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Nonpharmacological treatment of dyscognition in schizophrenia: effects of aerobic exercise

Isabel Maurus, MD; Astrid Röh, MD; Peter Falkai, MD; Berend Malchow, MD; Andrea Schmitt, MD; Alkomiet Hasan, MD

Cognitive symptoms are a core feature of schizophrenia and are related to an unfavorable disease outcome. So far, there are no satisfactory pharmacological approaches to address cognitive symptoms. For some time now, aerobic exercise has been demonstrated in various trials to be a promising candidate for this indication. The aim of this brief qualitative review was to present the most recent meta-analyses regarding the capacity of exercise to improve cognition in schizophrenia patients. Additionally, we give a short overview of the effects in other conditions, like healthy subjects and patients with major depression. We conducted a focused literature search using the PubMed database, concentrating on meta-analyses which are based on a systematic search. The most recent meta-analysis investigating the efficacy of aerobic exercise on cognitive impairments in schizophrenia patients provides evidence that exercise has positive effects on cognitive functioning in this population. However, the effect seems not to be specific; there were positive findings regarding healthy subjects and patients with depressive disorders as well, even if they were less consistent. As most available trials have a small to modest sample size and have no consensus with regard to the intervention regime, nor to the assessment of cognition, the findings are difficult to generalize. In the future, standardized clinical trials focusing on the long-term effects of exercise are needed to evaluate whether the improvements in cognition are sustainable.

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Keywords: schizophrenia; major depression; healthy subject; aerobic exercise; cognition; meta-analysis

Introduction

Cognitive symptoms are a core symptom of schizophrenia that can already be measured prior to the initiation of the first antipsychotic treatment.¹ Cognitive symptoms are related to unfavorable disease outcomes, long-lasting chronicity, and impairments in social and occupational functioning.² The management of the great variety of cognitive impairments covering all aspects of cognition including impairments in declarative memory, the ability to shift strategies, working

memory, and processing speed³ is one of the greatest challenges in clinical practice and in schizophrenia research. For a long period, there was the hope that antipsychotic treatment, especially with second-generation antipsychotics, would be effective in ameliorating at least some cognitive impairments. Despite their very high efficacy for positive symptoms,⁴ older and recent meta-analyses could not convincingly show their efficacy for cognitive symptoms.⁵⁻⁷ It has been established that cognitive symptoms can improve as a consequence of reduced positive symptoms (secondary effect of an antipsy-

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chotic treatment), but whether antipsychotics can directly improve impaired cognition remains elusive. Moreover, a blockade of D2 receptors and especially a treatment with anticholinergics to manage antipsychotic-induced motor side effects can even pronounce cognitive symptoms. Psychosocial treatments like cognitive training and cognitive remediation were shown to be effective in the management of cognitive impairments in schizophrenia⁸ and such programs should be offered to schizophrenia patients with cognitive impairments.

However, there is an urgent need to develop new strategies for this indication. At best, such strategies would be grounded in biological evidence derived from animal models. The potential of aerobic exercise to induce plasticity, and thus to improve cognition, was shown many years ago.⁹ Various factors to explain this effect, including neurogenesis, the increase in growth factors, or the normalization of an impaired excitation/inhibition balance have been discussed to be mechanistically involved in this process.¹⁰ Thus, the questions arose as to whether aerobic exercise can also improve cognition via increased neuroplasticity in patients with schizophrenia or other psychotic disorders. Exercise treatment has been an integral part of the broad array of psychosocial treatments in psychiatry for a long time, but the perspective of improving neural plasticity in cognition through exercise is still a rather new one. The landmark trial by Pajonk et al¹¹ showed in a small sample that 12 weeks of aerobic exercise could not only improve cognition in schizophrenia patients, but also induce structural plasticity in the hippocampus. Since then, some studies were able to confirm this finding, but negative findings were also observed.¹² Moreover, a magnitude of research of the last years¹³ confirmed a beneficial effect of exercise not only in schizophrenia patients, but also in healthy subjects and in patients with neurological disorders. Moreover, a substantial body of evidence indicates that exercise, but also physical activity in general, is linked to academic performance and later cognitive performance in adolescents.^{14,15} The aim of this brief qualitative review was to show the most recent meta-analyses regarding the capacity of exercise to improve cognition in humans focusing on schizophrenia patients. When discussing interventions like exercise that are on the one hand supported by strong

More endeavors should be made to increase physical activity in the everyday life of schizophrenia patients

biological evidence, but are on the other hand very likely to induce broad clinical effects rather than specific effects, it is important to ask questions regarding specificity. Therefore, we decided to give a short overview of the effects of exercise not only in other conditions like major depression, but also in healthy subjects. However, the literature presented here represents only a small excerpt from the available evidence.

