intervention: length (weeks), frequency (sessions per week), duration (session length in minutes), exercise type (e.g. aerobic, resistance, combined), training protocol outline, control/comparator condition details.

(iii) Cognitive outcomes: including the effect size (where reported) and statistical significance of change in cognitive performance on any neuropsychological task (or task battery) in the exercise condition.

(iv) Neurobiological changes: any reported changes in the mechanistic factors (as specified above) which could relate to or account for the cognitive-enhancing effects of exercise interventions for schizophrenia.

Results

Search results

The full article screening and selection process is detailed in Figure 1.The initial database search was performed on 22nd September 2016. The search returned a total of 2342 results, which was reduced to 1748 after duplicates were removed. At the title and abstract screening stage, 1707 articles were excluded for not meeting eligibility criteria. Full text

versions for 42 articles were retrieved. Of these, 11 articles were eligible for inclusion. An additional search of the reference lists and Google Scholar identified a further five articles which were eligible for inclusion, although one of these reported data from the studies identified in the main search. Thus, 16 articles, reporting data from 14 independent studies, were included in this review.

Included studies and participant details

Study details are displayed in Tables 1 and 2. Across the 14 trials, data was available from a total of 423 patients; 370 with long-term schizophrenia/schizoaffective disorder (11 studies) and 53 with first-episode psychosis (3 studies). The mean age was 41.4 years (range = 20.2 – 58.9 years). Nine studies were RCTs, three were controlled clinical trials (CCTs) and two were single-arm studies.

A total of 247 patients were allocated to exercise interventions, and 176 to comparison conditions. Most exercise interventions lasted 12 weeks (8 studies), with others lasting either six months (2 studies), 10 weeks (2 studies), 8 weeks (1 study) or 20 weeks (1 study). Exercise interventions included moderate aerobic training alone (Pajonk *et al.*, 2010; Takahashi *et al.*, 2012; Kimhy, 2015; Lin *et al.*, 2015; Rosenbaum *et al.*, 2015; Malchow *et al.*, 2016), combined aerobic and resistance training (Scheewe *et al.*, 2013; Kim *et al.*, 2014; Cassilhas *et al.*, 2015; Svatkova *et al.*, 2015), low intensity exercise with some aerobic activity (Kuo *et al.*, 2013; Ho *et al.*, 2016), high-intensity interval training (HIIT)(Heggelund *et al.*, 2011) or bodyweight workout videos (Nuechterlein *et al.*, 2016). Two of the studied

embedded exercise within broader 'lifestyle programs' for encouraging healthy habits (Takahashi *et al.*, 2012; Kuo *et al.*, 2013) and two combined exercise with cognitive remediation therapy (Malchow *et al.*, 2016; Nuechterlein *et al.*, 2016) but controlled for this in the comparator condition. Other control conditions included occupational therapy (Scheewe *et al.*, 2013), tai chi (Ho *et al.*, 2016), table football (Malchow *et al.*, 2016), yoga (Lin *et al.*, 2015), video games (Heggelund *et al.*, 2011) and usual treatment (Takahashi *et al.*, 2012; Lin *et al.*, 2015; Svatkova *et al.*, 2015).

Seven studies used neuroimaging techniques to assess the effects of exercise in schizophrenia, and seven others used blood/salivary biomarkers to assess physiological response to exercise interventions. No studies used both neuroimaging and biomarker analysis.

Findings from imaging studies

The full details and outcomes of all studies examining the effects of exercise on brain structure and connectivity in people with schizophrenia are presented in Table 1. Additionally, the findings of these studies are systematically summarized below.

Five studies examined the effects of exercise on brain volume in people with schizophrenia. Each of these also reported changes in the hippocampus from exercise. Two studies (Pajonk *et al.*, 2010; Lin *et al.*, 2015) both found that 12-weeks of aerobic exercise delivered three times per week increased hippocampal volume more than the other study conditions (which included yoga, table football and waitlist control). Increased hippocampal volume

corresponded with a significant increase in short term memory. Furthermore, both studies reported indications that these increases in brain volume were linked to improved cardiorespiratory fitness. Pajonk *et al.* (2010) reported a strong correlation between increases in hippocampal size and maximal exercise capacity (r=0.83, p=0.01) and (Lin *et al.*, 2015) found trend-level improvements in cardiorespiratory fitness only occurred in the exercise group (which was also the only study condition to increase hippocampal volume).

