EXERCISE AS A NEUROBEHAVIORAL THERAPY FOR COGNITIVE CONTROL DEFICITS IN MAJOR DEPRESSIVE DISORDER

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ABSTRACT OF THE DISSERTATION

Exercise as a neurobehavioral therapy for cognitive control deficits in major depressive disorder

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Major depressive disorder (MDD) is associated with a number of symptoms, including cognitive dysfunction and maladaptive ruminative thought patterns. Although consistent evidence indicates that aerobic exercise is beneficial for reducing depressive symptoms in MDD, little is known about the influence of exercise on neurocognitive deficits found in depression. This is important for establishing exercise as a neurobehavioral therapy for depression, that is, an intervention that addresses biological mechanisms believed to underlie the disorder. Here, we investigated whether the N2 and P3 components of the human event-related potential (ERP) could be used to index cognitive impairments in MDD, and whether these neurophysiological measures were correlated with ruminative thought patterns. Although there were no differences in P3 amplitude by depression status, N2 amplitudes were significantly reduced in individuals with MDD relative to healthy controls, indicating that reductions were associated with higher rumination levels. These findings demonstrate that individuals with MDD may experience impaired cognitive control while attending to varying environmental stimuli. Because of our findings related to impaired cognitive control processes, we examined the

neurophysiological and behavioral correlates of cognitive control during single bouts of low- and moderate-intensity exercise in healthy young adults to determine if neurocognitive function is modifiable by aerobic exercise. Importantly, acute exercise was shown to modify these ERP components, such that increased N2 and P3 amplitudes were found during exercise at low and moderate intensities relative to rest. Although this study was performed in nondepressed participants, it suggests an upregulation of cognitive control during aerobic exercise that may be maintained through a program of chronic exercise. Finally, we examined the effects of a moderate-intensity aerobic exercise intervention performed three days/week for 8 weeks. The aerobic exercise condition exhibited enhanced cognitive control (i.e., N2 amplitude) and reduced depressive symptoms among individuals with MDD; however, these exercise-induced changes in cognitive control were not found to significantly mediate pre-to-post changes in symptom outcomes. These findings support the use of exercise as a neurobehavioral therapy for MDD and suggest the possibility of incorporating exercise as a stand alone or augmentation strategy for conventional treatments.

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Chapter 1 of this dissertation, entitled "Rumination in major depressive disorder is associated with impaired neural activation during conflict monitoring", was originally published in *Frontiers in Human Neurosciene*. I was involved in study design, data collection, statistical analysis, figure generation, original drafting of manuscript, and final manuscript revisions.

Chapter 2 of this dissertation, entitled, "Neurophysiological and behavioral correlates of cognitive control during low and moderate intensity exercise", was originally published in *NeuroImage*. I was involved in study design, data collection, statistical analysis, figure generation, original drafting of manuscript, and final manuscript revisions.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1

Chapter 2

Chapter 3

LIST OF ABBREVIATIONS

AB	Attentional blink
ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
AE	Aerobic exercise
ANOVA	Analysis of variance
BAI	Beck anxiety inventory
BDI	Beck depression inventory
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BPM	Beats per minute
CAU	Care-as-usual
CBT	Cognitive behavioral therapy
CCT	Cognitive control training
CHD	Coronary heart disease
Cox	Cerebral oxygenation
DSM-IV	Diagnostic and Statistical Manual, Fourth Edition
EEG	Electroencephalogram
EOG	Electrooculogram
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
GAD	Generalized anxiety disorder

HR	Heart rate
HRR	Heart rate reserve
HRSD	Hamilton rating scale for depression
ICA	Independent component analysis
ICBT	Internet-based cognitive behavioral therapy
ICD-10	International Classification of Diseases-10
IPAQ	International physical activity questionnaire
ISI	Inter-stimulus interval
KKW	Kcal per kilogram of body weight per week
LD	Low dose
MADRS	Montgomery–Äsberg Depression Rating Scale
MDD	Major depressive disorder
MINI	Mini-International Neuropsychiatric Interview
Ms	Milliseconds
NIMH	National Institute of Mental Health
PA	Physical activity
PAR-Q	Physical activity readiness questionnaire
PCA	Principal components analysis
PE	Placebo exercise
PFC	Prefrontal cortex
PHD	Public health dose
PVT	Peripheral vision training
RCT	Randomized controlled trial

RDoC	Research Domain Criteria
RER	Respiratory exchange ratio
RM	Repeated measures
RPE	Rating of perceived exertion
RPM	Revolutions per minute
RRS	Ruminative response scale
RSVP	Rapid serial visual presentation
RT	Reaction time
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
SSRI	Selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
TAU	Treatment as usual
TFSF	Temporal factor spatial factor
TREAD	Treatment with Exercise Augmentation for Depression
VO_2 peak	Maximal rate of oxygen consumption
WCST	Wisconsin card sorting task

GENERAL INTRODUCTION

Major depressive disorder and rumination

Major depressive disorder (MDD) is one of the most common mental health disorders in the U.S. with a lifetime prevalence of approximately 20%. Each year, nearly 7% of U.S. adults experience a major depressive episode, with younger adults (18-25 years old) displaying higher prevalence rates. MDD is characterized by a number of behavioral, emotional, and cognitive symptoms, including psychomotor agitation or retardation, insomnia or hypersomnia, altered appetite, fatigue, feelings of guilt and worthlessness, and suicidal ideation. Other hallmark symptoms include cognitive deficits, which are associated with an inability to focus, concentrate, or sustain attention, and rumination, wherein individuals retrieve and repetitively rehearse autobiographical and negatively-valenced content about past and current problems. Ruminative thought patterns may contribute to cognitive control deficits that affect an individual's ability to disengage attention from irrelevant information, thus leading to a persistent predisposition to negative thoughts. As a result, rumination may serve as a vulnerability factor for depression and may play a causal role in the development of multiple cognitive detriments associated with depression. As motivated by Aaron Beck's (1) cognitive model of depression and the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative for developing new ways of classifying mental health disorders based on behavioral dimensions and neurobiological measures, there has been a recent increase in identifying treatments that target neurocognitive impairments in MDD.

Exercise as treatment for MDD

Until recently, the first and most accepted line of treatment for depression has been psychotropic medications, most notably selective serotonin reuptake inhibitors (SSRIs) and mood stabilizers. However, recent studies indicate that these drugs may not be as effective as once thought and even when they are, relapse often occurs. Additionally, the chronic effects of drug therapy on brain structure and function are relatively unknown. Alternative forms of treatment, such as cognitive behavioral therapy (CBT), electroconvulsive treatment, and other forms of brain stimulation (e.g., transcranial direct current stimulation), can be efficacious but require considerable time and commitment on the part of the patient, in addition to trained professionals to administer care. Thus, there is a need to establish evidence-based alternative or adjunctive treatments for depression.

One potential candidate for the treatment of depression is aerobic exercise (AE). Evidence from randomized controlled trials (RCTs) on the effects of exercise on mental health have consistently reported that AE is at least as effective as common antidepressants in reducing depression and may even be superior in preventing relapse (2, 3). Many mechanisms for these benefits have been proposed, including adaptive regulation of the autonomic nervous system, increased hippocampal neurogenesis, and more efficient stress responses. More recently, functional deficits in the hippocampus, amygdala, and frontocingulate brain regions have been proposed as potential treatment targets (4), especially considering their link to impaired cognitive control processes.

Among patients with MDD, impaired cognitive function is a common complaint (5-9) and is associated with considerable disability and limited functional recovery (10-12). Further, these cognitive complaints are common residual symptoms that remain even

after antidepressant treatment in MDD. Thus, increased focus on cognitive symptoms associated with MDD is warranted in order to better understand its relationship to emotion regulation.

Specifically, prefrontal-dependent cognitive control has recently been proposed as a neurobiological mechanism of symptomatology in MDD, with cognitive control being the target of novel, neurobehavioral therapies that aim to reduce depressive symptoms by ameliorating underlying neurocognitive deficits (13). Cognitive control refers to the ability to adjust and orient cognitive resources to optimize performance, make decisions, and complete goal-directed behaviors (14). With recent research assessing cognitive control deficits in MDD, it has been suggested that improvements in cognitive control processes may help remediate emotional dysregulation and information processing biases, and consequently aid in the treatment of depression. Although exercise is widely recognized as an effective behavioral intervention for reducing symptoms of depression, few studies have evaluated the efficacy of exercise to alleviate cognitive impairments in this population. Although exercise was not specifically designed as a neurobehavioral intervention, given its widespread neurobiological benefits, it is important to determine if exercise can be used to target distinct neurocognitive deficits in MDD and whether these changes mediate reductions in primary symptom outcomes.

Exercise and neurocognitive function

It is well established that exercise and fitness are related to enhanced cognitive performance. As early as 1997, meta-analyses suggested that exercise results in small, but significant effects on cognition (15). More recent meta-analytic findings by Colcombe

and Kramer (16) suggested that exercise has general and selective effects on cognitive function, with disproportionately larger effects for tasks or task components that recruit executive functions. Executive function, or cognitive control, has also been defined as a series of top-down cognitive processes needed when you have to concentrate and pay attention, when automatic instincts or intuitions are insufficient or inappropriate (17). There is general agreement that cognitive control is composed of at least three domains: inhibition, working memory, and cognitive flexibility.

Studies investigating cognitive deficits in MDD and those examining the putative cognitive benefits from exercise have traditionally relied on overt behavioral performance measures (e.g., response accuracy and reaction time) to assess cognitive performance outcomes; however, these measures often lack the requisite sensitivity for detecting subtle changes in cognitive processes. To address this limitation, techniques from neuroscience can be used to measure this relationship. In particular, the high temporal sensitivity of event-related brain potentials (ERPs) allows for precise measurements of processes that occur between stimulus presentation and response production, including early sensory and later psychological processing. Because electrical potentials travel close to the speed of light, the transmission through the brain, meninges, skull, and scalp are essentially instantaneous. Thus, ERPs reflect patterns of voltage fluctuations in the continuous electroencephalogram (EEG) that are time-locked to a specific event, such as the onset of a stimulus or the execution of a manual response and provide a direct, instantaneous measure of brain activity related to neurotransmission (18). Two ERP components that have received increased attention in assessing cognitive control processes, are the N2 and P3 components. The N2 component is a negative deflection in

the stimulus-locked ERP with a frontocentral scalp distribution peaking approximately 200-350 ms post-stimulus (19-22), and has been implicated in the detection of conflict, mismatch of stimuli from a mental template, and cognitive control during response inhibition (23-25). On the other hand, the P3 component is a positive deflection in the stimulus-locked ERP with a maximal centroparietal scalp distribution that peaks approximately 250-500 ms following stimulus onset (26, 27) and is generally believed to reflect attentional resource allocation during task performance that varies depending on task difficulties (27). Accordingly, the N2 and P3 components may serve as potential targets in the development of neurobehavioral interventions aimed at enhancing cognitive control deficits in MDD.

