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Aerobic Exercise in People with Schizophrenia: Neural and Neurocognitive Benefits

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Abstract

Schizophrenia is characterized by extensive neurocognitive deficits, which are linked to greater disability, poorer functional outcome, and have been suggested to impact daily functioning more than clinical symptoms. Aerobic exercise (AE) has emerged as a potential intervention. This review examines the impact of AE on brain structure and function along with neurocognitive performance in individuals with schizophrenia. Preliminary evidence indicates that AE can increase hippocampal volume and cortical thickness, in addition to exerting a neuroprotective effect against hippocampal volume decrease and cortical thinning. There is also evidence that AE is able to significantly increase serum brain-derived neurotrophic factor (BDNF) levels, which are implicated in neurogenesis, neuroplasticity, and cognitive improvement. Finally, evidence suggests that AE plays a significant role in improving overall cognition, including improvements in processing speed, working memory, and visual learning. The authors discuss the implications of the findings and provide recommendations for future research and areas of inquiry.

Keywords

Schizophrenia; Aerobic exercise; Aerobic fitness; Cognition; Neurotrophins; BDNF; Neuroplasticity; Hippocampal volume; Brain structure

Introduction

Neurocognitive deficits are well documented in individuals with schizophrenia, including impairments in memory, attention, processing speed, and executive functioning [1, 2]. These deficits predate the onset of illness and remain stable over time [3, 4]. Such impairments

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

have also been linked to greater disability and poorer functional outcome in this population [5, 6], including decreased ability to maintain daily routines [7], independent living [8], social functioning [9, 10], and employment [11, 12]. In a large cohort of stable outpatients (*N*=672), the most prevalent impairments were in the domains of executive functioning and processing speed, while working memory impairment predicted the degree of functional disability [13]. Similarly, in a longitudinal study examining individuals with first-episode schizophrenia over 7 years, changes in verbal memory, processing speed, and attention significantly predicted functional impairment in relationships, employment, and ability to engage and enjoy recreational activities [14]. Overall, it has been suggested that neurocognitive deficits play a larger role in functional impairment than positive symptoms of schizophrenia [15], and consequently, cognitive impairment has emerged as a critical target for treatment [16].

Cognitive deficits in individuals with schizophrenia have been linked to structural and functional brain abnormalities. A review examining the link between brain structure and cognitive deficits in this population found that enlarged ventricles correlated significantly with cognitive inflexibility and deficits in language, attention, and psychomotor speed, while abnormalities in the hippocampus were associated with impairments in declarative memory and executive functioning [17]. Abnormalities in white matter integrity have also been reported, particularly in frontal and temporal cortices [18], and abnormal myelination of tracts responsible for communication between these regions has been implicated [19]. Smaller gray matter volumes in older individuals with schizophrenia have been reported [20, 21], though the progressive nature of these deficits is controversial. Larger structural deficits have been associated with increased exposure to antipsychotic treatment [22], leading some researchers to suggest both structural and cognitive deficits inherent to the illness are relatively stable over time [23]. Complementing these findings, neuroimaging studies have shown evidence of cortical tissue loss, ventricular enlargements, smaller thalamus and temporal lobes (including the hippocampus), enlarged caudate nucleus, and reversed cerebral asymmetries [24]. Similarly, cognitive deficits in people with schizophrenia have also been linked with the regulation of neurotrophins. In particular, brain-derived neurotrophic factor (BDNF) has attracted much research interest. A member of the neurotrophin family, BDNF is the most prevalent neurotrophin in the brain and is heavily involved in neuronal growth, development, and maintenance [25]. A recent meta-analysis of 16 studies showed evidence of significantly lower serum BDNF levels in schizophrenia [26], which has been linked to memory impairment [27] and smaller hippocampal volumes [28].

Treatment approaches for cognitive deficits in schizophrenia have primarily focused on pharmacology and cognitive remediation. Initially, second-generation antipsychotic medication appeared promising in addressing not only symptoms, but also cognitive impairment in this population [29]. However, results from the NIH-sponsored CATIE study examining the effects of typical and atypical antipsychotic medications on cognition in schizophrenia found only minimal improvement [30]. Investigations of novel add-on pharmacological compounds have yielded mixed results, with compounds targeting single receptors resulting in limited to no improvement [31–34] and compounds that have anti-inflammatory and/or anti-oxidant properties showing more promise [35, 36]. Cognitive remediation was also beneficial among individuals with first-episode psychosis [37, 38], as

well as chronically ill individuals [39, 40]. However, a meta-analysis including 2104 individuals with schizophrenia demonstrated only small to moderate effect sizes on global cognitive improvement [41], and some studies failed to find any significant impact of cognitive training [42]. As a result, there remains a need for novel approaches to treating neurocognitive deficits in schizophrenia, particularly focused on fostering synaptogenesis and neurogenesis.

Recent studies have indicated a potential benefit of aerobic exercise (AE). Evidence from animal studies suggests that AE can have a positive impact on cognitive functioning [43], as well as strengthen neuronal growth and development [44, 45]. Most recently, mouse models of schizophrenia demonstrated that voluntary AE significantly increased BDNF levels in the hippocampus, improved spatial working memory, and encouraged increased social interaction [46]. Yet, studies investigating the effects of AE in animal models have noted differential effects of voluntary (spontaneous wheel running) versus involuntary or forced exercise (treadmill running). Both types of AE appear to upregulate BDNF levels in the hippocampus [47], improve spatial learning and memory, and increase activity-dependent BDNF in the hippocampus [48]. Leasure and Jones [49] reported that forced exercise actually resulted in more hippocampal neurogenesis as evidenced by more surviving progenitor cells compared to voluntary exercise at the expense of increased anxiety and emotional defecation. The authors also noted that animals engaging in voluntary exercise ran faster and for less time, while those in the forced exercise condition ran slower and for longer durations, suggesting the former group demonstrated greater exertion. In contrast, Ke et al. [50] found that voluntary exercise resulted in significantly higher hippocampal BDNF levels as compared to forced exercise and control groups, and forced exercise may induce greater stress resulting in downregulation of BDNF. These findings were contradictory to those reported by Leasure and Jones [49], who found that corticosterone levels were not significantly different between groups at end of study, and any increase in initial stress may be accounted for by habituation [48].

Similarly, findings among non-clinical and other clinical populations also provide support for AE positively affecting health outcomes [51–53], serum BDNF levels [54, 55], and cognition [56, 57]. Specifically, a meta-analysis of randomized clinical trials with 2049 adult participants demonstrated that exercise could lead to improvement in executive functioning, processing speed, attention, and declarative memory [58]. This is notable, since individuals with schizophrenia are often sedentary [59], and decreased physical activity has been implicated in cognitive impairment [60] and brain volume deficits [61•]. AE improves cardiopulmonary fitness in people with schizophrenia [62, 63] and preliminary evidence suggests AE may have a beneficial effect on cognitive functioning in schizophrenia. However, a comprehensive review of the current research literature is not available.