However, conflicting evidence for hippocampal growth following exercise is presented by Rosenbaum *et al.* (2015) and Malchow *et al.* (2016), both of which also used 12-weeks of aerobic exercise with 3-sessions per week. These studies failed to observe any significant increases in hippocampal volume from exercise, despite successfully increasing fitness (Rosenbaum *et al.*, 2015) and short term memory (Malchow *et al.*, 2016). Nonetheless, Malchow *et al.* (2016) did find a significant increase in left anterior lobe volume (p=0.05).

Additionally, the study by Scheewe *et al.* (2013), which used combined aerobic-resistance training twice-weekly for six months, also found no change in hippocampal volume, or any of the other brain regions studied. However, they did find that increased cardiorespiratory fitness over the six months was predictive of changes in brain structure, including increases in total cerebral volume (p=0.045), decreases in the lateral (p=0.035) and third ventricle (p=0.013), and left-hemisphere cortical thickening (p=0.024).

Svatkova *et al.* (2015), used the same training protocol as (Scheewe *et al.*, 2013) to examine effects of exercise on white matter integrity in people with schizophrenia. Results showed a

significant improvement in various fibre tracts implicated in motor functioning. Again, these improvements were significantly associated with increased cardiorespiratory fitness over intervention period (p=0.016). However, the improvement in global cognitive functioning (measured using IQ scores) was not statistically significant, and did not correlate with neurological changes.

Finally, Takahashi *et al.* (2012) was the only study to examine changes in brain activation from exercise in schizophrenia, using fMRI techniques. The intervention incorporated aerobic exercise and daily participation in basketballgroups as part of a 'healthy lifestyle program'. Participants' brain activation while watching sports-related videos and non-sports videos was measured before and after the 3-month program, and compared to a group who were not participating in the lifestyle program. Brain activation increased in the extrastriate body area of posterior temporal cortex when watching sports-related videos following the 3-month intervention, whereas no change was observed in the control condition. The degree of change in the intervention group strongly predicted improvements in general symptomatology ($r=0.78$, $p<0.01$).

Mechanistic findings from biomarker studies

The details and outcomes of all studies examining the effects of exercise on cognitive biomarkers in people with schizophrenia are presented in Table 2. Additionally, the effects of exercise on each biomarker are summarized below.

The most widely-studied biomarker was BDNF. This was examined in five studies with a total of 145 participants with schizophrenia. Of these, three interventions which combined aerobic exercise with cognitive training (Nuechterlein *et al.*, 2016), resistance training (Kim *et al.*, 2014), and healthy lifestyle advice (Kuo *et al.*, 2013) reported increases in BDNF. However, Cassilhas *et al.* (2015) found no effects on BDNF from 20-weeks of either resistance training or combined aerobic-resistance training.Kimhy et al. (2015) also failed to observe a main effect of exercise on BDNF, as the moderate increases in BDNF observed in this small sample (n=26) fell short of statistical significance.

Three studies explored the factors associated with exercise-induced improvements in BDNF using correlation analyses. Kimhy et al. (2015) found a significant main-effect of exercise on global cognition, and further reported that increases in BDNF predicted 14.6% of the improvements in cognitive performance from exercise, while increases in cardiorespiratory fitness accounted for 25.4% of the improvements observed. Kim *et al.* (2014) also found that increases in BDNF were significantly associated with improvements in cardiorespiratory fitness ($r=0.404$, $p=0.035$). Finally, Kuo *et al.* (2013) found that elevation in BDNF was positively associated with reductions in bodyweight and BMI following the 10-week multi-component lifestyle program ($p<0.001$).