The purpose of these experiments were threefold: First, to determine the extent of cognitive control deficits in MDD as reflected by N2 and P3 ERP components and the relationship between these neurocognitive indicators and symptoms of depression and rumination. Second, to determine whether these neurophysiological measures are modifiable by exercise. Since chronic exercise is the accumulation of individual bouts of exercise, demonstrating that these ERP components are sensitive to acute bouts of exercise is an important criterion for conducting a chronic exercise intervention in individuals with MDD. Critically, the final aim was to assess the influence of a chronic 8-week AE intervention on improving cognitive control and symptom outcomes in a sample of university students with a current diagnosis of MDD.

Specific Aims

Aim 1: To determine relationships between ruminative thoughts and cognitive control processes in individuals diagnosed with MDD compared to healthy controls. We hypothesized that individuals with a current diagnosis of depression would display deficits in cognitive control, manifested as reductions in N2 and P3 amplitudes, as well as impaired behavioral task performance outcomes. It was also predicted that individual differences in rumination would covary with both ERP and behavioral performance measures elicited by a cognitive control task. This aim will establish whether ruminative thought patterns in MDD are related to impaired cognitive control, and if these clinical and neurocognitive outcomes are effective targets for neurobehavioral interventions.

Aim 2: To assess whether N2 and P3 components are state-dependent and altered during an acute bout of aerobic exercise performed at 40% and 60% of peak aerobic fitness (VO2 peak). A secondary goal was to examine cognitive control processes at 5, 15, and 25 min time points during steady-state exercise. It was hypothesized that N2 and P3 ERP components would be sensitive to acute exercise such that they would be enhanced during exercise compared to the no exercise control condition. We also expected greater cognitive control when assessed at 25-min following exercise onset relative to earlier assessment times. This aim will provide a more stringent test of the hypothesis and demonstrate that acute exercise can modulate cognitive control processes in an otherwise healthy population. This will also allow for the determination of an appropriate exercise dose (intensity and duration) to augment cognitive control in future exercise interventions.

Aim 3: To determine the effects of an 8-week moderate-intensity aerobic exercise intervention on cognitive control, depressive symptoms, and rumination in individuals with MDD. We hypothesized that an 8-week moderate-intensity exercise intervention would result in improved cognitive control and concomitant reductions in depressive symptoms and ruminative thought patterns in depression. Regarding cognitive control, we expected cognitive control processes (i.e., N2 and P3 amplitudes) to be restored following the AE intervention, resulting in normalization relative to non-depressed individuals and individual baseline values. Lastly, we expected improvements in cognitive control to mediate reductions in rumination from pre-to-post intervention. This aim will identify mechanisms of action for the antidepressant effects of exercise that should be targeted in future randomized controlled trials to reduce rumination and depression.

CHAPTER 1: Rumination in major depressive disorder is associated with impaired neural activation during conflict monitoring

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INTRODUCTION

Major depressive disorder (MDD) is one of the most common mental health disorders in the United States with a lifetime prevalence of approximately 16.6% (28). Globally, more than 350 million people suffer from depression, and by 2020 it is predicted to be the second largest cause of disability, for all ages and both sexes (29). MDD is characterized by a number of behavioral, emotional, and cognitive symptoms, including psychomotor agitation or retardation, insomnia or hypersomnia, decreased or increased appetite, fatigue, feelings of guilt and worthlessness, and suicidal ideation (30). Other hallmark symptoms include rumination, wherein individuals retrieve and repetitively rehearse autobiographical and negatively valenced content about past and current problems, and attentional problems associated with an inability to focus, concentrate, or sustain attention (4, 30). These latter symptoms are indicative of deficits in cognitive functioning, which may further contribute to disability and poor quality of life (31-33).

Rumination is one of the most problematic cognitive symptoms associated with depression. These negative thought processes heighten negative affect and interfere with

an individual's ability to engage in effective problem-solving and adaptive behaviors (34-36). A number of studies suggest that MDD is associated with impairments in cognitive control processes, specifically those involved in regulating conflict (4, 20, 37, 38). In general, cognitive control reflects a person's ability to flexibly and voluntarily regulate behavior or thoughts in the service of goal-directed and purposive behaviors while resisting the retrieval and distraction of competing undesirable information (39-41). Although less well studied, recent studies also suggest that excessive rumination, as is often found in individuals with MDD, is associated with less cognitive control (42, 43). These control processes are involved in many aspects of healthy cognition and may be involved in delay of gratification and impulse control, as well as self-reflection and the intrusion of negative thought patterns. Structural and functional neuroimaging studies implicate prefrontal and anterior cingulate brain regions in cognitive control (4, 33, 44, 45). However, the temporal dynamics of conflict monitoring and cognitive control are not well described, especially as they relate to rumination.

According to the conflict monitoring hypothesis (19, 46, 47), an essential aspect of cognitive control involves conflict monitoring and conflict detection, both of which are believed to involve important connections between the anterior cingulate cortex (ACC) and lateral prefrontal regions. Several laboratory-based assessments including the go/no-go, stop signal, antisaccade, Stroop, and flanker interference tasks have been used to manipulate and assess conflict monitoring and cognitive control. The flanker interference task represents a canonical example of this response conflict, such that the presence of competing responses associated with the incongruent condition results in impaired performance relative to the congruent task conditions. Successful performance on this

task, particularly on the more challenging trials where the flanking arrows are incongruent with the target arrow, requires greater top-down cognitive control. That is, the incongruent task condition requires competition at the level of response activation and a person's ability to suppress inappropriate or prepotent responses. Task performance deficits have been reported in a number of clinical populations in which disturbances in conflict and response monitoring are present, such as schizophrenia, depression, and substance use disorders (45, 48). Functional magnetic resonance imaging (fMRI) and event-related brain potential (ERP) studies suggest a critical role of the ACC in detecting and evaluating conflicts as they emerge during the action selection process, and using this information to signal for increased recruitment of cognitive control from lateral PFC regions (45-47, 49). The N2 ERP component has been instrumental in studying ACC-mediated conflict monitoring in cognitive control and has also been used to study frontocingulate dysfunction in depression. The conflict N2 (sometimes referred to as flanker N2) is a negative deflection in the stimulus-locked ERP with a frontocentral scalp distribution that peaks approximately 200-350 ms after stimulus presentation (19, 20, 23). As an index of conflict processing, this ERP component has been shown to be more negative (i.e., larger) for incongruent flanker trials as a result of conflict that arises during response selection between the responses queued by the target stimulus and those queued by the incompatible flanking stimuli (20, 47). This response conflict can also be measured behaviorally, and it has consistently been shown that incongruent or conflicting task conditions result in impaired accuracy and increased reaction time relative to congruent task conditions (24, 47, 50).

Previous research examining conflict monitoring processes and the N2 in MDD has been mixed (51, 52). For instance, Ruchsow et al. (53) examined N2 and P3 ERP components elicited by a hybrid flanker go/no-go task where participants responded to the appearance of letters B or U as centrally located flanker stimuli ("go" condition) and withheld a response to the appearance of letters D or V. Although individuals with MDD evidenced reduced ("less positive") no-go P3 amplitudes compared to matched healthy controls, no between group differences were noted for the N2 component. Similarly, no between-group differences in response time, error rate, or N2 indices of conflict adaptation were found between 55 individuals diagnosed with MDD and demographically similar control participants using a modified flanker task (20). Although no between group differences were found in conflict adaptation, a cognitive control process involving the influence of previous trial congruency on current-trial performance, higher depressive symptom scores based on the BDI-II were associated with smaller mean N2 conflict adaptation scores for individuals with MDD, suggesting that N2 conflict adaptation may be associated with depressive symptoms rather than a clinical diagnosis per se. Alternatively, using an auditory go/no-go task, Kaiser et al. (52) reported a reduction of inferior frontotemporal positivity in the N2 latency range (i.e., polarity-inverted N2) among patients with unipolar depression. This was interpreted to reflect a specific deficit in the response inhibition component of executive control, and was accompanied by impaired behavioral task performance during the no-go task condition. Differences in the specific tasks used, clinical characteristics of MDD participants, or medication status may have contributed to the mixed findings in the

literature. However, the relation between N2 amplitude indices of conflict monitoring and cognitive control and maladaptive rumination remains to be studied.

In addition to deficits in conflict monitoring, individuals with MDD often experience a selective loss of attention and/or attentional inflexibility (32, 54), which may impair their ability to multitask, maintain conversations, and ignore distractions. These problems, in turn, often lead to impaired focus and forgetfulness (55). Several studies have demonstrated attentional deficits in individuals with MDD using a variety of attention-related neuropsychological measures (54, 56, 57). However, there is some inconsistency across studies. Ottowitz, Dougherty, and Savage (58) published a review suggesting that the evidence for selective deficits in attention in MDD was equivocal. Indeed, less than half of the studies (44%) included in the review demonstrated attentional impairments in MDD. The lack of consistent findings may have been due to variability in study designs, subtyping of depression (e.g., melancholic versus atypical depression), or may simply reflect the multifaceted nature of attention. That is, MDD may impair only select aspects of attention, and these impairments may be best characterized by tests specifically designed to evaluate a particular component of attention (58). Further, rumination may contribute to many of the cognitive biases and impairments found in MDD, including deficits found in attentional processes (59), but this suggestion has received only limited research attention.

Attentional processes in the brain depend on finely-timed sequences that result in the allocation of attentional resources for perception and processing of sensory stimuli across time. One approach that has been used to probe the temporal dynamics of attention is the rapid serial visual presentation (RSVP) paradigm and the attentional blink

phenomenon (AB; 60). First described in 1992, the AB is typically observed during RSVP tasks whereby individuals exhibit a reduced ability to report the second (T2) of two different target stimuli presented among a very rapid stream of visual distractors when T2 appears within approximately 100–500 ms of the first target (T1; 60, 61). Although no current theoretical explanations fully account for this phenomenon (62), most point to a limited capacity attentional resource system, indicating that sensory information is not transferred efficiently from early sensory processing stages (and brain regions) to those involved in working memory (63, 64). The magnitude of the AB (i.e., the time it takes to recognize T2 following presentation of T1) has been shown to be larger in clinical populations (65, 66), the elderly (67, 68), and children with attention-deficit/hyperactivity disorder (69, 70). Neuroimaging evidence suggests an interactive neural network consisting predominantly of overlapping lateral-frontal, inferotemporal, posterior-parietal, and occipital brain regions underlying the AB response (71, 72).

For the AB paradigm, we assessed the classic cognitive P3 ERP component, which is thought to reflect the allocation of attentional resources during the updating of working memory (73, 74). Previous studies have demonstrated a completely suppressed P3 but no change in amplitude or latency for earlier ERP components (e.g., P1, N1, N400), when the AB phenomenon occurs. These findings suggest that the AB occurs after early perceptual processing is complete. It also has been speculated that the blink response may reflect a failure to input or consolidate the second stimulus (T2) into working memory while T1 is being processed (75), thus supporting the utility of the P3 in documenting this effect. Consequently, the AB paradigm may help to elucidate the temporal nature of attention deficits in MDD and explain how select attentional processes

are influenced by rumination levels. Although the P3 component in MDD has received scant attention using the RSVP paradigm, in general depressed patients show some reduction of the parietally-maximal P3 component using a variety of oddball and go/no-go tasks (51).

