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INVITED REVIEW

Neurobiological effects of aerobic exercise, with a focus on patients with schizophrenia

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Abstract

Schizophrenia is a severe neuropsychiatric disease that is associated with neurobiological alterations in multiple brain regions and peripheral organs. Negative symptoms and cognitive deficits are present in about half of patients and are difficult to treat, leading to an unfavorable functional outcome. To investigate the impact of aerobic exercise on various neurobiological parameters, we conducted a narrative review. Add-on aerobic exercise was shown to be effective in improving negative and general symptoms, cognition, global functioning, and quality of life in schizophrenia patients. Based on findings in healthy individuals and animal models, this qualitative review gives an overview of different lines of evidence on how aerobic exercise impacts brain structure and function and molecular mechanisms in patients with schizophrenia and how its effects could be related to clinical and functional outcomes. Structural magnetic resonance imaging studies showed a volume increase in the hippocampus and cortical regions in schizophrenia patients and healthy controls after endurance training. However, results are inconsistent and individual risk factors may influence neuroplastic processes. Animal studies indicate that alterations in epigenetic mechanisms and synaptic plasticity are possible underlying mechanisms, but that differentiation of glial cells, angiogenesis, and possibly neurogenesis may also be involved. Clinical and animal studies also revealed effects of aerobic exercise on the hypothalamus–pituitary–adrenal axis, growth factors, and immune-related mechanisms. Some findings indicate effects on neurotransmitters and the endocannabinoid system. Further research is required to clarify how individual risk factors in schizophrenia patients mediate or moderate the neurobiological effects of exercise on brain and cognition. Altogether, aerobic exercise is a promising candidate in the search for pathophysiology-based add-on interventions in schizophrenia.

Keywords Schizophrenia · Aerobic exercise · Neurobiology · Plasticity · Epigenetics · Molecular mechanisms

Introduction

Schizophrenia is one of the most debilitating psychiatric disorders. Although antipsychotic medication is effective in reducing positive symptoms in schizophrenia patients, it is less successful in treating negative symptoms [1] and cognitive deficits [2]. These symptoms, however, cause the most long-term disability and disease-associated burden [3]. Thus, novel treatment strategies that promote functional recovery by decreasing negative symptoms and cognitive deficits are warranted. Studies have suggested that aerobic exercise as an add-on therapy may meet this need [4, 5]. Aerobic exercise was shown to be superior to various control conditions in improving positive, negative, and general symptom severity, global and social functioning, need of care, and quality of life in schizophrenia patients [3, 6–8] (Fig. 1). Furthermore,

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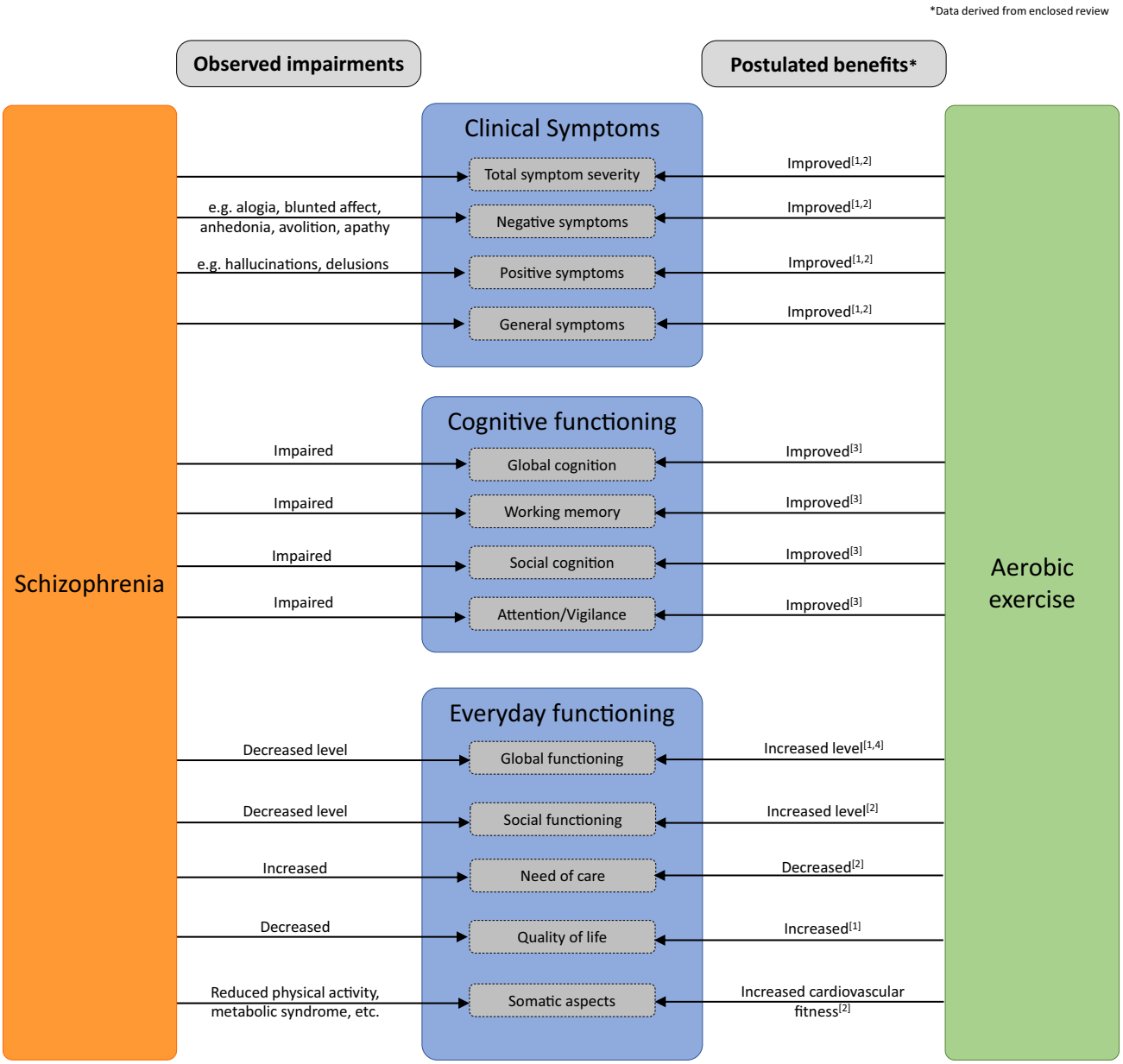

