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A randomized trial of aerobic exercise on cognitive control in major depression

Ryan L. Olson [a,*], Christopher J. Brush [b], Peter J. Ehmann [b], Brandon L. Alderman [b]

[a] Department of Kinesiology, Health Promotion, and Recreation, University of North Texas, Denton, TX, USA
[b] Department of Kinesiology and Health, Rutgers, The State University of New Jersey, New Brunswick, NJ, USA

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HIGHLIGHTS

- Eight weeks of aerobic exercise improves cognitive control, as indexed by increased N2 amplitude.
- Symptoms of depression were reduced, despite no changes in cardiorespiratory fitness.
- Aerobic exercise may be a neurobehavioral therapy for targeting cognitive control in depression.

ABSTRACT

Objective: The aim of this study was to examine the effects of an 8-week moderate-intensity aerobic exercise training intervention on cognitive control in individuals with major depressive disorder (MDD).
Methods: Participants with a current diagnosis of MDD ($n = 30$; 21.1 ± 2.0 years) were stratified by depressive symptoms and randomized to an 8-week intervention of aerobic exercise (AE) or placebo exercise (PE). AE consisted of three sessions/week of moderate-intensity exercise training while PE consisted of three sessions/week of light-intensity stretching. Cognitive control was assessed pre- and post-treatment using behavioral performance (i.e., reaction time and accuracy) and event-related potentials (i.e., N2 amplitude). Depressive symptoms and rumination were also assessed before and after the intervention.
Results: Compared with PE, the AE treatment arm was associated with an increase in N2 amplitude to incongruent flanker task trials, reflecting an increase in cognitive control processes. Symptoms of depression also decreased after AE although the treatments did not differ in their effects on rumination. Exploratory mediation analysis indicated that changes in N2 amplitude did not mediate pre-to-post treatment reductions in depressive symptoms.
Conclusions: An 8-week moderate-intensity AE program is associated with improved neural indices of conflict monitoring and reduced depressive symptoms among individuals with MDD.
Significance: Future research examining the influence of exercise in combination with behavioral and pharmacological treatments for neurocognitive function in MDD is warranted.

1. Introduction

Major depressive disorder (MDD) is one of the most common psychiatric disorders in the United States, affecting nearly 20% of individuals in their lifetime (Kessler and Bromet, 2013). Despite a vast array of available treatments, many patients fail to achieve and maintain remission while others are unable to continue treatment because of intolerable side effects (Thase, 2016). Given the heterogeneity of depression and variability in response to traditional therapies, a number of alternative or adjunctive treatments for MDD have received increasing attention. In particular, accumulating evidence supports aerobic exercise as an effective treatment for depression (Rethorst et al., 2009; Trivedi et al., 2011; Rimer et al., 2012), which is noteworthy because it can be self-administered, is cost-effective, and may result in additional health benefits (e.g., improved cardiovascular and metabolic health). This is especially important considering the mental health benefits of exercise are more pronounced among clinical populations relative to healthy individuals. Indeed, aerobic exercise has

* Corresponding author at: Department of Kinesiology, Health Promotion, and Recreation, University of North Texas, 1155 Union Circle #310769, Denton, TX 76203, USA. Fax: +1 940 565 4904.
E-mail address: Ryan.Olson@unt.edu (R.L. Olson).

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been shown to be as effective as first-line antidepressant treatments (e.g., sertraline and escitalopram) in reducing depression (Blumenthal et al., 1999), as well as in improving coronary heart disease risk factors and reducing relapse rates (Babyak et al., 2000; Sherwood et al., 2016). However, the precise mechanisms underlying the antidepressant effects of exercise remain unknown and comparatively understudied.

One proposed treatment approach for depression involves targeting impaired neurocognitive function, especially for treatment-resistant cases. In MDD, cognitive impairment is frequently observed and is a common residual symptom despite treatment with antidepressants (Greer et al., 2015). For instance, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, approximately 70% of of the 428 responders (those who achieved ≥50% reduction in depressive symptoms without symptomatic remission) reported difficulties concentrating and making decisions despite a positive clinical response to citalopram treatment (McClintock et al., 2011). In terms of neural substrates, depression is associated with functional deficits in different areas of the prefrontal (PFC) and anterior cingulate cortices (ACC; Davidson et al., 2002; Siegle et al., 2007), regions implicated in attention, working memory, and cognitive control (Ridderinkhof et al., 2004). Cognitive control refers to the successful guidance and management of more basic cognitive functions and emotions and is critical for physical and mental health. Deficits in cognitive control may not only be related to the persistence of other symptoms, such as emotion dysregulation (Levens et al., 2009; Krompinger and Simons, 2011), but may also play a role in increasing vulnerability for rumination, a known risk factor for depression and other forms of psychopathology (Gotlib and Joormann, 2010). As treatment efforts continue to revolutionize, it is important to consider their influence on potential neurocognitive targets in MDD.

