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INVITED REVIEW

# The effects of physical exercise in schizophrenia and affective disorders

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**Abstract** Affective and non-affective psychoses are severe and frequent psychiatric disorders. Amongst others, they not only have a profound impact on affected individuals through their symptomatology, but also regarding cognition, brain structure and function. Cognitive impairment influences patients' quality of life as well as their ability to work and being employed. While exercise therapy has been implemented in the treatment of psychiatric conditions since the days of Kraepelin and Bleuler, the underlying mechanisms have never been systematically studied. Since the early 1990s, studies emerged examining the effect of physical exercise in animal models, revealing stimulation of neurogenesis, synaptogenesis and neurotransmission. Based on that body of work, clinical studies have been carried out in both healthy humans and in patient populations. These studies differ with regard to homogenous study samples, sample size, type and duration of exercise, outcome variables and measurement techniques. Based on their review, we draw conclusions regarding recommendations for future research strategies showing that modern therapeutic approaches should include physical exercise as part of a multimodal intervention programme to improve psychopathology and cognitive symptoms in schizophrenia and affective disorders.

**Keywords** Schizophrenia · Affective disorders · Physical exercise · Symptoms · Cognitive remediation · MRI

## Introduction

Prospective epidemiological studies show that together with obesity, low diet quality and smoking, reduced physical activity belongs to the combination of lifestyle factors being responsible for up to 55 % of deaths [140]. However, only little is known regarding the effects of physical exercise on symptoms of mental disorders. In a longitudinal epidemiological study, subjects with regular physical activity had lower incidence of mental diseases in general, anxiety, somatoform and dysthymic disorder, while the incidence of bipolar disorder was increased

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[130]. Accordingly, adolescents who engaged regularly in physical activity have been characterised by lower depression and anxiety symptoms [83]. Vice versa, little or no physical activity has been linked to the development of depressive symptoms [37]. In this review, we intend to summarise effects of physical exercise in severe mental disorders and to recommend future research strategies.

## Schizophrenia

Schizophrenia is a severe mental disorder with prevalence in the range of 0.7–1 % [75, 98], which in the majority of cases already starts at a young age [80]. Negative symptoms like alogia, blunted affect, anhedonia, avolition and apathy occur early in prodromal states and remain persistent during the course of the illness, if at all responding poorly to antipsychotic treatment [57, 74, 84]. Patients' cognitive deficits, which also occur at an early stage and mainly affect memory, attention, executive functioning and perceptual processes, remain stable over time, represent a core feature of the disease, and are the main predictor for poor social-functioning outcome [24, 46, 61, 65, 66]. As a consequence of persisting negative symptoms and cognitive impairment, the disease often leads to lifelong disabilities thus constituting an enormous burden for patients and their families as well as health care systems [105]. These impairments have a distinct negative influence on patients' ability to function in all facets of daily life and therefore represent an important therapeutic target [49, 50, 78] which cannot be treated satisfactorily with currently available antipsychotics [47, 57]. Thus, new therapeutic approaches are needed which can fundamentally alter mechanisms in neuronal plasticity [157]. This, for instance, can be achieved via aerobic exercise, which has been proven to ameliorate cognition deficits and increase hippocampal blood flow in both mice [35, 141, 143] and healthy humans [110]. Furthermore, aerobic exercise was shown to have beneficial effects on hippocampal volume and metabolism in schizophrenia patients [109, 121].

Additionally, it should be kept in mind that patients with schizophrenia tend to lead a less healthy lifestyle [14, 20, 92, 128]. Due to medication [45] and genetic liability [145], they also run a high risk for developing a metabolic syndrome, diabetes and cardiovascular diseases [13, 14, 40, 56]. This risk might be increased in combination with reduced physical activity [18].

## Affective disorders

Affective disorders, including unipolar or major depressive disorder (MDD) and bipolar disorder (BD), are amongst the most prevalent psychiatric diseases [2, 101, 156].

Both types of affective disorders display cognitive deficits. Impaired cognitive performance mainly relating to attention, memory and executive tasks has indeed been found in both types of affective disorders (meta-analysis by Torres et al. [136]). These cognitive symptoms are thought to contribute to deterioration of social skills, to loss of autonomy and job-related problems. However, little attention has been paid to the development of specific treatment options for cognitive symptoms apart from the established pharmacological and psychotherapeutic therapies in MDD and BD. Considering current pathophysiological concepts in affective disorders, which emphasise the relevance of adult neurogenesis, hippocampal dysfunction and atrophy and neurotrophic signalling [122], there is good reason to hypothesise beneficial effects from physical exercise interventions.

## Effect of physical exercise on neurobiological mechanisms

Several biological mechanisms have been proposed to be influenced by physical exercise. Colcombe et al. [19] for instance reported that exercise not only has a positive influence on the number of synaptic connections through developing new neurons but also increases the cortical capillary blood supply. In mice, voluntary exercise is known to stimulate adult hippocampal neurogenesis, learning and memory [141–143], and this stimulation also increases exploratory behaviour [119]. Additionally, vigilance and memory are improved [42]. Physical exercise may exert antidepressant effects via the peptide precursor of neurotrophic factors VGF [73] or serotonergic 5-HT1A receptors [51] and via neurogenesis [41]. Furthermore, positive effects of physical exercise on mood symptoms have been associated with increased production of brain neurotrophic factors, like insulin-like growth factor 1 (IGF1), brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF), and increased activity and production of neurotransmitters (serotonin, norepinephrine and dopamine) related to psychiatric disorders [26, 103, 108]. Moreover, Floel et al. [38] linked cognitive functioning and physical activity through the effects of neurotrophines which are up-regulated through physical exercise and induce neuronal growth and synaptogenesis in animal models [8, 79, 104]. To the best of our knowledge, there is merely one animal study examining the effects of exercise in a schizophrenia risk mouse model [158] and only very few on the neuroprotective effect of exercise to decrease prenatal stress, a known risk factor for psychiatric diseases, including schizophrenia [4, 93]. In humans, one main focus of interventional trials on physical exercise is to evaluate effects on cognitive performance, individual psychopathology as well as brain function and structure. In light of the obvious limitations of current pharmacotherapy with respect to residual symptoms and cognitive deficits, unravelling the neurobiological effects of physical exercise in severe psychiatric diseases may contribute to finding novel treatment strategies—presumably acting by neuroplastic processes in specific brain regions. In this review, we intend to focus on effects of physical exercise in clinical studies of schizophrenia and affective disorders and to discuss critically methodological aspects leading to variable results.

