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Review article

Exercise effects on depression: Possible neural mechanisms

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ABSTRACT

Depression is a syndrome of stress- and emotion-dysregulation, involving compromised structural integrity of frontal-limbic networks. Meta-analytic evidence indicates that volumetric reductions in the hippocampus, anterior cingulate cortex, prefrontal cortex, striatum, and amygdala, as well as compromised white matter integrity are frequently observed in depressed adults. Exercise has shown promise as an effective treatment for depression, but few studies have attempted to characterize or identify the neural mechanisms of these effects. In this review, we examined the overlap between structural brain abnormalities in depression and the effects of exercise on brain structure in adults, to highlight possible neural mechanisms that may mediate the positive effects of exercise on depressive symptoms. The prefrontal cortex, anterior cingulate cortex, hippocampus, and corpus callosum emerged as structural neural markers that may serve as targets for exercise-based treatments for depression. These findings highlight the need for randomized exercise interventions to test these proposed neurobiological mechanisms of exercise on depression.

1. Introduction

Depression is a significant global public health concern; it is the leading cause of disability worldwide and is currently estimated to affect 350 million people [1]. Depression is characterized by significant impairment in social and occupational functioning, and the majority of depressed individuals have recurrent episodes (~50%) [2] and/or chronic depression (~20%) [3]. Exercise has recently shown promise as an effective non-pharmaceutical treatment for depression [4]. A recent Cochrane Review and meta-analysis of 35 randomized controlled trials (N = 1356) found that exercise was moderately effective at reducing depressive symptoms relative to a control condition in depressed adults (Standardized mean difference (SMD) = − 0.62 (95% CI: –0.81 to –0.42)) [4]. Subgroup analyses indicated that there was no evidence for a difference in the effectiveness of exercise relative to psychotherapy (7 trials) and pharmacotherapy (4 trials) in treating depression. A sensitivity analysis (8 studies, N = 377) suggested that exercise has a small long-term effect on depressive symptoms post-treatment (SMD –0.33, 95% CI –0.63 to − 0.03). In sum, meta-analytic evidence suggests that exercise is a promising treatment for depression in adults, showing effects that are comparable to other first-line treatments for depression [4] (see Table 1).

Despite the antidepressant effects of exercise, we have a limited understanding of the underlying neural mechanisms by which exercise alleviates depression. Converging evidence suggests that exercise and antidepressant medication may alleviate depression through common neuromolecular mechanisms [5,6], including increased expression of neurotrophic factors (i.e., BDNF) [5,6], increased availability of serotonin and norepinephrine [7], regulation of HPA-axis activity [8], and reduced systemic inflammatory signaling [9] (see [10] for Review). These processes influence the development of new neurons, increase synaptic connections between neurons, and increase cerebral vasculature [11,12]. Considering that exercise and antidepressant medication may exert effects on depression through overlapping molecular pathways, it is possible that they also influence overlapping neural systems. Antidepressant treatment may increase the volume of the hippocampus, anterior cingulate, and orbitofrontal cortex, increase white matter integrity, and induce changes in functional dynamics of frontal-limbic neural networks in depressed adults [13]. While there have been few studies examining effects of exercise on neural systems in depressed individuals, we may predict that exercise leads to similar neural changes as antidepressant medication.

The goal of this review is to describe structural brain abnormalities in depression that may also be influenced by exercise. Much of the exercise literature we review is from studies of older adults, because the effects of exercise on brain structure have been most studied in the

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Table 1
Comparison of short-term effectiveness of various treatments for depression.

Treatment modality	Meta-analysis	Effect Size	Pros	Cons
Cognitive behavioral therapy (CBT)	[91]	0.71 (0.62–0.79)	Evidence-based treatments: CBT, BA, and IPT	Requires:
Behavioral activation (BA)	[92]	0.74 (0.31–1.17)		❖ Access to a skilled practitioner
			❖ Learn emotion regulation skills	❖ Psychological mindedness
			❖ Long-term effects	❖ Regular participation
			❖ Clinician support	
Interpersonal psychotherapy (IPT)	[93]	0.63 (0.36–0.90)		
Pharmacotherapy	[94]	0.49 (0.32–0.67)	Common classes: SSRIs, SNRIs	❖ Side effects
				❖ Poor treatment adherence
			❖ Easy to administer	❖ Does not reduce risk of future depressive episodes
			❖ Effective for severe depression	
			❖ Little motivation required	
Exercise	[4]	0.62 (0.42–0.81)	❖ Cost-effective	❖ Requires prolonged motivation
			❖ Easy to administer	❖ Appropriateness determined by health-related factors
			❖ Improves overall health	

context of aging. We expect that this review may improve our understanding of the biological pathways involved in both the pathophysiology of depression and the anti-depressant effects of exercise.

