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Review article

Evaluation of the benefits of exercise on cognition in major depressive disorder

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ABSTRACT

Background: Cognitive impairment is increasingly recognized as a significant symptom in patients with major depressive disorder (MDD). While exercise is already recommended in many treatment guidelines for patients with MDD and has been shown to improve cognition in other disorders (e.g., Alzheimer's, Parkinson's, schizophrenia), limited research is available evaluating the effect of exercise on cognition in MDD.

Methods: We provide a narrative review of existing literature regarding the effect(s) of exercise on cognition across several neurodegenerative and psychiatric diseases, and particularly in MDD, with specific emphasis on study design and methodology that may impair adequate synthesis of the results. We also describe mechanisms by which exercise may improve cognition in depression and other brain disorders.

Results: Of existing studies with MDD, data are equivocal, as some are supportive of improved cognition, whereas others demonstrate no benefit. Several limitations were noted, including insufficiently-powered designs, variability in interventions examined (e.g., aerobic, anaerobic, mind-body) or control groups, lack of attention to the status of baseline cognitive impairment, and/or heterogeneity across outcome measures and clinical characteristics.

Conclusions: While preliminary results suggest the potential for exercise as a beneficial treatment or augmentation strategy for impaired cognition in MDD, the aforementioned limitations necessitate further investigation.

1. Introduction

Cognitive impairment is increasingly recognized as an important symptom of major depressive disorder (MDD), particularly with respect to its detrimental impact on functioning and quality of life. Although assessment of concentration (i.e., “diminished ability to think or concentrate, or indecisiveness”; p. 161, APA, 2013) has long been a part of the MDD diagnostic criteria, measurements of cognition are sparsely included on symptom severity scales that generally track clinical course as part of measurement based care and serve as the main outcome measure for research evaluating depression [1,2]. Only recently has more comprehensive objective and subjective evaluation of cognition become increasingly utilized as a research outcome in studies of depression, and perhaps more slowly incorporated as a consideration in clinical care, despite the importance of cognition and overall function to patients. This is a departure from other psychiatric illnesses, such as schizophrenia, where cognition is more commonly recognized as a core component of the disorder.

The cognitive impairments observed in depressed individuals include executive functioning and working memory, visual and verbal learning and memory, and attention and concentration [3,4]. Psychomotor slowing associated with depression tends to be reflected in poor performance across cognitive domains on relevant outcome measures (e.g., processing speed, reaction time). Thus, depression is associated with impairments across a fairly broad range of cognitive domains, although effect sizes in MDD tend to be smaller (on the order of .5 to 1 SD lower than healthy individuals) [5,6] as compared to those seen in bipolar disorder, schizophrenia, or Alzheimer's disease, where impairments are closer to 2 SD below healthy individuals. However, this may also be an artifact of the usage of group means within depressed samples for which baseline cognitive deficits are not required for study eligibility. For example, Gualtieri and Morgan (2008) estimate that as many as 28-37% of depressed individuals score between 1-2 SD below healthy controls, and 16-39% score 2 SD or greater [7].

The etiology of cognitive deficits in depression is as yet unclear, but there are overlapping neural circuits implicated in both cognition and mood, including regions of the basal ganglia, amygdala, thalamus, frontal cortex, and the hypothalamic-pituitary-adrenal (HPA) axis [8,9]. It has been suggested that disruption of the integrated circuity and subsequent functioning of these regions may be of greatest

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relevance to the cognitive impairments associated with mood disorders [9]. Similarly, interactions amongst serotonergic, noradrenergic, and dopaminergic neuronal circuits, as well as other neuromodulators, such as cytokines and neurotrophic factors, are frequently associated with both cognitive impairment and depression [8,10].

Regarding onset and development, cognitive performance deficits are not restricted to multi-episodic or treatment resistant depression; rather, significant cognitive impairments have been reported in first-episode depression that are similar (with respect to affected cognitive domains and magnitude of effects) to those seen in general depressed samples [11]. Additionally, some evidence suggests that altered cognitive processes and neurobiological changes may precede the onset of mood symptoms in depressed youth and/or individuals with first-episode depression, although many of these studies were inadequately powered and had significant limitations that suggest the need for replication [12–15]. Late life depression (typically defined as depression in adults ages 60 or older), on the other hand, has been referred to by some as a prodrome to dementia, due to the fact that older depressed adults have a 50% increase in risk of developing dementia [16,17]. Thus, cognition plays an important role in depression across the lifespan.

Cognition appears to be more impaired with increased depressive symptom severity [18,19]. However, cognitive impairments are frequently observed even in the presence of symptomatic remission [20–24], thereby suggesting at least some independence between overall depressive symptomatology and cognitive performance. Furthermore, some data suggest that antidepressant treatment is associated with improved cognitive performance, independent of improved mood [25,26].