## Search algorithms

To achieve a comprehensive overview of the available studies dealing with our topic, we performed a systematic literature search and study evaluation according to the Cochrane criteria, using the computerised search databases PubMed (1966–2012) and Web of Knowledge. Only studies published in English were considered for this review. The keywords used for this search were ''schizophrenia'' or ''psychosis'', "depression" or "depressive disorder", "bipolar disorder" or "mania", "physical exercise" or "exercise" or "aerobic exercise", ''sMRI'' or ''structural imaging'', "symptoms" or ''symptomatology'' and ''cognition'' or ''cognitive function" or ''cognitive dysfunction". Although our search was limited to studies in humans', relevant animal studies were also included in this review. The obtained literature was then carefully screened based on title and abstract. After selecting all pertinent articles, their full text was reviewed followed by a critical evaluation of study outcomes. Finally, we carefully checked the reference lists of these articles for other relevant studies on the field that might have been overlooked in our initial search.

## Methodology of exercise interventions in schizophrenia

There are a number of different approaches for designing the adequate physical training intervention and selecting primary outcome parameters. Tables 1 and 2 display various exemplary solutions for schizophrenia and affective disorders.

Exercise therapy studies reveal a great variety of interventions ranging from team sports like basketball [133] over aerobic exercise [109, 120] to yoga [7, 31], which incidentally is not easily classifiable into a strict category because it contains physical as well as mental aspects and is connected to religious or spiritual teachings [7]. While there are also a number of studies focussing on different relaxation techniques [147], a clear preference for aerobic exercise seems to emerge [1, 6, 27, 82, 109, 129, 153]. Some articles also describe resistance training as an add-on to aerobic endurance training [96, 115, 120]. Several interventions also contain educational aspects concerning healthy lifestyle and diet [102, 133, 153]. Exercise intensity ranges from a daily activity level [102] to 85 % or even 95 % of the highest heart rate resulting from the pre-test [59]. Likewise, the duration of these interventions also varies: some lasting only 8 weeks [59], while others went on for 18 months [115]. The duration of the training sessions varies similarly from less than 30 or 30 min maximally [5, 27, 153] to 60 min [7, 31, 96, 115, 120].

A number of studies assess physical performance [6, 27, 59, 96, 109, 120, 129], while others reveal methodological deficits in this area [1, 5, 7, 31, 39, 82, 102, 115, 132, 133, 151, 153]. Without a standardised assessment of physical performance, its correlations with symptoms, cognitive performance and neuroimaging cannot be generated. This also applies to the individual exercise intensity which otherwise is not determinable. Furthermore, the applied methods of assessment of physical performance are not comparable and fundamentally different from each other. While the 6-min walking test [6, 27, 96] measures the distance that a person can walk in 6 min and is practically simple [90], exercise tests on treadmills or cycle ergometers can be more complex and may therefore provide data in higher quality for more parameters. The 6-min walking test is suitable for patients with low cardiorespiratory fitness, reflects the intensity of daily life activities and allows a rough estimation of physical performance. Other exercise tests can be carried out with a maximal [59, 109] or submaximal [27, 129] intensity. Maximal exercise tests have a higher cardiovascular demand and thus are not recommendable for all patients. Contraindications need to be respected [137]. In addition, maximum values depend on the patient's motivation, which can be disturbed in mental illness. Maximal test protocols, however, can be used and result in data for the highest oxygen uptake [59, 109, 121, 129], but maximum values for oxygen uptake should be interpreted carefully because it is discussible whether mentally ill patients are able to reach exhaustion as defined for healthy individuals.

Guaranteeing the predictability, measurability and interpretability of training effects should not only be the basic design principle for clinical trials, but should always also be included and discussed in the respective publications. In detail, we recommend that authors report (a) exercising parameters (period of time, frequency, duration of single exercise sessions, intensity, equipment and type of exercise—in order to intentionally create an efficient training stimulus), (b) the selection of measured variables for the documentation and control of the training progress (e.g. heart rate, blood lactate concentration and

**Table 1** Applied methods in intervention and assessment of physical performance in studies with schizophrenic patients from 2001 to 2012