Fig. 1 Effects of aerobic exercise on symptoms and level of functioning in schizophrenia patients. Legends: Dauwan et al. [6], Firth et al. [11], Firth et al. [9], Vancampfort et al. [3]

it was found to significantly ameliorate cognitive deficits in schizophrenia, with specific effects on working memory, attentional processes, and social cognition [9]. It was also shown to be effective in promoting physical health and reducing the risk of patients with schizophrenia to develop a somatic comorbid disorder [10–12]; this is of particular importance, because people with schizophrenia consistently have higher morbidity and mortality than the general population. The life expectancy of people with schizophrenia is shortened by 10–20 years [4, 13], because they have a higher risk than the general population for cardiovascular disease [14], metabolic syndrome [15], diabetes [16], and respiratory diseases [17]. Unhealthy lifestyle habits, such as heavy smoking [18], poor diet [19], and low levels of physical activity [20], are likely to play important roles in the development of these conditions. Finally, certain antipsychotics and the symptoms of the disease itself often lead to weight gain and metabolic syndrome [21].

Impairments in neuroplasticity, inhibitory functioning, and connectivity that result in failed neuroregeneration have been discussed as the underlying causes of negative symptoms and cognitive deficits in patients with schizophrenia

[22]. Aerobic exercise has been suggested as a promising intervention to target these deficits by modulating neuroplasticity. However, there is still some ambiguity regarding the underlying neurobiological mechanisms of exercise in schizophrenia patients. Unfortunately, this current lack of understanding has hampered the design of efficient exercise programs intended to have the greatest possible benefits in schizophrenia.

Based on findings in healthy individuals and animal models, this narrative review aims to give an overview of different lines of evidence on how exercise impacts brain structure and function and molecular mechanisms in patients with schizophrenia (Fig. 2) and how these effects could be related to the clinical and functional outcomes of this severe disorder.

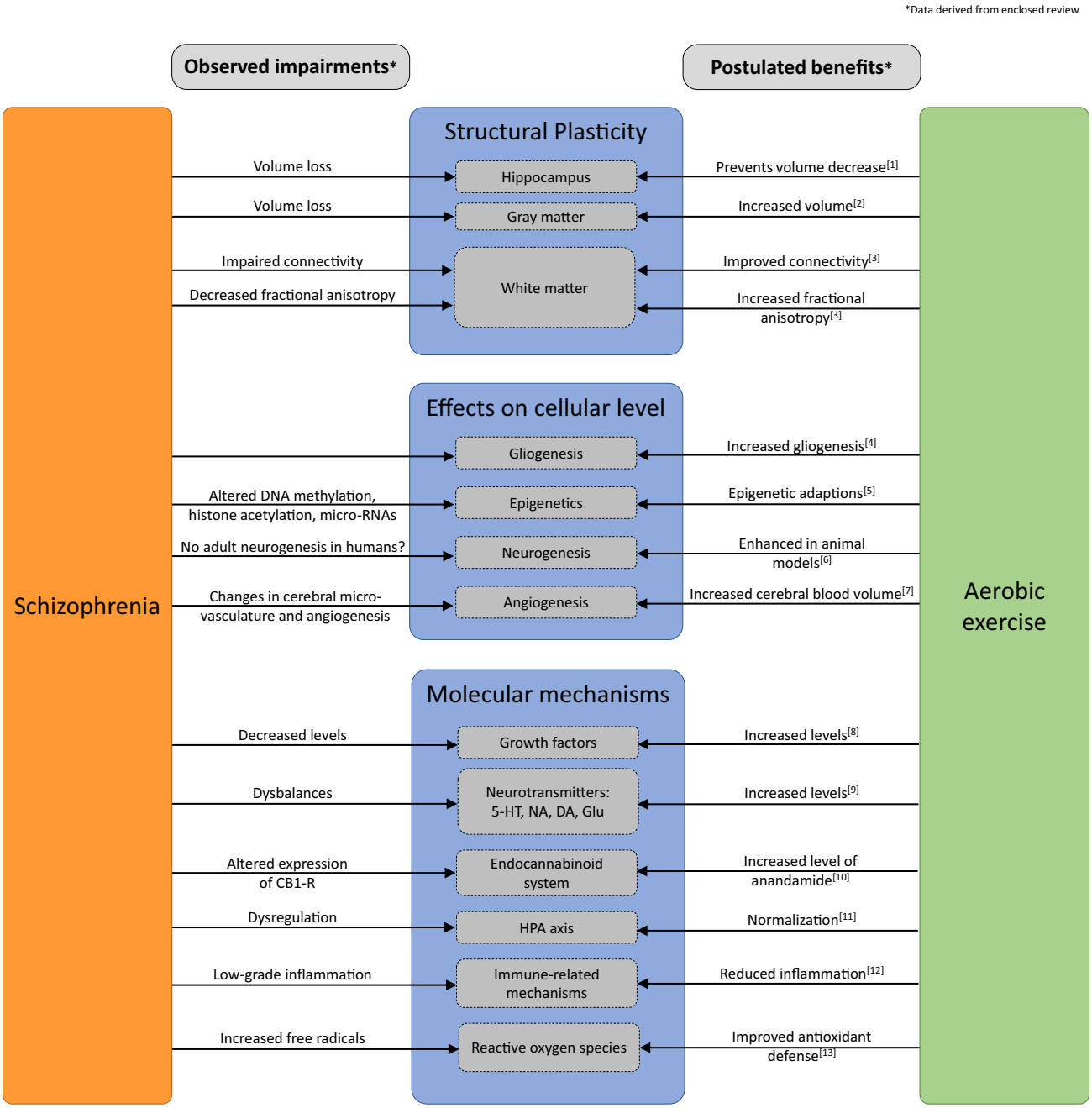

Fig. 2 Postulated neurobiological effects of aerobic exercise in schizophrenia patients. Legends: Firth et al. [33], Weinstein et al. [35], Svatkova et al. [51], Brockett et al. [68], Voisin et al. [85], van Praag [26], Pereira et al. [77], Szuhany et al. [110], Meeusen and De Meirleir [144], Tantimonaco et al. [177], Stranahan et al. [183], Gomes da Silva et al. [200]

Thereby, we covered several research areas, ranging from structural findings to the effects on cellular level and molecular mechanisms. The literature was not systematically searched, extracted, and synthesized. However, for every of the following topics, a focused literature search based on the PubMed database has been conducted. So far, research has focused on aerobic formats of exercise, which seem to be most promising. On the basis of previous recommendations for schizophrenia patients [23, 24], we will concentrate on the effects of long-term aerobic training.