The present study used the flanker task and the RSVP paradigm to examine the relationship of rumination to response conflict and the temporal dynamics of attention in individuals diagnosed with MDD compared to healthy controls. Although recognizing the lack of agreement in the literature concerning the N2 potential in MDD, we hypothesized that individuals with a current diagnosis of depression would display relative deficits in conflict monitoring using a modified flanker task. We expected these deficits to manifest as reductions in N2 amplitude as well as impaired behavioral task performance outcomes. It was also hypothesized that individuals with MDD would exhibit selective deficits in attention (i.e., evidence a larger blink) during the rapid presentation of visual stimuli and larger T1- and T2-elicited P3 amplitudes. These findings would indicate that individuals with MDD have less efficient neural resource allocation, resulting in impaired ability to consolidate two temporally close items into working memory. It was predicted that individual differences in rumination would covary with both ERP and behavioral deficits in the performance of both tasks.

METHODS

Participants

Individuals with MDD were solicited from a university counseling and psychiatric services clinic, where they were diagnosed prior to participation by a psychologist,

psychiatrist, or primary care provider. Control participants were recruited through advertisements posted in numerous locations around the university campus and local community. Recruitment was for a mental and physical skill training program aimed at improving physical and psychological health; the data presented herein represent findings from the initial baseline assessment. Participants of all ethnic origins between 18 and 35 years of age were included in the study. Only right-handed participants with normal or corrected-to-normal vision were included in the current analyses. Participants in the MDD group were included if they met diagnostic (DSM-IV-TR) criteria for current MDD (76) and confirmed by the Mini-International Neuropsychiatric Interview (MINI; 77). Exclusion criteria included a diagnosis of a bipolar spectrum disorder, schizophrenia spectrum disorder, self-injurious or suicidal behavior, or a history of neurological disorders or head injuries resulting in a loss of consciousness. All clinical interviews and suicide risk assessments were completed by trained graduate students working with the study PIs, and all were trained to competence by a licensed clinical psychologist (EAS), who supervised all study clinical assessments and is a member of the clinical psychology PhD training program at Rutgers University. Prior to participating in clinical interviews, all clinical interviewers completed extensive clinical training regarding the clinical symptoms assessed with the MINI, including depression. This training included formal team meetings outlining the structure and content of the diagnostic interview, discussions on troubleshooting and differential diagnoses with the interview, extensive shadowing of Dr. Selby who completed all assessments during the first semester of data collection, and an examination interview that required rating the correct diagnoses for a case presenting pre-specified symptoms that all interviewers were required to pass. During the course of

the study any concerns regarding diagnostic symptom endorsement or suicide risk concerns were discussed with the supervisor to ensure patient risk protection. The MINI is an appropriate tool for assigning threshold level psychiatric diagnoses in research settings and has been found to have strong diagnostic agreement with other clinical interviews such as the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; 78), which are frequently used in clinical settings because they explore symptoms in more depth than is needed for a research study (79). Healthy comparison participants who did not meet criteria for MDD via the MINI were also recruited and included if they reported no previous or current history of neuropsychiatric disorders, neurological disorders, or head injuries. All eligible individuals were invited to visit the laboratory for a more extensive clinical interview and neurophysiological testing. The final sample consisted of 33 MDD participants and 36 healthy controls. MDD and control participants did not differ with respect to age, sex, ethnicity, or educational level, *p*s>.05. Six of the 33 MDD (18%) participants had a confirmed comorbid diagnosis at the time of participation (1 with post-traumatic stress disorder, 5 with generalized anxiety disorder [GAD]) and three of these participants reported current antidepressant drug use. Additionally, two other participants were currently taking either antidepressant (*n*=1) or ADHD (*n*=1) medication. No medication use was reported among the control participants. As expected, MDD participants reported significantly increased levels of depressive symptoms assessed by the Beck Depression Inventory-II (BDI-II; 80, 81) and rumination as assessed by the Ruminative Responses Scale (RRS; 35). Table 1 shows participants' demographic and behavioral data according to group status. The research

protocol was approved by the university's Institutional Review Board and written informed consent was obtained from all participants prior to participation.

Table 1. Demographic and clinical characteristics of participants by group status. Values equal means ± *SD*.

Characteristic	Control	MDD	Total
n	36	33	69
Age (years)	21.0 ± 3.1	20.7 ± 2.9	20.9 ± 2.9
Gender (male/female)	12/24	9/24	21/48
Height (cm)	166.6 ± 8.5	164.9 ± 7.9	165.8 ± 8.2
Weight (kg)	67.4 ± 15.0	66.3 ± 15.6	66.9 ± 15.2
BMI (kg/m^2)	24.3 ± 5.1	24.3 ± 4.9	24.3 ± 5.0
BDI-II score	7.4 ± 4.8	23.9 ± 8.3*	15.4 ± 10.7
RRS Total	41.9 ± 10.6	59.1 ± 10.2*	50.2 ± 13.5
Depression	21.8 ± 5.9	33.2 ± 6.6*	27.3 ± 8.4
Brooding	9.7 ± 2.5	13.5 ± 3.6*	11.5 ± 3.6
Reflection	10.4 ± 3.9	12.4 ± 3.2*	11.4 ± 3.7

Note. MDD = Major Depressive Disorder; BMI = Body Mass Index; BDI = Beck Depression Inventory; RRS = Ruminative Responses Scale. Asterisks indicate statistically significant unpaired student's *t* test between control and MDD participants, $p < .05$.

Procedures

Individuals meeting the initial study inclusion criteria were invited for a baseline testing session to complete a clinical interview and provide behavioral and neurophysiological data. After receiving a general description of the study and providing written informed consent, participants completed a set of questionnaires pertaining to their demographics, attitudes, mood, and health, including the BDI-II and RRS. Next, participants were fitted

with a 64-channel Geodesic Sensor Net (Electrical Geodesics, Inc, OR) and seated approximately 0.5 m directly in front of a 17" Dell computer monitor. After completing a 5-min rest period, participants completed the flanker and AB tasks in counterbalanced order. Following the neurocognitive assessments, participants completed a cardiovascular and physical fitness test battery that was part of the larger intervention study.

MDD diagnosis, depression symptoms, and rumination assessment

Mini neuropsychiatric diagnostic interview (MINI). The MINI (manic/hypomanic episodes, obsessive-compulsive disorder, substance and alcohol use disorders) was used to confirm clinical diagnosis of MDD. The MINI is a brief structured interview that has been used extensively to aid in making diagnoses of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and International Classification of Diseases-10 (ICD-10) psychiatric disorders. The reliability and validity of this instrument have been previously established (82, 83). The point biserial correlation coefficient of MDD diagnosis with BDI-II scores was 0.80, $p < .001$.

Depressive symptoms. Participants completed the BDI-II (81), a 21-item, self-report inventory of the severity of current depressive symptoms. Higher total scores reflect greater subjectively perceived depressive symptomatology. The BDI-II in this sample demonstrated good internal consistency (α=.92).

Rumination. Participants completed the RRS (35), which includes 22 items describing thoughts and responses to depressed mood that are focused on the individual themselves,

possible symptoms, and potential consequences/causes of the mood. They were asked to rate each item on a scale from 1 (almost never) to 4 (almost always). An example of one of the items is: "Analyze recent events to try to understand why you are depressed." The RRS scale demonstrated appropriate internal consistency (α= .93).

Cognitive tasks

Eriksen flanker. A modified arrow version of the Eriksen flanker task (84) was presented with E-prime version 2.0 software (Psychology Software Tools, Inc., Pittsburgh, PA). The flanker task is composed of two conditions, congruent and incongruent, during which participants are asked to press a button corresponding to the direction of a centrally positioned target arrow (see Figure 1). The congruent trials consisted of the target arrow being flanked by arrows facing the same direction (i.e., <<<<< or >>>>>), while incongruent trials involved the target arrow being flanked by arrows facing the opposing direction (i.e., <<><< or >><>>). A set of instructions preceded the first trial that explained which button press would be used to indicate the direction of the central or target arrow. Participants performed a button press with their left thumb when the target arrow, or 3rd arrow from the left, pointed to the left (<) and a button press with their right thumb when the target arrow pointed to the right (>). Following task instructions, participants completed 20 practice trials. Performance feedback was provided on the computer screen and any remaining questions were answered during the practice trials to ensure participants sufficiently understood the task. Each trial began with a black screen containing a white fixation cross (+) in the middle of the screen for 500 ms, following which 7.6 cm tall stimuli were presented focally on a computer screen in white letters on

a black background for 100 ms with a response window of 1500 ms and a variable inter-stimulus interval (ISI) of 1100, 1300, or 1500 ms. Participants were instructed to respond as quickly and accurately as possible for each trial. Two blocks of 110 trials were administered with equiprobable congruency and directionality of stimuli.

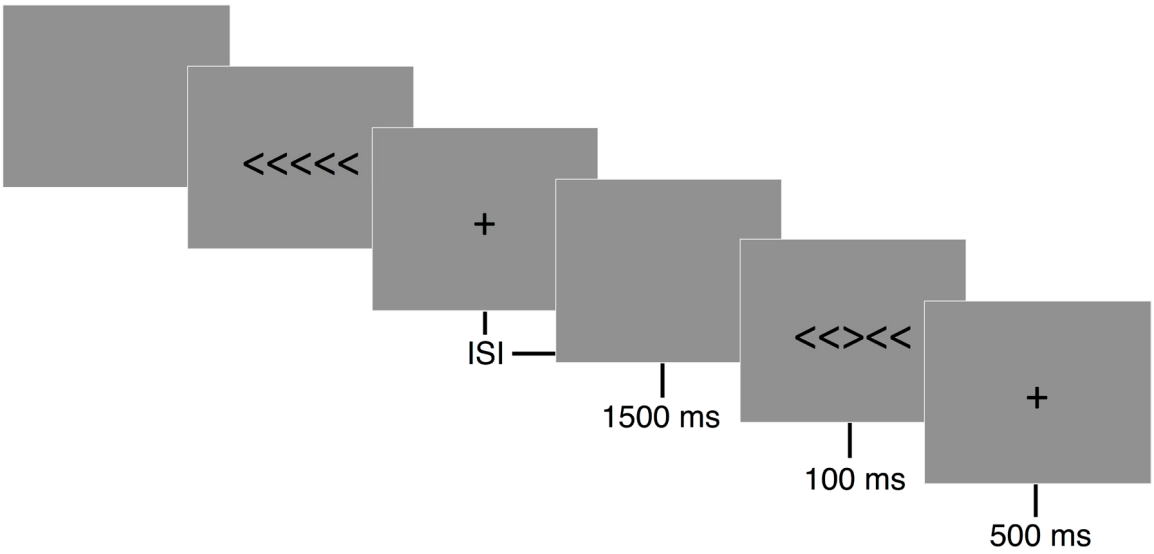

Figure 1. Eriksen flanker task. Following a 500 ms fixation cross (+), either congruent (< < < < <) or incongruent (< < > < <) stimuli were displayed focally for 100 ms on a computer screen. Participants were instructed to respond to the direction of a centrally positioned target arrow as quickly and accurately as possible. A button press corresponding to the direction of the centrally positioned arrow was recorded during a 1500 ms response window. A random inter-stimulus interval (ISI) of 1100, 1300, or 1500 ms occurred following the participant's response to reduce expectancy effects.