Two studies examined changes in inflammatory markers following exercise interventions. Heggelund *et al.* (2011) studied changes in c-reactive protein (CRP) following 8 weeks of HIIT in comparison to a video games control condition. Although there was a 66% reduction in

CRP from the exercise intervention and no change in the control condition, the difference between the two groups was not statistically significant. Kuo *et al.* (2013) also found no significant changes in CRP, IL-6 or TNF-a from their 10-week lifestyle intervention.

Changes in IGF-1 and salivary cortisol following exercise interventions were reported in one study each. Cassilhas *et al.* (2015) found no change in IGF-1 from a 20 week combined aerobic-resistance training program. Ho *et al.* (2016) found that low-intensity exercise moderately increased in salivary cortisol ($p<0.05$), while also increasing working memory as measured by the Forward Digit Span test ($p<0.05$).

Discussion

This review aimed to identify and evaluate all existing studies which have examined the neurobiological mechanisms through which exercise may reduce cognitive deficits in people with schizophrenia. Whereas a previous meta-analysis has demonstrated the efficacy of exercise for improving cognition in schizophrenia (Firth *et al.*, 2016a), this is the first systematic review of the mechanisms which may underlie these effects. Of the 14 eligible independent studies, 7 investigated effects of exercise on brain structure and functioning, and 7 investigated effects on peripheral markers which may indicate or produce cognitive improvements.

Exercise and/or improved cardiorespiratory fitness was associated with increased brain volumes in certain regions, for all but one study that assessed structural brain changes (which may be due to the null study having small sample size of only five participants

(Rosenbaum *et al.*, 2015)). These findings are consistent with the increased brain volume found in response to exercise in other populations (Erickson *et al.*, 2011; Voss *et al.*, 2013). Thus, stimulation of neurogenesis could be one mechanism through which exercise may have its pro-cognitive effects.

However, the effect of exercise on specific brain regions was inconsistent across studies. For instance, two studies found significant increases in hippocampal volume (Pajonk *et al.*, 2010; Lin *et al.*, 2015). These changes were observed in the schizophrenia group, but not the healthy control sample (Lin *et al.*, 2015). This suggests that exercise could attenuate the deterioration in hippocampal volume that can occur in the early phases of schizophrenia (Velakoulis *et al.*, 2006). Indeed, these findings are similar to those found in aging populations, where neuronal loss in the hippocampus, was also attenuated through exercise (Erickson *et al.*, 2011). However, two other studies using an identical training protocol failed to replicate these findings, despite significantly increasing cognitive performance and grey-matter volume in other brain regions (Malchow *et al.*, 2016). The same applied for the link between cardiorespiratory fitness and neurological improvements: whereas some studies found no relationship of exercise with cortical regions, but did find significant correlations between increased fitness and hippocampal volume (along with short term memory; a cognitive function often associated with this brain area) (Pajonk *et al.*, 2010; Falkai *et al.*, 2011), other studies found the opposite; reporting significant associations between fitness improvement and cortical thickness, but with no association with hippocampal change (Scheewe *et al.*, 2013). Given these inconsistencies, further evidence is required to

determine if and how the cognitive benefits of exercise relate to growth in particular brain regions. Nonetheless, it should be noted that studies which compared effects of exercise across hemispheres did consistently find that the left hemisphere was more sensitive to exercise-induced improvements than the right (Scheewe *et al.*, 2013; Lin *et al.*, 2015; Malchow *et al.*, 2016).

