Effects of aerobic exercise on cognitive performance and individual psychopathology in depressive and schizophrenia patients

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Abstract Cognitive deficits are core symptoms in patients with schizophrenia (SZ) and major depressive disorder (MDD), but specific and approved treatments for cognitive deterioration are scarce. Experimental and clinical evidence suggests that aerobic exercise may help to reduce psychopathological symptoms and support cognitive performance, but this has not yet been systematically investigated. In the current study, we examined the effects of aerobic training on cognitive performance and symptom severity in psychiatric inpatients. To our knowledge, to date, no studies have been published that directly compare the effects of exercise across disease groups in order to acquire a better understanding of disease-specific versus general or overlapping effects of physical training intervention. Two disease groups (n = 22 MDD patients, n = 29 SZ patients) that were matched for age, gender, duration of disease and years of education received cognitive training combined either with aerobic physical exercise or with mental relaxation training. The interventions included 12 sessions (3 times a week) over a time period of 4 weeks, lasting each for 75 min (30 min of cognitive training + 45 min of cardio training/mental relaxation training). Cognitive parameters and psychopathology scores of all participants were tested in pre- and post-testing sessions and were then compared with a waiting control group. In the total group of patients, the results indicate an increase in cognitive performance in the domains visual learning, working memory and speed of processing, a decrease in state anxiety and an increase in subjective quality of life between pre- and post-testing. The effects in SZ patients compared with MDD patients were stronger for cognitive performance, whereas there were stronger effects in MDD patients compared with SZ patients in individual psychopathology values. MDD

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patients showed a significant reduction in depressive symptoms and state anxiety values after the intervention period. SZ patients reduced their negative symptoms severity from pre- to post-testing. In sum, the effects for the combined training were superior to the other forms of treatment. Physical exercise may help to reduce psychopathological symptoms and improve cognitive skills. The intervention routines employed in this study promise to add the current psychopathological and medical treatment options and could aid the transition to a multidisciplinary approach. However, a limitation of the current study is the short time interval for interventions (6 weeks including pre- and post-testing).

**Keywords**  Sports · Exercise · Schizophrenia · Depression · Cognitive training

**Introduction**

Schizophrenia (SZ) and major depressive disorders (MDD) represent severe mental diseases that rank among the ten most frequent causes of mental disability (for SZ: [59], for MDD: [19]). The symptoms of schizophrenia include ‘positive’ (e.g., hallucinations, delusions) and ‘negative’ symptoms (e.g., social retardation, loss of energy, affective flattening). Some of the negative symptoms of SZ, including loss of energy, social withdrawal and affective flattening, and mirror depressive symptoms, observed in MDD. In addition, both patient groups suffer from cognitive deficits, especially in the domains executive functioning, memory and attention (for SZ: [66], for MDD: [57]). As Iosifescu et al. [33] mentioned, beside disease-specific psychopathological symptoms, cognitive impairment may be an important independent dimension of depression and schizophrenia and may lead to deterioration of social abilities, loss of autonomy and job-related problems.

While antipsychotic medication in SZ and antidepressant medication in MDD target primarily psychotic and depressive symptoms, respectively, there are to date no pharmacological options available that are specifically approved for the treatment of cognitive symptoms in psychiatric diseases. Cognitive training programs have been developed targeting cognitive deficits in various psychiatric conditions, especially in psychosis (e.g., Cogpack® [44], Cognitive Remediation [46, 72]). As Twamley et al. [62] showed in his review of studies investigating the effects of cognitive training in schizophrenia patients, 14 out of 17 studies revealed small to medium effect sizes regarding the improvement of neuropsychological performance. However, novel therapeutic approaches attempt to integrate pharmacological and psychotherapeutic elements into multimodal treatment concepts (see for SZ: [50], for MDD: [27]). Despite these efforts, there is currently still no causal treatment for cognitive deficits available, driving the urgent need to develop alternative approaches to ameliorate cognitive symptoms in psychiatric patients.

However, newer approaches have suggested that physical training may improve cognitive functioning and psychopathology in psychiatric patients. Malchow et al. [43] summarized in their review of current clinical studies the effect of exercise on affective and schizophrenia patients and revealed positive effects in both disorders. The underlying causes of beneficial effects of physical exercise have been investigated through animal models and in humans have been linked to neurogenesis, neuronal plasticity (cortical capillary supplies, number of synaptic connections, development of new neurons), synaptogenesis and neurotransmission (see review by Malchow et al. [43]). Van Praag [63] showed in his review of exercise studies in mice that running increases neuronal plasticity as well as learning and memory. Experimental studies in animal models and humans showed that aerobic physical exercise improve growth factors such as glucocorticoids, brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) (see review by Voss et al. [67]). BDNF is of special interest regarding its role in synaptic plasticity and growth [15, 42]. Furthermore, Voss et al. [67] noted in their review that a high number of animal studies (e.g., [47, 51, 52]) and several studies on humans [20, 23, 58] verified associations between exercise and changes in BDNF levels.

Of further interest is the role of the hippocampus, a core structure of cognitive functioning in the brain, in relation to plasticity and growth factors. Cotman et al. [14] reported in their review that aerobic exercise enhances hippocampal plasticity and memory through hormonal and inflammatory factors, such as glucocorticoids, and neurotrophins. In particular, Whiteman et al. [69] noted that neurotrophins and neurotrophin-related genes are involved in synaptic plasticity and show increased level in the hippocampus after physical exercise. Additionally, Pajonk et al. [54] showed that aerobic exercise leads to an increase in hippocampal volume and improve short-term memory in schizophrenia patients. Another study by Falkai et al. [18] revealed that 3 months of aerobic exercise leads to an increase in cortical thickness in healthy probands. However, only very few studies have investigated the effects of physical exercise on the cognitive performance of patients with affective disorder or schizophrenia (see review by Malchow et al. [43]), and no study compared the effects in both conditions.