Attentional blink. A modified version of the AB task was adapted from Slagter et al. (85) and used to assess competition between targets for limited attentional resources (66, 86). Stimuli were presented focally on a computer screen in white letters on a black background. Following the presentation of a 1780 ms fixation cross (+), a rapid serial visual presentation (RSVP) of 15 or 19 capital letters was presented. Participants were

instructed to identify two target numbers (T1 and T2) embedded within the rapid visual stream of letters (distractors). Each stimulus was presented for 50 ms, followed by a 34-ms blank slide (Figure 2). For each trial, the letter (distractor) was randomly selected (without replacement) from the alphabet. Within each trial, one (single-target) or two (dual-target) letters were replaced with a randomly drawn (without replacement) number ranging from 2-9. In the case of single-target trials, the second target was replaced with a blank screen (T2-absent trial). The time between T1 and T2 (or the blank) was either 336 ms (short) or 672 ms (long). The shorter timeframe between targets (T2-present/short trials) has been shown to reliably produce a blink (misidentified T2) compared to the longer timeframe (T2-present, long trials). This occurs during peak competition for limited attentional resources (85). T2 and the blank screen were presented in positions 3-5 from the end of the stream. Due to similarities, letters B, I, O, Q, and S and numbers 1 and 0 were omitted from the visual stream.

Prior to the task, participants were instructed that there could be one or two numbers (targets) in the letter stream. At 1000 ms after the stream was completed, participants were instructed to enter the numbers on a keyboard in the order they were presented. If participants were unable to identify T2, they were instructed to guess its identity. Participants entered zero if they were absolutely certain there was no second target presented. A new trial began 200 ms after the second number (or blank) was identified. In addition to verbal instructions, on-screen instructions and a 1-minute practice block, with feedback, were provided prior to actual testing. Participants then performed two blocks of 112 trials each. There were a total of 116 T2-present/short trials,

36 T2-present/long trials, 36 T2-absent/short trials, and 36 T2-absent/long trials, which were randomly selected during each block.

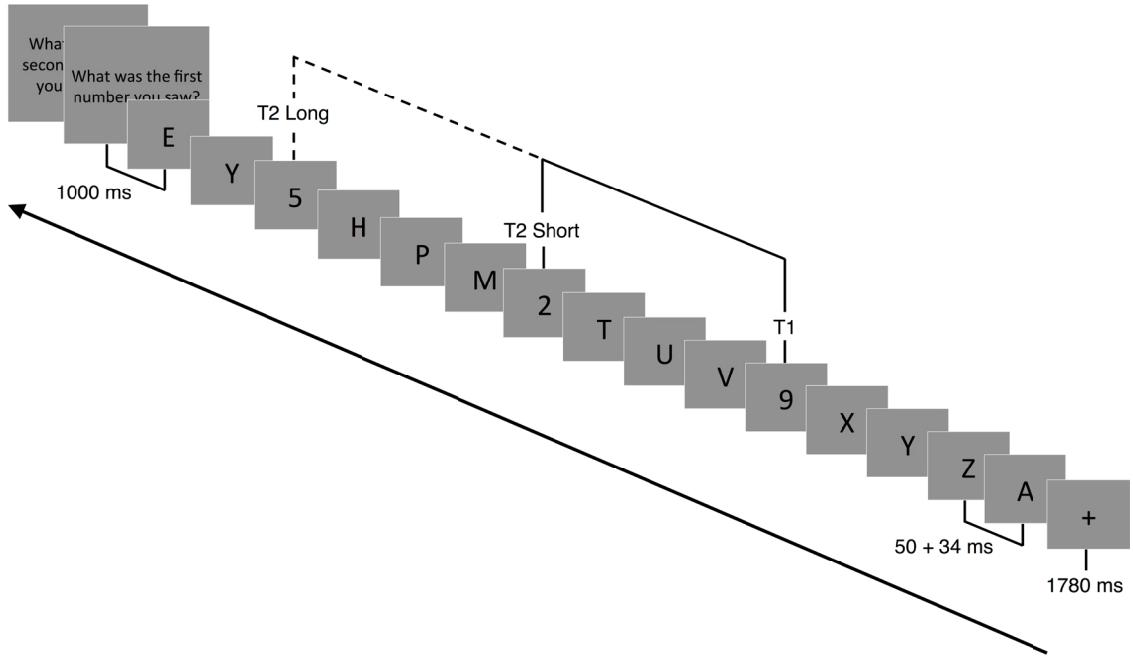

Figure 2. Attentional blink paradigm. Following a 1780 ms fixation cross (+), a RSVP of 15 or 19 capital letters (distractors) were displayed focally on a computer screen. Embedded within the RSVP were 1 (T1 present-T2 absent) or 2 (T1 present-T2 present) target numbers. Each slide was presented for 50 ms followed by a 34 ms blank slide. Participants had to detect T1 and T2 (if present) and report their response at the end of each trial. In T2 absent trials, T2 was replaced with a blank screen. The temporal lag between T1 and T2 could vary between 336 ms (short trials) and 672 ms (long trials).

ERP data

Electroencephalographic (EEG) activity was recorded using a 64-channel Geodesic Sensor Net system (Electrical Geodesic, Inc, OR) arranged according to the International

10–10 system (87). The electrooculogram (EOG) was recorded from electrodes located above and below each eye. Individual electrode impedances were kept below 50 kΩ in accordance with standard data collection procedures (88). Although lower impedances are typically recommended (18), previous research has shown excellent EEG signals when data were collected with higher scalp impedance (88, 89), and similar values have been used in the study of ERP components in MDD (20). Data were sampled at 250 Hz and collected with a .1-100 Hz bandpass hardware filter. Continuous data were recorded during each task condition referenced to the vertex electrode (Cz). Following collection, data were re-referenced (90, 91) to the mastoids and filtered with a 35 Hz low-pass filter. Data were visually inspected for eye-blinks, eye-movements, and bad channels before and after artifact rejection tools were applied to correct and remove ocular artifact using NetStation 4.0 (Electrical Geodesic Inc., EGI). Briefly, segments were marked "bad" if they contained 1) eye movements exceeding 55 μV, 2) eye blinks exceeding 140 μV, or 3) greater than or equal to 10 bad channels exceeding 200 μV. In each case, a moving average of 20 samples combined with threshold values were used. Using spherical spline interpolation, bad channels were then replaced from the remaining channels in "good" segments.

For the flanker task, epochs of individual trials were created from 100 ms pre- to 1000 ms post-stimulus presentation and baseline adjusted using the 100 ms pre-stimulus period. ERPs were constructed by averaging across congruent and incongruent trials separately for each participant. N2 amplitude was captured using a mean-amplitude approach. Consistent with previous research and based on visual inspection of waveforms (18, 89, 92), we used a window spanning 200-350 ms post-stimulus to evaluate the N2

(23, 93). For the AB task, epochs of individual trials were created from 200 ms pre- to 2000 ms post-stimulus (relative to T1). All epochs were baseline corrected using the 200 ms pre-stimulus period. For short trials, the T1-elicited P3 components were defined within a 295-365 ms window post-stimulus, while the T2-elicited P3 components were defined within a 847-1151 ms window (85). Additionally, on long trials, T1-elicited P3 components were averaged across a 295-651 ms window while the T2-elicited P3 components were defined within a 1147-1451 ms window (85). We used a mean amplitude approach to isolate ERP components since this is viewed as a more unbiased estimation of ERP amplitude (18, 94). Artifact-free waveforms where the arrow directions were correctly identified (flanker) or both T1 and T2 targets were identified (attentional blink) were subsequently grand averaged.

Data analysis

Behavioral data. Only trials in which a response was attempted were considered. To reduce the potential effect of outliers, trials with RTs beyond the individual mean ± 3 *SD* for each trial type were excluded. Exploratory analyses using one-way ANOVAs revealed no significant effects of sex or ethnicity on any of the cognitive performance measures; therefore, these variables were not further considered. Behavioral performance data (i.e., response time and accuracy) from the flanker task were submitted to a 2 (Group: MDD patients, controls) x 2 (Task Congruency: Congruent, Incongruent) ANOVA with repeated measures. To assess performance on the AB task, average T1 and T2 accuracy data were submitted to a 2 (Group: MDD patients, controls) x 2 (Lag: Short, Long) ANOVA. Only trials in which T1 was identified correctly were examined. In order

to determine the relationship between self-reported rumination and behavioral task performance, a bivariate Pearson correlation between rumination scores and accuracy and RT data for both cognitive tasks was performed.

ERP data. In light of the frontocentral nature of the N2 component elicited by the flanker task, a mixed 2 (Group: MDD patients, controls) x 2 (Task Congruency: Congruent, Incongruent) x 3 (Site: Fz, FCz, Cz) ANOVA with repeated measures was conducted on mean N2 amplitudes. Less negative values were interpreted as reflecting less cognitive control in response to the stimulus. To investigate the relationship between rumination and N2, we performed bivariate Pearson correlations between self-reported rumination scores and N2 amplitudes for congruent and incongruent flanker trials. For the AB task, mixed 2 (Group: MDD patients, controls) x 2 (Lag: Short, Long) x 4 (Site: Fz, FCz, Cz, Pz) with repeated measures were conducted for P3 amplitudes corresponding to T1 and T2. Since previous research indicates that comorbid anxiety-related disorders and psychotropic medications may influence neural activation patterns (95-97) and psychomotor speed, we reanalyzed the behavioral and ERP outcomes while excluding those participants with comorbid diagnoses or current psychotropic medication use. We performed similar bivariate correlations for P3 amplitudes on T1 and T2 trials of the AB task. Partial eta squared (η^2_p) values are reported to demonstrate the magnitude of effect sizes following ANOVAs, with .01–.059 representing a small effect, .06–.139 a medium effect, and > .14 a large effect (98). Post hoc comparisons were conducted using univariate ANOVAs and Bonferroni corrected *t* tests. Effect sizes (ES) were calculated

for any pairwise comparisons by using Hedges' g statistic (99). A critical alpha level of $p \leq 0.05$ was adopted for all significance tests.

RESULTS

Behavioral data. For accuracy on the flanker task, the mixed 2 (Group) x 2 (Task Congruency) ANOVA revealed a main effect of congruency, $F(1,67) = 34.97$, $p < .001$, η^2_p=0.34, indicating that participants performed worse on incongruent relative to congruent trials. No main effect of group or group by congruency interaction was observed, indicating that MDD and healthy controls did not differ in terms of overall accuracy. This test also confirmed that a comparable number of data points in each group were available for subsequent ERP analysis. The ANOVA for RT similarly showed a main effect of congruency, $F(1,67) = 397.52$, $p < .001$, η^2_p =0.86, due to faster response times for congruent versus incongruent trials. The main effect of group and the group x congruency interaction were not statistically significant. For the AB task, T2 accuracy was significantly higher on long trials (74%) than on short trials (61%), $F(1,67) = 69.33$, $p < .001$, η^2_p =0.51, confirming an AB effect whereby T2 was detected less frequently on the short trials. However, no significant group main effect or interaction with group was observed. In sum, MDD and healthy control participants did not differ in terms of behavioral task performance for either task (see Figure 3). These findings remained consistent when we reanalyzed the data to account for comorbid diagnoses or current medication use. No significant correlations emerged between self-reported rumination and behavioral performance measures for either cognitive task.