To address this gap in the literature, the primary aim of the present review is to examine the feasibility and efficacy of AE as an intervention for cognitive deficits in individuals with schizophrenia and bring the reader up to date regarding the most recent empirical evidence of AE's impact on: (1) neurobiological structure and function and (2) neurocognitive performance. The secondary aim is to identify areas in need of further study. In order to obtain the most current literature, a search was conducted through January 2016 on Medline,

Web of Science, and PsycNET for clinical trials examining the impact of AE on brain structure and function and neurocognition. Search words and terms included the following: “exercise” or “aerobic exercise,” “schizophrenia” or “psychosis,” “neurocognition” or “cognition,” “neurotrophin” or “BDNF” or “IGF” or “NGF” or “NT-3,” “brain structure,” and “hippocampal volume.” Relevant articles were pulled and reference lists examined for additional studies. The search yielded 11 studies, 8 of which are summarized in Table 1 and discussed more thoroughly below. Three remaining studies were only briefly mentioned in the review due to lack of comparison group ($N = 1$) and presentation of additional outcomes for a sample already included in review ($N = 2$).

Impact of Aerobic Exercise on Brain Structure and Functioning

Three randomized control trials examined the effects of AE on brain structures. Pajonk et al. [64] compared males with schizophrenia ($N = 8$) and age-matched healthy male controls ($N = 8$) who engaged in 3-month AE program (30 min per session, three times per week), along with a schizophrenia patients comparison group ($N = 8$) that played table football for a similar duration and frequency. Comparison of changes in hippocampal volumes assessed indicated significant increase in volume in both the schizophrenia and control AE groups (12 and 16 %, respectively) versus a 1 % decrease in hippocampal volume in the non-exercise schizophrenia group. No changes were found in total brain or gray matter volume in either group. A second article examining cortical thickness in the same sample found no significant changes in either group [65]. Overall, these findings demonstrate that despite neuronal atrophy [66, 67] and lower levels of presynaptic proteins [68] in the hippocampus of individuals with schizophrenia, some degree of neurogenesis in the region was possible through AE.

A second trial by Scheewe et al. [69] randomized 32 individuals with schizophrenia and 52 age-matched healthy controls to exercise and control conditions. The exercise program, which included both cardiovascular and strength training exercises, lasted for 6 months, but at reduced frequency compared to Pajonk et al. (twice per week for 60 min; 40 min of AE and 20 min of strength training). At baseline, participants with schizophrenia had smaller cerebrum, gray matter, and ventricle volumes, as well as reduced cortical thickness compared to healthy controls. Post-intervention, the authors failed to find significant differences in brain volume, hippocampal volume, or cortical thickness. There was a trend ($p = .05$) reported for hippocampal volume change; schizophrenia group demonstrating mild decrease in volume post-exercise, while volume did not change significantly in health individuals post-intervention. The study also reported a significant association between improved aerobic fitness and increased volume of cerebral cortex and ventricles, as well as cortical thickening. Supporting these results, a recent small pilot study conducted by Rosenbaum et al. [70] also reported no changes in hippocampal volumes post-exercise treatment, despite significant improvement in aerobic fitness. However, a study revisiting the sample examined by Sheewe et al. revealed that all participants who engaged in AE irrespective of clinical status demonstrated some improvement in white matter integrity within the motor tracts, while non-exercising participants showed a decrease in integrity in the same regions [71]. These findings indicate that overall, exercise improved brain connectivity in this sample and highlight the importance of outcome variable selection when

evaluating the effects of AE. Taken together, results suggest that while exercise at the frequency implemented by Scheewe et al. may not directly promote change in brain structures, it may play a neuroprotective role through improvement in cardiorespiratory fitness and attenuating the expected decreases in brain volume and white matter integrity observed in schizophrenia.

The most recent trial exploring the link between exercise and brain structures appears to support this hypothesis. Malchow et al. [72] utilized the same exercise intervention as Pajonk et al. [64] with a larger sample per group (range = 19–21). However, they failed to find significant changes in hippocampal volumes in both the schizophrenia and control groups post-treatment, though the authors reported observing a temporary increase in gray matter volume in the temporal lobe for the duration of the intervention in the schizophrenia exercise group. The study also evaluated participants 3 months post-intervention to assess lingering effects of exercise. Interestingly, the gray matter volume increase was no longer found in the schizophrenia exercise group, and the schizophrenia control group displayed evidence of a statistically significant decrease in volume. This appears to be in line with Scheewe et al.'s finding and supports the hypothesis that exercise may exert a neuroprotective effect.

A possible explanation for the discrepancy in imaging findings is differences in the frequency and intensity of the provided intervention. Preliminary findings indicate that fidelity with target training intensity is significantly correlated with improvement in cognitive performance in this population [73]. Similarly, a recent meta-analysis of exercise interventions in schizophrenia found that trials that administered at least 90 min per week of moderate-to-vigorous exercise that saw significant improvement not only in fitness, but also in psychiatric symptoms [74•]. Additional data regarding frequency, duration, and in-session intensity would be helpful in determining if the dose-response relationship is a contributor to seeing significant structural and neurobiological changes.

Four additional studies examined brain functioning by exploring the link between AE and circulating neurotrophins, with three studies focusing on BDNF and one study focusing on insulin-like growth factor (IGF-1) and insulin-like growth factor-binding protein (IGFBP-3). Kuo et al. [75] led the first investigation of the link in comparing obese individuals with schizophrenia ($N = 33$) and age- and weight-matched healthy controls ($n = 30$) before and after a 10-week weight reduction intervention, which included AE, dietary changes, and nutritional counseling. BDNF serum levels in the schizophrenia group were significantly lower at baseline. Post-intervention, those individuals who participated in the program demonstrated 4.65 ng/ml (21 %) increase ($p < .001$) in serum BDNF. Of note, the primary aim of the study was to determine the effects of weight reduction on circulating BDNF. Given the multi-faceted approach of the program to reduce weight, our inferences regarding the impact of exercise alone are limited. However, the authors were able to demonstrate that methods to reduce weight may have a significant impact on serum BDNF, supporting a further investigation of AE.

Kim et al. [76] took this step further by implemented a 3-month exercise program that combined 25 min of AE with 25 min of strength training three times per week. The

participants were all individuals with schizophrenia, randomized into exercise and non-exercise groups. Post-treatment, the authors found that the exercise group had significantly higher serum BDNF levels. In addition, the group also displayed a significant improvement in aerobic fitness, which positively correlated with BDNF levels. Given decreased serum BDNF levels in schizophrenia [77] and its implication in various cognitive processes [78, 79], this study was the first to explore directly a combined exercise program as a method of modulating serum BDNF levels in this population.