Structural plasticity

Structural magnetic resonance imaging (sMRI) findings, with a focus on gray matter

The hippocampus plays a vital role in declarative learning and memory formation. Notably, several psychiatric and neurological disorders, including schizophrenia, have been associated with hippocampal dysfunction. This may be because some symptoms are common to these disorders, such as aspects of cognitive impairment [25]. At the same time, the hippocampus has been identified as a brain region that is sensitive to the effects of physical activity, an aspect that has been extensively studied in rodents [26, 27]. In particular, aerobic training seems to promote hippocampal volume and function, as specified below.

An increase in hippocampal volume in response to aerobic exercise has been consistently observed in animal models [28, 29], and a number of human studies have also found that aerobic exercise can lead to improvements in learning and memory performance and that these improvements are associated with increased hippocampal volume. For example, Erickson et al. [30] showed that a correlation between fitness and short-term memory in a large sample of healthy elderly adults was mediated by increases in hippocampal volume. Similar results were found in another study in healthy adults, which showed increases in bilateral hippocampal volume after 10 weeks of an aerobic exercise intervention program [31]. However, despite these and other promising findings [32, 33], overall evidence from studies on the effects of aerobic exercise on hippocampal volume in humans is less robust. Firth et al. recently undertook a meta-analysis of controlled trials on this topic. Across 14 eligible controlled trials in a total of 737 participants, they found no significant effect of aerobic exercise on total hippocampal volume ($g = 0.120$, 95% CI 0.02–0.26, $p = 0.082$). However, compared with control conditions, aerobic exercise had positive effects on left hippocampal volume in terms of a volume increase. As post hoc analyses revealed, these findings were driven through aerobic exercise preventing the physiological volumetric decrease in comparison to control conditions [33]. Studies in older adults in particular have shown that exercise interventions can counteract age-related brain atrophy [34]. This effect might mediate the association between aerobic fitness and executive function [35]. Moreover, higher physical fitness levels have been associated not only with larger hippocampi [36] but also with larger cortical areas, especially frontal regions [35, 37, 38]. Again, systematic research on this issue is lacking.

Four of the studies in the meta-analysis by Firth et al. [33] investigated the impact of exercise on hippocampal volume in patients with schizophrenia. When analyzing these studies in a total of 107 people with schizophrenia or first-episode psychosis, the authors detected no significant increase in the total, right, or left hippocampal volume compared with control conditions ($g = 0.149$, 95% CI −0.31 to 0.60, $p = 0.53$) [33]. However, because of the relatively small sample sizes across the studies, which did not allow for further subgroup analysis, they were unable to rule out possible benefits of aerobic exercise on hippocampal volume in schizophrenia on the basis of the null findings [33]. In patients with schizophrenia, individual risk factors may contribute to conflicting results [39, 40]. Indeed, schizophrenia polygenetic risk scores have been shown to significantly influence the exercise-mediated volume increase of specific subregions of the hippocampus [41].

Effects on white matter

Although most of the current literature focuses on assessing gray matter changes, some papers also report on the impact of aerobic exercise on white matter integrity [25]. White matter tracts interconnect distant cortical regions and are required to allow complex information processing in large-scale networks [42, 43]. In cross-sectional studies, both aerobic fitness and endurance exercise have been shown to affect white matter tracts in healthy individuals [32, 44]. In a study by Burdette et al., older adults at risk for cognitive decline (because they were aged 70–85 years and had self-reported memory loss) participated in an exercise intervention (150 min/week of aerobic training), cognitive training, a combined treatment of exercise and cognitive training, or a healthy aging educational control group. After 4 months of the intervention, MRI measures of resting brain blood flow and connectivity were performed. The authors showed that physical exercise was associated with increased connectivity between prefrontal, cingulate, and hippocampal areas, which resulted in better performance on several cognitive tasks [45].

A recent meta-analysis assessed the effects of aerobic exercise on white matter volume, lesions, and microstructure in older healthy adults. The authors concluded that, across all 29 eligible studies, physical activity correlated with greater white matter volume, resulting in small but significant effect sizes [46].

Abnormalities in white matter integrity have been reported in patients with schizophrenia, particularly in frontal and temporal cortices, by studies using diffusion tensor imaging (DTI), a method that assesses the diffusion properties of water molecules to infer microstructural white matter changes [47, 48]. Other studies have shown an abnormal myelination of the tracts responsible for communication between these regions [49, 50]. Svatkova et al. [51] conducted a longitudinal intervention study in 33 patients with schizophrenia and 48 healthy controls. The participants were randomly assigned to either 6 months of training (1 h training session, consisting of 40 min of aerobic and 20 min of anaerobic exercise, twice weekly) or a life-as-usual condition. Using DTI, the researchers showed that the training led to an increased integrity in particular of white matter fiber tracts related to motor functioning, such as the corpus callosum, corticospinal tract, and superior longitudinal fascicle, whereas life-as-usual led to a decreased fiber integrity. Remarkably, this benefit was seen in both the patients with schizophrenia and the healthy controls [51].

In summary, these studies demonstrate that aerobic exercise is able to induce structural adaptations in motor function-related brain regions and associated fiber connections. Furthermore, the beneficial effects of exercise with respect to cerebrovascular health play an important role in white matter integrity. These benefits include the preservation of arterial elasticity and wall integrity and a reduction in arterial stiffness and blood pressure [46].