Recent interventional trials showed preventive and therapeutic effects of physical exercise on depressive mood (see meta-analysis of 23 studies by [45]).
patients with MDD indicated that physical exercise might be effective in treating [34] and preventing depressive episodes (compared with psychotherapy or antidepressants) [4, 40]. Furthermore, there is some emerging evidence that physical activity may enhance cognitive performance in patients with MDD [39, 65]. However, the evidence for cognition-enhancing effects in MDD is equivocal: Hoffman et al. [31] compared four different interventions in patients with MDD [supervised exercise, home-based exercises, a third group received an anti-depressive drug (sertraline) and a fourth group received a placebo] and did not find any differences in neuropsychological tests across the groups, despite the exercise groups performed better than placebo and antidepressant groups in tests of executive functioning.

Studies investigating the effectiveness of various physical training interventions in schizophrenia indicate that physical exercise may ameliorate positive and negative symptoms of schizophrenia [1]. Pelham and Campagna [55] showed a reduction in severity of depressive symptoms and increased well-being in a sample of 40 outpatients with schizophrenia. The study by Pajonk et al. [54] examined the effects on cognitive performance in schizophrenia patients after 3 months of physical exercise and revealed positive effects on short-term memory in the patient group, but no significant effects on long-term memory.

Overall, the existing number of controlled randomized trials that systematically examined the effects of aerobic physical exercise in SZ and MDD patients on cognitive and clinical symptoms is limited and effect sizes are largely unknown. We hypothesized that the effects of established cognitive training programs would be significantly facilitated by concomitant aerobic physical exercise. Moreover, we hypothesized that aerobic exercise may have additive or synergistic effects with cognitive training, thus allowing for better overall clinical and cognitive outcome compared with each intervention alone.

Therefore, the aim of this study was to examine whether aerobic physical training may substantially improve cognitive performance in psychiatric patients (MDD and SZ) beyond effects typically achieved with cognitive interventions alone. To our knowledge, to date, no studies have been published that directly compare the effects of exercise combined with cognitive training across disease groups. The rationale of our approach to include two parallel disease groups is to acquire a better understanding of disease-specific versus general or overlapping effects of physical training intervention. We expected an improvement of cognitive performance, increased scores in parameters of quality of life and reduced psychopathological symptoms in MDD and SZ patients after a combined cognitive and exercise training.

We expect this treatment to be superior to a cognitive training combined with a relaxation training or medical drug therapy alone.

Materials and methods

Participants

Fifty-one patients [mean age (M) = 39.65 (SD = 12.81) years, 28 females, 23 males] completed the intervention. Twenty-nine patients were diagnosed with schizophrenia (SZ) disorder [mean age (M) 39.42 (SD = 12.32) years, 17 females, 12 males] and 22 patients with MDD [mean age (M) 40.00 (SD = 14.10) years, 11 females, 11 males] according to DSM-IV criteria [3]. To ensure the diagnosis, the Structured Clinical Interview for DSM-IV (SCID-I and SCID-II: German version: [70]) was carried out with all participants, followed by an interview to examine sociodemographic factors. The participants were all inpatients of the Department of Psychiatry, Goethe-University, Frankfurt, Germany. All patients fulfilled the DSM-IV criteria for an acute state of illness (see ‘Results’ section for initial scores). Also, we made sure that no participant fulfilled the criteria for any comorbid Axis-I or II disorders (see Table 1 for further details).

The duration of disease had to be at a minimum of 5 years in order to select long-term patients. Mean duration of disease across groups was M = 10.67 [SD = 4.32] years. All patients had to be in stable medication status during the last month preceding pre-testing and during the intervention until post-testing. We ensured that there was no significant change in the medication status between pre- and post-testing in all participants. Therefore, we computed the chlorpromazine equivalents for each SZ patient using the formula by Woods [71], and ‘amitryptiline equivalents’ for each MDD patient as described by [2].

Before starting the intervention phase, the participants were, blind to pre-test results, randomly assigned to one of the following groups: The first group received both cognitive and physical exercise training (physical exercise group, n = 16); the second group underwent cognitive and relaxation training (relaxation group, n = 17). In addition to the intervention groups, we had a ‘waiting control group,’ including n = 18 participants, to control for potential bias factors.

The recruitment and randomization process has been done as follows: the different interventions were numbered (1 = exercise, 2 = relaxation, 3 = waiting control). All participants were informed that they will be randomly distributed to one of the possible interventions. Every patient who was interested to participate in the study has
been allocated a random number (1, 2, 3) using Microsoft Excel software. Thereafter, each patient has been informed about the allocated intervention.

The ‘exercise group’ included eight SZ and eight MDD patients according to DSM-IV criteria [3]; the ‘relaxation group’ included 11 SZ and 6 MDD patients (view Table 1 for further details). The waiting control group included ten SZ and eight MDD patients and received no intervention, but conducted the pre- and post-testing. The three groups were matched regarding age, gender, duration of disease, duration of medication (for SZ and MDD patients separately) and years of education. Statistical tests (\(\chi^2\) tests, \(t\) tests) for differences between the groups revealed no significant group differences (all \(p\) values \(< 0.05\)) regarding age, gender, duration of disease, duration of medication and years of education.

After finishing the main study, we did a control experiment with a ‘cognitive training group’ whose participants did not take part in the randomization process. The intervention of the ‘cognitive training group’ was conducted in similar conditions than the main treatment (4 weeks, 3 sessions per week, each session lasting 30 min) with a group size of \(n = 19\) participants (\(n = 10\) SZ and \(n = 9\) MDD patients). The results of the ‘cognitive training group’ were compared with the other intervention groups (see ‘Results’ section).