Silva et al. [80] examined whether resistance training plays a significant role in upregulating neurotrophins. Male individuals with schizophrenia were assigned randomly to three groups: resistance training, combination of resistance and AE, and control group. Intervention was 60 min, two times per week, for 20 weeks. Baseline assessments of neurotrophins BDNF, IGF-1, and IGFBP-3 (IGF's binding protein) were reported; however, no data was provided regarding statistical significance between groups. Furthermore, the authors failed to find any significant differences in neurotrophin levels within or between groups post-intervention. Although these results are surprising, several limitation of the study could account for the variation in results. The authors did not assess for aerobic fitness, but noted that participants experienced no weight reduction. Both aerobic fitness and loss of body weight were significantly associated with elevations in BDNF, as reported earlier. Furthermore, antipsychotic medication dosages, which have been shown to impact serum BDNF levels [81], were significantly different between groups. Finally, similar to the imaging findings described earlier, the dose and intensity of the intervention could be impacting these findings.

A recent study by Kimhy et al. [82] examined individuals with schizophrenia who were randomized to attend AE ($N = 16$) or control (treatment as usual; $N = 17$). The intervention consisted of 60-min sessions, three times per week, for 12 weeks, and participants exercised from 60 to 75 % of their maximal heart rate, increasing gradually across the initial first 4 weeks of treatment. Post-intervention, changes in serum BDNF levels significantly contributed to the variance in neurocognitive functioning, accounting for 14.6 % of the variance in AE-associated cognitive improvement. The difference between groups was not significant (11 vs. 1.9 %, respectively); however, potentially due to the small sample size.

Overall, three out of four studies demonstrated that AE significantly impacts serum BDNF levels. In turn, higher BDNF levels were correlated with improved aerobic fitness and accounted for a significant portion of cognitive improvement in one of the trials. One study failed to find any differences in serum neurotrophin levels [80]. Interestingly, this study employed a similar exercise regimen to a trial that also failed to find significant changes in brain volume, hippocampal volume, or cortical thickness [69], suggesting that an insufficient weekly dose of intervention could potentially explain the difference in results.

Impact of Aerobic Exercise on Neurocognitive Performance

Three studies examined the link between AE and neurocognition. Pajonk et al. [64] assessed short- and long-term memory using Rey Auditory Verbal Learning Test (RAVLT) and visuospatial short-term memory using the Corsi block-tapping test. Results indicated that

after a 12-week AE intervention, individuals with schizophrenia in the exercise group showed a 34 % increase in short-term memory while the scores of exercising healthy controls dropped by 17 %. In addition, non-exercising patients' scores dropped by 6 %. Interestingly, the authors also examined associations between short-term memory scores and hippocampal volume, which were positively correlated, but only when the schizophrenia was combined to include both exercising and non-exercising participants. Results for long-term memory and visuospatial memory were more complex. The former decreased and the latter increased somewhat in the combined exercise group (healthy and schizophrenia participants), though the there was no significant group × time interaction in the combined schizophrenia group (exercising and non-exercising participants). Taken together, these results suggest that the mechanisms by which exercise exerts its effects on memory may differ between healthy controls and individuals with schizophrenia.

Oertel-Knöchel et al. [83] examined the effects of AE and cognitive training on neurocognitive functioning in schizophrenia. The study consisted of an AE + cognitive training group, relaxation + cognitive training group, and a waiting control group (no intervention), to which participants were randomly assigned. AE intervention involved 45-min sessions three times per week for 1 month. Cognitive training consisted of 30-min sessions three times per week. Cognition was assessed using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB). MCCB assesses eight major cognitive domains, including verbal and non-verbal working memory, processing speed, attention, verbal learning, visual learning, problem-solving, and social cognition. Oertel-Knöchel et al. [83] assessed five of the eight domains, excluding attention, problem-solving, and social cognition. The results from post-intervention assessment indicated that cognitive performance improved in both the relaxation and AE groups; however, the effect was much stronger in the combined treatment group. Specifically, participants demonstrated significant improvement in processing speed, working memory, and visual learning. This indicates that AE played a crucial role in improving cognitive functioning independent of cognitive training. Contrary to expectations, the authors failed to find significant post-treatment effects in verbal learning. This is surprising, as recent studies have found significant improvements in this domain with exercise intervention [84].

Our group has also examined neurocognitive functioning as part of the 12-week BDNF study described earlier [82]. In this protocol, neurocognition was also assessed using the MCCB pre and post-treatment phase. Individuals with schizophrenia in the exercise group demonstrated 15.1 % improvement in overall cognitive functioning, while performance in the treatment as usual group decreased by 2 %. The AE intervention produced a large effect (d = .93) with 77 % of the participants improving in performance by 5 % or more. Of note, improvement in aerobic fitness was significant in the exercise group, and it positively correlated with improvements in the social cognition and visual learning domains of the MCCB. Further analysis revealed that after controlling for demographic and clinical variables, aerobic fitness explained 25.4 % of the variance in neurocognitive improvement. Given that cognitive deficits assessed by the MCCB in individuals with schizophrenia have been found to be between one and two-and-a-half standard deviations below the norms for healthy individuals [85, 86], AE-associated changes in neurocognitive functioning accounted

for 24 % in improvement in the current sample, and suggesting the elimination of approximately 16–40 % of neurocognitive deficit generally reported in this population. These results provide strong support for AE as a safe, feasible, and effective intervention.

Conclusion and Future Directions

Empirical research investigating the neural and neurocognitive effects of AE in schizophrenia remains limited, but the emerging evidence is promising. In terms of AE impacting brain structure, the literature is divided. One study observed lasting increases in hippocampal volumes of exercising individuals in schizophrenia, while another observed temporary changes in gray matter volume that disappeared shortly after the intervention ended. A third one failed to find any increases in gray matter volume but noted that participants who did not receive an exercise intervention displayed decreases in gray matter, suggesting that AE and improvement in aerobic fitness may play a neuroprotective role in schizophrenia. This is a plausible hypothesis, as research in neurodegenerative illnesses such as Alzheimer's and dementia has come to similar conclusions about the neuroprotective role of AE in brain structure and function [87, 88].

The majority of studies reviewed also demonstrated evidence that AE is able to significantly increase serum BDNF levels. This is particularly crucial, since improvement in cognitive functioning is related to the brain's ability to modify neural connectivity and function. Such neuroplasticity is dependent on the support of neurotrophins that regulate neuronal survival, differentiation, and growth [89, 90], and influence cellular energy metabolism [91]. Indeed, our group demonstrated an increase in serum BDNF accounted for 14.6 % of the variance in AE-associated cognitive improvement in schizophrenia [82]. Future research should confirm these findings and examine the effects of AE interventions on other neurotrophin serum levels, as well as the impact of neurotrophin levels on mediating the link between AE and cognition. In particular, assessing the impact of AE interventions on vascular endothelial growth factor (VEGF), is also indicated. AE has been shown to upregulate VEGF in the periphery [92] and increased VEGF has been linked to greater hippocampal neurogenesis in animal studies [93]. Other potential targets of investigation include nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4).