Functional imaging findings

In addition to brain imaging with MRI, electrophysiological techniques, including electroencephalography (EEG), functional magnetic resonance imaging (fMRI), functional near-infrared spectroscopy (fNIRS), and transcranial magnetic stimulation (TMS), may also be helpful in providing insight into the effects of aerobic exercise on brain activity and functioning [52]. For example, in healthy older adults, changes in task-related brain activation and functional connectivity through long-term exercise were demonstrated with fMRI [53, 54]. In addition, aerobic training was shown to increase functional connectivity between the frontal, posterior, and temporal cortices in both the default mode network (DMN) and the frontal executive control networks [55]. Compared with sedentary individuals, healthy, active individuals showed differences in motor cortical excitability, as assessed by motor cortex TMS, and motor cortical plasticity via paired-associative stimulation could only be induced in physically active people [56]. Older studies indicate changes in EEG amplitude and visual-evoked potentials (VEPs) after marathon running [57, 58]. One recently published study showed that 3 months of aerobic endurance training (30 min, 3 times/week) on bicycle ergometers increased motor cortical inhibition, assessed by TMS, in both healthy controls and schizophrenia patients, with no significant group differences [59].

Neurogenesis

Neurogenesis refers to the process of generating new neurons from precursor cells. Evidence from genetic studies, animal models, and imaging studies suggests that aberrant neurogenesis may contribute to the pathogenesis, pathophysiology, and symptoms of schizophrenia [60].

Improvements in spatial learning and memory after chronic aerobic exercise have been associated with physiological and structural neuronal changes, including neurogenesis [26, 61]. In rodents, studies demonstrated that aerobic exercise promotes neurogenesis in the dentate gyrus subregion of the hippocampus [26, 27]. Moreover, in humans, regular aerobic exercise has been shown to increase cell density and shape in a number of hippocampal regions [62, 63]. These changes in brain cell composition after exercise have been shown to relate to greater volumes of subregions of the hippocampus and to the total size of the hippocampus seen with structural MRI in rodents [64–66].

Until recently, the adult human hippocampus was considered to be able to continue generating new neurons up to adulthood, and aerobic exercise was thought to be a possible way to enhance neurogenesis [67]. However, evidence from human studies on hippocampal volume increase in response to aerobic exercise is less robust than that from animal studies [32, 33]. Findings regarding neurogenesis as the underlying mechanism are also equivocal in humans. Whereas some studies have suggested that new neurons are added to the adult dentate gyrus every day, others have found many fewer putative new neurons [67]. To get to the bottom of the contradictory data, Sorrells et al. examined surgical resection samples from patients with epilepsy and postmortem samples from controls and detected no young neurons in the dentate gyrus [67]. In the monkey hippocampus, they found proliferation of neurons in the subgranular zone in early postnatal life, but decreased neurogenesis during juvenile development. The group concluded that even though a recruitment of young neurons to the primate hippocampus occurs during the first years of life, neurogenesis in the dentate gyrus does not continue, or is extremely rare, in adult humans. Their findings raise important questions about how the function of the dentate gyrus differs between humans and species in which adult hippocampal neurogenesis is preserved, such as rodents. It follows that even though exercise-induced neurogenesis could be shown in animals, it probably does not occur in humans.

Gliogenesis

In rodents, studies examined whether exercise could alter the structure and function of astrocytes. Astrocytes form the majority of glial cells in the human central nervous system (CNS) and play an important role in the regulation of blood flow and trophic support, both functions that have numerous implications for neuronal functioning and synaptic growth [68]. Moreover, astrocytes modulate glutamate metabolism and transmission. Abnormality in these processes is highly correlated with schizophrenia phenotypes [69].

Using immunolabeling for astrocyte and synaptic markers in rodents, two studies observed an increase in astrocyte cell body size in the hippocampus, medial prefrontal cortex, and orbitofrontal cortex in response to running compared with the sedentary control condition [68, 70]. The authors concluded that aerobic exercise alters astrocyte morphology and leads to specific changes in astrocyte markers.

Animal models have also provided some evidence to suggest an association between exercise and the proliferation of oligodendrocyte progenitor cells. Throughout adulthood, oligodendrocyte progenitor cells continue to differentiate into mature oligodendrocytes, a process that is essential for continued myelination. For example, running was shown to increase the number of immature and mature oligodendrocytes in the spinal cord of the mouse [71] and to increase differentiation of oligodendrocyte precursors after hypoperfusion of the brain [72]. These results suggest the existence of complex interactions between environmental factors, oligodendrocyte lineage development, and brain function [73].

The effects of aerobic exercise on glia proliferation and differentiation in schizophrenia patients or healthy controls are widely unknown. Positive findings, for example from DTI studies, as mentioned above, could reinforce the relevance of physical exercise as a strategy for the regeneration of white matter tracts.

Angiogenesis

Angiogenesis is broadly defined as the formation of new blood vessels from the existing vasculature and is regulated by angiogenic growth factors, among others [74]. The maintenance of adequate cerebral blood flow is essential for a constant supply of oxygen and nutrients, which, in turn, is essential for the energy-requiring processes memory formation and consolidation [43]. Morphological, genetic, neuroimaging, and postmortem gene expression studies implicate cerebral microvasculature and changes in angiogenesis as a potential contributor to the pathophysiology of schizophrenia [74].

However, studies have shown that, in healthy older adults, greater aerobic capacity, achieved through regular physical activity, leads to higher cerebral blood flow and that dementia is associated with a reduced cerebral blood flow [75, 76]. A 3-month aerobic exercise intervention by Pereira et al. in healthy middle-aged participants resulted in an increased cerebral blood volume in the dentate gyrus region of the hippocampus, which correlated with improved learning and better memory performance [77], indicating that the vascular adaptations might contribute to subsequent neuroplasticity [78]. In schizophrenia patients, angiogenesis as a result of aerobic exercise still requires further investigation.