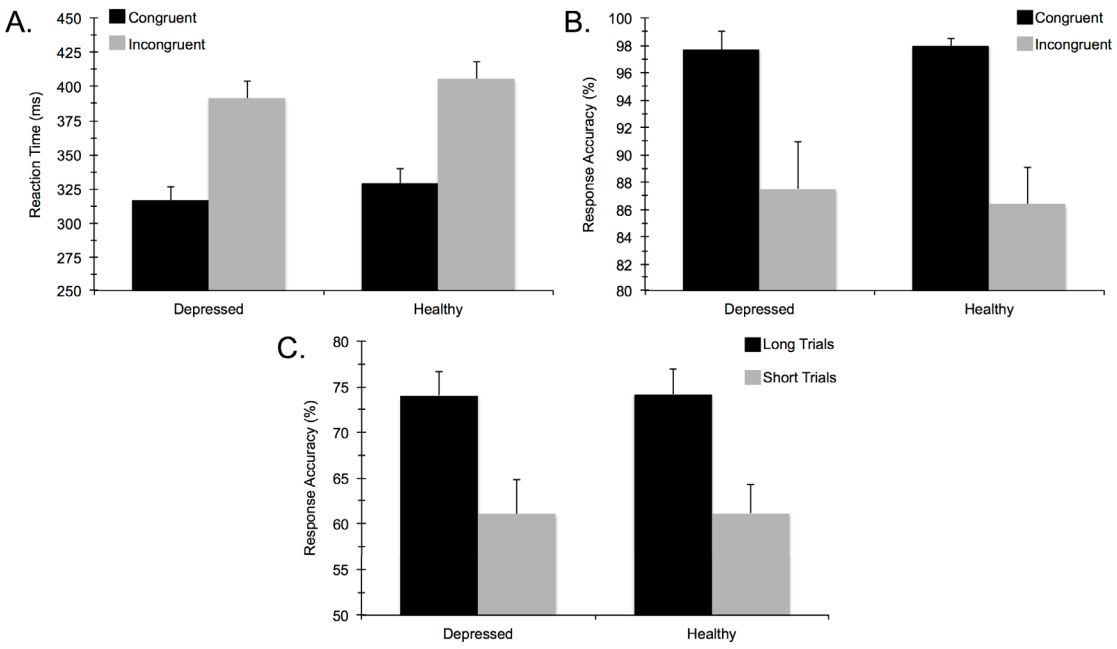

Figure 3. Mean (±) SE behavioral task performance for: (A) reaction time (ms) on the flanker task, (B) response accuracy (%) on the flanker task, and (C) response accuracy on the attentional blink task.

ERP data. Figure 4 illustrates the grand averaged ERP waveforms for each group at the three frontocentral midline electrode sites (Fz, FCz, Cz) to congruent and incongruent flanker task stimuli. The total number of flanker trials used for ERP analysis did not differ by group or condition. ERPs for MDD participants included a total of 88 ± 16 trials for the incongruent condition and 88 ± 15 trials for the congruent condition and ERPs for control participants included a total of 93 ± 12 trials for the incongruent condition and 92 ± 13 trials for the congruent condition (mean ± standard deviation). For the N2 component, a Group (MDD, controls) x Task Congruency (Congruent, Incongruent) x Site (Fz, FCz, Cz) ANOVA revealed a main effect of Group, $F(1,67) = 6.28$, $p = .015$, $\eta^2_p = .09$, Task Congruency, $F(1,67) = 16.48$, $p < .001$, $\eta^2_p = .20$, and Site, $F(2,66) = 27.63$, p

< .001, η^2_p = .46. Post hoc Bonferroni corrected *t* tests of the Group main effect indicated that healthy controls demonstrated overall more negative activity (.348 μV) in the N2 latency time window than the MDD group (-1.483 μV), *p* = .015. The Congruency main effect showed that N2 displayed a larger response (more negative amplitude) for incongruent (-.967 μV) relative to congruent (-.167 μV) flanker trials, *p* < .001. Decomposition of the Site main effect revealed significantly more negative amplitudes for Fz (-1.442 μV) and FCz (-1.036 μV) sites relative to Cz (.777 μV), *p*s <.05. The Group and Task Congruency main effects were superseded by a significant Group x Task

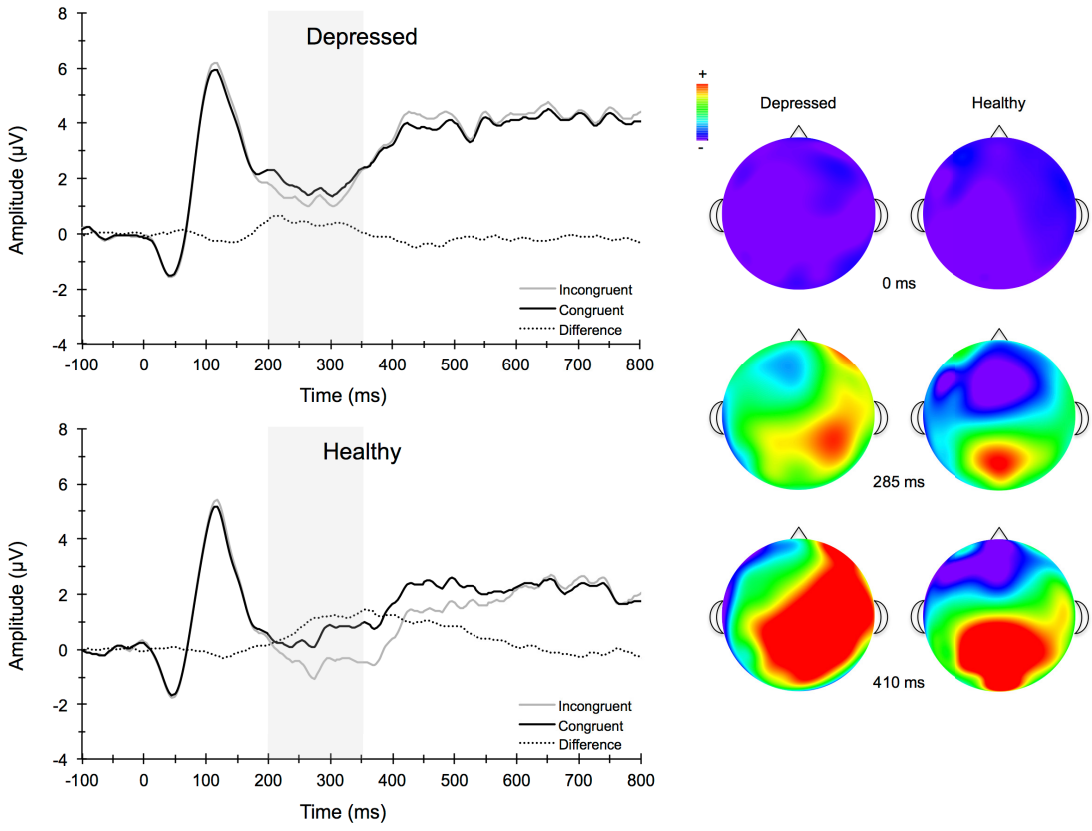

Figure 4. Stimulus-locked grand average ERP waveforms for depressed (top left) and healthy (bottom left) participants during the flanker task averaged across frontocentral midline electrode sites (Fz, FCz, and Cz). Topographic scalp maps (right) collapsed across congruency for depressed and healthy participants.

Congruency interaction, $F(1,67) = 4.20$, $p < .05$, $\eta^2_p = .06$. This interaction revealed a larger flanker N2 effect (i.e., larger N2 for incongruent versus congruent task conditions) for healthy participants (1.204 μV), ES = 0.38, $p < .001$, compared to MDD participants (.396 μV), ES = 0.13, $p = .131$. Significant main effects of Group, Congruency, and the Group x Task Congruency interaction remained significant when accounting for comorbid diagnosis and current medication use (Fs > 3.7, ps < .05), suggesting that these differences did not alter the overall pattern of findings. Importantly, self-reported rumination was also significantly correlated with N2 amplitude, $r = .28$, $p = .02$ (see Figure 5). This positive correlation indicates that as rumination scores increased, N2 amplitude became more positive (i.e., less negative N2 amplitude reflects reduced cognitive control).

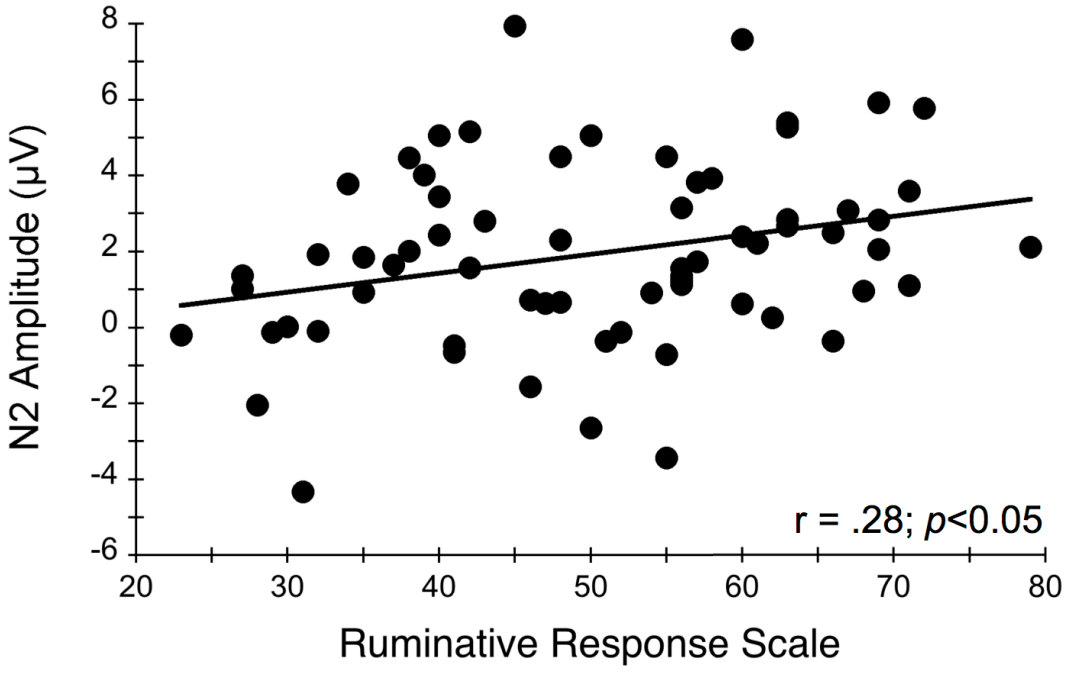

Figure 5. Relationship between N2 amplitude averaged across frontocentral midline electrode sites Fz, FCz, and Cz and self-reported rumination levels during the flanker task. More positive N2 amplitudes are interpreted as an index of impaired conflict monitoring.