Methods

For this brief qualitative review, we conducted a focused literature search using the PubMed database. On March 26, 2019, we searched the database using the search terms “exercise” OR “physical activity” AND “cognition” using the meta-analyses filter. We were able to identify 133 meta-analyses. These publications were screened at the abstract level by IM and the selected references were discussed between IM and AH. We decided to focus on meta-analyses as this approach allows for a literature selection based on systematically searched literature (meta-analytical evidence). Our aim was to provide an overview of the topic; a separate meta-analysis was not carried out for this purpose. Thus, our review presented here is not the result of a full systematic search, but is based on sources of evidence that were systematically searched. To put the results in a schizophrenia perspective, we decided not only to include meta-analyses focusing on schizophrenia patients, but also those focusing on major depressive disorder (MDD), bipolar disorder (BD), and healthy subjects (including children, adolescents, and older adults). The results of the selected meta-analyses are presented in *Table 1* and include the most matching published meta-analyses regarding exercise as intervention to improve cognition in patients with MDD and BP, and in and healthy subjects. The following text focuses on schizophrenia patients.

Results

From the identified 133 publications, we decided to add 15 studies to *Table 1*¹⁶⁻³⁰ to give the reader a focused overview regarding this topic. Below we present the findings by the latest meta-analysis investing the efficacy of aerobic exercise on cognitive impairments in schizophrenia patients¹⁶ in more detail. Firth et al evaluated ten trials with cognitive outcome

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data for 385 patients with schizophrenia, among them seven randomized controlled studies. In their meta-analysis they could show, that exercise significantly improved global cognition ($g=0.33$, 95% CI=0.13–0.53, $P=.001$) with no statistical heterogeneity ($I^2=0\%$), providing evidence that exercise has positive effects on cognitive functioning among people with schizophrenia. When only the RCTs were considered, the effect size was even $g=0.43$ ($P<.001$). Using meta-regression analyses the authors concluded, that greater amounts of exercise were associated with larger improvements in global cognition ($\beta=.005$, $P=.065$). Moreover, interventions which were supervised by physical activity professionals were also more effective ($g=0.47$, $P<.001$). Regarding the subdomains of cognition, exercise significantly improved working memory ($g=0.39$, $P=.024$), social cognition ($g=0.71$, $P=.002$), and attention/vigilance ($g=0.66$, $P=.005$). As social cognitive impairments are negatively associated with employment and independent living^{31,32} and attention/vigilance is a strong predictor of functional recovery particularly after a first episode of schizophrenia,³³ both domains are important variables regarding the patients' outcome in real-world functioning.³⁴ As for processing speed, verbal memory, visual memory and reasoning, and problem solving, the authors found no significant effects. Firth et al concluded that exercise is similarly effective in improving cognition in schizophrenia to cognitive remediation therapy, which had an average effect size of $g=0.45$ (95% CI=0.31–0.59) in randomized trials.^{16,35} They therefore suggest combining exercise with cognitively demanding tasks to confer maximal benefits for cognition in schizophrenia patients in the future, as this has already been done in some studies with preliminary positive results.³⁶ Please see *Table I* for the description of the other selected meta-analyses.

Conclusions

Aerobic exercise has shown the potential to improve cognitive impairments in schizophrenia patients, though this effect does not seem to be specific, or rather restricted, to this condition. When discussing the effects of exercise on cognition, it is important to differentiate two aspects. First, the effects of physical exercise early in life or the effects of being active in older age on cognitive functioning. The importance of exercise/physical activity has been confirmed by epidemiological studies.³⁷ Second, the effects of exercise in terms of direct treatment in schizophrenia patients or other psychiatric or neurological conditions. Such evidence came from controlled

or uncontrolled clinical trials that applied specific training (eg, cycling, yoga) for a specific time period and measured cognitive function prior to and after the treatment. These trials are the basis for the available meta-analyses and as shown in the most recent one by Firth et al,¹⁶ exercise can improve global and specific cognitive functions in schizophrenia patients (see results, and *Table I* for details). The effects for depressive disorders¹⁸ were less consistent, suggesting a more specific effect of exercise in schizophrenia. Taking the more pronounced cognitive impairments in schizophrenia, compared with depression, into consideration, one could speculate that a more severe presentation of symptoms is more likely to respond to a given intervention.