Effects of exercise on biomarkers were also inconsistent across studies, including in relation to BDNF. BDNF is the most abundant neurotrophic factor in humans, and is upregulated in response to exercise (Szuhany *et al.*, 2015). It has been found to predict cognitive benefits of exercise in healthy populations (Griffin *et al.*, 2011). Animal studies have indicated a critical role of BDNF in exercise-related cognitive enhancement, as blocking the BDNF channels prevents the improvements usually observed in rats from regular physical activity (Vaynman *et al.*, 2004). However, the role of BDNF in exercise treatments for schizophrenia has yet to be established. Whereas serum BDNF levels did notably increase in 4 of the 5 studies which examined this possible mechanism (Kuo *et al.*, 2013; Kim *et al.*, 2014; Kimhy et al., 2015; Nuechterlein *et al.*, 2016), only 2 observed a statistically significant improvement (Kuo *et al.*, 2013; Kim *et al.*, 2014). However, this may have been due to the small sample sizes of n=13 and n=4 in the intervention arms of these studies. Nonetheless, increases in BDNF did hold significant associations with exercise-induced improvements in fitness, body composition, and most importantly cognitive functioning in each study which examined these relationships (Kuo *et al.*, 2013; Kim *et al.*, 2014; Kimhy et al., 2015). Previous meta-analyses

have also found that populations with depression are more sensitive to upregulation of BDNF in response to exercise than healthy samples (Szuhany *et al.*, 2015).

Existing studies have found no effect of exercise on inflammatory markers in people with schizophrenia (Heggelund *et al.*, 2011; Kuo *et al.*, 2013). This is an interesting finding given that patients with schizophrenia show low-grade systemic inflammation (Potvin *et al.*, 2008) which may impact upon cognitive functioning (Dickerson *et al.*, 2007), and exercise is known to have anti-inflammatory effects in other populations (Petersen *et al.*, 2005). However, levels of circulating pro-inflammatory cytokines in the blood are confounded by many factors, including smoking and obesity, both common in schizophrenia (McCreadie, 2003) and do necessarily reflect inflammation in the brain (Bergink *et al.*, 2014). Thus, the positive effects of exercise in reducing neuroinflammation may not be captured using these peripheral measures. Future research using positron emission tomography to assess microglial activation and magnetic resonance spectroscopy to measure brain glutathione could derive more valid information on the anti-inflammatory and anti-oxidative effects of exercise in schizophrenia. If such studies did find a reduction of neuroinflammation and oxidative stress in response to exercise, this could inform the development of interventions targeting these processes in order to reduce cognitive dysfunction

One limitation in this review is the substantial variation between studies in the exercise interventions applied, the comparison groups used, and the outcomes studied, making it difficult to compare findings across studies. It is possible that the inconsistencies across

study findings arose as a result of the differences between the interventions applied. However, whereas this review focused on pro-cognitive mechanisms from any type of exercise, other recent reviews which have examined neural and cognitive effects of exercise in schizophrenia have also found broad inconsistencies and significant heterogeneity across studies, even when focusing entirely on aerobic exercise interventions (Firth *et al.,* 2016a; Vakhrusheva*et al.,* 2016a).

Along with training type, exercise dosage is another factor which may impact upon the neurobiological changes which occur from physical activity interventions, since studies which use greater amounts of exercise also tend toresult in greater cognitive improvements among people with schizophrenia (Firth*et al.,* 2016a). Exercise intensity may also be a critical factor, as intervention studies have observed that the patients who achieve greater adherence to moderate-to-vigorous exercise are more likely to experience cognitive enhancements (Kimhy*et al.,* 2016; Firth *et al.*, 2016b). Further mechanistic research is needed to establish the importance of exercise dosage vs. exercise type for designing optimal programs for cognitive enhancement.

However, it is also important to consider that people with severe mental health problems engage in less moderate and vigorous activity than the general population (Schuch *et al.,* 2016; Stubbs *et al.*, 2016; Vancampfort *et al.,* 2016), due to a combination of psychological and social barriers (Firth *et al.*, 2016c). Previous studies have shown that providing exercise facilities and advising patients to be physically active fails to increase physical activity

(Archie *et al.*, 2003). Nonetheless, taking into account patients' individual motivations and preferences for exercise, in order to create personalised training programs, does enable people with schizophrenia to engage in sufficient amounts of exercise (Firth *et al.*, 2016b; Firth *et al.*, 2016d).