The literature on both animal and, to a limited extent, human studies suggests that gliogenesis, vascular adaptations, and possibly neurogenesis represent the primary mechanisms on the cellular level, and that all three are promoted by exercise. These adaptations are followed in turn by changes in molecular pathways, which will be further considered below.

Epigenetic alterations

Epigenomic profiling means linking genotype to differential gene expression [79]. A major epigenetic mechanism is methylation of cytosine bases within the genome. If this methylation occurs within the promoter region of genes, it results in repression of transcription, thus enabling transcriptional control [80]. Histone modification of chromatin is another epigenetic mechanism that influences gene expression [81]. Altered DNA methylation and histone post-translational modifications have been detected in the brain and blood cells of patients with schizophrenia [82–84]. In addition, micro-RNAs (miRNAs) that regulate the transcriptome, such as miR137, have been shown to be differentially expressed in brain regions of schizophrenia patients [82, 83]. Because environmental factors play a major role in epigenetic regulation [82], studies have investigated the respective effects of aerobic exercise. A review of 25 studies on the effect of physical activity on DNA methylation in humans concluded that long-term exercise can change methylation in a highly tissue- and gene-specific manner [85]. Studies that examined these mechanisms in rodents showed that exercise regulates DNA methylation and histone acetylation in the hippocampus [86]. Interestingly, animal studies even showed an influence of paternal exercise on the offspring's hippocampal DNA methylation compared with the offspring of sedentary fathers [87, 88]. These findings indicate that exercise-induced epigenetic mechanisms have trans-generational effects.

Exercise enhances the activity of histone acetyltransferases and histone deacetylases, both of which play an important role in the regulation of histone acetylation and modulate gene transcription [89]. These mechanisms may contribute to the transcriptional regulation underlying the improvements in cognitive function seen in rodents after long-term aerobic exercise [89]. Moreover, in animals,

BDNF expression was shown to be enhanced through epigenetic mechanisms [86].

In addition, aerobic exercise is able to modulate the expression of memory-related miRNAs [86]. There are multiple interactions between miRNAs and epigenetic factors. On one hand, in many cell types, the expression of some miRNAs is silenced by DNA methylation and modulated by histone modifications. On the other hand, miRNAs can directly target epigenetic factors, such as DNA methyltransferases and histone deacetylases, which lead to adaptations in chromatin structure [90]. Exercise-induced memory improvements were shown to be accompanied by changes in the hippocampal miRNA-mRNA regulatory network in animals [91–93]. A comparison of endurance athletes and healthy controls found linear correlations between miRNA and both resting heart rate and maximum oxygen uptake [94]. The authors concluded that muscle-enriched miRNAs are regulated by aerobic exercise training and can serve as biomarkers of cardiorespiratory fitness [94]. However, there is a need for more research exploring epigenetic effects in human populations and patients with schizophrenia.

Synaptic plasticity

After being exposed to internal and external influences, the brain is able to respond on the synaptic level. A study in rodents showed that hippocampal dendritic length and dendritic spine complexity can be enhanced through exercise [63]. Kohman et al. [95] conducted a study with a microarray on whole hippocampal samples from adult and aged mice that were housed with or without a running wheel. The results showed that running increased the expression of genes related to cell growth, and attenuated the expression of genes involved in immune function and chromatin remodeling. A study with a similar design demonstrated an upregulation of genes involved with synaptic trafficking (synapsin I, synaptotagmin, and syntaxin), signal transduction pathways (Ca^{2+}/calmodulin-dependent protein kinase II, CaM-KII, mitogen-activated/extracellular signal-regulated protein kinase, MAP-K/ERK I and II, protein kinase C, and PKC-delta) and transcription regulators (cAMP response element-binding protein, and CREB) [96].

Exercise can also promote synaptic plasticity by facilitating long-term potentiation (LTP), as shown in animals [97–99]. LTP refers to the strengthening of synaptic connections between neurons and is considered as a cellular model of learning and memory [100]. In young rodents, aerobic exercise was able to stimulate LTP and reverse the age-related decline of LTP compared with sedentary controls [32]. Alongside morphological changes to the neural cells and their vasculature, these mechanisms may contribute to ameliorating learning and memory impairments. Their significance in patients with schizophrenia needs to be further investigated in future studies.

Growth factors

The upregulation of various neurotrophic factors is assumed to be one of the underlying mechanisms mediating neuroplasticity through physical activity [76]. It is well documented that neurotrophic factors can facilitate the maturation, proliferation, and survival of neurons [38, 101].

BDNF

Brain-derived neurotrophic factor (BDNF) not only has an integral role in supporting neuronal survival and growth, but also improves functional connectivity by increasing synaptogenesis and dendritic spine density [100]. It is widely distributed throughout the CNS and can be found in particularly high concentrations in the hippocampus, neocortex, cerebellum, striatum, and amygdala [101]. BDNF unfolds its effects on neurogenesis and synaptic transmission by binding to one of its receptors, high-affinity tropomyosin-related kinase-B (Trk-B). Binding to Trk-B results in receptor dimerization and trans-autophosphorylation of tyrosine residues in the cytoplasmic domains of the receptor, which in turn initiates a number of intracellular signaling cascades [38]. In models of normal aging and neurodegenerative conditions, treating cultured hippocampal or cortical neurons with exogenous BDNF protects them against dysfunction and degeneration [102, 103]. Moreover, BDNF has been shown to be essential for the maintenance of synaptic plasticity [102]. After applying BDNF to organotypic hippocampal slices in culture, a higher density of dendritic spines and synapses can be observed and the expression of synaptic proteins such as synaptophysin, synaptobrevin, and synaptotagmin rises [104].

The strongest evidence for acute exercise-induced increases of BDNF in the brain is derived from rodent studies [38, 105]. Using BDNF-mutant mice, Korte and colleagues first demonstrated that BDNF has a functional role in memory formation [106]. In the same year, it was reported that rats showed increased BDNF gene expression in the hippocampus and certain layers of the caudal neocortex after 7 days of wheel running [107], providing the first evidence that growth factors may be responsible for the beneficial effects of exercise on the brain [43]. Blocking BDNF receptors, however, abolished the downstream effects of exercise on cognitive performance and memory [100]. This defect was rescued with BDNF replacement, either by injecting the BDNF-expressing adenovirus [108] or by supplying exogenous BDNF [109].