All participants underwent a complete physical examination, an exercise electrocardiogram (ECG) and routine blood investigation. Exclusion criteria for all participants were drug addiction or drug abuse (for minimum of 1 year preceding the intervention), any physical illness, neurological disorders or other medical condition or disease, which may represent an exclusion criterion to participate in exercise training and an inability to provide informed consent. We also ensured that the fitness level of the participants was appropriate (based on medical criteria, e.g., heart frequency, pulse, blood pressure) to participate in sports. Participants were provided with a description of the study and gave written informed consent before participating. Experimental procedures were approved by the ethical board of the medical department of the Goethe-University, Frankfurt/Main, Germany.

Study design

The total intervention consisted of three weekly sessions each lasting 75 min over 4 weeks, totaling 12 sessions (see Fig. 1). Depending on the group, each session included 30 min of cognitive training and 45 min of either physical exercise or relaxation. The physical exercise was led by a trained physical exercise instructor, with previous experi-

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**Table 1** Sociodemographic and clinical characteristics and cognitive performance of the different intervention groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>Exercise group Mean (SD)</th>
<th>Relaxation group Mean (SD)</th>
<th>Waiting control group Mean (SD)</th>
<th>Total Mean (SD)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>PAT</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>51</td>
<td>(\chi^2 = 0.07, p = 0.65) (Chi-square)</td>
</tr>
<tr>
<td></td>
<td>SZ</td>
<td>8</td>
<td>11</td>
<td>10</td>
<td>29</td>
<td>(\chi^2 = 0.98, p = 0.29) (Chi-square)</td>
</tr>
<tr>
<td></td>
<td>MDD</td>
<td>8</td>
<td>6</td>
<td>8</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>PAT</td>
<td>7:9</td>
<td>6:11</td>
<td>10:8</td>
<td>23:28</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SZ</td>
<td>3:5</td>
<td>4:7</td>
<td>5:5</td>
<td>12:17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MDD</td>
<td>4:4</td>
<td>2:4</td>
<td>5:3</td>
<td>11:11</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>PAT</td>
<td>41.13 (13.74)</td>
<td>38.07 (12.01)</td>
<td>40.41 (14.22)</td>
<td>39.65 (12.81)</td>
<td>(t = 0.12, p = 0.91)</td>
</tr>
<tr>
<td></td>
<td>SZ</td>
<td>44.63 (13.78)</td>
<td>34.91 (9.33)</td>
<td>38.33 (4.51)</td>
<td>39.42 (12.32)</td>
<td>(t = 0.05, p = 0.91)</td>
</tr>
<tr>
<td></td>
<td>MDD</td>
<td>36.63 (12.91)</td>
<td>41.37 (15.69)</td>
<td>42.21 (8.31)</td>
<td>40.00 (14.10)</td>
<td>(t = 0.05, p = 0.91)</td>
</tr>
<tr>
<td>Years of education</td>
<td>PAT</td>
<td>14.44 (2.64)</td>
<td>15.40 (3.86)</td>
<td>15.01 (3.01)</td>
<td>14.90 (3.27)</td>
<td>(t = 0.05, p = 0.91)</td>
</tr>
<tr>
<td></td>
<td>SZ</td>
<td>14.69 (3.4)</td>
<td>15.41 (3.58)</td>
<td>15.34 (2.46)</td>
<td>15.11 (3.43)</td>
<td>(t = 0.05, p = 0.91)</td>
</tr>
<tr>
<td></td>
<td>MDD</td>
<td>14.19 (1.79)</td>
<td>15.37 (5.19)</td>
<td>14.98 (2.34)</td>
<td>15.08 (2.34)</td>
<td>(t = 0.05, p = 0.91)</td>
</tr>
<tr>
<td>Duration of diseases</td>
<td>PAT</td>
<td>10.20 (7.19)</td>
<td>10.23 (5.67)</td>
<td>10.67 (4.32)</td>
<td>10.45 (2.89)</td>
<td>(t = 0.56, p = 0.87)</td>
</tr>
<tr>
<td></td>
<td>SZ</td>
<td>11.01 (6.54)</td>
<td>10.43 (5.01)</td>
<td>9.95 (3.43)</td>
<td>10.34 (2.99)</td>
<td>(t = 0.56, p = 0.87)</td>
</tr>
<tr>
<td></td>
<td>MDD</td>
<td>10.01 (5.56)</td>
<td>10.08 (4.56)</td>
<td>10.98 (3.43)</td>
<td>10.55 (3.56)</td>
<td>(t = 0.56, p = 0.87)</td>
</tr>
<tr>
<td>Duration of medication</td>
<td>PAT</td>
<td>8.23 (5.65)</td>
<td>8.78 (6.01)</td>
<td>9.45 (5.34)</td>
<td>8.99 (3.23)</td>
<td>(t = 1.12, p = 0.24)</td>
</tr>
<tr>
<td></td>
<td>SZ</td>
<td>7.87 (4.78)</td>
<td>9.09 (5.67)</td>
<td>9.34 (3.45)</td>
<td>8.23 (2.89)</td>
<td>(t = 1.12, p = 0.24)</td>
</tr>
<tr>
<td></td>
<td>MDD</td>
<td>8.65 (4.57)</td>
<td>8.02 (4.53)</td>
<td>9.89 (4.01)</td>
<td>9.23 (2.89)</td>
<td>(t = 1.12, p = 0.24)</td>
</tr>
</tbody>
</table>

SZ schizophrenia patients, MDD major depressive patients, PAT SZ and MDD patients together

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\(\chi^2\) chi-square test, \(t\) Student’s \(t\) test
ence in working with psychiatric patients. Cognitive training and relaxation were conducted by trained psychologists. Minimum criteria of expertise for a trained psychologist or trained physical exercise instructor were defined as an experience of 2 years or more as psychiatric group instructor. The components of the interventions were tested in an exploratory study for efficacy, safety and feasibility. Acceptance for exercises was defined as ‘feasible for all participants,’ ‘feasible in a group session’ and ‘could be performed based on instructions only.’ All groups of the intervention program consisted of between eight and twelve participants per session. We attempted to achieve a comparable psychosocial situation across physical exercise and relaxation training. Therefore, all sessions were done in similar settings, including time of the day, room, structure of the sessions and number of participants per group.