A further limitation in this review is heterogeneity of samples in terms of age and duration of illness, as participants ranged between 20 years to almost 60 years old and we included 3 studies of first episode psychosis, along with 11 of long-term schizophrenia. There is a possibility that findings may not generalise between these two groups, since other cognitive enhancement interventions have been found to be more effective in first-episode psychosis than long-term illness (Bowie *et al.*, 2014). Indeed, the two controlled trials of exercise in first-episode psychosis found improvements in cognitive functioning across various domains, accompanied by increased hippocampal volume (Lin *et al.*, 2015) and serum BDNF (Nuechterlein *et al.*, 2016). This is consistent with the findings that the early stages of schizophrenia are associated with more inflammation compared to chronic illness (Miller *et al.*, 2011; Upthegrove *et al.*, 2014). Furthermore, the early stages of illness may be the optimal time period to target cognitive deficits in order to improve real-world functioning and facilitate full recovery (Bowie *et al.*, 2014; Cotter *et al.*, 2014).

In conclusion, there is preliminary evidence that the cognitive benefits of exercise for schizophrenia are accompanied by improvements in brain structure and connectivity, although the mechanisms of exercise-induced cognitive improvements cannot be attributed

to growth in any particular area as of yet. Similarly, although increase in BDNF is a promising finding for explaining the cognitive effects of exercise, information is too limited to draw any firm conclusions. Furthermore, peripheral markers of inflammation have yet to show any relationship with exercise in schizophrenia. Future studies which directly compare alternative physical activity regimes (differing in terms of either dosage or exercise modality) are needed. Additionally, there is currently a complete lack of intervention studies which combine neuroimaging with biomarker measurement and fitness assessment in order to elucidate the neurobiological pathways through which exercise enhances cognition in schizophrenia. This is an important area for future research to gain further insight into pro-cognitive mechanisms of exercise. This in turn would lead to optimal intervention development and exercise prescription for reducing cognitive deficits in schizophrenia, and thus improving functional recovery for patients.

Author contributions

JF, JC and RC conducted the article screening and data extraction. All authors contributed to the conception and writing of the manuscript, and have approved the final version.

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Table 1. Studies assessing the impact of exercise on brain structure and connectivity in people with schizophrenia

	Exercise n=	Control n=	Mean age	Design	Exercise Intervention	Cognitive outcomes of Exercise	Exercise effects on brain structure and connectivity
Lin et al. 2015	17	13	24.9	RCT comparing 12 weeks of aerobic exercise to yoga and usual treatment.	45-60 minutes of treadmill walking and stationary cycling at 50%-60% VO_2 max. Three sessions per week.	↑Verbal Acquisition p=0.02, d=0.83. ↑Verbal Retention p=0.016, d=0.56. ↑Forward Digit Span p=0.014, d=0.59. ↑Backwards Digit Span p<0.01, d=1.08. NC Stroop task.	Hippocampal grey matter volume was only increased by the exercise condition (F=7.52, p=0.01), with largest increases in the left hippocampus (F=5.13, P=0.03). Yoga or usual treatment did not produce any change. There was no correlation between improved cognition and increases in physical fitness (VO2 max r=0.07, p=0.42)
Malchow et al. 2015a ; Malchow et al 2015b	22	21	36.5	RCT comparing 12 weeks of aerobic exercise to table football. Both groups augmented with cognitive training. Assessments at 6 and 12 weeks.	30 minutes of stationary cycling at gradually increasing intensity. Three sessions per week.	From 6-12 weeks: ↑Wisconsin card sorting p=0.008, Z=−2.6. ↑Verbal STM p=0.03, +10.2%. ↑Verbal LTM p=0.03, +12.7%. NC Trail-Making Task.	Increased grey matter volume in left anterior temporal lobe after 3 month exercise intervention compared to baseline (x=−48, y=0, z=−26; p=0.05) No significant changes in bilateral hippocampal volumes (in medial temporal lobe).