| Study | Intervention of the active groups (applied methods) | Assessment of physical performance (applied methods) | Results (physical performance) | Sample sizes | | |
|---|---|---|---|---|---|---|
| | | | | SZE | SZC | HC |
| Acil et al. [1] | 10 weeks, 3 sessions/week, 25–40 min/session, 10 min warming up, 25 min aerobic exercise, 5 min cooling down, no exceedance of the maximal heart rate (220-age) | – | – | $n = 15$ | $n = 15$ | – |
| Ball et al. [5] | 10 weeks<br>Weight watchers meetings: 1 session/week<br>Supervised exercise sessions: 3 sessions/week, walking, 0.1–1.0 miles, 5–25 min | – | – | $n = 11$ | $n = 11$ | – |
| Beebe et al. [6] | 16 weeks, 3 sessions/week, 10 min warming up, 5–30 min, walking, treadmill, target heart rate | 6-min walking test | Level of aerobic fitness: +152 feet walking distance (ca. 10 %) | $n = 4$ | $n = 6$ | – |
| Behere et al. [7] | 3 months (first month instructed training, second and third month practicing at home), 60 min/session<br>Yoga group: “loosening exercises, breathing practices, suryanamaskara, sitting, supine and prone posture asanas along with pranayama and relaxation techniques”<br>Exercise group: “brisk walking, jogging, and exercises in standing and sitting postures and relaxation” | – | – | Yoga: $n = 27$<br>Exercise: $n = 17$ | $n = 22$ | – |
| Dodd et al. [27] | Familiarisation period: 4 weeks, 1 session/week, low intensity<br>Circuit exercise: 6 months, 2 sessions/week, max. 30 min/session, treadmill, stationary bicycle, aerobic metabolism, 65–75 % of maximal heart rate<br>Walking programme: 6 months, 1 session/week, 30 min/week | Submaximal cycle ergometer test, 6-min walking test | Cardiorespiratory fitness: no changes<br>Exercise endurance: no changes | $n = 8$ | – | – |
| Duraiswamy et al. [31] | Instructed sessions: 3 weeks, 5 sessions/week, 60 min/sessions practices at home: 3 months<br>Yoga therapy group: Sithilikarana Vyayama, asanas, breathing practice, relaxation techniques<br>Exercise therapy group: “brisk walking, jogging and exercises in standing and sitting postures and relaxation” | – | – | Yoga: $n = 21$<br>Exercise: $n = 20$ | – | – |
| Fogarty et al. [39] | 3 months, individual exercise programmes | | | $n = 6$ | – | – |
| Heggelund et al. [59] | 8 weeks, 3 sessions/week, treadmill, high aerobic intensity training, 4 × 4 min intervals, 85–95 % of HRpeak (interval), 70 % of HRpeak (active resting period), 80 % adherence | Exercise test (treadmill): 10 min warming up, 6-min 60 Watt (testing of mechanical efficiency), 3–6 min increasing speed every min to exhaustion (measurements of $VO_2$ peak and HRpeak) | 12 %* mechanical efficiency increase<br>12 %* $VO_2$ peak increase | $n = 12$ | $n = 7$ | – |
| Killackey et al. [82] | 9 weeks, 3 sessions/week, 30 min/session, running and walking at home using applications (“Nike+” and “Couch to 5 k”) downloaded onto iPod touch to instruct, control and document sessions and twitter to post results and feedback | Posts on twitter, face-to-face interviews | Self-reported fitness: results not published | – | – | – |
| Marzolini et al. [96] | Aerobic training: 12 weeks, 2 sessions/week, 60 min/session, walking, 1.6–6.4 km, 60–80 % of the heart rate reserve; 11–14 on the Borg rating of perceived exertion scale (RPE) combined with resistance training: 20 min/session, 1–2 sets/session, 10–15 repetitions/set, hand-held dumbbells, half squat, heel raises, biceps curls and triceps extensions, 60 % of one repetition maximum, >15 on the Borg RPE scale | Six minute walk test, one repetition maximum test (bicep curls) | Functional exercise capacity: 27.7 ± 22.3 m increase in walking distance, maximal strength: 28.3 ± 8.8 %* improvement in one repetition maximum | $n = 7$ | $n = 6$ | – |

**Table 1** continued

| Study | Intervention of the active groups (applied methods) | Assessment of physical performance (applied methods) | Results (physical performance) | Sample sizes | | |
|---|---|---|---|---|---|---|
| | | | | SZE | SZC | HC |
| Methapatara et al. [102] | Educational leaflet<br>Motivational interviewing programme: 1 week, 5 sessions/week, 60 min/session, motivational interviewing, group education, pedometer practice, feedback<br>Walking programme: 12 weeks, 3,000–8,000 steps/day at home, using pedometers for measurements | – | – | $n = 32$ | $n = 32$ | – |
| Pajonk et al. [109] and Falkai et al. [36] | 12 weeks, 3 sessions/week, 30 min/session<br>Aerobic exercise group: ergometer, cycling, heart rate corresponding to a blood lactate concentration of 1.5–2.0 mmol/l (pre-test)<br>Tabletop football group (control group) | Incremental cycle ergometry: 3 min duration of stages, 25 or 50 Watt initial stage, 25 or 50 watt stage increment, until exhaustion, EKG, blood pressure, gas exchange, blood lactate concentration measurements | Aerobic fitness: aerobic exercise group: 11 % increase in power (Wpeak/kg)<br>5 % relative $VO_2$ peak increase<br>Tabletop football group: 1 % increase in power (Wpeak/kg)<br>3 % relative $VO_2$ peak decrease | $n = 8$ | $n = 8$ | $n = 8$ |
| Poulin et al. [115] | Single "educative activity about dietary and physical activity counseling", 90 min<br>Exercise programme: 18 months, 2 sessions/week, 60 min/session, treadmills, stationary cycles, cardiovascular workouts, free weights, resistance bands, flexibility and balance drills, strength training | – | – | $n = 59$ | $n = 51$ | – |
| Scheewe et al. [120, 121] | 6 months, 1–2 sessions/week, 60 min/session, cardiovascular exercises, graduate increase of intensity (3 weeks 45 % of heart rate reserve, 9 weeks 65 %, 14 weeks 75 %), muscle strength exercises [6 exercises/week, 16 weeks, 3 times 10–15 repetitions maximum, 10 weeks 3 times 8–12 repetitions maximum; muscles of arms, legs and trunk (biceps, triceps, quadriceps, pectoral and deltoid muscles, abdominal muscles)] | Cardiopulmonary exercise test (cycle ergometer) | Intention-to-treat analyses: Cardiorespiratory fitness: +7.2 %* in peak work rate (Wpeak)<br>Per protocol analyses: +9.7 %* in peak work rate (Wpeak), –0.3 % highest relative oxygen uptake ($VO_2$ peak) | $n = 31$ | $n = 32$ | $n = 55$<br>Exercise: $n = 27$<br>No intervention: $n = 28$ |
| Strassnig et al. [129] | 6 weeks, 3 sessions/week, 30 min/session, treadmill, running, 65 % of maximal heart rate (220-age) | Submaximal exercise test | Physical capacity: increase in relative $VO_2$ max from 26.5 ± 5.4 ml/kg/min (pre-test) to 31 ± 4.4 ml/kg/min (post-test) | $n = 6$ | – | – |
| Takahashi et al. [132] | Single session, watching basketball in video clips | – | – | $n = 12$ | – | $n = 12$ |
| Takahashi et al. [133] | 3 months, 2 session/day, 12 sessions/week, 30–60 min/session, aerobic exercise, walking, jogging, muscle-stretching exercise (static and dynamic), basketball, 11–13 on the Borg rating of perceived exertion scale<br>Nutrition education | – | – | $n = 13$ | $n = 10$ | – |
| Visceglia et al. [151] | 8 weeks, 2 sessions/week, 45 min/session, Yoga (relaxation, breathing exercises, stretching and movements) | – | – | $n = 10$ | $n = 8$ | – |
| Wang et al. [152] | 4 days, individual everyday physical activity | Accelerometer (actigraph model WAM7164) for assessment of amount and intensity of physical activity | Minutes of moderate-to-vigorous physical activity per day: 29.6 ± 24.7 min/day | $n = 73$ | – | – |