Figure 6 illustrates the grand averaged ERP waveforms for each group averaged across the Cz, CPz, and Pz midline electrode sites to short and long trials of the attentional blink task. The total number of attentional blink trials used for ERP analysis did not differ by group or condition. ERPs for MDD participants included a total of 80 ± 21 trials for the short lag condition and 23 ± 5 trials for the long lag condition. Similarly, ERPs for control participants included a total of 80 ± 26 trials for the short lag condition and 22 ± 4 trials for the long lag condition (mean ± standard deviation). For the AB task, the omnibus analysis for P3 amplitude to T1 yielded a significant main effect for Lag, $F(1,67) = 11.25$, $p < .001$, $\eta^2_p = .14$, and Site, $F(3,65) = 21.79$, $p < .001$, $\eta^2_p = .50$, with post hoc analyses for Lag revealing significantly larger T1-elicited P3 amplitudes in long trials compared to short trials and for Site revealing a central-parietal distribution, with the parietal and central sites showing significantly larger amplitudes than the frontal and frontocentral sites, ps < .01. No group level main effects or interactions were evident for T1-elicited P3 amplitude. The 3-way mixed model ANOVA for P3 amplitude elicited by T2 similarly revealed a significant main effect for Lag, $F(1,67) = 19.66$, $p < .001$, $\eta^2_p = .23$, and Site, $F(3,65) = 4.75$, $p < .01$, $\eta^2_p = .18$, with post hoc analyses revealing larger T2-elicited P3 amplitudes on long trials compared to short trials and for Site revealing larger P3 amplitudes over central and parietal electrode sites compared to frontal and frontocentral sites. No significant main effects or interactions by Group were found. Self-reported rumination levels were not associated with T1- or T2-elicited P3 amplitudes for short or long trials ($p > 0.05$).

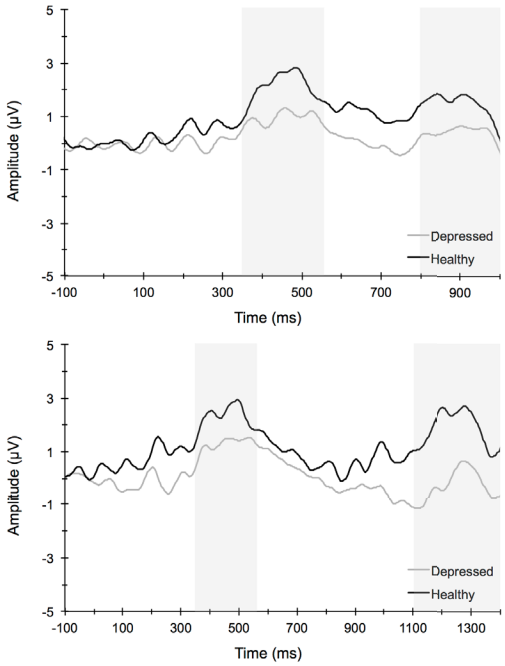

Figure 6. Stimulus-locked grand average waveforms for short (top) and long (long) attentional blink trials averaged across centroparietal midline electrode sites Cz, CPz, and Pz.

DISCUSSION

Individuals who suffer from MDD often experience deficits in learning, memory, selective attention and cognitive control (32, 100-102). These various processes allow one to initiate actions, evaluate risks, make decisions, plan for the future, inhibit habitual or prepotent responses, and resist temptations. During depressive episodes, individuals often ruminate about the past, which further interferes with cognitive control processes and the ability to inhibit unwanted thought patterns. In this study, we examined conflict monitoring using a modified flanker task and the ability to process two temporally close stimuli using a RSVP paradigm in depressed individuals and healthy controls, as well as the relationship of these cognitive processes to rumination. We examined how these behavioral and psychological measures related to neural indices of cognitive control and attention as evident in ERPs elicited by the flanker and AB tasks. The present findings indicate that although behavioral task performance was comparable between the two groups, there were differences between the groups' respective ERP responses to environmental stimuli. ERPs may be more sensitive to subtle cognitive dysfunction in MDD and provide some insight into the underlying mechanisms involved. Consistent with our hypotheses, the amplitude of the N2 was significantly

reduced in depressed participants when compared to non-depressed participants. These neuronal responses were particularly observed in response to the incongruent flanker task condition (i.e., the task condition requiring greater amounts of conflict monitoring) and were maximal at frontocentral recording sites. Moreover, correlational analyses indicated that participants who reported greater rumination levels also expressed significantly smaller N2 amplitudes. Contrary to expectations, behavioral performance and P3 amplitudes for the AB task were similar among depressed and non-depressed individuals, suggesting preserved temporal dynamics of attentional processes and neural resource allocation during the AB task in MDD. The implications of these findings are discussed below.

First, similar to several previous studies (20, 92) we failed to observe any differences in behavioral performance measures between individuals with MDD and typical controls. Moreover, no significant correlations were found between self-reported rumination and accuracy or reaction time measures for either cognitive task. In contrast, although Holmes and Pizzagalli (33) reported no difference in accuracy, they found significantly longer response times for MDD patients relative to controls for the more challenging incongruent Stroop task trials. The participants in this latter study were older than those used in our study or in these previous studies of cognitive control deficits in MDD (20, 92). Many of the participants in our study were also university students. It is possible that select neurocognitive deficits in MDD are not observable using behavioral performance measures in such a young, otherwise high functioning population. One advantage of ERPs over behavioral measures is that they can provide information regarding the covert subset of neural processes that occur between stimulus engagement

and motor response execution. Therefore, they may be more suitable to detecting any underlying impairment in conflict monitoring and attentional processes that may be present yet not observable through other measures. Future studies aimed at investigating the temporal sequence of cognitive deficits and MDD as well as any developmental variations in these neurocognitive processes are warranted.

Depressed individuals displayed lower N2 ERP amplitudes during the flanker task, a task requiring variable amounts of cognitive control. The ERP data suggested impairment in early conflict processing stages of information processing. This suggests that the MDD group recruited less cognitive control during task performance compared to healthy controls. Previous studies examining the N2 component in MDD have resulted in mixed findings, and several recent studies have not found between group (MDD vs. controls) differences in N2 amplitude (20, 53). Clawson et al. (20) examined N2 amplitudes in the context of conflict adaptation, wherein previous trial congruency influences current trial performance through available cognitive control resources. Although no group differences were found, depressive symptoms assessed through the BDI-II were significantly correlated with N2 conflict adaptation scores. The authors noted that the relationship between symptoms of depression and reduced conflict adaptation processes may be dimensional rather than categorical in nature, and that individuals who experience levels of depression that fail to meet diagnostic thresholds may still evidence cognitive dysfunction, including those processes involved in conflict adaptation. In contrast, Mao et al. (103) assessed an N2 component (labeled the N270 in their study) during a visual S1-S2 mismatch paradigm and found smaller N270 amplitude among the depressed patients compared to controls at frontal and parietal electrode sites.

This finding was interpreted as evidence of impaired conflict processing, involving ACC and lateral PFC regions. Differences in the tasks used, clinical characteristics of the participants, and precise timing of the component amplitudes across studies may have resulted in the mixed findings in the literature. Future studies should incorporate tasks that are believed to be sensitive to both early and later stages of cognitive control processes to elucidate the precise temporal nature of dysfunction in MDD. Moreover, it will be important for future research to examine this relationship across a wider domain of depression severity to determine whether this relationship is stronger for more severely depressed individuals versus those with mild to moderate depression.

Several previous studies have also studied other ERP components associated with cognitive control processes in depressed patients using both emotional (104, 105) and nonemotional (20, 33, 92, 106) tasks. Using a Stroop task, Holmes and Pizzagalli (33) found that individuals with MDD showed larger Stroop interference effects and reduced N2 and N450 amplitudes. The N450 component belongs to the conflict-monitoring family of ERPs and is believed to represent similar cognitive control processes related to conflict monitoring (i.e., N2), although it may not be as sensitive to conflict adaptation processes (24). Moreover, source localization analyses revealed reduced activation within dorsal ACC and left dorsolateral PFC regions 620 ms after stimulus presentation among MDD participants, and the reduced activation resulted primarily in response to incongruent trials (33). Krompinger and Simons (92) similarly found overall reduced Stroop N450 amplitudes in undergraduates with high BDI scores relative to those with lower BDI scores; however, a large Stroop congruency effect was found for the N450 for the high but not for the low depressive group, amid comparable behavioral task

performance scores. This hyperactivation was also related to rumination and suggests that trait ruminators might over engage cognitive control processes, including the affective subdivisions of the ACC, in the process of performing at normative levels. It is also possible that depressed individuals have less efficient neuronal resources due to other psychological processes that occur during performance of the task, which may happen with trait ruminators. To examine this possibility, we assessed the correlation between individual differences in rumination and N2 amplitudes elicited by the flanker stimuli. We found that N2 amplitudes were significantly related to self-reported rumination levels, such that higher rumination scores were related to lower N2 amplitude. Thus, rumination appears to be associated with less efficient conflict monitoring resources used to attend to stimuli in the environment that may be unexpected and require the upregulation of cognitive control. This diminished cognitive control at the neurological level may partially explain why some depressed individuals have difficulty disengaging from negative environmental experiences and a diminished ability to reappraise situations to find positive perspectives about the situation (107). These findings are consistent with other studies, which report that clinically depressed individuals have difficulty inhibiting the emotional effects of negative content (108, 109), even after the depression has remitted (110, 111).

Deficits of cognitive control in depression could be caused by a number of neurobiological factors such as epigenetic influences, neurovascular changes, stress exposure, or environmental and social influences, among others. These influences likely interact to confer risk for MDD in particular and psychopathology more broadly. A recent meta-analysis of 193 structural neuroimaging studies across six diverse psychiatric

diagnostic groups (schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety) found gray matter loss in three specific brain regions across diagnostic categories: the dorsal anterior cingulate, right insula, and left insula (112). This finding was important not only in demonstrating a possible shared disrupted neural circuitry across diagnoses, but highlights the potential importance of executive functioning or cognitive control in these conditions. Others have previously noted important brain regions in depression (prefrontal cortex, hippocampus, and amygdala; 4), and, importantly, these structures also emerged as critical to depression in the meta-analysis (112). Depression may result in underlying neurobiological changes that in turn cause impairment in cognitive control (113). The causal pathway may be explained by underlying impairments in cognitive control contributing to risk for or relapse of depressive episodes, possibly by contributing to an inability to inhibit feelings of frustration, helplessness and low self-worth (32). As mentioned previously, there is a need for longitudinal studies to examine the directional links between cognitive control processes and depression at both a behavioral and neurobiological level.

A number of different attentional processes have been studied in relation to mood disorders and MDD (32, 54). Previous studies have indicated that the temporal dynamics of attentional processes can be influenced by demographic, lifestyle, or health factors, as reflected by the size of the AB as well as P3 amplitude (85, 114, 115), but how temporal dynamics of attention are affected by MDD is not well understood. In the present study, we observed no group differences in attentional resources devoted to the AB task in participants with MDD. Specifically, no significant differences in the magnitude of the AB or P3 amplitude were observed between depressed and healthy groups. It is possible

that individuals with depression can maintain attention through basic attentional tasks (e.g. simple organization tasks), but have more difficulty as the tasks require greater response monitoring or conflict (e.g., cognitive evaluation, aspects of social engagement). It is important in future research to examine the temporal sequence between MDD and conflict monitoring aspects of cognitive control. Our results suggest the possibility that an initial target of treatment in MDD should be the reduction of rumination.