Pajonk et al. 2010 ; Falkai et al. 2013	8	8	35	RCT of 12-weeks aerobic exercise vs. table football control group.	Three days of 30 minutes stationary cycling per-week, at an individually-defined intensity that was gradually increased over the intervention.	↑Verbal STM p=0.04, *d*=1.19. NC Verbal LTM NC Visuospatial STM	Hippocampal volume in the exercise group increased by 12%, significantly more than control condition (F=13.8, p=0.002). Exercise group also had a 35% increase in NAA:Cr ratio in the hippocampus. Increases in cardiorespiratory fitness were correlated with increased hippocampal volume (r=0.83; p=.01) and improved verbal STM (r=0.51; p=0.05). For cortical regions, there was no overall effect from exercise, and no correlation with improved cardiorespiratory fitness.
Rosenbaum et al. 2015	5	0	20.2	Single-arm study of 12-weeks aerobic exercise	Twice-weekly, 45-minute sessions of stationary cycling at 65% heart-rate of their VO2 max.	Spatial Span; +15%, ns. Verbal learning; -17%, ns.	No significant change in hippocampal volume ↑0.4%; ↑33.0mm^3;t=0.5, ns, despite significant improvements in VO2 max (p=0.02)
Scheewe et al. 2013	18	14	30	RCT of 6 months exercise program vs. occupational therapy.	Twice weekly combined aerobic-resistance training: 40 minutes of cycling/treadmill/ elliptical at up to 75% of max heart rate, then 20 minutes of resistance training.	N/R	No main effect from exercise on global brain volume, hippocampal volume, or cortical thickness. Improvements in cardiorespiratory fitness (peak wattage)were significantly associated with improvements in brain structure, including;increased total cerebral matter volume (0.164ml/W; p=0.045), decreased lateral ventricle (0.018 ml/W; p=0.035), decreased third ventricle volume (0.0018 ml/W; p=0.013), cortical thickening in the left hemisphere (t=2.29, p=0.024), and, at trend-level significance, cerebral grey matterincreases (0.159 ml/W; p=0.059).

Svatkova et al. 2015	16	17	30.1	RCT comparing 6 months exercise to usual treatment	Twice weekly combined aerobic-resistance training: 40 minutes of cycling/treadmill/ elliptical at up to 75% of max heart rate, then 20 minutes of resistance training.	↑Global IQ p=0.33, +4.1 points	Exercise significantly improved white matter integrity in fibre tracts implicated in motor functioning. Overall improvement in white matter integrity held a significant correlation with cardiorespiratory fitness (V02 peak; r=0.27, p=0.016). However, there were no significant associations between fitness and IQ, or between brain changes and IQ.
Takahashi et al. 2012	13	10	41.9	CCT comparing 3 months healthy lifestyle program to usual treatment	Exercise module of the lifestyle program was delivered twice daily for 30-60mins, comprising of walking and jogging, muscle-stretching exercises, and sports group (basketball).	N/R	Exercise intervention significantly increased brain activation in the extrastriate body area of the posterior temporal cortex when watching basketball clips (peak: x=42, y=74, z=4, Z score=4.12). No change in control condition. Greater extrastriate body area activation was associated with greater reduction in the general symptoms subscale of the PANSS(r=0.78, p=0.002), but not for positive or negative symptom subscales (all p>0.05).

CCT, controlled clinical trial; IQ, intelligence quotient; LTM, long term memory; NAA:Cr, n-acetylaspartate to creatine ratio; NC, no change; N/R, not reported; PANSS, positive and negative syndrome scale; RCT, randomized clinical trial; STM, short term memory.