**Table 1** continued

| Study | Intervention of the active groups (applied methods) | Assessment of physical performance (applied methods) | Results (physical performance) | Sample sizes | | |
|---|---|---|---|---|---|---|
| | | | | SZE | SZC | HC |
| Warren et al. [153] | 10 weeks<br>Exercise programme: 3 sessions/weeks, 20 min/session, 2–5 min increases/week, walking, jogging, pedometer, log<br>Education programme: 10 weeks, 1 session/week, 30 min/session, healthy lifestyle<br>5-km event at the end of the intervention | – | – | $n = 17$ | – | – |

*SZE* schizophrenia patients participating in an intervention group with exercise, *SZC* schizophrenia patients participating in a control group without exercise, *HC* healthy controls

* Statistically significant

written logbook) and (c) the consideration of the reasonableness and feasibility of the intervention in light of the reduced capability of the patients.

Physiological adaptations to regular physical exercise afford a certain amount of time. Investigations in sport science led to the development of a model, which proposes that after approximately 6 weeks of training, a new level of adaptation is reached [33, 72, 107]. Subsequently, training intensity should be modified accordingly. Physical exercise according to the continuous method with no changes in intensity needs neither warming up nor cooling down and is feasible even with cognitively impaired patients [64, 144]. High-intensity interval training seems to be very promising as well, especially concerning the improvement of peak oxygen uptake levels [62]. Training durations of at least 30 min provide stimuli for metabolic as well as neurologic, muscular and cardiovascular systems [106]. In addition, 30 min are well tolerated by the patients [109, 129]. As experiences from current studies show even patients only accustomed to shorter continuous physical activity are able to exercise for 30 min after a short habituation phase. There are indications, however, that longer training sessions show an even greater positive effect on positive and depressive symptoms in schizophrenia [27, 96, 120]. Unless a deliberate decision in favour of high-intensity training is made, exercise intensity should be equivalent to 10–13 points (fairly light to moderately difficult) on the scale of perceived exertion (BORG scale) [12]. Although experiences in using the BORG scale for mentally ill patients [96, 133] exist, it is still uncertain whether it can be used with these patients in the same way as with healthy controls. If the training load corresponds to both the mental and physical precondition of the patient, the exercise sessions themselves should not be too stressful for the patients [72]. Thus, training intensity should always be chosen according to patients' individual results on the assessments of their physical performance. Blood lactate concentrations of approximately 2.0 mmol/l are recommended to ensure a predominantly aerobic energy metabolism and prevent stressful experiences with increasing anaerobic metabolism and overload [69, 70]. We propose exercise tests both before and after exercise intervention since changes in heart rate (Physical Working Capacity 130) and blood lactate concentration (performance with 2 mmol/l) within stages similar to training intensities are to be expected, while the highest oxygen uptake will not necessarily change. Exercise testing allows generating different training intensities by applying concepts of ventilatory or lactate thresholds. Further research is needed to ensure that these parameters can be used for patients. Control of patients' individual exercise intensity through blood lactate concentrations can be used to back up training in an aerobic zone. The heart rate can be influenced by a number of pharmacological treatments, which is why an electrocardiogram (ECG) is also essential. Regarding the higher cardiovascular mortality rate in schizophrenia [126, 134, 161], some safety precautions should be considered, e.g. a doctor on call, emergency equipment and as mentioned an exercise testing with stress ECG before the intervention [137]. The use of bicycle ergometers in the intervention assures an exact measurement of training intensity and provides the option to standardise. Cycling is, above all, also a type of exercise that is feasible with patients who are obese or have orthopaedic problems because it is joint-friendly [89, 135]. Its circular movement is easy to practice and seems to also have a relaxing influence because of the rhythmic repetitions [87]. During a long-term exercise therapy regimen, other cardio-respiratory exercises like running on a treadmill might also be appealing to patients and will help to avoid monotonous training stimuli.

## Methodology of exercise interventions in affective disorders

A majority of studies in affective disorders do not fulfil adequate methodological requirements. In their review, Wolff et al. [159] excluded all studies not meeting

**Table 2** Applied methods in intervention and assessment of physical performance in studies with unipolar and bipolar affective disorders from 2001 to 2012