Research has also examined potential mechanisms via which AE is able to upregulate neurotrophin levels, specifically BDNF. Cotman and colleagues [94, 95] suggest that IGF-1 is directly upregulated by exercise in the periphery, and increased IGF-1 increases BDNF signaling in the central nervous system and periphery by both increasing BDNF's signaling during AE and increasing the availability of BDNF's binding receptor, tropomyosin receptor kinase B (TrkB). Additionally, findings have linked lower BDNF levels with increased hypertension [96] and metabolic syndrome [97]. This is particularly relevant in schizophrenia, as this population is at increased cardiometabolic risk after initiating antipsychotic treatment [98]. AE has been shown to effectively reduce this risk [99], suggesting that AE may be responsible for reducing impact of systematic risk factors on BDNF levels. Further study of the processes by which AE is able to upregulate BDNF and other neurotrophins in the context of schizophrenia-related co-morbidities would clarify the mechanism of action of AE in this population.

Regarding cognitive performance, preliminary evidence supports AE as an effective intervention to significantly improve global cognitive functioning. However, there is some disagreement regarding which cognitive abilities are improved through exercise. Future studies can elucidate and confirm initial findings that AE can specifically improve processing speed, working memory, visual learning, and verbal learning in this population.

In addition, the degree to which AE is able to produce changes in neurocognition, as well as brain structure and functioning, appears to be governed by a dose-response relationship. Future studies should confirm these preliminary findings and include close monitoring of adherence to intensity targets that will improve assessment of interventions and allow for comparison between studies. To increase enjoyment and decrease attrition in future programs, employment of engaging activities as part of AE programs is encouraged. For instance, integration of active-play video game systems has recently been shown to be safe and effective in this population [100•]. Current literature also highlights the importance of aerobic fitness and its positive correlation with volume changes in brain structures. Implementation of a standardized measure of aerobic fitness, such as the maximal oxygen consumption fitness test (VO_2 max), is recommended in future trials.

Finally, the majority of studies in the current review also reported clinical and functional improvements for individuals participating in AE, though information was limited. This supports findings that increased sedentary behavior and lower aerobic fitness in schizophrenia are associated with functional deficits in the domains of physical functioning, interpersonal relationships, daily activities, and work skills [59]. Similarly, significant associations between higher body mass index (BMI) and more extensive cognitive impairment [59, 101] have been reported, and studies have suggested that improvement in aerobic fitness may lead to greater health-related quality of life [102]. Taking into account the evidence thus far, future research should include measures of daily, social, work, and community functioning to better capture the real-world impact of AE-associated neural and neurocognitive changes. Overall, the present review found preliminary evidence for the benefits of AE to enhance neural and neurocognitive outcomes among individuals with schizophrenia.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

1. Gold JM, Harvey PD. Cognitive deficits in schizophrenia. Psychiatr Clin N Am. 1993; 16:295–312.
2. Harvey PD, Keefe RS. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. Am J Psychiatr Am Psychiatri Publ. 2001; 158:176–84.
3. Jones P, Rodgers B, Murray R, Marmot M. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet. 1994; 344:1398–402. [PubMed: 7968076]
4. O'Carroll R. Cognitive impairment in schizophrenia. Adv Psychiatr Treat. 2000; 6:161–8.
5. Bowie CR, Harvey PD. Cognitive deficits and functional outcome in schizophrenia. Neuropsychiatr Dis Treat. 2006; 2:531–6. [PubMed: 19412501]
6. Barch DM, Keefe RSE. Anticipating DSM-V: opportunities and challenges for cognition and psychosis. Schizophr Bull. 2010; 36:43–7. [PubMed: 19923191]

7. Velligan DI, Mahurin RK, Diamond PL, Hazleton BC, Eckert SL, Miller AL. The functional significance of symptomatology and cognitive function in schizophrenia. Schizophr Res. 1997; 25:21–31. [PubMed: 9176924]
8. Bowie CR, Leung WW, Reichenberg A, McClure MM, Patterson TL, Heaton RK, et al. Predicting schizophrenia patients' real-world behavior with specific neuropsychological and functional capacity measures. Biol Psychiatry. 2008; 63:505–11. [PubMed: 17662256]
9. Addington J, Addington D. Neurocognitive and social functioning in schizophrenia: a 2.5 year follow-up study. Schizophr Res. 2000; 44:47–56. [PubMed: 10867311]
10. Addington J, Addington D. Neurocognitive and social functioning in schizophrenia. Schizophr Bull. 1999; 25:173–82. [PubMed: 10098920]
11. Midin M, Razali R, Zamzam R, Fernandez A, Hum LC, Shah SA, et al. Clinical and cognitive correlates of employment among patients with schizophrenia: a cross-sectional study in Malaysia. Int J Ment Health Syst. 2011; 5:14. [PubMed: 21624111]
12. Sánchez P, Ojeda N, Peña J, Elizagárate E, Yoller AB, Gutiérrez M, et al. Predictors of longitudinal changes in schizophrenia: the role of processing speed. J Clin Psychiatry. 2009; 70:888–96. [PubMed: 19422757]
13. Zaragoza Domingo S, Bobes J, García-Portilla M-P, Morralla C. Cognitive Performance associated to functional outcomes in stable outpatients with schizophrenia. Schizophr Res Cogn. 2015; 2:146–58.
14. Milev P, Ho B-C, Arndt S, Andreasen NC. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. Am J Psychiatry. 2005; 162:495–506. [PubMed: 15741466]
15. Lepage M, Bodnar M, Bowie CR. Neurocognition: clinical and functional outcomes in schizophrenia. Can J Psychiatry. 2014; 59:5–12. [PubMed: 24444318]
16. Gold JM. Cognitive deficits as treatment targets in schizophrenia. Schizophr Res. 2004; 72:21–8. [PubMed: 15531404]
17. Antonova E, Sharma T, Morris R, Kumari V. The relationship between brain structure and neurocognition in schizophrenia: a selective review. Schizophr Res. 2004; 70:117–45. [PubMed: 15329292]
18. Fitzsimmons J, Kubicki M, Shenton ME. Review of functional and anatomical brain connectivity findings in schizophrenia. Curr Opin Psychiatr. 2013; 26:172–87.
19. Reid MA, White DM, Kraguljac NV, Lahti AC. A combined diffusion tensor imaging and magnetic resonance spectroscopy study of patients with schizophrenia. Schizophr Res. 2016; 170:341–50. [PubMed: 26718333]
20. Cahn W, van Haren NEM, Hulshoff Pol HE, Schnack HG, Caspers E, Laponder DAJ, et al. Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. Br J Psychiatry. 2006; 189:381–2. [PubMed: 17012664]
21. Hulshoff Pol HE, Schnack HG, Bertens MGBC, van Haren NEM, van der Tweel I, Staal WG, et al. Volume changes in gray matter in patients with schizophrenia. Am J Psychiatry. 2002; 159:244–50. [PubMed: 11823266]
22. Fusar-Poli, P.; Byrne, M.; Valmaggia, L.; Day, F.; Tabraham, P.; Johns, L., et al. J Psychiatr Res. Vol. 44. Elsevier Ltd; 2010. Social dysfunction predicts two years clinical outcome in people at ultra high risk for psychosis; p. 294-301.
23. Zipursky RB, Agid O. Recovery, not progressive deterioration, should be the expectation in schizophrenia. World Psychiatry. 2015; 14:94–6. [PubMed: 25655164]
24. Buckley PF. Neuroimaging of schizophrenia: structural abnormalities and pathophysiological implications. Neuropsychiatr Dis Treat. 2005; 1:193–204. [PubMed: 18568069]
25. Nieto R, Kukuljan M, Silva H. BDNF and schizophrenia: from neurodevelopment to neuronal plasticity, learning, and memory. Front Psychiatry. 2013; 4:45. [PubMed: 23785335]
26. Green MJ, Matheson SL, Shepherd A, Weickert CS, Carr VJ. Brain-derived neurotrophic factor levels in schizophrenia: a systematic review with meta-analysis. Mol Psychiatry. 2011; 16:960–72. [PubMed: 20733577]