Table 2. Studies examining cognitive biomarkers following exercise interventions for schizophrenia

	Exercise n=	Control n=	Mean age	Design	Exercise Intervention	Cognitive outcomes of Exercise	Exercise effects on biomarkers
Cassilhas et al. 2015	21	13	33.3	RCT of 20 weeks resistance training vs. combined aerobic-resistance training vs. low intensity control group.	60 minutes, twice weekly, of either: (i) progressively-difficult resistance exercises targeting large muscle groups, (ii) half resistance exercises, half treadmill running, or (iii) control group of very low-weight resistance exercise with slow treadmill walking.	N/R	No change in BDNF or IGF-1
Heggelund et al. 2011	12	7	33.5	CCT comparing 8 weeks of HIT to computer games.	Sessions consisted of 4x4- bouts of high-intensity treadmill running at 85-95% max heart rate, interspersed with 3 minute rest periods (walking).	N/R	Hs-CRP (mg/l) in the exercise group went from 8.09 (s.d.=18.15) to 2.67 (s.d.=2.11) after 8 weeks. In the control group, hs-CRP went from 4.41 (s.d.=5.34) to 4.26 (s.d.=5.09). No significant difference between groups.
Ho et al. 2016	51	49	54.9	3-arm RCT comparing 12 weeks of exercise or tai chi to waitlist control	60 minutes of low-intensity activity designed to match physical exertion of tai chi (50-60% maximal oxygen consumption) e.g. stretching, walking, mild weight training.	↑Forward Digit Span $p<0.05$, $d=0.42$. NC Backward span.	Salivary cortisol in exercise group significantly increased significantly more than waitlist control ($p<0.05$, $d=0.46$)
Kim et al. 2014	24	12	49.4	12-week RCT of combined aerobic-resistance training vs. low-intensity control	3 days per-week of 25 mins resistance exercise (using elastic bands) plus 25 mins treadmill walking at 60% max heart rate.	N/R	BDNF increased following the exercise program (13.2 ng/ml to 16.0 ng/ml, p=0.007), significantly more than the control condition. Increases in BDNF correlated with improvements in cardiovascular fitness (YMCA step test; r=0.404, p=0.035) and leg strength (r=0.446, p=0.021), but not with grip strength (r=0.03, p=0.45).

Kimhy et al. 2015	13	13	36.9	RCT comparing 12-weeks of aerobic exercise to usual treatment	60 mins at 60-75% V02 peak of multi-modal exercise including treadmill running, elliptical training and interactive video gaming. 3 sessions per week.	↑Global Cognition p=0.031, *d*=0.93.	BDNF increased by 11.0% in exercise group vs. 1.9% in usual treatment, but with no significant difference between-groups (*d*=0.3, p=0.46). Regression analyses found that improvements in cognitive performance were predicted by bothincreased BDNF (F=4.11, p=0.05) and increased fitness (F= 8.16, p=0.009).
Kuo et al. 2013	33	0	37.8	Single-arm study of 10 week healthy lifestyle program	Weekly group exercise class (1hr), plus encouragement to engage in regular low-intensity activity and moderate intensity activity (fast walking or cycling) 5 times per-week.	N/R	BDNFincreased from 4.5 ng/ml to 9.1ng/ml after the multi-element program (p<0.001). There was no change in CRP, IL-6 or TNF-*α*. Increases in BDNF were strongly correlated with reductions in bodyweight (r=0.773, p<0.001) and BMI (r=0.63, p<0.001).
Nuechterlein et al. 2016	7	9	22.7	CCT of 10-weeks of aerobic exercise combined with cognitive training vs. cognitive training alone.	4-times weekly aerobic exercise at 60-80% of max heart rate, using 30-45 mins bodyweight workout videos (doing lunges, squats, pushups etc.)	↑Global Cognition p: N/R, *d*=0.96. ↑Social Cognition p: N/R, *d*=1.3. ↑Working Memory p: N/R,*d*=1.0. ↑Processing Speed p: N/R,*d*=0.76. ↑Attention/Vigilance p: N/R,*d*=0.66.	BDNF increased from baseline to follow-up inthe exercise group (mean change: 4.22 ng/ml), with an accompanying change in cardiorespiratory fitness (*D*=0.94)

BDNF, brain-derived neurotrophic factor (serum levels of); BMI, body mass index; CCT, controlled clinical trial; *D*, cohen's d;Hs-CRP, high sensitivity c-reactive protein; IL-6, interleukin 6; NC, no change; Ng/mL, nanogram per millilitre; N/R, not reported; RCT, randomized clinical trial; TNF-a, tumor necrosis factor alpha.