| Author | Intervention of the active groups (applied methods) | Assessment of physical performance (applied methods) | Results (physical performance) | Sample sizes |
|---|---|---|---|---|
| Babyak [3] | 16 weeks, 3 sessions/week, 45 min.; cycle ergometry or brisk walking/jogging.<br>Participants were assigned training ranges equivalent to 70–85 % of heart rate reserve<br>(1) Aerobic exercise<br>(2) Medication (sertraline)<br>(3) Sertralin + exercise | Treadmill test for max. heart rate<br>Heart rate, perceived exertion (recorded 3 times/session) | 64 % of subjects in the exercise group and 66 % of subjects in the combination group reported that they continued to exercise, 48 % of participants in the medication group initiated an exercise programme during the 6-month follow-up period | $n = 156$ MDD |
| Blumenthal [9] | 16 weeks, 3 sessions/week; graded treadmill exercise<br>(1) aerobic exercise<br>(2) pharmacological treatment<br>(3) aerobic exercise + pharmacological treatment (sertraline) | Aerobic capacity | – | $n = 156$ MDD |
| Blumenthal [10] | 16 weeks, 3 sessions/week<br>Training ranges equivalent to 70–85 % maximum heart rate reserve.<br>(1) graded treadmill exercise: 3 supervised group exercise sessions per week<br>(2) supervised aerobic exercise ($n = 51$)<br>(3) home-based aerobic exercise ($n = 53$); same as group 1 but at home without supervision<br>(4) sertraline ($n = 49$), medication provided daily<br>Placebo ($n = 49$) | Patients' fitness assessment via graded treadmill exercise testing<br>Duke–Wake Forest protocol: workloads are increased at a rate of 1 metabolic equivalent per minute Expired air was collected by mouthpiece for quantification of minute ventilation, oxygen consumption ($VO_2$), and carbon dioxide production | The exercise groups displayed significantly higher levels of aerobic capacity (peak $VO_2$) compared with placebo and medication pill conditions.<br>Differences in aerobic capacity between exercise treatment conditions, with supervised exercise participants achieving higher levels of post-treatment aerobic capacity than home-based exercisers.<br>Patients in the two exercise conditions exhibited greater treadmill times compared with patients who received pills; supervised exercisers attaining longer treadmill times than those patients who exercised at home. Participants in home-based exercise showed an improvement of 3.5 % in peak $VO_2$ and 7.5 % in treadmill time; supervised exercise improved by 8.3 % in peak $VO_2$ and 18.8 % in treadmill time; the medication group showed a 0.8 % decrease in peak $VO_2$ and 3.9 % improvement in treadmill time; and the placebo group declined by 4 % in peak $VO_2$ and 2.3 % in treadmill time | $n = 202$ MDD |
| Deslandes [23] | 12 months, 2 sessions/week, 35 min<br>(1) Aerobic: continuous treadmill walking, +pharmacological treatment<br>(2) Control group: only pharmacological treatment | Functional capacity: time to up and go (TUG) test and multiple-sit-to-stand (MSTS) test<br>Heart rate and perceived exertion (Borg scale) were monitored and recorded every 5 min during each exercise session by physical education instructors | Improvement of functional capacity (TUG, MSTS) after 1 year in exercise group. | $n = 20$ MDD |
| Dimeo [25] | 10 days, 30 min/day<br>Aerobic exercise: walking on a treadmill, interval training pattern | – | – | $n = 12$ MDD |
| Dunn [29] | 12 weeks, 2 sessions/week, 4 groups, low dose (LD), high dose (HD)<br>(1) Aerobic exercise: 4 groups, 12 weeks, 2 times<br>(2) under supervision<br>(3) individually in rooms by themselves, monitored by laboratory staff<br>(4) Placebo group: 3 times a week flexibility training for 15–20 min | Energy expenditure exercise frequency | No main effect of exercise frequency | $n = 80$ MDD |

**Table 2** continued

| Author | Intervention of the active groups (applied methods) | Assessment of physical performance (applied methods) | Results (physical performance) | Sample sizes |
|---|---|---|---|---|
| Heh [60] | 3 months<br>(1) Exercise support programme: 1 h/week at the hospital; another two sessions at home, +support guide: a 45-min, whole-body, gentle stretching exercise programme, CD record<br>(2) Control group: standard care | Physical activity record | Increase PA level, improved physical fitness, improved psychological well-being | $n = 80$ MDD |
| Hoffmann [67] | 16 weeks, 3 sessions/week, graded treadmill exercise; individual training ranges equivalent to 70–85 % of their HR reserves<br>4 Groups:<br>(1) Supervised aerobic exercise<br>(2) Home-based aerobic exercise: Participants received an initial exercise training session, guidance regarding how to implement their exercise programme<br>(3) Sertraline<br>(4) Placebo Pill | Graded treadmill exercise testing before and after treatment. Patients exercised to exhaustion or standard end points (e.g., >2 mm ST-segment depression, abnormal blood pressure response, etc.) using the Duke–Wake Forest protocol; workloads are increased at a rate of 1 METImin$^{-1}$. Expired air was collected by mouthpiece for quantification of minute ventilation, oxygen consumption and carbon dioxide production | Participants in the exercise groups: higher levels of aerobic capacity (peak $\dot{V}O_2$) and greater treadmill times compared with participants who received pills. Differences in aerobic capacity and treadmill endurance between exercise treatment conditions, with supervised exercise participants achieving higher levels of aerobic capacity and longer treadmill times than participants who exercised at home<br>Home-based exercise: improvement of 3.5 % on peak $\dot{V}O_2$ and 7.5 % on treadmill time<br>Supervised exercise: improved by 8 % on peak $VO_2$ and 19 % on treadmill time<br>Sertraline group: 1 % decrease in peak $\dot{V}O_2$ and 4 % improvement in treadmill time<br>Placebo group: declined by 4 % on peak $\dot{V}O_2$ and 2 % on treadmill time | $n = 202$ MDD |
| Hoffmann [68] | 4 months, 3 sessions/week, aerobic exercise<br>(a) Supervised exercise<br>(b) Home-based exercise<br>(c) Sertraline<br>(d) Placebo pill | Self-reported exercise (Godin Leisure-time exercise questionnaire) assessment: after 4 months, at 1-year follow-up | After 4 months: comparable benefits exercise/sertraline<br>1-year follow-up: neither initial treatment group nor antidepressant medication use during the follow-up period were significant predictors of MDD remission<br>Regular exercise during follow-up period predicted HRSD and MDD status | $n = 172$ MDD |
| Kerse [81] | 6 months, 3 sessions/week, 30 min Exercises and walking<br>Control condition: social visits<br>6 months; 8 visits → 7 times during first 3 months; 1 time after 6 months | Physical function: ascertained by 2 measures. (1) Short Physical Performance Battery (SPPB): gait speed, muscle strength as measured by repeated standing from a chair, and balance measurement. (2) self-report Nottingham Extended activities of daily living (NEADL) scale: to assess functional status and the ability to perform activities of daily living mobility outside the home, meal preparation, shopping, and housekeeping) | After 12 months follow-up: trend towards a differential impact of the physical activity intervention on walking behaviour, most notable at 6 months<br>There was a significant decline in functional status (NEADL) for all participants during the 12 months but no differential change between the physical activity and social groups.<br>There was no differential change between the groups in physical function and no change over time | $n = 193$ MDD |
| Knubben [85] | Modified Bruce treadmill test; daily walking on a treadmill for 10 days. Five times for 3 min with a mean (SD) intensity corresponding to a lactate concentration of 3 (0.5) mmol/l in capillary blood, heart rate of 80 % of the maximum<br>Placebo group: daily 30-min programme: light stretching exercises and relaxation exercises. Total activity time <10 min/day | Intensity of effort daily assessed by Borg rating of perceived exertion scale<br>Heart rate to evaluate the training intensity | Patients reported no negative effects of exercise (muscle pain, tightness or fatigue) in the course of the programme<br>The maximum oxygen uptake of the endurance training group remained unchanged during the study | $n = 38$ MDD |