However, the reader should bear in mind that no systematic searches in different databases were carried out, but that a focused literature search based on systematically searched literature in meta-analyses was used for this article. In addition, despite the promising results from the meta-analysis shown here, most available trials are from a small to modest sample size, no multicenter trial is available yet, and neither the applied interventions nor the used measures to access cognition are comparable. Thus, the question of the generalizability of these findings cannot be answered. Moreover, long follow-up periods are needed, as are studies evaluating whether the improvement in cognition is sustained after the termination of the clinical trial. Without these trials, it remains unclear if exercise treatment has a long-lasting effect on cognition in schizophrenia or whether the effect is restricted to the setting of a clinical trial.

When discussing the effects of exercise on cognition in schizophrenia, the aspect of exercise as an environmental factor needs to be considered. As detailed above, being active in general improves cognition and seems to be protective regarding cognitive decline. Schizophrenia patients suffer from a sedentary lifestyle and it has been consistently shown that patients are less active in general compared with healthy controls.³⁸ The reasons for this include the effects of negative symptoms, the effects of sedation, and the lack of social stimuli for these patients. Thus, for future research two strategies should be followed. First, we do need better clinical trials in this area specifically focusing on the long-term outcomes of exercise treatments. For such trials, a consensus of the intervention scheme and the outcome measures is needed. For the latter, consensus approaches from other fields of schizophrenia research³⁹ should be

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POPULATION	AUTHORS	JOURNAL, YEAR	TITLE	INCLUDED TRIALS, SAMPLE SIZE
SCHIZOPHRENIA				
	Firth J, Stubbs B, Rosenbaum S, et al ¹⁶	<i>Schizophrenia Bulletin</i> . 2017	Aerobic exercise improves cognitive functioning in people with schizophrenia: a systematic review and meta-analysis.	10, n=385
	Dauwan M, Begemann MJ, Heringa SM, Sommer IE ¹⁷	<i>Schizophrenia Bulletin</i> . 2016	Exercise improves clinical symptoms, quality of life, global functioning, and depression in schizophrenia: a systematic review and meta-analysis.	29, n=1109
MAJOR DEPRESSIVE DISORDER				
	Brondino N, Rocchetti M, Fusar Poli L, et al ¹⁸	<i>Acta Psychiatrica Scandinavica</i> . 2017	A systematic review of cognitive effects of exercise in depression.	8, n=637
BIPOLAR DISORDER				
	No systematic reviews/ meta-analyses could be identified.			
HEALTHY CHILDREN				
	Álvarez-Bueno C, Pesce C, Cavero-Redondo I, Sánchez-López M, Martínez-Hortelano JA, Martínez-Vizcaíno V ¹⁹	<i>Journal of the American Academy of Child & Adolescent Psychiatry</i> . 2017	The effect of physical activity interventions on children's cognition and metacognition: a systematic review and meta-analysis.	36, n=5527
	De Greeff JW, Bosker RJ, Oosterlaan J, Visscher C, Hartman E ²⁰	<i>Journal of Science And Medicine I in Sport</i> . 2018	Effects of physical activity on executive functions, attention and academic performance in preadolescent children: a meta-analysis.	31, n=4593

Table I (continued overleaf). Descriptive overview of the selected meta-analyses. Results are in parts been adapted as direct quote. Please see the respective references for further information: BP, bipolar disorder; MDD, major depressive disorder; SZ, schizophrenia.

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RESULTS

Exercise significantly improved global cognition ($g=.33$, $P=.001$) with no statistical heterogeneity. The effect size in the 7 studies which were randomized controlled trials was $g=0.43$ ($P<.001$). Greater amounts of exercise were associated with larger improvements in global cognition ($P=.065$). Interventions which were supervised by physical activity professionals were also more effective ($g=0.47$, $P<.001$). Exercise significantly improved the cognitive domains of working memory ($g=0.39$, $P=.024$), social cognition ($g=0.71$, $P=.002$) and attention/vigilance ($g=0.66$, $P=.005$). Effects on processing speed, verbal memory, visual memory and reasoning and problem solving were not significant.