In humans, immediately preceding exercise has also been shown to increase peripheral BDNF levels

significantly. A meta-analysis by Szuhany and colleagues revealed that, after regular aerobic training, healthy individuals showed a higher increase in peripheral BDNF after immediately preceding physical activity ($g = 0.59$) than previously sedentary individuals showed after only a single session of exercise ($g = 0.46$) [110]. Regarding resting BDNF levels after a program of regular exercise, Szuhany et al. found a low but significant effect size of $g = 0.27$. Moreover, exercise-induced expression of BDNF seems to be age-dependent and less pronounced in older individuals [111] and women [110].

In patients with schizophrenia, serum BDNF levels were shown to be significantly lower than in healthy controls [112, 113], and were associated with cognitive impairment [114]. Several studies have examined the link between aerobic exercise and BDNF in schizophrenia patients. Peripheral BDNF was shown to increase after aerobic exercise compared with an inactive control group consisting of either patients with schizophrenia receiving treatment as usual [115–118] or healthy controls [119]. Moreover, after aerobic exercise, positive correlations were demonstrated between BDNF and cognitive enhancements [120], providing an important clinical link to enhanced neuroplasticity.

Although there are several growth factors that may play a role in the chronic effects of exercise, besides BDNF insulin-like growth factor (IGF-1) and vascular endothelial growth factor (VEGF) have received the most interest. BDNF interacts with both IGF-1 and VEGF, both of which stimulate the growth of endothelial cells, which express nitric oxide synthase. Nitric oxide synthase in turn is required for exercise-induced upregulation of BDNF in the hippocampus [38, 121].

IGF-1

Studies comparing trained and sedentary individuals demonstrated that IGF-1 levels are significantly higher in trained individuals [32]. In addition, both animal and human studies revealed that exercise is associated with an increased peripheral level of IGF-1 [122]. Circulating IGF-1 crosses the blood–brain barrier [123], enhances synaptic plasticity and neuronal survival, and increases concentrations of BDNF [124]. IGF-1 replacement was shown to enhance learning and memory in rats [125].

Compared with healthy controls, schizophrenia patients exhibit reduced levels not only of BDNF but also of IGF-1 [126, 127]. To the best of our knowledge, so far, only one study has assessed changes in peripheral IGF-1 levels in schizophrenia patients after aerobic exercise: Andrade et al. found no differences in peripheral IGF-1 levels induced by 20 weeks of aerobic exercise [128].

VEGF

VEGF is produced by skeletal muscle cells and secreted into the circulation. Acute exercise increases VEGF mRNA in skeletal muscle, whereas VEGF protein itself is reduced immediately after acute exercise [129]. However, chronic exercise is able to restore and even increase skeletal muscle VEGF mRNA and protein levels [130]. Even though VEGF does not readily cross the blood–brain barrier, in animals, increased levels were shown in the hippocampus after exercise [131].

Regarding patients with schizophrenia, a meta-analysis by Misiak and colleagues in 15 eligible studies revealed no significant differences in VEGF levels between patients and controls [132]. However, heterogeneity across the studies was significant in the majority of the analyses [132]. Insufficient data were available on exercise-induced changes in VEGF levels in patients with schizophrenia.

Other growth factors that represent potential targets for future investigations, because they have been shown to change with exercise, include nerve growth factor (NGF) [96], neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), fibroblast growth factor type 2 [133], VGF growth factor [134], and galanin [48, 135, 136].

Neurotransmitter systems

Because of technical challenges, only a few studies have examined the effects of exercise on the neurotransmitter systems in the brain of awake humans. Instead, most studies have been conducted in rodents, using techniques such as in vivo microdialysis or high-performance liquid chromatography (HPLC) analysis of postmortem brain tissue [137, 138]. These studies have shown that aerobic exercise influences several neurotransmitter systems in the brain, such as serotonin (5-hydroxytryptamine, 5-HT), dopamine, acetylcholine, and norepinephrine. We will discuss these effects below to indicate future research areas that may identify possible beneficial effects of aerobic exercise on neurotransmitters in schizophrenia patients.

Serotonin

The monoamine neurotransmitter serotonin (5-HT) is known to play an important role in the process of learning and memory in the hippocampus [139]. However, its transmission in the hippocampus is disrupted in schizophrenia [25, 140], which likely contributes to the deficits in memory often associated with the disorder [65, 141, 142].

Animal studies have shown that chronic exercise increases 5-HT concentrations in the brain, particularly in the striatum, hippocampus, hypothalamus, and frontal cortex [143, 144]. Physical activity is presumed to increase

the relative proportion of free tryptophan peripherally as the underlying mechanism for the increases in 5-HT concentrations: During exercise, free fatty acids displace tryptophan from binding with albumin, and the unbound tryptophan is able to cross the blood–brain barrier and form 5-HT [145]. Moreover, an exercise-induced modulation of enzymes results in an altered metabolism of 5-HT [146]. The extent to which these mechanisms occur in patients with schizophrenia and how they contribute to neuroplasticity and reduced negative symptoms has not yet been examined.

Norepinephrine

The effect of exercise on brain concentrations of norepinephrine has also been evaluated in animal studies. Meeusen et al. reported that chronic exercise leads to an increase in the concentration of norepinephrine in the whole brain [144]. Moreover, a study in mice showed that exercise-induced reductions in depression-like behavior were correlated with an increase in hippocampal norepinephrine [147]. Although norepinephrine is involved in a variety of cognitive processes [148], changes in cognitive functioning related to exercise-induced effects on norepinephrine have not yet been well evaluated in healthy humans or patients with schizophrenia [52].