27. Zhang XY, Liang J, Chen DC, Xiu MH, De YF, Kosten TA, et al. Low BDNF is associated with cognitive impairment in chronic patients with schizophrenia. Psychopharmacology. 2012; 222:277–84. [PubMed: 22274000]

28. Rizos, E.; Papathanasiou, MA.; Michalopoulou, PG.; Laskos, E.; Mazioti, A.; Kastania, A., et al. A longitudinal study of alterations of hippocampal volumes and serum BDNF levels in association to atypical antipsychotics in a sample of first-episode patients with schizophrenia. In: Hashimoto, K., editor. PLoS One. Vol. 9. 2014. p. e87997

29. Woodward ND, Purdon SE, Meltzer HY, Zald DH. A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. Int J Neuropsychopharmacol. 2005; 8:457–72. [PubMed: 15784157]

30. Keefe RSE, Bilder RM, Davis SM, Harvey PD, Palmer BW, Gold JM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch Gen Psychiatry. 2007; 64:633–47. [PubMed: 17548746]

31. Buchanan RW, Keefe RS, Lieberman JA, Barch DM, Csernansky JG, Goff DC, et al. A randomized clinical trial of MK-0777 for the treatment of cognitive impairments in people with schizophrenia. Biol Psychiatry. 2011; 69:442–9. [PubMed: 21145041]

32. Javitt DC, Buchanan RW, Keefe RSE, Kern R, McMahon RP, Green MF, et al. Effect of the neuroprotective peptide davunetide (AL-108) on cognition and functional capacity in schizophrenia. Schizophr Res. 2012; 136:25–31. [PubMed: 22169248]

33. Egan FM, Zhao X, Gottwald R, Harper-Mozley L, Zhang Y, Snavely D, et al. Randomized crossover study of the histamine H3 inverse agonist MK-0249 for the treatment of cognitive impairment in patients with schizophrenia. Schizophr Res. 2013; 146:224–30. [PubMed: 23523692]

34. Haig GM, Bain E, Robieson W, Othman AA, Baker J, Lenz RA. A randomized trial of the efficacy and safety of the H3 antagonist ABT-288 in cognitive impairment associated with schizophrenia. Schizophr Bull. 2014; 40:1433–42. [PubMed: 24516190]

35. Levkovitz, Y.; Mendlovich, S.; Riwkes, S.; Braw, Y.; Levkovitch-Verbin, H.; Gal, G., et al. J Clin Psychiatry. Vol. 71. Physicians Postgraduate Press, Inc; 2010. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia; p. 138-49.

36. Berger GE, Proffitt T-M, McConchie M, Yuen H, Wood SJ, Amminger GP, et al. Ethyl-eicosapentaenoic acid in first-episode psychosis: a randomized, placebo-controlled trial. J Clin Psychiatry. 2007; 68:1867–75. [PubMed: 18162017]

37. Wykes T, Newton E, Landau S, Rice C, Thompson N, Frangou S. Cognitive remediation therapy (CRT) for young early onset patients with schizophrenia: an exploratory randomized controlled trial. Schizophr Res. 2007; 94:221–30. [PubMed: 17524620]

38. Lee RSC, Redoblado-Hodge MA, Naismith SL, Hermens DF, Porter MA, Hickie IB. Cognitive remediation improves memory and psychosocial functioning in first-episode psychiatric out-patients. Psychol Med. 2013; 43:1161–73. [PubMed: 23237010]

39. Hogarty GE, Flesher S, Ulrich R, Carter M, Greenwald D, Pogue-Geile M, et al. Cognitive enhancement therapy for schizophrenia: effects of a 2-year randomized trial on cognition and behavior. Arch Gen Psychiatry. 2004; 61:866–76. [PubMed: 15351765]

40. Sartory G, Zorn C, Groetzinger G, Windgassen K. Computerized cognitive remediation improves verbal learning and processing speed in schizophrenia. Schizophr Res. 2005; 75:219–23. [PubMed: 15885513]

41. Wykes, T.; Huddy, V.; Cellard, C.; McGurk, SR.; Czobor, P. Am J Psychiatry. Vol. 168. American Psychiatric Publishing; Arlington, VA: 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes; p. 472-85.

42. Rass O, Forsyth JK, Bolbecker AR, Hetrick WP, Breier A, Lysaker PH, et al. Computer-assisted cognitive remediation for schizophrenia: a randomized single-blind pilot study. Schizophr Res. 2012; 139:92–8. [PubMed: 22682988]

43. Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci. 2008; 9:58–65. [PubMed: 18094706]