Exercise was not superior to control conditions in improving any of the cognitive subdomains (attention & executive functioning: $g=.07$, $P=.55$; Processing speed: $g=.15$, $P=.24$; Working memory: $g=.23$, $P=.09$; Long-term memory: $g=.14$, $P=.19$; However, moderator analyses for the type of exercise revealed a significant effect of yoga in improving the cognitive subdomain long-term memory ($g=.32$, $P<.05$).

There were no significant effects on global cognition or specific domains.

There were positive effects of exercise on nonexecutive cognitive functions ($g=.23$; 95% CI=.09-.37); core executive functions ($g=.20$; 95% CI=.10-.30), working memory ($g=.14$; 95% CI=.00-.27), selective attention-inhibition ($g=0.26$; 95% CI=0.10-0.41), and metacognition ($g=0.23$; 95% CI=0.13-0.32), including higher-level executive functions ($g=0.19$; 95% CI=0.06-0.31) and cognitive life skills ($g=0.30$; 95% CI=0.15-0.45).

Acute physical activity had a positive effect on attention ($g=.43$; 95% CI=.09, $P=.77$; 6 studies), while longitudinal physical activity programs had a positive effect on executive functions ($g=.24$; 95% CI=.09, $P=.39$; 12 studies), attention ($g=.90$; 95% CI=0.56, 1.24; 1 study) and academic performance ($g=.26$; 95% CI=.02, $p=.49$; 3 studies).

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POPULATION	AUTHORS	JOURNAL, YEAR	TITLE	INCLUDED TRIALS, SAMPLE SIZE
HEALTHY ADULTS				
	Smith PJ, Blumenthal JA, Hoffman BM, et al ²¹	<i>Psychosomatic Medicine.</i> 2013	Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials.	29, n=2049
	Rathore A, Lom B ²²	<i>Systematic Reviews.</i> 2017	The effects of chronic and acute physical activity on working memory performance in healthy participants: a systematic review with meta-analysis of randomized controlled trials.	15, n=1315
	Chang YK, Labban JD, Gapin JI, Etnier JL ²³	<i>Brain Research.</i> 2012	The effects of acute exercise on cognitive performance: a meta-analysis.	79, n=2072
	McMorris T, Sproule J, Turner A, Hale BJ ²⁴	<i>Physiology & Behavior.</i> 2011	Acute, intermediate intensity exercise, and speed and accuracy in working memory tasks: a meta-analytical comparison of effects.	
HEALTHY OLDER ADULTS				
	Colcombe S, Kramer AF ²⁵	<i>Psychological Science.</i> 2003	Fitness effects on the cognitive function of older adults: a meta-analytic study.	18, n=197
	Roig M, Nordbrandt S, Geertsen SS, Nielsen JB ²⁶	<i>Neuroscience and Biobehavioral Reviews.</i> 2010	The effects of cardiovascular exercise on human memory: a review with meta-analysis.	21, n=2224
	Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B ²⁷	<i>Br J Sports Med.</i> 2018	Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis.	39
	Barha CK, Davis JC, Falck RS, Nagamatsu LS, Liu-Ambrose T ²⁸	<i>Frontiers in Neuroendocrinology.</i> 2017	Sex differences in exercise efficacy to improve cognition: A systematic review and meta-analysis of randomized controlled trials in older humans.	41
	Kelly ME, Loughrey D, Lawlor BA, Robertson IH, Walsh C, Brennan S ²⁹	<i>Ageing Res Rev.</i> 2014	The impact of exercise on the cognitive functioning of healthy older adults: a systematic review and meta-analysis.	25, n=731
	Young J, Angevaren M, Rusted J, Tabet N ³⁰	<i>The Cochrane Database of Systematic Reviews.</i> 2015	Aerobic exercise to improve cognitive function in older people without known cognitive impairment.	12, n=754

Table I (continued). Descriptive overview of the selected meta-analyses. Results are in parts been adapted as direct quote. Please see the respective references for further information: BP, bipolar disorder; MDD, major depressive disorder; SZ, schizophrenia.