1.1. Study selection

Literature search was conducted using PubMed, Google Scholar, and references from included studies and review articles from inception until September 2016. To search for meta-analyses examining structural abnormalities in depression, the following strategy was used: ("depress*") AND ("MRI") AND ("meta-analysis") AND ("brain volume") OR ("brain structure") OR ("white matter"). To search for cross-sectional, longitudinal, and intervention studies examining exercise effects on brain structure, the following strategy was used: ("exercise" OR "PA" OR "CRF") AND ("brain volume") OR ("brain structure") OR ("white matter").

Eligibility of articles was determined by reviewing titles and abstracts. All included studies were published in English. The inclusion criteria for the depression literature were 1) meta-analysis, 2) inclusion of clinically depressed patients (diagnosis of MDD), and 3) use of structural MRI data. The inclusion criteria for the exercise studies were 1) original studies (epidemiological, cross-sectional, and intervention studies), 2) use of structural MRI data, 3) evaluation of the effect of physical activity (PA), cardiorespiratory fitness (CRF), or exercise on regional volumetric assessments, and 4) gray matter volume in regions commonly linked with depression: hippocampus, anterior cingulate cortex, prefrontal cortex, striatum, and amygdala. Meta-analyses from the depression literature were not reviewed if they combined participants with depression and other psychiatric diagnoses (i.e., bipolar disorder) into one group. Articles from the exercise literature were excluded if they included patients with cognitive comorbidities (i.e., dementia).

1.2. Structural abnormalities in depression that may be influenced by exercise

Regional gray matter abnormalities have been have identified in acutely depressed adults relative to age-matched non-psychiatric control subjects in numerous meta-analytic studies [14–28]; the most reliable regional abnormalities identified through structural MRI studies include the bilateral hippocampus, anterior cingulate cortex, regions within the prefrontal cortex, striatum, and amygdala. The literature of neuroimaging studies examining structural abnormalities in depression is vast and has been reviewed extensively; therefore, only meta-analytic studies and reviews will be described here.

1.3. Hippocampus

The hippocampus is one of the most studied brain regions in the context of depression. The hippocampus plays an important role in stress regulation, as it exerts inhibitory control over HPA-axis activity, and is also more broadly involved in cognitive and affective processing via its widespread connections with other limbic and prefrontal regions [29]. Reduced hippocampal volume has been consistently shown to be about 5% smaller in depression [15–17,19,21–23,25]. Interestingly, these meta-analyses indicate that reductions in hippocampal volume are present throughout the lifespan [26], not explained by comorbid psychiatric comorbidities [19], and are not solely a consequence of medication-effects [25]. A recent meta-analysis (N = 1728 depressed; N = 7199 control subjects) [16] confirmed that depression was associated with smaller hippocampal volumes with larger reductions for those with an early age of onset (< 21 years). Given that early onset depression increases the risk for recurrent depressive episodes, it is possible that volumetric reductions in the hippocampus may persist even after remission and may increase vulnerability for further volumetric reductions during subsequent episodes.

There may be several factors that moderate the association between depression and hippocampal volume. For example, in the context of chronic stress dysregulation, lower hippocampal volume may represent a risk marker, rather than a consequence, of depression [15,30,31]. However, some meta-analyses suggest that hippocampal differences exist only in the context of chronic or recurrent depression [16,23], or among individuals experiencing their first depressive episode [15]. This may indicate that the studies included in these meta-analyses may represent different subgroups of depressed individuals that modify the effects of depression on hippocampal volume. For instance, variability in depression severity, age-of-onset of the first depressive episode, Alzheimer's disease pathology in older adults, or lifestyle factors (e.g., physical activity) may influence hippocampal volumetric reductions in depressed individuals. Nonetheless, reductions in hippocampal volume are a robust structural marker observed in depression.

1.4. Exercise effects on hippocampal volume

The association between fitness or exercise and hippocampal volume is a highly replicated finding (see Table 2). In cognitively and psychiatrically healthy older adults, Erickson et al. [32] found that higher CRF was associated with larger hippocampal volumes. CRF refers to an individual's aerobic capacity, and is commonly used in this literature as a proxy for physical activity habits over a prolonged period of time (also see [33,34]). Another cross-sectional study in older adults found that high levels of exercise engagement may mitigate the cumulative adverse effects of lifetime stress on hippocampal volume in