44. van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci. 1999; 2:266–70. [PubMed: 10195220]
45. van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci U S A. 1999; 96:13427–31. [PubMed: 10557337]
46. Kim T-W, Kang H-S, Park J-K, Lee S-J, Baek S-B, Kim C-J. Voluntary wheel running ameliorates symptoms of MK-801-induced schizophrenia in mice. Mol Med Rep. 2014; 10:2924–30. [PubMed: 25323073]
47. Liu Y-F, Chen H, Wu C-L, Kuo Y-M, Yu L, Huang A-M, et al. Differential effects of treadmill running and wheel running on spatial or aversive learning and memory: roles of amygdalar brain-derived neurotrophic factor and synaptotagmin I. J Physiol. 2009; 587:3221–31. [PubMed: 19451201]
48. Alomari MA, Khabour OF, Alzoubi KH, Alzubi MA. Forced and voluntary exercises equally improve spatial learning and memory and hippocampal BDNF levels. Behav Brain Res. 2013; 247:34–9. [PubMed: 23499703]
49. Leasure JL, Jones M. Forced and voluntary exercise differentially affect brain and behavior. Neuroscience. 2008; 156:456–65. [PubMed: 18721864]
50. Ke Z, Yip S-P, Li L, Zheng X-X, Tam W-K, Tong K-Y. The effects of voluntary, involuntary, and forced exercises on motor recovery in a stroke rat model. Conf Proc … Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf. 2011; 2011:8223–6.
51. DiLorenzo TM, Bargman EP, Stucky-Ropp R, Brassington GS, Frensch PA, LaFontaine T. Long-term effects of aerobic exercise on psychological outcomes. Prev Med (Baltim). 1999; 28:75–85.
52. Bize R, Johnson JA, Plotnikoff RC. Physical activity level and health-related quality of life in the general adult population: a systematic review. Prev Med. 2007; 45:401–15. [PubMed: 17707498]
53. Penedo FJ, Dahn JR. Exercise and well-being: a review of mental and physical health benefits associated with physical activity. Curr Opin Psychiatry. 2005; 18:189–93. [PubMed: 16639173]
54. van Praag H. Neurogenesis and exercise: past and future directions. NeuroMolecular Med. 2008; 10:128–40. [PubMed: 18286389]
55. van Praag H. Exercise and the brain: something to chew on. Trends Neurosci. 2009; 32:283–90. [PubMed: 19349082]
56. Guiney H, Machado L. Benefits of regular aerobic exercise for executive functioning in healthy populations. Psychon Bull Rev. 2013; 20:73–86. [PubMed: 23229442]
57. Masley S, Roetzheim R, Gualtieri T. Aerobic exercise enhances cognitive flexibility. J Clin Psychol Med Settings. 2009; 16:186–93. [PubMed: 19330430]
58. Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, et al. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom Med. 2010; 72:239–52. [PubMed: 20223924]
59. Kimhy D, Vakhrusheva J, Bartels MN, Armstrong HF, Ballon JS, Khan S, et al. Aerobic fitness and body mass index in individuals with schizophrenia: Implications for neurocognition and daily functioning. Psychiatry Res. 2014; 220:784–91. [PubMed: 25219618]
60. Leutwyler H, Hubbard EM, Jeste DV, Miller B, Vinogradov S. Associations of schizophrenia symptoms and neurocognition with physical activity in older adults with schizophrenia. Biol Res Nurs. 2013; 16:23–30. [PubMed: 24057223]
61•. McEwen SC, Hardy A, Ellingson BM, Jarrahi B, Sandhu N, Subotnik KL, et al. Prefrontal and hippocampal brain volume deficits: role of low physical activity on brain plasticity in first-episode schizophrenia patients. J Int Neuropsychol Soc. 2015; 21:868–79. While many AE studies are conducted in chronically ill populations, this paper underscores the effects of high vs. low baseline physical activity on brain structure in early phase of schizophrenia. [PubMed: 26581798]
62. Armstrong HF, Bartels MN, Paslavski O, Cain D, Shoval HA, Ballon JS, et al. The impact of aerobic exercise training on cardiopulmonary functioning in individuals with schizophrenia. Schizophr Res. 2016

63. Vancampfort D, Rosenbaum S, Probst M, Soundy A, Mitchell AJ, De Hert M, et al. Promotion of cardiorespiratory fitness in schizophrenia: a clinical overview and meta-analysis. Acta Psychiatr Scand. 2015; 132:131–43. [PubMed: 25740655]
64. Pajonk F-GG, Wobrock T, Gruber O, Scherk H, Berner D, Kaizl I, et al. Hippocampal plasticity in response to exercise in schizophrenia. Arch Gen Psychiatry. 2010; 67:133–43. [PubMed: 20124113]
65. Falkai P, Malchow B, Wobrock T, Gruber O, Schmitt A, Honer WG, et al. The effect of aerobic exercise on cortical architecture in patients with chronic schizophrenia: a randomized controlled MRI study. Eur Arch Psychiatry Clin Neurosci. 2013; 263:469–73. [PubMed: 23161338]
66. Deicken RF, Zhou L, Schuff N, Fein G, Weiner MW. Hippocampal neuronal dysfunction in schizophrenia as measured by proton magnetic resonance spectroscopy. Biol Psychiatry. 1998; 43:483–8. [PubMed: 9547926]
67. Heckers S, Konradi C. Hippocampal neurons in schizophrenia. J Neural Transm. 2002; 109:891–905. [PubMed: 12111476]
68. Sawada K, Barr AM, Nakamura M, Arima K, Young CE, Dwork AJ, et al. Hippocampal complexin proteins and cognitive dysfunction in schizophrenia. Arch Gen Psychiatry. 2005; 62:263–72. [PubMed: 15753239]
69. Scheewe TW, van Haren NEM, Sarkisyan G, Schnack HG, Brouwer RM, de Glint M, et al. Exercise therapy, cardiorespiratory fitness and their effect on brain volumes: a randomised controlled trial in patients with schizophrenia and healthy controls. Eur Neuropsychopharmacol. 2012c:675–85. [PubMed: 22981376]
70. Rosenbaum, S.; Lagopoulos, J.; Curtis, J.; Taylor, L.; Watkins, A.; Barry, BK., et al. Psychiatry Res Neuroimaging. Vol. 232. Elsevier; 2015. Aerobic exercise intervention in young people with schizophrenia spectrum disorders; improved fitness with no change in hippocampal volume; p. 200-1.
71. Svatkova A, Mandl RCW, Scheewe TW, Cahn W, Kahn RS, Hulshoff Pol HE. Physical exercise keeps the brain connected: biking increases white matter integrity in patients with schizophrenia and healthy controls. Schizophr Bull. 2015; 41:869–78. [PubMed: 25829377]
72. Malchow B, Keeser D, Keller K, Hasan A, Rauchmann B-S, Kimura H, et al. Effects of endurance training on brain structures in chronic schizophrenia patients and healthy controls. Schizophr Res. 2015:1–10.
73. Kimhy D, Lauriola V, Bartels MN, Armstrong HF, Vakhrusheva J, Ballon JS, et al. Aerobic exercise for cognitive deficits in schizophrenia—the impact of frequency, duration, and fidelity with target training intensity. Schizophr Res. 2016; doi: 10.1016/j.schres.2016.01.055
74•. Firth, J.; Cotter, J.; Elliott, R.; French, P.; Yung, AR. Psychol Med. Vol. 45. Cambridge University Press; 2015. A systematic review and meta-analysis of exercise interventions in schizophrenia patients; p. 1343-61.This systematic meta-analysis demonstrates important findings regarding the effective dose of exercise required to see substantial changes in neurocognition and functional outcomes
75. Kuo FC, Lee CH, Hsieh CH, Kuo P, Chen YC, Hung YJ. Lifestyle modification and behavior therapy effectively reduce body weight and increase serum level of brain-derived neurotrophic factor in obese non-diabetic patients with schizophrenia. Psychiatry Res. 2013; 209:150–4. [PubMed: 23219101]
76. Kim H, Song B, So B, Lee O, Song W, Kim Y. Increase of circulating BDNF levels and its relation to improvement of physical fitness following 12 weeks of combined exercise in chronic patients with schizophrenia: a pilot study. Psychiatry Res. 2014; 220:792–6. [PubMed: 25446461]
77. Buckley PF, Mahadik S, Pillai A, Terry A Jr. Neurotrophins and schizophrenia. Schizophr Res. 2007; 94:1–11. [PubMed: 17524622]
78. Castrén E, Rantamäki T. The role of BDNF and its receptors in depression and antidepressant drug action: reactivation of developmental plasticity. Dev Neurobiol. 2010; 70:289–97. [PubMed: 20186711]
79. Castrén E, Tanila H. Neurotrophins and dementia—keeping in touch. Neuron. 2006; 51:1–3. [PubMed: 16815323]