One week before and 1 week after the intervention phase, all participants were tested with a cognitive and clinical test battery.

Cognitive training

Both intervention groups received three sessions a week of cognitive training, lasting 30 min each. The cognitive training was a combined training program of two manuals established for cognitive training in psychiatry (‘COGPACK’ [44]; German version of the ‘cognitive training after Stengel’ [61]), which had been designed for psychiatric participants. Both programs address multiple cognitive domains, including motor skills, executive functioning, memory, concentration, attention, vigilance, learning and problem solving across multiple sensory systems. The cognitive training started with a group task (e.g., for memory skills), followed by individual tasks to train multiple cognitive domains. The participants were instructed to solve the tasks as fast and as accurate as possible. The instructors ensured that all participants worked on the tasks. The subdomains that were trained were randomly selected during the whole intervention time.
span (4 weeks). All stimulus material used for the pre- and post-testing has been excluded from the training sessions.

After a break of approximately 10 min, the intervention was followed by physical exercise or relaxation.

Physical exercise

Each physical exercise session consisted of three phases, starting with a warm-up (10 min), followed by cardio training (25 min) and ending with a cool-down phase (10 min), lasting altogether 45 min. The warm-up consisted of pep rally, ball games, stretching and motivation exercises. The cardio training included aerobic exercise, aerobic with boxing and circuit training in alternate order. The instructors ensured that the training intensity was set at an aerobic endurance level of 60–70% of individual maximum heart rate, which was calculated individually for each participant using the maximum heart rates of the ECG [10]. Heart rate of each participant was measured by instructors every 10 min during the training sessions. The exercise equipment for the circuit training used in this study included a trampoline, weights, physiotherapy balls, staves and flexi bars. The circuit training comprised six different ‘circuit stations’ focusing on arms, legs, chest, back, shoulders and abdomen. It included endurance exercise with and without weights and other materials, with 2–3 circuits per training per participant. Each exercise had to be performed for 60 s with a break of 20 s. The exercises were arranged to be comparable, but adjusted to the individual level of the participants.

The aerobic training comprised exercises for arms and legs and included boxing elements and learning step rates. First, the aerobic training started with easy arms and legs movement (without any choreography). During the intervention phase, the exercises became more difficult, e.g., through combined arms and legs exercises or through building a small choreography (e.g., arms – legs – arms + legs – arm, etc.). To ensure that all participants were able to do the aerobic exercises, the choreography was simple and was repeated as often as necessary by the instructor. The aerobic training with boxing comprised the same order than the simple aerobic training, but included special boxing elements. The cool-down phase included stretching and slow-motion exercising.

Relaxation

The relaxation period lasted for 45 min. At the beginning of the session, the participants were instructed about the benefits of relaxation training. The interventions were modified from standardized therapeutic routines (see concepts by [8, 25, 29, 56]). The exercises included breathing exercises, ‘imagery journey,’ ‘enjoy exercises’ for all sensory modalities, relaxation or acceptance and awareness training. Yoga or progressive muscle relaxation or related exercises were decidedly not applied because of their acknowledged physiological effects similar to those of active training.

Pre- and post-testing

One week before (pre-testing) and 1 week after the intervention (post-testing), a cognitive test battery and psychopathological assessments were conducted in all participants by independent psychologists. Assessors were blind to treatment group. Only the diagnoses of SZ and MDD were known to the assessors without reference to the applied rating scales for cognitive functioning and severity of psychopathological symptoms.

All participants were tested for cognitive status using the MATRICS consensus battery, which was conducted to evaluate cognitive performance in seven cognitive domains relevant for psychiatric disorders especially for SZ patients [53]. In the current study, we assessed the domains: working memory [Wechsler Memory Scale®-Third Edition: Spatial Span (WMS-III SS), Letter–Number–Span (LNS)], psychomotor speed [Trail Making Test: Part A (TMT A), Brief Assessment of Cognition in Schizophrenia: Symbol Coding (BACS SC), Category Fluency: Animal Naming], verbal learning [Hopkins Verbal Learning Test-Revised (HVLT-R)] and non-verbal (visual) learning [Brief Visuospatial Memory Test-Revised (BVMT-R)] (view Table 2 for further details).

In order to assess state anxiety in both patient groups, all participants were instructed to fill in the self-rating instrument State-Trait-Anxiety-Inventory (STAI; [41]). The STAI consists of two subscales, measuring state or trait anxiety, each with 20 items. For the current study, we used only the state subscale of the STAI in order to assess acute and temporarily state symptomatology. State anxiety was defined by the authors as an arousal of the autonomic nervous system combined with feelings of fear, discomfort and nervousness induced by actual situations. The participants were instructed to rate their state anxiety on a 4-point Likert scale, and scores range from 20 to 80 points. Higher scores indicate higher state anxiety. The majority of the items are anxiety present questions, as they represent the occurrence of an anxiety statement, but some items of the scale are scored inversely that means that they represent anxiety-absent questions indicating the absence of anxiety in a statement.

