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Optimizing the exercise prescription for depression: the search for biomarkers of response

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There is growing support for the efficacy of exercise interventions for the treatment of individuals who present with mild-to-moderate depression. The variability in treatment response across studies and individuals suggests that the efficacy of exercise for depression will be most optimal when prescribed to individuals who are most prone to respond. The present article reviews contemporary theoretical accounts and recent empirical data pointing to neuroinflammatory states and neurotrophin production as possible biomarkers of the antidepressant response to exercise. The larger exercise and depression literatures provide justification for elevated levels of pro-inflammatory cytokines and deficits in BDNF production as putative matching variables. Although there is some empirical support for these hypotheses, it is clear that this research warrants replication and extension. We offer a few suggestions for future research in this emerging area.

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Introduction

While there are a variety of antidepressant medications available for treatment of depression there are no reliable methods to determine which antidepressant treatment will be effective for which patients. Toups and Trivedi [1] discussed the need to identify characteristics for antidepressant medication matching as only a little over a third of patients seeking antidepressant medication treatment achieve remission with their first two treatment steps, and nearly a third of all patients only achieve minimal or no improvement on any given antidepressant medication [2,3]. Therefore, the road to recovery for patients is often long, as months can be spent trying a series of medications, and still, many may never recover through medication.

Several randomized controlled trials have supported the efficacy of exercise interventions to alleviate symptoms of mild-to-moderate depression to a degree comparable to other evidence-based treatments, including medications and cognitive behavior therapy [4,5]. Additionally, there is some — however limited — evidence suggesting that exercise may be useful for treating patients with 'treatment-resistant' depression [6]. As a single-modality or adjunctive to standard medication treatment or psychotherapy, exercise interventions appear to be most efficacious when the prescription is moderate-to-vigorous-intensity aerobic activity performed 3–5 days per week for a length of 6–12 months [7–9]. In addition, trials that include follow-up assessments up to 12 months indicate that the benefits of exercise may outlast those observed with medication treatments [7].

Similar to medication interventions, exercise interventions have their limitations. For certain people exercise does not alleviate their depression. Indeed, exercise interventions also exhibit fairly high non-response and non-remission rates. In a well-controlled study comparing four doses of exercise, only the highest dose of exercise, one that meets the public health recommendations for physical activity performed 5 times per week, achieved the response and remission rates similar to a multistep medication intervention of approximately 60% [10]. All other doses, including one that met the public health recommendations for physical activity performed 5 times per week, only achieved response and remission rates ranging from about 20 to 30% [10].

Another challenge to exercise interventions is that exercise prescriptions for depressed individuals are marked by meaningful non-compliance rates [11,12], thus possibly reducing their effectiveness. A major exercise treatment dissemination trial conducted in the United Kingdom assigned depressed adults to clinician-recommended exercise or standard care alone and showed that patients prescribed exercise exhibited poor rates of adherence to their recommendations with most participants only attaining small deviations from their pretreatment sedentary patterns [13]. Because of the patients' non-compliance tendencies there were no differences in depressive symptoms between the treatment groups at posttreatment and 4-month follow-up.

Without understanding for whom exercise is most effective, exercise interventions may become another step

along the long road to establishing an alternative or complimentary effective antidepressant treatment. In this paper, we review recent theoretical accounts and empirical research pointing to neuroinflammatory state and neurotrophin production (brain-derived neurotrophic factor; BDNF) as possible biomarkers of the response to exercise in the treatment of depression. Aiding the goal to personalize the exercise prescription for depression, we suggest a few useful avenues for future research in this emerging area.