**Table 2** continued

| Author | Intervention of the active groups (applied methods) | Assessment of physical performance (applied methods) | Results (physical performance) | Sample sizes |
|---|---|---|---|---|
| Kubesch [87] | 30 min, one time, aerobic endurance 2 different workload levels (40, 60 % of their predetermined individual 4-mmol/l lactic acid exercise capacity) | – | – | $n = 24$ MDD<br>$n = 10$ HC |
| Mather [97] | 10 weeks, 2 sessions/week, 60 min., aerobic exercise; training contained elements of endurance, stretching and muscle strengthening<br>Control group: health education talks, 60 min each | – | – | $n = 85$ MDD |
| Silveira [123] | 6 weeks, 2 sessions/week, 30 min., aerobic exercise; 10-min warm-up (40 % of the $VO_2$ max), 20 min treadmill walking (60 % $VO_2$ max), 5 min cool-down<br>Control group: no exercise | – | – | $n = 20$ MDD |
| Van Citters [139] | 9 month SHAPE health promotion programme; individualised, community-integrated; exercise and dietary modification | Physical activity | Participation was associated with increased exercise, vigorous activity and leisurely walking | $n = 76$ psychiatric patients |
| Vasques [150] | 30-min walk, electric treadmill; workload levels: 65–75 % of the maximum heart rate estimated for their age (220-age) | – | – | $n = 10$ MDD |
| Weinstein [154] | 1* graded treadmill exercise, 50 min; Four stages: 5-min warm-up period at 3.0 mph with a grade of 2.0°; 10-min treadmill exercise at approximately 70 % of $VO_2$ max; 5-min exercise at approximately 85 % of $VO_2$ max; 5-min cool-down period at 3.0 mph with a grade of 2° | Heart rate (HR)<br>Aerobics centre longitudinal<br>Study physical activity questionnaire: to evaluate initial physical activity level at time of study enrolment | No differences between depressed participants and controls for perceived exertion<br>(Borg scale) and duration of exercise performed<br>Control group had a higher percentage of individuals completing the protocol (80 %) than the depressed group (65 %) (not statistically significant) | $n = 30$ MDD<br>$n = 16$ HC |

Participants are MDD or BD patients unless stated otherwise

*HC* healthy controls

minimum methodological criteria and suggested only moderate effect sizes in studies comparing physical exercise with pharmacological treatment. A review of existing studies on BD and physical exercise also proposes that most do not meet methodological standards [160]. Furthermore, doses of training might again influence results. Dunn et al. [30] systematically investigated the effects of low versus high doses of aerobic exercise finding high doses to be more effective in reducing depressive symptoms in MDD than low doses and that after 12 weeks of intervention exercise, frequency had not shown influence on the severity of depressive symptoms. Compared with a control condition (social visits), for instance, an individualised physical activity programme for older patients with depressive symptoms was not more effective in ameliorating the severity of their symptoms [81]. It must be kept in mind, however, that participants of the study by Kerse et al. had engaged in only moderate levels of physical activity. In addition, findings of sport intervention studies might also be influenced by the point in time of assessing main outcome measures: Weinstein et al., for example, [154] reported that in a group of depressive patients, depressive symptoms had decreased directly after exercise, while 30 min after exercise, depressive symptoms and fatigue had again increased in the patient group.

## Effects of physical exercise on schizophrenia symptomatology

After having been neglected as a therapeutic intervention despite its cost-effectiveness for a long time, exercise has been in the focus as therapeutic add-on in various psychiatric disorders since the late 1990s [16, 118]. In the beginning, the effects of exercise on schizophrenia were seen mainly with regard to physiological changes like obesity or metabolic syndrome while psychological alterations, not to mention neurobiological changes, were being ignored. Additionally, there were many methodological limitations in these early studies [16]. Major concerns, e.g., are missing healthy and/or patient control groups, too small sample sizes and non-randomized or non-controlled design [1, 27, 148]. Until now, many exercise studies still only focus on body weight as sole outcome parameter without paying attention to psychopathological changes [5, 32, 102, 152] or measure only unspecific global outcomes with scales not tailored to the specific schizophrenia psychopathology [96, 129].

As for other psychiatric disorders [159], a number of studies point to a significant improvement of schizophrenia symptoms via aerobic exercise, which has been confirmed by a first meta-analysis [48]. Some authors measured quality of life as additional outcome parameter and unanimously report respective improvement as well [1, 6, 7, 31]. Scheewe et al. used the Camberwell Assessment of Need (CAN) [114] also finding significant improvement [120]. In a randomized controlled trial (RCT), Beebe et al. [6] were able to show reductions of positive and negative symptoms in chronically ill schizophrenia patients after aerobic exercise, though the differences did not reach statistical significance. Another RCT in chronically ill schizophrenia patients with aerobic exercise (indoor cycling) compared to a patient control group and healthy controls found a reduction in the severity of total symptoms of up to 9 % in the cycling group, while non-exercising patients presented a total symptom increase of 13 % measured by the positive and negative symptom scale (PANSS); again the findings did not reach statistical significance most likely due to small sample sizes [109]. This is in accordance with the results of Takahashi et al. [133] who found an improvement of the general psychopathology scale but not in the positive and negative symptom scale of the PANSS after exercising. This finding is further verified by an RCT with a large sample of schizophrenia patients reporting a significant reduction in the PANSS total score, especially by decreasing positive symptoms, disorganisation, excitement, emotional distress and a trend level significance in the decrease in negative symptoms. Also, exercise therapy had a positive effect on depressive symptoms [120]. Only one study with a relatively small sample of chronically ill schizophrenia patients undergoing aerobic high-intensity training compared to patient controls playing computer games did not find an improvement of positive, negative or depressive symptoms in either group via using PANSS and the Calgary Depression Scale for Schizophrenia (CDSS) [59]. The noted missing effects in this study could be due to the relatively small sample sizes and overall duration of the intervention, but also an effect of the different exercise intensities. After combining aerobic exercise (walking) and training of muscular strength in a small sample, persons with schizophrenia or schizoaffective disorders showed significantly reduced depressive symptoms plus significant improvement in their total score on the Mental Health Inventory, using a structured self-report questionnaire, as compared with controls [96].