All participants were also screened for their subjective quality of life, using the German version of a questionnaire asking for physical and mental health, the self-ratings scale

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Table 2 Overview over the cognitive and clinical tests for the pre- and post-testing

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Construct</th>
<th>Processing</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMT—part A [53]</td>
<td>Speed of processing</td>
<td>Connect numbers</td>
</tr>
<tr>
<td>BACS SC [36]</td>
<td>Speed of processing</td>
<td>Symbol coding</td>
</tr>
<tr>
<td>Category fluency: animal naming [53]</td>
<td>Speed of processing</td>
<td>‘Please name as lot animals as possible’</td>
</tr>
<tr>
<td>LNS [22]</td>
<td>Working memory</td>
<td>Learning and organize verbal components (numbers and letters)</td>
</tr>
<tr>
<td>HVLT-R™ [9]</td>
<td>Verbal learning</td>
<td>Learning and retrieval of word lists</td>
</tr>
</tbody>
</table>

Individual psychopathology

<table>
<thead>
<tr>
<th>Test</th>
<th>Scale/Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAI [41]</td>
<td>State anxiety</td>
</tr>
<tr>
<td>BDI II [28]</td>
<td>Depression symptoms</td>
</tr>
<tr>
<td>RHS [48, 49]</td>
<td>Predisposition toward hallucinations</td>
</tr>
<tr>
<td>PANSS [35]</td>
<td>Individual psychopathology (psychosis symptoms)</td>
</tr>
</tbody>
</table>

TMT Trail Making Test, BACS SC Brief Assessment of cognition in Schizophrenia: Symbol Coding, WMS-III SS Wechsler Memory Scale®-3rd Ed.: Spatial Span, LNS letter–number–span, HVLT-R Hopkins Verbal Learning Test-Revised™, BVMT-R Brief Visuospatial Memory Test-Revised™, STAI State-Trait-Anxiety-Inventory, SF-12: PSK Psychic scale of the SF 12, BDI II Beck Depression Inventory, PANSS positive and negative affect schedule

We computed ANCOVAs with repeated measurements, with the t-scores of the cognitive domains [working memory (sum of t-scores of WMS-III SS and LNS, corrected for age and gender), speed of processing (sum of t-scores of TMT A, BACS SC, Animal naming, corrected for age and gender), verbal learning (t-scores of the HVLT-R, corrected for age and gender), visual learning (t-scores of the BVMT-R), corrected for age and gender] and the clinical variables (STAI) as dependent variables, and time of measurement (pre-test, post-test, diagnosis (schizophrenia, depression) and intervention group (relaxation, exercise, waiting control) as independent variables; age, gender, duration of disease and years of education were used as covariates. The scores of the SF-12: PSK were analyzed using the nonparametric Wilcoxon test. We also computed Scheffé post hoc single contrasts to assess group differences across groups. We corrected all analyses for multiple comparisons using the Bonferroni correction option in the SPSS software package.

For the control experiment, we conducted additional ANCOVAs with repeated measurements for the ‘cognitive training group’ after the main experiment. This was done to ensure potential effects of a single cognitive training on cognitive performance and individual psychopathology. This was done separately of the main analysis.

In order to examine the effect sizes of the different interventions on cognitive performance and individual psychopathology scales across groups, we calculated power analyses according to the formula by Cohen [13]. Here, we compared the means of the cognitive tests and individual psychopathology scales of pre- and post-testing across...
groups. Following the recommendation by Cohen [13], effect sizes of $d = 0.2$ were set as small, effect sizes of $d = 0.5$ as middle and effect sizes of $d = 0.8$ as high.

**Results**

Cognitive performance

For the cognitive domain ‘speed of processing,’ there was a significant effect of time and diagnosis [time: $F(46) = 37.55, p < 0.001$; diagnosis: $F(46) = 11.52, p < 0.05$], but no significant effect of intervention group ($p > 0.05$). Both patient groups significantly increased their speed of processing between pre- and post-testing. There were no significant interactions between diagnosis $\times$ intervention group $\times$ time ($p > 0.05$).

The domain working memory showed significant effects of time, diagnosis and intervention group [time: $F(46) = 9.34, p < 0.05$; diagnosis: $F(46) = 8.43, p = 0.02$; intervention group: $F(46) = 10.23, p = 0.02$]. Moreover, there was a significant interaction effect of intervention group $\times$ diagnosis $\times$ time [$F(46) = 14.32, p < 0.01$]. Post hoc tests revealed a significant interaction effect of intervention $\times$ time ($t = 18.82, p < 0.001$), which can be attributed to the higher increase in working memory scores in the SZ patients group relative to MDD patients between pre- and post-testing in the aerobic physical exercise group.

The domain verbal learning showed no significant differences of time, diagnosis or intervention and no significant interaction effects ($p > 0.05$).

The ANCOVA with repeated measurements revealed significant differences between pre- and post-testing in the cognitive domain visual learning [$F(46) = 9.53, p = 0.004$]. Also, there was a significant effect of diagnosis [$F(46) = 6.34, p = 0.01$]. These differences can be explained by a significantly lower score of the schizophrenia patients in these domains at pre-testing and a significant increase between the first and the second measurement time point in contrast to MDD patients [see Fig. 2; Table S1 (supplementary material)].

Individual psychopathology

MDD patients had a mean initial score in the BDI II (depressive symptoms) of 25.50 [11.83] points across intervention groups, which indicate that they were in an acute clinical state of illness at the beginning of the intervention. However, they showed a significant reduction in depressive symptoms (BDI II) between pre- and post-testing [$F(19) = 24.10, p < 0.001$] and a significant interaction time $\times$ intervention group [$F(19) = 4.19, p = 0.03$], which can be explained by significant differences between pre- and post-testing for the relaxation and exercise group but not for the waiting control group.