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RESULTS

Modest improvements in attention and processing speed ($g=.158$; 95% CI .055-.260; $P=.003$), executive function ($g=.123$; 95% CI, .021-.225; $p=.018$), and memory ($g=.128$; 95% CI, .015-.241; $P=.026$) could be found.

Meta-analysis of chronic physical activity revealed a significant, small effect size ($g=.27$; 95% CI:.12-.42, $P=.0005$), while analysis of acute physical activity revealed a non-significant, trivial result ($P=.53$).

Analyses indicated overall effect of acute exercise was positive but small ($g=.097$; $P\leq.001$).

Significant, beneficial effect size of acute exercise for response time, ($g=-1.41$; $P<.001$) and for accuracy ($g=.40$; $P<.01$).

Robust but selective benefits for cognition, with the largest fitness-induced benefits occurring for executive-control processes ($g=.68$, $P<.05$). Exercisers also improved reliably more than control subjects on controlled ($g=.461$, $P<.05$), spatial ($g=.426$, $P<.05$), and speed tasks ($g=.274$, $P<.05$).

Acute exercise had moderate (SMD=.26; 95% CI=.03-.49; $p=.03$) whereas long-term had small (SMD=.15; 95% CI=.02-0.27; $P=.02$) effects on short-term memory. On long-term memory, acute exercise showed moderate to large (SMD=.52; 95% CI=.28-0.75; $P<.0001$) and long-term exercise insignificant effects (SMD=.07; 95% CI=-.13-.26; $P=.51$).

The effect of exercise on cognition was statistically significant for all domains (SMD=.29; 95% CI=.17-.41; $P<.01$), except global cognition, regardless of the cognitive status of participants.

Overall pooled analysis showed that exercise improved executive functioning compared to controls ($g=2.064$, $P<.001$).

There were significant improvements for resistance training compared to stretching/toning on measures of reasoning ($P<.005$); and for Tai Chi compared to 'no exercise' controls on measures of attention ($P<.001$) and processing speed ($P<.00001$). There were no significant differences between exercise and controls on any of the remaining 26 comparisons.

No evidence of benefits from aerobic exercise in any cognitive domain.

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applied. Second, exercise and physical activity programs must be implemented in the clinical routine of in- and outpatient settings and societal programs to involve schizophrenia patients in eg, sport or fitness clubs must be set up. Such approaches will not only improve cognitive functioning in schizophrenia patients, but also help to reduce the high cardiovascular mortality and foster the integration of those persons. However, we are aware that the second approach is difficult and that is not very likely that such programs will be implemented. On the other hand, we believe that exercise in schizophrenia patients must not be restricted to clinical trials. The effects on cognition are promising but not convincing enough to give evidence based-recommendations at a high level. In schizophrenia patients, the recent German treatment guideline recommends physical exercise (aerobics, yoga) with an evidence level B based on the Scottish Intercollegiate Guidelines Network (SIGN) classification.⁴⁰ The National Institute for Health and Clinical Excellence (NICE) guidelines have recommended physical activity programmes for adults with psychosis or schizophrenia⁴¹ and for people with persistent subthreshold depressive symptoms or mild-to-moderate depression.⁴² Physical activity should be delivered in groups with support from a competent practitioner, consist typically of three sessions per week of moderate duration (45 minutes to 1 hour) over 10 to 14 weeks (average 12 weeks).⁴² The SIGN guidelines for nonpharmaceutical management of depression in adults have recommended that structured exercise may be considered as a treatment option for patients with depression.⁴³ Still, the effects of exercise on general human development and on cardiovascular parameters allow already justify such programs. The World Health Organization's Global Recom-

mendations on Physical Activity for Health⁴⁴ address three age groups and state that children and adults should engage in regular moderate-to-vigorous intensity aerobic physical activity (eg, running, walking, cycling) and muscle-strengthening activity. According to this recommendation and those of the American College of Sports Medicine⁴⁵ adults aged 18 to 64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity. Such a moderate to intense training mode should also be applied in aerobic exercise studies including in patients with mental disorders.

In summary, exercise has a positive impact on cognitive functions in schizophrenia, but more research is needed as detailed above. In particular, more endeavors should be made to increase physical activity in the everyday life of schizophrenia patients. ■

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