80. Silva, BAe; Cassilhas, RC.; Attux, C.; Cordeiro, Q.; Gadelha, AL.; Telles, BA., et al. A 20-week program of resistance or concurrent exercise improves symptoms of schizophrenia: results of a blind, randomized controlled trial. Rev Bras Psiquiatr. 2015; 37:271–9. [PubMed: 26375919]
81. Chen C-C, Huang T-L. Effects of antipsychotics on the serum BDNF levels in schizophrenia. Psychiatry Res. 2011; 189:327–30. [PubMed: 21320726]
82. Kimhy D, Vakhrusheva J, Bartels MN, Armstrong HF, Ballon JS, Khan S, et al. The impact of aerobic exercise on brain-derived neurotrophic factor and neurocognition in individuals with schizophrenia: a single-blind, randomized clinical trial. Schizophr Bull. 2015; 41:859–68. [PubMed: 25805886]
83. Oertel-Knöchel V, Mehler P, Thiel C, Steinbrecher K, Malchow B, Tesky V, et al. Effects of aerobic exercise on cognitive performance and individual psychopathology in depressive and schizophrenia patients. Eur Arch Psychiatry Clin Neurosci. 2014:1–16. [PubMed: 24370997]
84. Hötting K, Schauenburg G, Röder B. Long-term effects of physical exercise on verbal learning and memory in middle-aged adults: results of a one-year follow-up study. Brain Sci. 2012; 2:332–46. [PubMed: 24961197]
85. Kern RS, Gold JM, Dickinson D, Green MF, Nuechterlein KH, Baade LE, et al. The MCCB impairment profile for schizophrenia outpatients: results from the MATRICS psychometric and standardization study. Schizophr Res. 2011; 126:124–31. [PubMed: 21159492]
86. August SM, Kiwanuka JN, McMahon RP, Gold JM. The MATRICS Consensus Cognitive Battery (MCCB): clinical and cognitive correlates. Schizophr Res. 2012; 134:76–82. [PubMed: 22093182]
87. Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med. 2006; 144:73–81. [PubMed: 16418406]
88. van Gelder BM, Tijhuis MAR, Kalmijn S, Giampaoli S, Nissinen A, Kromhout D. Physical activity in relation to cognitive decline in elderly men: the FINE Study. Neurology. 2004; 63:2316–21. [PubMed: 15623693]
89. Hennigan A, O'Callaghan RM, Kelly AM. Neurotrophins and their receptors: roles in plasticity, neurodegeneration and neuroprotection. Biochem Soc Trans. 2007; 35:424–7. [PubMed: 17371291]
90. Vaynman S, Gomez-Pinilla F. License to run: exercise impacts functional plasticity in the intact and injured central nervous system by using neurotrophins. Neurorehabil Neural Repair. 2005; 19:283–95. [PubMed: 16263961]
91. Gomez-Pinilla F, Vaynman S, Ying Z. Brain-derived neurotrophic factor functions as a metabotrophin to mediate the effects of exercise on cognition. Eur J Neurosci. 2008; 28:2278–87. [PubMed: 19046371]
92. Kraus RM, Stallings HW, Yeager RC, Gavin TP. Circulating plasma VEGF response to exercise in sedentary and endurance-trained men. J Appl Physiol. 2004; 96:1445–50. [PubMed: 14660505]
93. Fabel K, Fabel K, Tam B, Kaufer D, Baiker A, Simmons N, et al. VEGF is necessary for exercise-induced adult hippocampal neurogenesis. Eur J Neurosci. 2003; 18:2803–12. [PubMed: 14656329]
94. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci. 2002; 25:295–301. [PubMed: 12086747]
95. Cotman CW, Berchtold NC, Christie L-A. Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci. 2007; 30:464–72. [PubMed: 17765329]
96. Prigent-Tessier A, Quirié A, Maguin-Gaté K, Szostak J, Mossiat C, Nappey M, et al. Physical training and hypertension have opposite effects on endothelial brain-derived neurotrophic factor expression. Cardiovasc Res. 2013; 100:374–82. [PubMed: 24092446]
97. Chaldakov GN, Fiore M, Stankulov IS, Manni L, Hristova MG, Antonelli A, et al. Neurotrophin presence in human coronary atherosclerosis and metabolic syndrome: a role for NGF and BDNF in cardiovascular disease? Prog Brain Res. 2004; 146:279–89. [PubMed: 14699970]
98. Mitchell AJ, Vancampfort D, De Herdt A, Yu W, De Hert M. Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. Schizophr Bull. 2013; 39:295–305. [PubMed: 22927670]

99. Carroll S, Dudfield M. What is the relationship between exercise and metabolic abnormalities? A review of the metabolic syndrome. Sports Med. 2004; 34:371–418. [PubMed: 15157122]

100•. Kimhy D, Khan S, Ayanrouh L, Chang RW, Hansen MC, Lister A, et al. Use of active-play video games to enhance aerobic fitness in schizophrenia: feasibility, safety, and adherence. Psychiatr Serv. 2016; 67:240–3. This study highlights the integration of technology in aerobic exercise training programs to increase efficacy and enjoyment, and decrease attrition. [PubMed: 26423100]

101. Friedman JI, Wallenstein S, Moshier E, Parrella M, White L, Bowler S, et al. The effects of hypertension and body mass index on cognition in schizophrenia. Am J Psychiatry. 2010; 167:1232–9. [PubMed: 20634363]

102. Vancampfort D, Guelinckx H, Probst M, Stubbs B, Rosenbaum S, Ward PB, et al. Health-related quality of life and aerobic fitness in people with schizophrenia. Int J Ment Health Nurs. 2015; 24:394–402. [PubMed: 26215311]

Table 1

Experimental design and outcomes of studies assessing impact of aerobic exercise in schizophrenia from 2010 to 2015