SZ patients showed a mean initial score of 15.01 [SD = 2.12] in the positive subscale of the PANSS and a mean initial score of 15.55 [SD = 3.01] in the negative subscale of the PANSS at the beginning of the intervention across intervention groups. However, the positive symptoms (PANSS pos) showed no changes between pre- and post-testing ($p > 0.05$), but there was a significant main effect of interventions in the subscale Negative of the PANSS (PANSS neg) [$F(26) = 8.34, p = 0.02$]. Post hoc tests revealed a significant reduction in PANSS neg scores in the exercise and in the relaxation group. There was also a significant interaction intervention group $\times$ time [$F(26) = 4.78, p = 0.04$] in the PANSS negative symptoms scores, which was due to no significant differences in the waiting control group ($p > 0.05$).

There were no significant differences between pre- and post-testing across intervention groups in the scores of the predisposition toward hallucinations (RHS) in the SZ patient group ($p > 0.05$).

Regarding psychopathology values that have been assessed across disease groups, the state anxiety scores (STAI) showed a significant effect of time [$F(46) = 6.06, p = 0.02$]: both intervention groups (relaxation, aerobic exercise) had a decrease in state anxiety (STAI) from pre- to post-testing. Results revealed also significantly stronger effects of time for the aerobic exercise group compared with relaxation group and wait control group (significant effect of intervention group; $F(46) = 3.18, p = 0.04$). These effects can be explained by the stronger decrease in state anxiety (STAI) in the MDD group in comparison with the SZ patient group between pre- and post-testing [see Fig. 3; Table S2 (supplementary material)]

The values of the SF-12: PSK showed a significant increase between first and second measurement time point [effect of time: $F(46) = 18.62, p < 0.001$] in both the aerobic exercise and the relaxation group. This result can be explained by a stronger increase in SF-12: PSK values in the MDD patient group. The increase in SF-12: PSK scores between pre- and post-testing was independent of the kind of intervention (exercise vs. relaxation) in both groups, which resulted in no significant interaction effect of intervention group $\times$ time $\times$ diagnosis ($p > 0.05$).

Power analyses

We compared the means of the cognitive test scores for speed of processing, working memory, verbal learning and visual learning of pre- and post-testing across groups. Here,
the results indicated middle effect sizes in the exercise group regarding speed of processing, working memory, verbal learning, and visual learning ($d = 0.47–0.57$), and high effect sizes for visual learning ($d = 0.91$). In the relaxation group, middle effect sizes have been shown for speed of processing and visual learning ($d = 0.43–0.47$) and low effect sizes for working memory and verbal learning ($d = 0.18–0.24$). In the waiting control group, speed of processing revealed middle effect size ($d = 0.50$); the other cognitive test scores showed low effect sizes ($d = 0.23–0.35$).

We also compared means of the psychopathology scores (STAI, SF-12: PSK, BDI II, RHS, PANSS) between pre-
Fig. 3 Results of the group comparisons (means [SD]) regarding the clinical scales (SF-12: PSK, SCL-90, STAI, BDI II, RHS, PANSS).SZ pre schizophrenia patients group at pre-testing, SZ post schizophrenia patients group at post-testing, MDD pre major depressive patients group at pre-testing, MDD post major depressive patients group at post-testing. Exercise = physical exercise group, Relaxation = relaxation group, waiting = waiting control group. STAI State-Trait-Anxiety-Inventory, SF-12: PSK Psychic scale of the SF 12, BDI II Beck Depression Inventory (only MDD patients), RHS Revised Hallucination Scale (only SZ patients), PANSS pos Positive and Negative Symptom Scale subscore positive (only SZ patients), PANSS neg Positive and Negative Symptom Scale subscore negative (only SZ patients)
and post-testing. The results indicated high effect sizes for the state anxiety (STAI), the SF:12 PSK and the BDI II (only MDD patients) in the exercise group \((d = 0.70–0.93)\), and low effect sizes for predisposition toward hallucinations (RHS), PANSS positive and negative symptoms in SZ patients in the exercise group \((d = 0.11–0.24)\). In the relaxation group, high effect sizes have been found for state anxiety and SF:12 PSK \((d = 0.82–0.95)\), middle effect size for depressive symptoms in MDD patients \((d = 0.58)\) and low effect sizes or predisposition toward hallucinations (RHS) and PANSS positive and negative symptoms \((d = 0.12–0.24)\). In the waiting control group, the SF:12: PSK revealed middle effect sizes; the other psychopathology scores showed only low effect size \((d = 0.10–0.18)\) (see Table S3, supplementary material).

Results of the control condition: cognitive training group

The ‘cognitive training group’ revealed effects on cognitive performance comparable with those found in the wait control group in both MDD and SZ patients, the only exception being the domain of psychomotor speed, where participants of the cognitive training group a trend toward improved on psychomotor speed in the post-test in both groups (see supplementary material).

Drop-out rate and intention-to-treat analysis (ITT)

Initially, \(n = 75\) patients took part in the study, but only fifty-one patients completed the intervention (drop-out rate 32 %). The drop-out rate was equally distributed across disease and intervention groups. We assessed the reasons for drop-out and divided them into two categories called ‘organization reasons’ and ‘motivation reasons.’ For instance, ‘end of inpatient treatment’ and ‘changes in medication load’ (exclusion criteria) were the main reasons for drop-outs in the category ‘organization reasons,’ and ‘motivation reasons’ included statements like ‘absence of motivation’ and ‘too much effort needed.’ In sum, the drop-out rate concerning the category ‘organization reasons’ was 20 %, whereas the drop-out rate in the category ‘motivation reasons’ was 12 %.