Dopamine

Optimal dopamine levels are important, because dopamine plays a key role in motivation [149] and mood, and is involved in the pathogenesis of schizophrenia [150]. Repeated exercise leads to adaptations in the dopaminergic system through several mechanisms, as has been shown in animals. These mechanisms include modulation of dopaminergic turnover [151] and optimization of enzyme functions, such as tyrosine hydroxylase activity [152], and calcium levels [153, 154]. Peripheral catecholamines do not cross the blood–brain barrier. However, aerobic exercise leads to increased levels of serum calcium, which is transported to the brain via the calcium–calmodulin system. This, in turn, enhances the brain dopamine synthesis through a calmodulin-dependent system [155]. An increase in dopamine concentrations after aerobic exercise is region-specific. Whereas dopamine levels were higher in the hypothalamus and midbrain after aerobic exercise training, they were lower in the prefrontal cortex, hippocampus, and striatum [137, 144]. However, research regarding adaptations in the dopaminergic system through aerobic exercise in schizophrenia patients is still lacking.

Glutamate

Glutamate plays a central role in synaptic plasticity [156], and alterations in the glutamate system, such as a hypofunction of the N-methyl-D-aspartate receptor, have been linked to the pathogenesis of schizophrenia [157, 158]. Aerobic exercise is able to enhance glutamate turnover [159] by improving calcium regulation [160] and, as has been demonstrated in animals [161], leads to increased glutamate levels in the anterior cingulate cortex. Exercise upregulates glutamatergic-related genes [96, 162] and increases both the expression of NR2A and NR2B glutamatergic receptors [163] and mRNA and protein expressions of NMDA receptors [164] in the hippocampus; these effects are associated with neurogenesis and synaptic plasticity [154, 163]. In healthy humans, a proton magnetic resonance spectroscopy (H-MRS) study visualized changes in glutamate in the primary visual cortex and the anterior cingulate cortex after exercise: aerobic exercise increased glutamate in both cortical areas, leading to higher resting states after 1 week [161]. Nevertheless, future studies are needed to investigate the relationship between exercise-induced changes in the glutamate system and cognition in schizophrenia patients.

Acetylcholine

The nicotinergic acetylcholine (nAch) receptors α7 and α4β2 have been reported in postmortem studies to be lower in the prefrontal cortex and hippocampus in patients with schizophrenia than in healthy controls and to be related to cognitive deficits [165, 166]. Decreased receptor function is related to cognitive deficits, especially learning and memory. Agonists of the nAch receptor α improve cognition and may be effective in the treatment of schizophrenia [167]. In an animal model of schizophrenia, the DISC1 transgenic mouse, voluntary exercise improved hippocampus-dependent spatial memory and social recognition [168]. In exercising rats, 24 h after spatial memory testing, an upregulation of muscarinic receptor density and an increase in high-affinity choline uptake were found, concomitant with a reduction in hippocampal high-affinity choline uptake [169]. Moreover, the animals demonstrated an enhanced depolarization-induced activation of high-affinity choline uptake. Animal models showed that brain acetylcholine levels increase during aerobic exercise, specifically in the hippocampus and cortex. This increase in acetylcholine supports the generation of hippocampal theta activity, which enhances synaptic plasticity and memory formation [170, 171]. Therefore, changes in the acetylcholine system may be involved in exercise-induced improvements in cognitive function; however, this relationship has not yet been investigated in patients which schizophrenia.

Endocannabinoid system

The endocannabinoid system, including altered expression of the cannabinoid 1 (CB1) receptor, has been implicated in the pathophysiology of schizophrenia [172, 173]. It represents a neuromodulatory system that is known to regulate emotional and cognitive processes, resulting in analgesia, sedation, anxiolysis, and a sense of wellbeing [155, 174]. This system comprises cannabinoid 1 and 2 (CB1 and CB2) receptors, which are expressed at high density in the brain and periphery [175].

Sparling et al. [176] reported the first evidence that exercise is able to activate the endocannabinoid system by showing elevated plasma anandamide levels in healthy runners and cyclists when compared with sedentary controls. Exercise can help to modulate the endocannabinoid system, which may mediate some of the beneficial impacts of exercise on cognition and mood [177, 178]. Although this hypothesis has not yet been further investigated, the effects of exercise on the endocannabinoid system might contribute to its positive effects on cognition and mood in schizophrenia patients.

Hypothalamus–pituitary–adrenal (HPA) axis hormones

HPA axis dysregulation and altered blood cortisol levels are implicated in mental stress, and are suggested to be a pathophysiological factor in schizophrenia, especially during acute episodes [179–181]. In addition, BDNF expression is suppressed under conditions of chronic adverse stress, because hippocampal BDNF mRNA is negatively correlated with plasma glucocorticoid levels. This has been shown in animals to lead to an impaired ability of neurons to protect themselves against injury and disease, as outlined previously [182].

Although physical exercise is an acute stressor, chronic exercise can have neuroprotective effects. Some of the hypotheses presented in the literature that address the correlation between the HPA axis and exercise suggest that biological changes in the activity of the HPA axis could be an effective feedback mechanism via enhanced density and efficiency of mineralocorticoid receptors, lower cortisol levels, and inhibition of cortisol synthesis [183]. However, results concerning brain HPA axis hormones are somewhat equivocal. There is only weak evidence that exercise alters cortisol concentrations in humans [184]. Regarding the expression of corticotrophin-releasing hormone (CRH) mRNA, some authors stated that it is decreased in the hypothalamus after long-term exposure to exercise [185], whereas others found either no significant effect [186] or an initial increase followed by a return to original levels [187].

The findings concerning the effect of chronic exercise on brain corticosteroid receptor mRNA gene expression are contradictory [119, 186].

Summing up, there is no clear evidence for biological changes in the activity of the HPA axis after exercise in either healthy individuals or schizophrenia patients.

Immune-related mechanisms

In patients with schizophrenia, increased brain inflammatory markers [188] and a chronic low-grade systemic inflammation with microglia activation [189, 190] have been reported, and inflammation has been proposed to affect cognitive functioning [191]. However, in schizophrenia, a reduced expression of immune-related genes has also been detected and related to disturbed synaptic processes [192]. In this context, treatment with antipsychotics may influence the expression of pro-inflammatory genes [193].