Study	Participants			Exercise intervention*	Control intervention	Assessment measures	Neurobiological outcomes	Neurocognitive/clinical outcomes
	SZE	SZC	HCE					
Pajonk et al. [64]	8	8	8	12 weeks, 3 sessions/week, 30 min/session *Type*: AE via cycling	12 weeks, 3 sessions/ week, 30 min/session *Type*: tabletop football	*Physical*: VO_2max *Imaging:* SMRI *Cognitive*: RAVLT, Corsi block-tapping test *Clinical*: PANSS	*Intervention group*: hippocampal volume increased by 12 % in SZE 16 % in HCE *Control group:* hippocampal volume decreased by 1 % in SZC	*Intervention group:* STM increased by 34 % in SZE, decreased by 17 % in HCE. PANSS scores decreased by 9 % in SZE *Control group:* STM decreased by 6 % in SZC. PANSS scores increased by 13 % in SZC
Scheewe et al. [69]	18	14	25/27 (HC)**	6 months, 2 sessions/week, 60 min/ session *Type:* AE via cycling, rowing, crosstrainer (40 min) and 3 sets of muscle strength exercises, 10–15 repetitions/set (20 min)	6 months, 2 sessions/ week, 60 min/session *Type:* occupational therapy (SZC) and life as usual (HC)	*Physical:* VO_2max *Imaging:* SMRI *Clinical:* PANSS	*Intervention group:* no sig. changes in global brain volume, hippocampal volume, or cortical thickness in SZE or HCE *Control group:* no sig. changes in SZC or HC	No neurocognitive data *Intervention group:* PANSS scores decreased by 10.75 % in SZE *Control group:* no sig. changes in PANSS scores in SZC
Malchow et al. [72]	20	19	21	12 weeks, 3 sessions/week, 30 min/session *Type:* AE via cycling	12 weeks, 3 sessions/ week, 60 min/session *Type:* tabletop football	*Imaging:* SMRI and VBM *Clinical:* PANSS	*Intervention group:* no sig. increases in hippocampus or hippocampal substructure volumes in SZE and HCE. Increased gray matter volume of the left anterior temporal in SZE vs SZC ($p < .05$) only during intervention period; no sig. differences 3 months post-study *Control group:* during intervention, increase in gray matter volume in anterior cingulate cortex and motor cortex bilaterally ($p < .05$). Volume decrease in left hippocampus 3 months post-study ($p = .001$)	No neurocognitive data *Intervention group:* no sig. changes in PANSS scores in SZE *Control group:* no sig. changes in PANSS scores in SZC
Kuo et al. [75]	33	–	30	10 weeks, 5 sessions/week, 20–30 min/session and 1 session/ week, 60 min/session of group physical activity *Type:* house cleaning/slow walking (30 min) or faster walking/ cycling (20 min); group activity type not reported	None reported	*Physical:* weight, BMI, waist circumference *Neurotrophins:* serum BDNF	*Intervention group:* serum BDNF levels increased ($p < .001$); weight, BMI, waist circumference decreased ($p < .001$) *Control group:* none reported	
Kim et al. [76]	22	12	–	12 weeks, 3 sessions/week, 60 min/session	12 weeks, 1 session/ week, 60 min/session	*Physical:* weight, BMI, YMCA 3-min	*Intervention group:* serum BDNF values increased (p	

Study	Participants SZE	SZC	HCE	Exercise intervention*	Control intervention	Assessment measures	Neurobiological outcomes	Neurocognitive/clinical outcomes
				Type: combination of AE via moderate walking (25 min) and strength training (25 min)	*Type:* stretching, dancing, and recreational activity	step test and other physical functioning tests *Neurotrophins:* serum BDNF	= .007), and positively correlated with fitness (p = .035) *Control Group:* no changes.	
Silva et al. [80]	19	13	–	20 weeks, 2 sessions/week, 60 min/session *Type (two arms):* **1** Resistance training only **2** Resistance (30 min) and AE on treadmill (25 min)	20 weeks, 2 sessions/ week, 60 min/session *Type:* same protocol as AE intervention but equipment kept at lowest setting	*Physical:* weight, BMI, VO_2max *Neurotrophins:* serum IGF-1, IGFBP-3, and BDNF *Clinical:* PANSS, CDSS, SF-36	*Intervention group (1):* no changes *Intervention group (2):* no changes *Control group:* no changes	No neurocognitive data *Intervention group (1):* PANSS scores decreased in SZE (p < . 001); SF-36 physical role limitation scores improved (p = . 011). No sig. changes in CDSS *Intervention group (2):* PANSS scores decreased in SZE (p = . 003); SF-36 physical role limitation scores improved (p = . 014). No sig. changes in CDSS *Control group:* no sig. changes
Kimhy et al. [82]	16	17	–	12 weeks, 3 sessions/week, 60 min/session *Type:* AE via Xbox active-play video games focused on whole-body exercises, treadmills, bicycle, and elliptical	Treatment as usual	*Physical:* VO_2max *Cognitive:* MCCB *Neurotrophins:* serum BDNF	*Intervention group:* serum BDNF increased by 11 %. BDNF change explained 14.6 % of variance in neurocognitive improvement *Control group:* serum BDNF increased by 1.9 % (group difference was not sig.)	*Intervention group:* improved neurocognition by 15.1 %. Aerobic fitness explained 25 % of variance in neurocognitive improvement. *Control group:* 2.0 % decline in neurocognitive performance
Oertel-Knöchel et al. [83]	8	21	–	4 weeks, 3 sessions/week, 45 min/ session *Type:* AE via boxing and circuit training	*Two arms:* **1** 4 weeks, 3 sessions/ week, 45 min/ session *Type:* relaxation training, including breathing and imagery exercises (N = 11) **2** Waitlist (N = 10)	*Cognitive:* MCCB *Clinical:* PANSS, RHS		*Intervention group:* sig. improvement of performance in visual learning, working memory and processing speed, both compared to baseline and to control groups. Significant reduction of PANSS negative symptoms scores in SZE. No sig. change in RHS *Control group (1):* sig. reduction of PANSS negative symptoms scores in SZC *Control group (2):* no changes

AE aerobic exercise, *SZE* individuals with schizophrenia receiving exercise intervention, *SZC* individuals with schizophrenia receiving control intervention, *HCE* healthy individuals receiving exercise intervention, *HC* healthy individuals receiving control intervention, *Sig* significant, *SMRI* structural magnetic resonance imaging, *RAVLT* Rey Auditory Verbal Learning Test, *PANSS* the Positive and Negative Syndrome Scale, *STM* short-term memory, *VBM* voxel-based morphometry, *BMI* body mass index, *BDNF* brain-derived neurotrophic factor, *IGF-1* insulin-like growth factor 1, *IGFBP-3* insulin-like growth factor-binding protein 3, *CDSS* Calgary Depression Scale for Schizophrenia, *SF-36* Short Form-36 Health Survey, *MCCB* MATRICS Consensus Cognitive Battery, *SAPS* Scale for the Assessment of Positive Symptoms, *SANS* Scale for the Assessment of Negative Symptoms, *BDI* Beck Depression Inventory, *BAI* Beck Anxiety Inventory, *STAI* State-Trait Anxiety Inventory, *RHS* Revised Hallucination Scale

*All exercise interventions were in addition to treatment as usual in individuals with schizophrenia

**In this study, 25 healthy participants participated in exercise intervention and 27 additional healthy participants were recruited as exercise controls and continued life as usual (HC)