While these data suggest impaired conflict monitoring in MDD, several limitations should be noted. First, the current sample size was relatively small, which may have limited power in detecting group differences in subtle attentional processes. Second, although group differences emerged in ERPs that were elicited by the flanker task, we did not observe statistically significant differences in behavioral task performance between depressed and healthy participants. We also did not find any significant correlations between N2 and P3 amplitudes and task performance measures. Previous studies have shown a relation between N2 amplitudes and reaction time (47, 116, 117), suggesting that the degree of conflict as measured my N2 amplitude is reflected in impaired behavioral performance. It is possible that our version of the flanker task was not demanding enough to detect behavioral differences by depression status. Another possible explanation may be that our behavioral tasks did not involve a negative valence component, which may have activated depression symptomology more than the neutral behavioral stimuli used in this study. Further, it is possible that the MDD sample, consisting of enrolled undergraduate students, was functioning at a sufficiently high cognitive level to overcome potential neurocognitive limitations on the tasks employed. As mentioned previously, the precise temporal resolution of ERPs provides a more

sensitive approach for detecting cognitive deficits and their underlying neurophysiological mechanisms. Although we did not source-localize our ERP components, the nature of the cognitive tasks and the ERP findings nonetheless allow us to draw comparisons to those observed in other ERP studies examining cognitive control processes.

In spite of these limitations, the present findings suggest a potential link between conflict monitoring processes and rumination in MDD. This study represents an initial step in developing a more comprehensive understanding of depression by integrating neural and cognitive models of MDD. The ERP data combined with previous source localization and fMRI studies suggest dysregulation within anterior cingulate and prefrontal brain regions in MDD (33, 48). Given these and related data, it is important to develop clinical interventions which increase the neuronal response that underlies conflict monitoring processes and reduce the maladaptive levels of rumination that often are observed in individuals with MDD.

CHAPTER 2: Neurophysiological and behavioral correlates of cognitive control during low and moderate intensity exercise

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INTRODUCTION

It is now well accepted that acute exercise has a positive effect on cognitive functioning when cognition is assessed post-exercise (118-122). Indeed, meta-analytic reviews have reported small but significant effects of acute exercise on cognitive performance (119, 120). However, a majority of the studies in this area have assessed cognition following exercise to control for exercise-induced physiological arousal, with relatively fewer studies focusing on cognitive performance during exercise. This is important since a critical methodological factor that might explain the inconsistent findings in the literature relates to the time that cognition is assessed relative to exercise. Additionally, the mechanisms involved and moderators of the relationship are still widely unknown. Understanding important moderators as well as cognitive and brain processes during exercise may help to better understand the benefits of exercise participation on cognitive function and brain health.

Previous studies have reported that acute aerobic exercise exerts a small beneficial effect on cognitive performance when assessed during exercise (119, 121); however, not all studies are in agreement (123, 124). Several key moderating variables

that may impact this relationship have been identified in recent meta-analyses (119, 120). These moderators (e.g., exercise duration and intensity) may help to both explain the discrepant findings and advance our understanding of the complex relationship between acute exercise and cognition. Both meta-analyses suggest that exercise has a selective impact on cognition depending upon when cognition is assessed relative to exercise. Specifically, Lambourne and Tomporowski (120) reported that cognitive task performance was impaired during exercise; however, these impairments were only observed during the first 20 min. Beyond the initial 20 min of exercise, they observed enhanced performance on cognitive tasks that involved rapid decisions and automatized behaviors. Chang et al. (119) found no significant differences between effect size measures derived from three different acute exercise paradigms: those that assessed cognitive performance during exercise, immediately following exercise, and after a longer delay (> 1 min following exercise). However, based on those studies that assessed cognition during exercise, the largest effect sizes were observed when cognitive tasks were administered 20 min or longer following exercise onset. These meta-analytic findings are consistent with the conclusions drawn by Brisswalter et al. (118) who reported consistent positive effects of acute exercise lasting more than 20 min on cognitive performance. Although these reviews are suggestive of the notion that exercise lasting longer than 20 min in duration may facilitate or impair cognition depending on when cognition is assessed, this idea has received very little scientific attention. This research has important theoretical implications and may help to elucidate the optimal dose of exercise to prescribe to enhance cognitive performance.

A second key moderator that has been less well studied and may help to better characterize the effects of exercise on cognitive performance is exercise intensity. Examining the dose-response relationship between exercise intensity and cognition may help to elucidate the psychobiological processes induced by different exercise intensities, and how these processes help to explain the effects of exercise on select cognitive processes. Even fewer studies have examined the dose-response effects of exercise on cognitive control (125). Cognitive control is a construct from contemporary cognitive neuroscience that refers to top-down, goal directed operations that assist with the selection, scheduling, maintenance, and coordination of processes that underlie perception, memory, and action (126, 127). Utilizing the Karvonen or heart rate reserve (HRR) method to prescribe exercise intensity, which reflects the difference between maximal and resting heart rate (HR), Wang et al. (125) randomly assigned 80 typical college-aged adults to low (30% HRR), moderate (50% HRR), and high (80% HRR) intensity exercise conditions or to a no-exercise seated control and administered a cognitive control task (i.e., the Wisconsin Card Sorting Test, WCST) simultaneous with the interventions. They reported impaired WCST performance during high intensity exercise relative to the other three conditions, whereas similar performances were found for the low and moderate intensity exercise conditions. Alternatively, Schmit and colleagues (128) examined concurrent changes in cognitive control and cerebral oxygenation (Cox) in the prefrontal region during strenuous exercise performed to exhaustion. Although Cox values were found to decline linearly until exercise exhaustion, there was no systematic impairment of cognitive control during the intense bout of exercise. It remains to be determined whether these findings related to prefrontal

activation would persist beyond the first 20 min of exercise and whether there is a dose-response relationship between exercise intensity and cognitive performance. Moreover, it is possible that the intensity of exercise interacts with exercise duration to impact cognition. There is a need to examine the dose-response relationship between exercise intensity and in-task cognitive performance and whether this relationship changes within and beyond the initial 20 min of exercise.

Traditionally, studies in this area have used behavioral performance measures such as response accuracy and reaction time to gauge cognition both during and following exercise. Although these measures have undoubtedly enhanced our understanding of the effects of exercise on cognition, the high temporal sensitivity of event-related brain potentials (ERPs) may allow for greater understanding of covert aspects of cognitive processing, including processes that occur between stimulus presentation and response selection and action. ERPs reflect patterns of voltage fluctuations in the ongoing electroencephalogram (EEG) that are time-locked to a specific event, such as the onset of a stimulus or the execution of a manual response (129). Two components that have been leveraged to better understand the complex nature of cognitive processing during exercise are the N2 and P3 components of the ERP. The N2 component is a negative deflection in the stimulus-locked ERP with a frontocentral scalp distribution that peaks approximately 200-350 ms after stimulus presentation (19, 20, 23), and has been repeatedly associated with the detection of response conflict, the mismatch of a stimulus with a mental template, and/or increased cognitive control during response inhibition (23-25). The P3 component is a positive deflection in the stimulus-locked ERP observed at central and parietal scalp sites approximately 250–500 ms after

stimulus onset, and the component amplitude is believed to reflect the allocation of attentional resources during stimulus engagement (73, 74). The N2 and P3 components have been instrumental in advancing our understanding of cognitive and brain function both during and following acute exercise (124, 130, 131).

The few studies that have used ERPs to investigate cognition during exercise have reported equivocal results. Pontifex and Hillman (124) assessed cognition through ERPs while participants cycled at a steady-state corresponding to 60% of maximal HR for approximately 6.5 min. They found global reductions in N2 and increases in P3 amplitude across frontal and lateral electrode sites along with longer N2 and P3 latencies, suggesting cortical inefficiency during stimulus engagement and delays in stimulus evaluation and classification speed. In terms of behavioral performance, exercise resulted in impaired accuracy for the incongruent trials of the flanker task, reflecting the task condition requiring greater amounts of cognitive control. More recently, Vogt et al. (132) had participants perform mental arithmetic during a moderate intensity bout of self-paced cycling within a virtual environment while EEG was recorded. Although they found an increase in N2 and P3 amplitudes elicited by the virtual environment, these ERPs were not influenced by exercise. Moreover, no significant differences were observed in behavioral performance (response accuracy and reaction time) measures between exercise and control conditions. However, it was conceded that performing a cognitive task while cycling in a virtual environment may have created an increase in cognitive load, which might have obscured any effects of exercise *per se* on cognition. Taken together, these findings suggest either no changes or perhaps deficits in cognition during exercise, particularly for cognitive control tasks. However, in line with findings from

meta-analyses (119, 120), the influence of exercise lasting longer than 20 min on behavioral and neurophysiological correlates of cognitive control (i.e., N2 and P3 components) warrants investigation.

To date, no study has investigated the dose-response effects of aerobic exercise intensity on cognitive control by recording both behavioral and neuroelectric measures. Moreover, there is a need to investigate the effect of duration on cognitive control processes during the initial 20 min of exercise and thereafter to determine whether there is a delayed benefit of aerobic exercise on cognitive processing. Therefore, the purpose of this study was to assess neurophysiological and behavioral performance measures of cognitive control during a 31 min bout of aerobic exercise performed at 40% and 60% of peak aerobic fitness (VO_2 peak) and to examine the time course effects on cognition by assessing neurocognitive performance at 5, 15, and 25 min time points during steady-state exercise. We hypothesized that the ERP measures would exhibit greater sensitivity to the effects of acute exercise on cognitive performance than the behavioral performance measures (see 124, 133). Based on existing dose-response evidence during exercise, it was hypothesized that both the 40% and 60% exercise conditions would impair response accuracy and N2 and P3 ERP measures compared to rest. Lastly, based on current meta-analytic findings (119, 120), we expected cognitive benefits for both exercise conditions assessed at 25-min relative to earlier time points following exercise onset.

METHODS

Participants

Undergraduate students were recruited from Rutgers University and the surrounding community through the use of flyers and advertisements. Participants were required to meet the following inclusion criteria: between the ages of 18 and 35, native English speakers, right handed, and reporting normal or corrected-to-normal vision. Participants were excluded if they had a presence or history of cardiovascular, neurological, or musculoskeletal problems that would impact exercise ability, past or present history of psychiatric or neurological disorders (including attention deficit hyperactivity disorder (ADHD), clinical depression or anxiety, or any head injury with loss of consciousness), or were taking medication. Thirty participants who met the inclusion criteria were enrolled in the study. Three participants were eliminated because more than 50% of their trials contained artifacts after artifact detection (134), yielding a final sample of 27 participants. Prior to participation, participants provided written informed consent that was approved by the Institutional Review Board at Rutgers, The State University of New Jersey. Participant demographic and fitness data are provided in Table 2.

Procedures

Participants visited the laboratory on four separate days. Each testing day is referred to as a session. During the first session, participants were given a general description of the study, provided consent, and completed a health history and demographics questionnaire and a physical activity readiness questionnaire (PAR-Q) to ensure safety for the cardiorespiratory fitness assessment and subsequent testing sessions. Participants were asked to avoid exercise for 48 hours and caffeine or other stimulants for 3-4 hours prior to baseline testing. This was verified upon arrival to the laboratory. Participants were

accompanied to an exercise testing room and fitted with a Polar S810 heart rate monitor and had their height and weight measured with a stadiometer and digital scale (Health-O-Meter model 499KL, IL). A maximal cardiorespiratory fitness (VO_2 peak) test was then administered while participants cycled on a Lode Corival cycle ergometer. Upon completion of the fitness assessment, participants were scheduled for their remaining three testing sessions, which took place at approximately the same time of day as their initial visit.