Additionally, there are three RCTs pointing to a good if not even superior positive influence on schizophrenia symptoms through yoga compared to aerobic exercise: while one only compared patients with a yoga intervention to patients in a waiting list condition [151], both Behere et al. [7] and Duraiswamy et al. [31] investigated different outcomes of yoga therapy compared to a therapeutic exercise add-on. Each of the studies reported a significantly better total, positive and negative PANSS score plus a significantly improved socio-occupational status. This better outcome might be due to the yoga-intrinsic dual focus on physical and mental conditions, specifically including relaxation exercises. Nevertheless, the reported findings should be interpreted with caution since both studies present methodological weaknesses with regard to adherence, compliance rate, monitoring the therapeutic add-on under outpatient conditions and by not including healthy controls. Furthermore, the study designs were based on different yoga techniques, and the two latter were conducted in India where yoga might be better accepted than in Western countries [149].

## Effects of physical exercise on cognitive performance in schizophrenia

Although cognitive deficits are regarded as a core feature of schizophrenia (e.g. [24, 46, 61, 65]) and despite some evidence derived from studies in healthy humans (e.g. [19, 34, 71, 110]), macaque monkeys [116] and rodents [4, 35, 110, 141] that exercise enhances cognition, this aspect still is widely neglected in schizophrenia research. To our knowledge, only one RCT specifically focussed on neurocognitive effects induced by aerobic exercise in chronically ill schizophrenia patients. Here, aerobic exercise led to a 34 % improvement in the short-term memory of schizophrenia patients score of the German version of the Rey Auditory Verbal Learning Test. Somehow surprising, no improvement of memory scores were found in healthy controls. This may be due to the fact that controls already had a very high pre-test short-term memory level. Likewise, the long-term memory and Corsi direct block span score were investigated, but no significant effects were detected [109]. While we originally speculated these somewhat unexpected findings might to be due to the small sample size of our trial, Scheewe et al. also failed to find any changes in cognition in their larger sample of schizophrenia patients (personal communication).

## Neuroimaging studies on aerobic exercise in schizophrenia

At present, there are only three randomized structural imaging trials investigating the effects of aerobic exercise on brain volumes in schizophrenia patients. In a first pilot study, Pajonk et al. could demonstrate a mean hippocampal volume increase of 12 % in the schizophrenia exercise group and 16 % in the healthy control group positively correlated with fitness in comparison with the non-exercising group. Additionally, exercising patients presented a statistically significant increase of 35 % in the NAA/Cr ratio in magnetic resonance spectroscopy, whereas the patient control group showed a decline of 16 %. The authors did not find changes in total brain volume or total grey matter volumes [109]. In a far larger sample again, neither hippocampal volume changes nor changes in global brain volume or cortical thickness could be found. Nevertheless, fitness improvement was related to an increase in total cerebral matter volume (or attenuated volume decrease) and a decrease in lateral and third ventricle volume (or less increase) in patients with schizophrenia, but not in healthy controls. Additionally, an association of cardiorespiratory fitness improvement with cortical thickening in most left frontal, temporal and cingulate cortical areas was found in both schizophrenia patients and healthy controls, which may point to less volume decrease over time in the schizophrenia exercise group [121]. In contrast, using another method, Falkai et al. [36] found no difference in cortical thickness and surface expansion in schizophrenia patients after exercising, while healthy controls showed these changes in right frontal and occipital pole regions. According to a trial in healthy probands, increase in hippocampal volume seems to take place only in the anterior section and is related to greater serum levels of BDNF, which is known as a mediator of synaptic plasticity and neurogenesis [34].

In two recent studies focusing on the extrastriate body area, located in the posterior temporal-occipital cortex and associated with understanding others' behaviours, Takahashi et al. [132, 133] used functional magnetic resonance imaging and found increased activation of the extrastriate body area in the exercising patient group in comparison with non-exercising schizophrenia patients. This increase was associated with an improved general psychopathology measured by PANSS. However, both studies are no RCTs, and hence, general conclusions are limited.

## Effects of physical exercise on affective symptoms

The first study describing effects of physical exercise on symptoms of depression has been published in 1985 [95]. Levels of physical activity have been inversely associated with the severity of depressive symptoms and with prevalence rates of depression in the general population [43, 55, 99, 131]. Interestingly, one trial resulted in a significant association between more steps/day and lower prevalence of depression in women, but not in men [99]. Other studies observed the effect of regular physical exercise on the remission rate and onset of depression.

In their recent study, Jerstad et al. reported that physical exercise has a protective effect for the onset of major/minor depression in adolescents. They also suggested that the occurrence of depressive symptoms reduces physical activity in adolescents [77]. Assumptions of physical exercise being effective in preventing depression [91] were confirmed by the finding that an aerobic training programme was superior to pharmacological treatment in preventing a relapse in patients with MDD (6-month observation). This effect had been stronger in patients who had continued to exercise on their own [3].

To investigate systematically whether there is a causal relationship between physical activity and psychopathological symptoms, intervention studies with 2–3 weekly exercise sessions have been carried out [9, 63]. Interventional sports trials in MDD patients indicated a beneficial effect of moderate physical activity on depressive symptoms, as measured with well-established depression scales (e.g. Hamilton depression scale [54]; Beck depression scale [58]) [100, 159]. Moreover, an exercise support programme, lasting 3 months, reduced depression scores of mothers suffering from postpartum depression [60].