We conducted an additional ITT with all scores, which changed significantly between pre- and post-testing. To perform the ITT, we replaced all missing values in the post-testing with the mean of the respective group (‘mean replacement’) and repeated the analyses. The results of the ITT indicated that the previous significant results for the cognitive testing and the individual psychopathology remained significant without the results of the state anxiety (STAI), which was no longer significant \((p > 0.05)\).

Discussion

The current study examined the effects of a combined physical exercise and cognitive training program on cognitive performance and individual psychopathology of schizophrenia and major depressive patients. To our knowledge, this is the first time that a combination of cognitive and physical exercise training and two patient groups in one study was systemically investigated. All participants (except for the waiting control group) underwent the same cognitive training, but differed in the accompanying specific treatment [relaxation (control condition) vs. physical exercise]. Using this study design, we aimed to control important bias factors, particularly those introduced by psychotherapy-applied psychiatric inpatients, which in many cases includes some cognitive stimulation, which could interact with the effects of our aerobic exercise intervention on cognitive performance. However, the comparison between ‘cognitive training + relaxation’ versus ‘cognitive training + physical exercise’ would eliminate potential bias from different levels of cognitive stimulation during regular standard therapy procedures for inpatients and help to assess differential cognitive effects of aerobic training and control interventions.

Overall, our results indicate an increase in cognitive performance and a reduction in severity of illness across subject groups, with strongest effects found in patients undergoing combined cognitive and aerobic physical training. A combination of physical exercise and cognitive training may therefore be superior to the use of single interventions in the management of cognitive deficits and individual psychopathology in schizophrenia and MDDs.

Effects on cognitive performance and psychopathology: Schizophrenia patient group

In sum, schizophrenia patients in our study showed an improvement of cognitive performance and a reduction in psychopathology scores. The results of the cognitive testing indicate a significant increase in performance in the domains speed of processing, working memory and visual learning as an effect of the intervention program in the schizophrenia patient group. The results are in keeping with the results by Pajonk et al. [54] who showed beneficial effects of physical exercise on short-term memory. In our study, verbal learning was the only domain that revealed no significant differences between time points of measurement and different intervention groups (exercise, relaxation, waiting list control). One explanation for this finding is that verbal learning performance may be persistent across illness states, which has been reported by [66], and that 80 % of SZ patients overall suffer from cognitive deficits [46].
Evidence suggests that verbal learning performance is stable during the disease and thus may represent a trait rather than a state marker, relatively resistant to therapeutic interventions. Findings from a neuroimaging study revealed that the hippocampus volumes, a core brain structure associated with learning and memory, can be positively changed by exercise [54].

Furthermore, the interventions lead to an improvement in subjective well-being in the schizophrenia patient group. Accordingly, PANSS negative symptoms have been reduced after the intervention phase in both intervention groups. This is partly in line with the study by Acil et al. [1] who showed a reduction in psychopathology scores of patients with schizophrenia through controlled physical exercise. However, in our study, we could not replicate the finding of a reduction in hallucination severity and anxiety after physical exercise interventions as showed by Acil et al. [1].

Effects on cognitive performance and psychopathology: major depressive patient group

Overall, our results are in line with recent studies, which revealed the importance of physical exercise for cognitive performance and psychopathology (see review by Malchow et al. [43]). Depressive patients showed a significant improvement of cognitive performance in the domains speed of processing, working memory and visual learning as an effect of the intervention program without significant differences in the verbal learning ability between pre- and post-testing. Douglas and Porter [17] stated in their review of studies investigating neurocognitive functioning in MDDs that verbal learning and memory are the cognitive domains most sensitive to the clinical state.

The results of the other cognitive testing in MDD patients are in keeping with those of previous studies [39, 65], indicating that physical exercise can enhance cognitive performance of patients with MDD, especially on attention and inhibitory control function. The studies by Kubesch et al. [39] and Vasques et al. [65] assessed cognitive function immediately after the exercise sessions, whereas we did the cognitive testing 1 week after the intervention. Hoffman et al. [31] observed no differences between pre- and post-testing in diverse neuropsychological tests when comparing the effects of placebo, medication and exercise, without significant better performance of exercising participants in comparison with participants receiving sertraline in tests of executive functioning. Unfortunately, Hoffman et al. [31] did not report in detail all cognitive domains tested here.

The depressive patient group revealed also a reduction in depression scores, state anxiety and an improvement in subjective mental health in the relaxation and the exercise group, but not for the waiting control group. A reduction in depressive symptoms after several weeks of physical exercise has been observed in several studies in depressive patients (see recent review by Mead et al. [45]). Accordingly, our findings are supported by those of Bartholomew et al. [5], who demonstrated that exercises induce well-being, and studies reporting a reduction in anxiety symptoms through physical exercise in depressive patients [37, 60].

Comparison of the effects across disease groups

As a main part of our study, we directly compared the effects of a combined intervention program on schizophrenia versus major depressive patients. In some cognitive subscores/domains, schizophrenia patients showed a greater increase than major depressive patients. This suggests that the benefit of the interventions for these cognitive domains is higher for schizophrenia patients than for major depressive patients. This may be caused partly by a lower base level of the cognitive performance in schizophrenia patients, which is in accordance with the meta-analysis by Heinrichs and Zakzanis [30], who reported that schizophrenia patients particularly suffer from cognitive deficits. Moreover, we observed a specific effect of physical exercise training on the working memory performance in schizophrenia: working memory performance improved significantly in the group of schizophrenia patients and during physical exercise, but not in depressive patients and not during relaxation training in schizophrenia patients. Working memory deficits are most common in schizophrenia patients (see for example [24]), and the specific improvement of this cognitive domain corresponds to the study by [73]. In sum, working memory deficits may be a core feature of SZ patients, which particularly might be improved by physical exercise.