Animals with increased brain inflammatory factors (such as TNF-alpha, IL-6, CRP, and 1IL-1beta) show depression-like and sickness behavior [194, 195]. The levels of the neuroinflammatory mediators and also the sickness behavior can be attenuated by voluntary aerobic exercise [196]. Aerobic exercise has been shown to be a promising intervention to reduce inflammation in the periphery and the brain of animals [197, 198].

Acute exercise leads to a rapid elevation in peripheral levels of IL-6, but the rise of inflammatory markers is quickly followed by the induction of anti-inflammatory substances, such as IL-1ra, IL-10, and soluble tumor necrosis factor receptor. Regular exercise, on the other hand, downregulates systemic inflammation via homeostatic adaption [103, 199]. Several studies have shown an inverse association between regular exercise and various inflammatory biomarkers, such as TNF-α [200], IFN-γ [197], and IL-1β [198, 201, 202]. In addition, aerobic exercise leads to a reduction of IL-18, CRP, TNF-alpha, and IL-1beta [203, 204] and a marked increase in anti-inflammatory mediators, such as IL-10 [205, 206]. Moreover, exercise results in a decrease in pro-inflammatory visceral white fat mass [198, 204], in the proliferation of microglia [197], and in the hippocampal expression of immune-related genes [207, 208].

In schizophrenia patients, changes in C-reactive protein (CRP) were studied after 8 weeks of high-intensity interval training (HIIT). Although CRP decreased by 66%, the difference from the non-exercising control group was not statistically significant [209]. Another study examined serum CRP, IL-6, and TNF-alpha levels in obese patients with schizophrenia after a 10-week lifestyle intervention (including lifestyle modification, psychosocial treatment, behavior therapy, and aerobic exercise). The authors were not able to find any significant changes in comparison to the control group, which consisted of matched controls without

psychiatric disorders [117]. However, levels of circulating pro-inflammatory cytokines in the blood are confounded by many factors, including smoking, obesity, sleep disorders, and poor oral health, all of which are common in schizophrenia and further contribute to the inflammatory burden in schizophrenia patients [103, 120, 210]. Thus, to date, the extent to which aerobic exercise can improve cognitive functioning in schizophrenia via alterations in the expression of immune-related genes remains unclear.

Exercise-induced generation of reactive oxygen species

Increased free radical production and an impaired antioxidant defense system have been shown to be involved in the pathophysiology of schizophrenia [211]. In addition, oxidative changes have been shown to interfere with the stability of genomic DNA in the brain of schizophrenia patients [212]. Oxidative stress is defined as an imbalance between antioxidants and reactive oxygen species (ROS) (e.g., superoxide, hydrogen peroxide, and hydroxyl radical) [213]. It has been suggested that the beneficial effects of regular aerobic exercise are partly based on its ability to generate ROS [214]. Exercise-induced ROS production contributes to the induction of antioxidants, DNA repair, and protein-degrading enzymes [155]. Long-term exercise may be helpful in optimizing the enzymatic antioxidant system and mitigating oxidative damage in schizophrenia patients, but this issue has not been studied yet [154].

Discussion

The aim of this narrative review was to give an overview of different lines of evidence on how exercise impacts brain function at different levels in patients with schizophrenia. We wanted to clarify how those effects of exercise could be related to the clinical and functional outcomes.

The past years have seen a growing number of publications on the neurobiological mechanisms of exercise, but few have reported on these effects in patients with schizophrenia. Although the clinical effects of exercise in schizophrenia are becoming increasingly evident, more research on the underlying neuroadaptive processes is warranted.

Animal studies have provided consistent evidence that exercise results in brain morphological changes and functional adaptations, including an increase in the concentrations of neurotrophic factors and neurotransmitters.

Animal models provide a valuable source of information, because they enable experimental approaches and give insights into the molecular and cellular mechanisms that cannot be investigated in humans. Although animal models have revealed much about the potential neurobiological mechanisms of exercise effects on brain and cognition, the findings often cannot be easily generalized to humans because of the physiological and behavioral differences between humans and other species. Evidence from human studies on the neuroadaptive processes of exercise is limited to date. Because of the often small effect sizes and numerous negative findings, conclusions must be drawn cautiously. Given the rather limited amount of research, especially in patients with schizophrenia, it is currently not possible to either confirm or refute any of the above-mentioned neurobiological explanations. However, research to date indicates that, in schizophrenia patients, aerobic exercise has an impact on brain structure (e.g., as shown by MRI studies) and function (e.g., as shown by TMS studies), epigenetic mechanisms, gene expression, and neurotransmitters, restores BDNF levels, and may influence immune-related genes (Fig. 2).

In general, exercise research comes with some limitations, because the interventions depend on the participants' compliance. Patients with schizophrenia may often have a diminished motivation to be physically active, which is why research might represent a positive selection [76]. In addition, treatment with antipsychotics may increase sedation and muscular exhaustion. Therefore, patients performing aerobic exercise need concomitant supervision and encouragement by sports scientists [23]. Furthermore, the duration, frequency, and modality of aerobic exercise training differ between studies [215].

Additional research is needed to clarify the role of the cellular and molecular pathways in patients with schizophrenia. The field will profit from additional randomized-controlled trials, which have the potential to systematically establish a causal relationship between aerobic exercise, its neurobiological effects, and outcome parameters, such as negative symptoms and cognitive deficits.

We have little knowledge on the optimal intensity, duration, and frequency of exercise that may be required for exercise-induced changes to interact with schizophrenia or on the type of exercise that may be most beneficial [23, 216]. Further research is required to clarify in more detail how individual differences in patients with schizophrenia mediate or moderate the effects of exercise on the brain and cognition. In this context, it may be important to examine the effects of genetic and environmental risk factors on the individual response to aerobic exercise.

Limitations of this narrative review include the lack of systematic literature research, which increases the risk of selection and evaluation bias. However, the main aim of this review was to give an overview of the current knowledge about the impact of aerobic exercise on neurobiological functions from the macro- to the micro-level with a focus on schizophrenia patients to foster a general debate and discuss rationales for future research.

Even though its underlying neurobiological mechanisms have not yet been fully clarified, exercise remains a promising candidate in the search for interventions that address the negative and cognitive symptoms of patients with schizophrenia and, thus, improve their outcome.

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