However, a meta-analysis including 25 interventional trials revealed only small-to-moderate effect sizes on clinical symptoms in MDD [100]. Similarly, in a new Cochrane review and meta-analyses including 28 studies, physical exercise showed moderate clinical effects [117]. Another meta-analyses of randomized controlled trials showed only modest effects of exercise and little evidence of long-term beneficial effect of exercise in patient with depression [86]. In many of these studies, the sample sizes were small and other methodological shortcomings need to be considered. Therefore, to improve comparability between studies, there is a need for large controlled clinical trials meeting standard criteria for intervention and rater-based evaluation of symptoms. For example, using only self-reported ratings of depressive symptoms, Chalder et al. [17] found no improvement in the intervention group. Several studies reveal a reduction of depressive symptoms in MDD via a controlled physical exercise programme [10, 23, 25, 29, 85, 97, 123, 125, 127]. It has been suggested that the effects were particularly strong for positive mood and energy, and less strong for improving distress, confusion, fatigue, tension or anger [11].

Other studies comparing physical exercise with other treatments, e.g. pharmacological treatment, indicated that physical exercise was similarly effective as established therapies [159]. Hoffman et al. compared initial treatment assignment, antidepressant medication and physical exercise in a 1 year follow-up and found that physical exercise was the best predictor of depression scores compared with other conditions [67]. Comparing a 12-months lasting aerobic exercise group with a group receiving antidepressant medication showed that the exercise group had a significant decrease in depressive symptoms compared to controls [23]. One work group found antidepressant therapy to show better effects than physical exercise at the beginning of treatment. However, 4 months later, both treatment options were regarded as similarly helpful in reducing depressive symptoms [9]. Several studies have shown that after physical activity, decreased depressive symptoms and increased quality of life are not merely due to improvement of physical fitness [28, 94, 124]. Thus, neurobiological mechanisms may be altered before the physical fitness level rises.

To our knowledge, there are only few studies on physical exercise in BD patients [15, 76, 138, 139]. Wright et al. [160] assumed that physical exercise may reduce stress as well as depressive and anxious symptoms in BD. In a recent review, it has been shown that medical co-morbidity, lower education status and social isolation have been associated with decreased physical activity in bipolar patients [146]. Therefore, in prospective studies, these variables should be evaluated.

## Effects of physical exercise on cognitive performance in affective disorders

Studies investigating the effects of physical exercise on cognitive performance in affective disorders are rare [68, 87, 88, 150, 159]. For MDD, two studies investigated cognitive skills immediately after an exercise session and showed improved attention and inhibitory control function [87], as well as increased selective attention [150]. When compared with cognitive therapy or antidepressants in MDD, exercise was found to be as effective as either of these treatments [159]. In contrast, one trial compared four groups of patients with MDD: one group participated in supervised exercise; a second group engaged in home-based exercises; a third group received an antidepressive drug (sertraline) and a fourth group was given a placebo. There were no differences across all neuropsychological tests when comparing the effects of placebo and exercise, but exercising participants performed better than participants receiving sertraline on tests of executive functioning [68]. While two studies had assessed cognitive function immediately after the exercise sessions [87, 150], participants in the study by Hoffman et al. [68] were measured later and were of older age.

A recent review of BD revealed that the results in BD mirror those from studies in MDD, suggesting that exercise is a viable treatment option for neurocognitive dysfunction in BD [88]. Other reviews on physical exercise in BD reported exercise-induced neurobiological changes and effects on BDNF levels [2].

While there are a number of studies assessing the effect sizes of sports interventions in patients with cognitive decline and dementia, such analyses do not yet exist for trials in affective disorders. To sum it up, there is substantial evidence for significant effects of physical exercise interventions on individual psychopathology in MDD, while effects on cognitive performance in these patients are less well established.

## Neurophysiology and physical exercise effects in affective disorders

Relatively few studies have examined the influence of regular physical exercise on brain functioning in affective disorders, and none of them assessed BD patients. The existing studies mainly focused on electroencephalography (EEG), which has also been used to assess electrophysiological correlates of brain function in clinical studies of depression [21, 22]. Recent findings indicate that mood symptoms are associated with cortical asymmetry mainly in the alpha band (8–13 Hz) [52, 53, 111–113]. However, to the best of our knowledge, only two studies systematically examined the effects of exercise treatment on EEG activity patterns in patients with MDD [23, 123]. One study investigating a group of patients with MDD, receiving a combination of aerobic exercise and pharmacological treatment for 1 year, revealed no changes in EEG pattern after the treatment period. In contrast, a control group with only pharmacological treatment showed an increase in alpha band power in the right hemisphere. After 1 year, however, the authors reported a reduction in depressive symptoms after 1 year in the exercise group but not in the control group [23]. The second study showed increased EEG mean frequency for both, an aerobic exercise group (2 times a week, 6 months) and a control group of MDD patients, but no significant group differences [123]. In sum, the existing number of studies using imaging approaches in affective disorders is too small to fit these findings into a pathophysiological model. Assessing brain function with fMRI and brain morphological changes with volumetric methods may be better suited for the assessment of training effects. The findings in schizophrenia are of interest for studies in affective disorders, which mirror some of the negative symptoms of schizophrenia (depressive symptoms). Based on the recent findings, it might be of interest to systematically investigate brain volumes, especially hippocampus volumes, in trials on MDD patients.

## Standardised physical activity in psychiatric research: a recommendation

In summary, exercise therapy has shown effects on both cognition and symptoms in schizophrenia and affective disorders. However, exercise therapy interventions in psychiatric research should also be standardised in order to be comparable. Based on our experiences, we recommend the following standard programme for endurance training in clinical studies: a minimum of 12 weeks, 3 sessions per week, general aerobic endurance training (continuous training), a minimum of 30 min per training session, with blood lactate concentrations of ca. 2.0 mmol/l, intensities equivalent to 10–13 on the BORG scale, attendance rates of more than 75 % and finally assessment of physical performance by incremental bicycle ergometry (with measurements of gas exchange, blood lactate concentration and heart rate). This design corresponds to recent research findings in sports medicine and the most recent consort statement by the American College of Sports Medicine [44, 107, 155] and ensures compliance of mentally ill patients [109]. However, to date, it is uncertain whether this scale is applicable in the same way to psychiatric patients, and future studies should address this. In spite of encouraging first results, further exercise therapy studies should comprise larger patient samples to provide more conclusive findings. Finally, it must be kept in mind that long-term exercise therapies call for different training methods to avoid monotonous and thus inefficient training stimuli [72].

**Conflict of interest** None.

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