Exercise has shown direct positive benefits on mood and cognitive symptoms in depression, and it impacts several of the neural regions and modulatory systems implicated in both cognitive and mood impairments. Several meta-analyses have concluded that exercise is an efficacious treatment for depression, both alone and as an augmentation to antidepressant medication, although effect sizes associated with exercise in depression tend to be smaller in more rigorously conducted trials [27–30]. Nonetheless, increasing literature supports the use of exercise as a treatment for depression, and it is included in several treatment guidelines and recommendations (e.g., CANMAT [as first-line treatment for mild-to-moderate MDD and adjunctive for moderate-severe MDD]; NICE [as first-line treatment for persistent subthreshold depressive symptoms or mild-to-moderate MDD]; and APA [as first-line treatment for mild MDD and adjunctive for all levels of severity [31]]). The evaluation of exercise specifically on cognitive impairments in depression has been more sparsely investigated, despite support for its efficacy on cognition in other disorders.

Namely, exercise has been shown to be effective in slowing or ameliorating deficits in neurodegenerative disorders such as mild cognitive impairment, dementia, and Parkinson's disease, and efficacious as a treatment for neurodegenerative disorders and other psychiatric disorders such as schizophrenia. Numerous meta analyses conducted across diverse clinical samples (e.g., healthy elderly, sedentary, mild cognitive impairment, Alzheimer's disease, multiple sclerosis, etc.) have demonstrated that aerobic exercise interventions [32] improve a variety of cognitive outcomes including domains of attention and processing speed, executive function, memory [32], verbal fluency [33], and global cognition [34]. Further, although out of scope of this review, there is substantial preclinical evidence supporting exercise as a mechanism for improving cognitive function in both healthy and diseased animal models.

While there are numerous clinical studies supporting direct benefits of exercise on cognitive performance in neurodegenerative disease, fewer studies examine this relationship of exercise and cognitive performance specifically in depression, which is the focus of the current review. Of the reports that evaluate the role of exercise on cognition in depression, results are heterogeneous, and many, including a recent meta-analysis, do not provide supportive evidence [35]. As we are attempting to describe the potential importance of exercise on cognition, we rely heavily on meta-analyses to interpret the existing data, particularly with respect to the effect of exercise on cognition in other clinical disorders, which have been studied in greater detail. We do acknowledge, however, that numerous individual reports have been published, many of which demonstrate conflicting results in all of the disorders studied, thereby indicating the need for further elucidation of potential study design issues that may contribute to the heterogeneity of results.

This review will discuss each of these issues in turn and highlight methodological and other limitations that may hinder our understanding of the efficacy of exercise on cognition in depression to date. We conclude that the effects of exercise on cognition in depression are promising, though currently scarce, and will discuss future directions that may help better clarify the role of this potentially beneficial intervention for cognition in depression.

2. Cognitive effects of exercise in neurological disorders

As the evaluation of exercise on cognition specifically in depression is an emerging field of study, we consider results from studies of exercise and neurodegenerative disease, which is an important link due to the high rates of depression comorbidity with neurological disorders. As many as 50% of Alzheimer's [36] and 17% of Parkinson's disease [37] patients also suffer from depression, and regardless of time-of-onset, individuals with depression have a significantly higher risk of developing cognitive dysfunction. Further, while depression is a known risk factor for Alzheimer's disease [17,38], evidence suggests that it may even modulate the progression from mild cognitive impairment to full dementia [39,40]. Lastly, several biological alterations are consistent across MDD and neurodegenerative disorders and are further discussed in detail below. Thus, while a clear cause vs. effect interaction remains unknown, there are clear parallels and links between MDD and neurodegeneration, which supports evaluating these studies to gain insight into the possible effects of exercise on cognition in depression.

2.1. Alzheimer's disease and dementia

In Alzheimer's disease (AD)—the most common form of dementia—several clinical trials demonstrate a positive effect of exercise on cognition, particularly with regard to executive functioning, and benefits are observed across patients in both the beginning stages of AD as well as those with severe impairment [34,41,42]. For example, Ohman et al. found that AD patients participating in home-based exercise programs performed significantly better on the Clock Drawing Test (CDT), a metric of executive function, as compared to control participants [42]. In AD patients, Yang et al. evaluated global cognition using two standard metrics, the ADAS-Cog (Alzheimer's Disease Assessment Scale-Cognitive) and MMSE (Mini Mental State Examination). They demonstrated that AD patients randomized to an aerobic cycling group exhibited improved ADAS-Cog scores, whereas those randomized to a health education control group did not. Interestingly, however, both groups achieved higher MMSE scores [43]. In a meta-analysis by Strohle et al., exercise resulted in moderate-to-strong improvements in cognitive composite measures in AD patients [34]. Conversely, Hoffmann et al. recently reported an overall lack of significance in cognitive improvement between supervised exercise intervention and control cohorts [44]. Importantly, however, in the Hoffmann study, only 62% of participants fell into the “high exercise” group (*a priori* defined as participants who attended more than 80% of the exercise sessions and exercised with an intensity of more than 70% of maximal heart rate). When data from the high exercise group alone were compared with data from controls, significant improvements were seen in the primary outcome measure, the Symbol Digit Modalities Test (SDMT), which assesses mental speed and attention. A meta-analysis by Groot and