Inflammatory markers

Recent research suggests that depressed patients have elevated levels of pro-inflammatory cytokines, with the most reliably observed elevations in Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-alpha) [14,15]. Since adipose tissue is a key source of cytokines and is often associated with depression [16,17], it is important to note the observed IL-6 elevations appear to be specific to the state of depression rather than the high levels of body mass index across many study samples [18]. Along with the elevated levels of pro-inflammatory cytokines among depressed individuals, several studies show lower than average levels of anti-inflammatory cytokines such as Interleukin-10 (IL-10) [19] and a lack of correlation between IL-10 and IL-6 that typically is present [20], suggesting there is a dysregulation of the inflammatory system among depressed patients (see Hiles *et al.* for a meta-analysis showing large amounts of variability of IL-10 levels between depressed and non-depressed [21]). Moreover, there are several findings suggesting that the administration of Interferon-alpha (IFN-alpha; increases IL-6 and TNF-alpha signaling) induces, along with depressed mood and what is sometimes referred to as 'sickness behavior' [22–24], pathophysiological states similar to those found in medically healthy depressed patients such as disruption of neurotransmitter metabolism [25] and alternations in brain circuitry related to information processing [26] (see Raison *et al.* for a review of these data [27]). Together, these findings provide support for the hypothesis that inflammatory deregulation is implicated in the maintenance and etiology of depression, thus highlighting a promising target for clinical intervention.

Exercise has emerged as an effective strategy to target inflammatory deregulation [28,29,30•] (see Eyre *et al.* for an excellent review of the neuroimmunological effects of physical exercise in depression [31,32]). For example, acting as a stressor, acute bouts of exercise result in the release of the pro-inflammatory cytokine IL-6 from muscles. This release of IL-6, in turn, activates the synthesis of anti-inflammatory cytokines such as IL-10 and inhibits release of pro-inflammatory cytokines such as TNF-alpha [29], suggesting that exercise promotes, in this way, an anti-inflammatory environment. Similarly, when occurring chronically, exercise (training) reduces the production of pro-inflammatory cytokines such as IL-6 and TNF-alpha [33,34] and increases the production of the anti-inflammatory cytokine IL-10 [35]. Interestingly, there is also some initial research suggesting that exercise may, in addition to reducing the neuroinflammatory state, buffer the risk this state confers for depression. Specifically, Rethorst and colleagues found that the relation between IL-6 and depression symptom severity was moderated by the level of participation in moderate-intensity physical activity, such the relation was positive and significant among those who were not active but not significant among those who were active [36]. No inferences with respect to the specificity of this exercise-inflammation-depression relation could be made because the authors only measured and modeled IL-6.

The rationale for prescribing exercise as an intervention for depression specifically for those who exhibit elevations in pro-inflammatory cytokines is further supported by the observation that these individuals may be less likely to respond to other established interventions. Indeed, high levels of TNF-alpha are associated with non-response to selective serotonin reuptake inhibitors (SSRIs) [37,38]. Initial support for this possible matching strategy comes from a recent study (TREAD) evaluating the efficacy of a 12-week exercise program to augment antidepressant treatment for non-responders to SSRIs. In this study, 126 sedentary men and women who remained on a stable dose of SSRI treatment were randomized to either a low (4 kcal per kg per week [KKW]) or high (16 KKW) dose exercise prescription and completed supervised as well as home-based exercise sessions to fulfill the prescription [39]. Seventy-three of these participants provided blood samples at baseline and immediately following the 12-week interventions that were analyzed for IL-6, and TNF-alpha, IFN-gamma, IL-1beta. Of these inflammatory markers, only TNF-alpha level at baseline was associated with the rate of decrease in depression severity over the course of treatment, such that the improvements were greater among those with high levels relative to those with low levels of TNF-alpha [40••]. This relation was not dose-dependent. In its early phases, this research requires replication and extension. It will be particularly important to demonstrate that the relation between depressive symptom severity improvement and levels of TNF-alpha (or other cytokines) at presentation is specific to exercise. Studies comparing the efficacy of different single modality (e.g. cognitive behavior therapy, antidepressant treatment, exercise) and or combination interventions that involve assessment of cytokines at baseline are required to achieve this aim.

BDNF

BDNF is a member of the neurotrophins, a family of structurally related proteins that promote neuronal differentiation and survival during development [41,42], and has been implicated in the development of and recovery