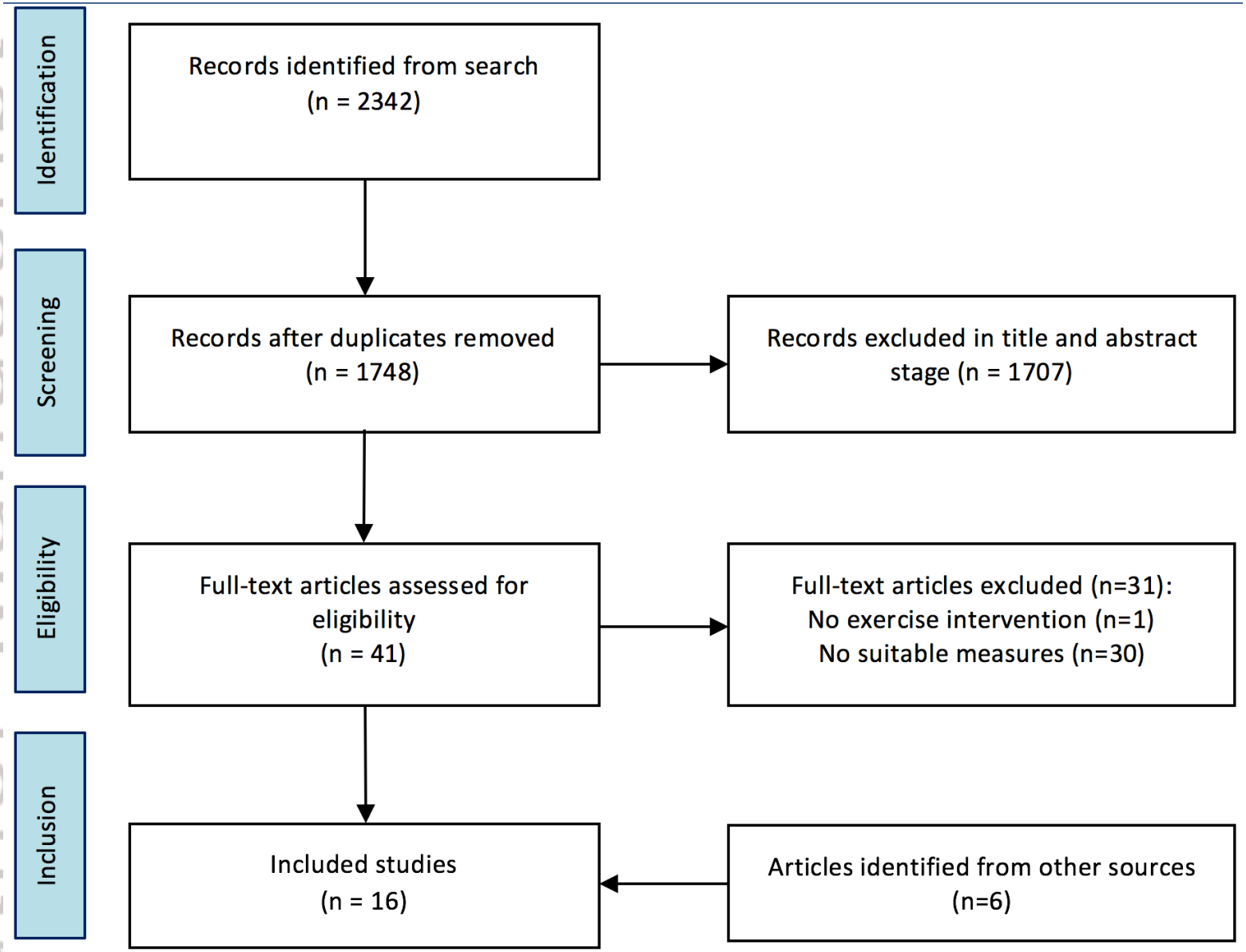

Fig 1

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