Motivated by Beck's cognitive model of depression (Beck, 1967) and the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative for developing new ways of characterizing mental health disorders based on behavioral and neurobiological dimensions, there has been recent interest in investigating risk factors and mechanisms, as well as identifying treatments that may specifically target neurocognitive impairments in MDD. Aerobic exercise may be particularly effective for ameliorating cognitive deficits in MDD, considering that a large body of empirical evidence supports the influence of exercise on cognitive function (Colcombe and Kramer, 2003; Hillman et al., 2008; Smith et al., 2010; Hotting and Roder, 2013). Despite the parallel lines of inquiry of the benefits of exercise for depression and cognitive function, insufficient research has investigated the effects of an exercise training intervention on neurocognitive function in MDD. This may be particularly important for cognitive control processes, which have been shown to be impaired in MDD in both neurophysiological studies (Vanderhasselt et al., 2012; Clawson et al., 2013) and systematic reviews (Snyder, 2013). In one of the few studies to date examining the effects of exercise on cognition in MDD, Greer et al. (2015) evaluated the effectiveness of exercise as an augmentation strategy for patients reporting persistent cognitive deficits following selective serotonin reuptake inhibitor (SSRI) treatment. In a 12-week randomized controlled trial (RCT), participants completed either a high (16 kcal per kilogram of body weight per week [KKW]) or low (4KKW) dose of exercise (see TREAD trial; Trivedi et al., 2006). Although both groups exhibited improved measures of psychomotor speed, visuospatial memory, and cognitive control, only the high dose condition benefitted spatial working memory. This study is an important first step towards establishing exercise as a neurobehavioral treatment for MDD, and future studies are warranted to elucidate the influence of exercise on established neurocognitive deficits in MDD.

Studies investigating the effects of exercise on cognitive processes in MDD have primarily relied on the use of behavioral performance outcomes (e.g., response accuracy and reaction time) as measures of neuropsychological function. More recent studies have incorporated neuroscientific techniques to investigate covert cognitive processes that may be influenced by exercise. One such approach is through the event-related potential (ERP) technique. ERPs are small voltage fluctuations in the continuous electroencephalogram (EEG) that are time-locked to specific events, such as visual stimuli or a manual response (Kappenman and Luck, 2012). The N2 component is a negative deflection in the stimulus-locked ERP with a frontocentral scalp distribution that occurs approximately 200–400 ms post-stimulus (Botvinick et al., 2004; Folstein and Van Petten, 2008; Clawson et al., 2013). The N2 is associated with the detection of conflict, mismatch of stimuli from a mental template, and cognitive control during response inhibition (Folstein and Van Petten, 2008). We previously found reduced N2 amplitude elicited by a flanker task in 33 individuals with MDD compared with 36 non-depressed, age- and sex-matched controls (Alderman et al., 2015). Levels of self-reported rumination among this sample also correlated with N2 amplitude, suggesting an important relationship between cognitive control and the ability to filter or disengage from negative thoughts. Accordingly, the N2 component may serve as a potential neurocognitive target to ameliorate cognitive control deficits in MDD.

The primary aim of this study was to examine the effects of an 8-week moderate-intensity aerobic exercise (AE) training intervention on neurocognitive function in individuals with MDD. Symptoms of depression and rumination were also assessed at baseline and following AE or a placebo exercise (PE) treatment consisting of an equivalent dose of low-intensity stretching. To better characterize whether AE leads to improved symptom outcomes (e.g., depressive symptoms and rumination) through improvements in cognitive control, a mediation analysis was conducted to determine if variation in N2 amplitude from pre-to-post intervention was predictive of treatment outcome. Thus, a secondary exploratory aim was to determine whether changes in depressive symptoms and rumination were mediated by changes in N2 amplitude. It was hypothesized that AE would improve neurocognitive function and reduce depressive symptoms and rumination relative to PE. Further, treatment-related changes in cognitive control (N2 amplitude) were hypothesized to significantly mediate symptom reductions in depression and rumination, such that larger reductions in symptoms would be found amongst individuals exhibiting the greatest improvements in cognitive control.

2. Methods

2.1. Participants

Individuals diagnosed with nonpsychotic MDD were recruited from university clinics, physician referrals, and advertisements around the university. Inclusion criteria included: (1) men and women aged 18–30 years; (2) confirmed MDD diagnosis; (3) no current psychological or pharmacological treatments for depression beyond stable (>6 weeks at stable dose) antidepressant (e.g., SSRI, serotonin and norepinephrine reuptake inhibitors; SNRI) or mood stabilizer treatment; (4) no regular exercise program (defined as energy expenditure of <35 kcal/kg/day or <3 days/week for ≤20 min/session over the past month); (5) no physical limitations or contraindications to exercise; and (6) normal or corrected-to-normal vision. Exclusion criteria included: (1) severe psychopathology (e.g., bipolar spectrum disorders, schizophrenia spectrum disorders, and substance dependence disorders); (2) evidence of suicide risk as assessed by the suicidality module of the