Moreover, the comparison of the results of the psychopathology scales used here suggest a specific effect of physical exercise on the state anxiety of depressive patients. As the baseline state anxiety symptoms are lower for SZ than for MDD patients, this specific effect might be explained by affective flattening symptoms in SZ, leading to lower anxiety severity when compared with MDD patients.

Our observations indicate that there was a high psychosocial effect of the exercise training, regarding social interest and interaction during the exercise procedure. The patients talked about their personal impressions regarding the training, about their symptoms and other topics. It has been suggested that exercise may also help in social interaction, leading to improved well-being, better stress
coping, improved social skills and self-confidence in individuals with chronic psychiatric disorders such as SZ (see reviews by [32, 38, 64]). However, as Knöchel et al. [38] stated it has not yet been systemically investigated whether the potential social benefits of physical exercise in groups are specific for the kind of intervention or may be suitable for all group interventions.

Limitations

The duration, intensity, frequency and kind of physical activity may have an impact on the effects on cognitive performance and affective symptoms, and duration of the intervention period was short with respect to adaptation of physical fitness. However, the intensity of the intervention used in the current study nearly reached the recommendations about the optimal frequency and duration of physical exercise of the American College of Sports Medicine [21].

A difficulty faced in this current study was the choice of the intervention in the comparison group. We selected those kinds of relaxation exercises, which could be performed under comparable conditions (room, social effect, time) as the physical exercise training, but without a strong effect on physical movement and muscles. This was done in order to evaluate the specific effects of physical exercise versus relaxation. In order to control for potential single effects of cognitive training, we added a control experiment to evaluate the specific effects of cognitive training. Another problem of our study was that the high number of conditions led to a relatively low sample size per condition. In future studies, we may reduce the number of conditions in order to clarify the aim of the study and to increase the number of participants per condition.

The high drop-out rate in our study indicates that patients with psychiatric disorder need to be convinced of the benefits of the intervention as they tend to have motivational problems. Furthermore, the high drop-out rate may be a selection bias toward a specific group of patients. For instance, the inclusion of patients with lower compliance would lead to a higher potency of the intervention, as this patient group may benefit most from the interventions. For further studies, it may be necessary to evaluate the group of drop-out patients in order to compare this group with the included patients. Moreover, it is necessary to reduce the drop-out rate through token systems and psychoeducation (see standardized psychotherapy programs by [26, 27]). However, as one main reason for the high drop-out rate concerned with organization reasons, an important point to discuss is how the structure in the hospitals may be revised to ensure that patients can take part on intervention after the end of their inpatient treatment.

A problem for all studies involving psychiatric patients is the potential uncontrolled effect of psychotropic medication, which may influence the severity of psychopathological symptoms and cognitive deficits. However, we ensured that all participants across groups were in stable medication since one last month before testing and during the intervention period. Furthermore, typically, antidepressant medication needs at least 1–2 weeks (more frequently 2–3 weeks) to elicit therapeutic response in patients who respond to the medication. Based on the fact that a part of the effects elicited by physical exercise training are overlap with biological effects of antidepressant medication (e.g., hippocampal neurogenesis, enhanced BDNF signaling), the psychopathological and cognitive effects of physical exercise would be expected to appear within the same time range as effects of antidepressant drug treatment.

The selection of suitable constructs and tests limits the information that one may derive from the current study. For instance, the state anxiety (STAI) questionnaire measures a specific construct, which is not typical for patients with schizophrenia. In addition, the SF-12: PSK subscale may not differentiate well between high scoring participants and low scoring participants due to the low number of items (n = 12). Furthermore, the mode of instruments to assess psychopathology differed between disease groups: while a clinician rating scale was used in schizophrenia patients (PANSS), a self-rating scale was administered in MDD patients (BDI II). Therefore, the severity of psychopathological symptoms reflected by respective scores was more objectively assessed in schizophrenia patients than in patients with MDD.

Conclusion

In the current study, we specifically addressed disease-specific versus general or overlapping effects of physical training intervention. This approach helped to recognize disease-specific variations in training effects in order to adapt training procedures to better suit specific patient groups or specific symptoms. In general, our findings showed that physical exercise may be a promising approach to improve cognitive and clinical symptoms in psychiatric patients. We showed an improvement in cognitive performance, in the subjective quality of life, and reduced psychopathological symptoms in MDD and SZ patients. However, further studies are needed to determine whether the effects of cognitive training, physical exercise or the combination of both generate the best effects. Of interest are the specific effects: patients with schizophrenia benefit more in their working performance, whereas depressive patients profit more in their state anxiety.
through a combination of physical exercise and cognitive training. This result leads to the assumption that it may be better to develop specific programs for each diagnosis in order to address symptoms more specifically.

Besides that, potential positive aspects of physical exercise, such as improvement of daily structure and lifestyle of psychiatric patients [16], may be of significance in particular if one considers the high rate of non-compliant schizophrenia patients regarding medical treatment [12].

In general, introducing physical exercise in therapeutic regimes would be an innovative approach that could significantly reduce the severity of psychopathological and cognitive symptoms in patients. For further studies, a longer time span of intervention, a higher number of participants and a reduction in drop-out rates might be necessary goals. Nevertheless, the results indicated positive effects on cognitive and clinical symptoms in depressive and schizophrenia patients after just 4 weeks of intervention. Physical exercise should be used in a multimodal therapeutic intervention as an add-on therapy, together with a medicinal therapy and psychotherapy.

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Conflict of interest None.

References