Table 2. Participant characteristics (M ± SD) overall and by gender.

Measure	Females	Males	Total
n	11	16	27
Age (years)	20.4 ± 1.5	20.5 ± 2.3	20.4 ± 2.0
Height (cm)*	160.1 ± 7.0	176.8 ± 5.8	170.0 ± 10.4
Weight (kg)*	57.6 ± 3.6	74.3 ± 11.4	67.5 ± 13.8
BMI (kg/m^2)	22.4 ± 3.6	23.7 ± 3.0	23.2 ± 3.3
VO_2 peak ($mL*kg^{-1}* min^{-1}$)*	33.7 ± 7.9	48.2 ± 10.1	42.3 ± 11.7

Note. VO_2 peak norms are available in the American College of Sports Medicine (2013) Guidelines for Exercise Testing and Prescription (9^{th} Edition). *Significant difference, unpaired Student's *t* test between females and males, $p < .05$.

For the three experimental sessions, participants completed a no-exercise seated control, a low intensity (40% VO_2 peak), and a moderate intensity (60% VO_2 peak) exercise bout in counterbalanced order, performed 2–3 days apart to allow adequate recovery from the previous session. The no-exercise seated control involved participants sitting at rest on the cycle ergometer while the exercise conditions consisted of cycling for 31 min at a HR intensity range corresponding to approximately 40% or 60% VO_2

peak as determined from the baseline fitness test (i.e., HR achieved at these intensities during maximal VO_2). HR ranges were determined prior to participants entering the lab and were monitored throughout each session. In order to standardize additional variables related to work output, data from the maximal fitness test were used to set the initial resistance (Watts) for the exercise sessions. At the start of each experimental session, participants were fitted with a Polar HR monitor and the bike was re-adjusted to the settings established during the baseline fitness test. A 64-channel Geodesic Sensor Net (Electrical Geodesic, Inc, OR) was applied to record continuous electroencephalographic (EEG) activity. In order to reduce head and upper body movement artifact during neuroelectric recording (133), participants were asked to maintain a posture where upper body movement was minimized without restricting lower body movement. To further reduce movement artifact and noise, the electrode wire harness was suspended and elevated away from the neck and back region. Participants were verbally read and provided with on-screen instructions for the flanker task. During the last two minutes of a 5 min low intensity warm-up on the bicycle ergometer (women, 70W; men, 80W), researchers adjusted the resistance until HR corresponding to 40% or 60% VO_2 peak was reached and maintained. Participants also completed a practice block of the flanker task during the 5 min warm-up. HR was continuously recorded and monitored at the beginning and end of each trial block to ensure participants were maintaining ± 5 beats per minute (bpm) of their individually prescribed range of intensity. During the control session, participants were required to maintain the same posture on the cycle ergometer without pedaling for an equivalent amount of time (31 min). Following completion of the

final experimental testing session, participants were compensated and briefed on the purpose of the study.

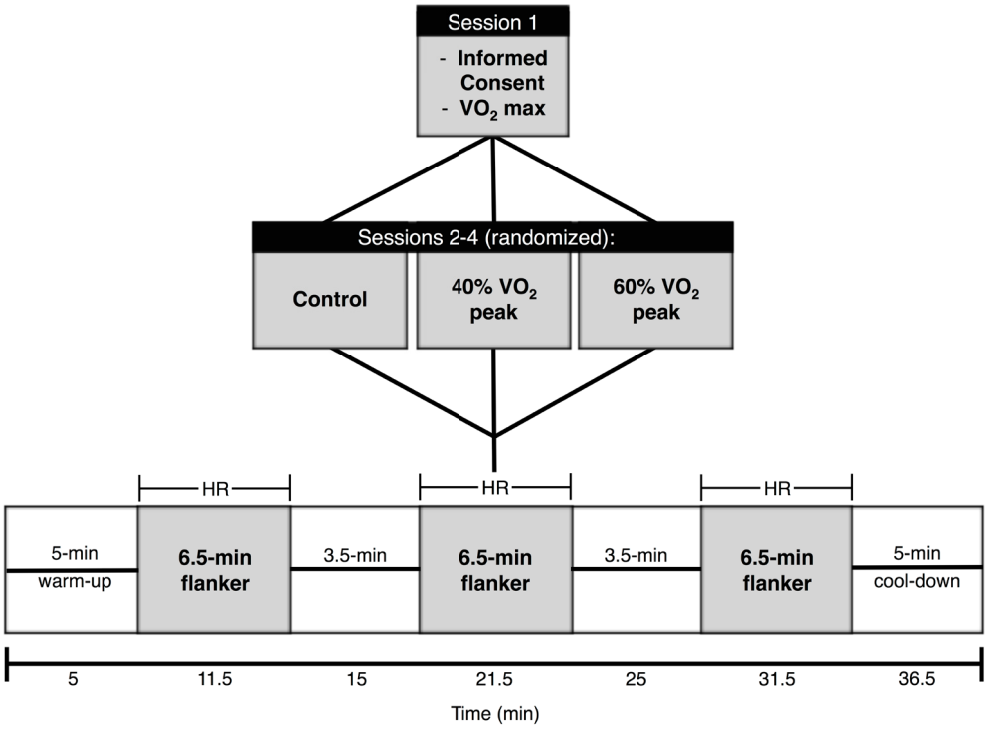

Figure 7. Study diagram. Following practice trials and a 5-min warm-up period, experimental sessions (2–4) contained three 6.5-min blocks of flanker trials separated by 3.5-min of steady- state exercise or rest (during the control condition). Sessions ended with a 5-min cool-down period.

Cardiorespiratory Fitness Assessment

Cardiorespiratory fitness was assessed by a maximal oxygen consumption (VO_2 peak) test performed on a Lode Corival (Lode B.V., Groningen, NLD) cycle ergometer. Prior to testing, participants sat on the ergometer so the seat height and aero bicycle handlebar angle could be adjusted so they were comfortable, yet steady, while maintaining an efficient cycling posture. The seat height was set such that participants' knees were bent by 10 to 20 degrees at full extension on the down stroke. A 2 min warm-up with very

light resistance (25 W) was completed prior to the ramped protocol. The protocol involved increasing the resistance of the ergometer by 5 W every 10 s while a steady cadence (RPM) was maintained until volitional exhaustion or VO_2 peak criteria were met. Speeds ranged from 50-75 RPM depending on the comfort level and experience of the participant. If the participant was unable to maintain a steady cadence (±5 RPMs of their selected speed) for greater than 10 s, they were given one warning that the test would be terminated unless the RPM was maintained. Following 15 s out of the determined range or on the second warning, the test was terminated and participants were allowed to cool-down. VO_2 peak ($mL * kg^{-1} * min^{-1}$) was determined from direct expired gas exchange data from a computerized metabolic system (Parvo Medics True Max 2400 Metabolic Cart, ParvoMedics, Inc., Sandy, UT) averaged over 15 s intervals. VO_2 peak was determined as the maximal relative rate of oxygen consumption when at least two of the following criteria were met: (1) a plateau in VO_2 values despite a progressive increase in workload, (2) maximal heart rate (HR) within 10 beats per minute (bpm) of age-predicted maximal values (220 bpm - age in years), or (3) a respiratory exchange ratio greater than 1.10. A 5 min cool-down was then performed at a self-selected pace with minimal resistance to ensure participants returned to baseline HR values prior to leaving the laboratory.

Eriksen Flanker Task

Participants completed a modified version of the Eriksen flanker task (84) to examine cognitive control. Stimuli consisted of five arrows presented in the center of the computer screen. The central arrow was the target, while the surrounding or flanking arrows on

each side of the target served as distractors. Each block of trials consisted of equally weighted congruent and incongruent trials presented in random order. The congruent trials consisted of the central target being flanked by arrows pointing in the same direction (e.g., <<<<<), while incongruent trials involved the target being flanked by arrows pointing in the opposing direction (e.g., <<><<; see Figure 1). After a practice block of 30 trials, which took place during the 5 min warm-up period, three 6.5 min blocks of trials were presented during each experimental session, separated by 3.5 min of cycling or rest, depending on condition (Figure 7). During the 3.5 min period between each trial block, participants either maintained steady-state exercise or remained sitting comfortably on the cycle ergometer during the control condition. Regardless of congruency, participants performed a button press with their left thumb when the central target pointed to the left (<) and a button press with their right thumb when the central target pointed to the right (>). Participants' responses were collected via response clickers (left and right) that were attached to custom aero bars affixed to the cycle ergometer. Participants were instructed to respond as quickly and accurately as possible by pressing the left or right response button with the hand that corresponded to the direction in which the target was pointing. The stimuli were presented on a monitor at a distance of 70 cm centered to the nasion. The stimuli were 1.5 cm tall x 8 cm long black arrows centered focally on a white background for 100 ms with a response window of 1500 ms. The vertical and horizontal visual angles were 1.2° and 6.6°, respectively. A random inter-stimulus time interval of 1100, 1300, or 1500 ms was used between each visual fixation (+) and the stimulus in order to reduce potential anticipatory responses. Performance feedback was provided only during the practice trials.

Electroencephalographic (EEG) Data

Continuous EEG activity was recorded from 64 scalp sites using a Geodesic Sensor Net and Electrical Geodesics, Inc. (EGI; Eugene, OR) amplifier system (20 K nominal gain, bandpass = .10–100 Hz). Continuous data were initially referenced to the vertex electrode (Cz) and digitized continuously at 250 Hz with a 24-bit analog-to-digital converter. Impedances were maintained below 50 kΩ. Although lower impedances are typically recommended, previous research has shown acceptable EEG signals when data were collected with higher scalp impedances, and similar values have been used in previous studies of cognitive control (135, 136).

Following collection, data were re-referenced to the average of the left and right mastoids (90, 91) and bandpass filtered with a low-pass frequency of 30 Hz and high-pass frequency of .1 Hz. The continuous EEG data were manually inspected and periods with large movement-related artifacts (eye-blinks and eye movement) were removed using NetStation 4.0 (Electrical Geodesic Inc., EGI). Stimulus-locked epochs were then created from 100 ms pre-stimulus to 1,000 ms post-stimulus and baseline adjusted using the 100 ms pre-stimulus period. Prior to artifact detection and removal and to control for potential DC drift often associated with gross movement artifact, a linear detrend was applied to the segmented data where a linear trend line was plotted, the slope was calculated and subtracted from the waveform (124). NetStation detection software, which allows for the adjustment of settings for detecting and marking artifacts and contaminated segments, was used to detect eye-blinks, vertical and horizontal eye-movements, and bad channels. Marked segments were visually inspected and rejected if they contained 1) eye movements exceeding 55 μV, 2) eye blinks exceeding 140 μV, or 3) greater than or equal

to 10 bad channels exceeding 200 μV. In each case, a moving average of 20 samples combined with threshold values was used. Using spherical spline interpolation, bad channels were then replaced from the remaining channels in "good" segments. Trials were also visually inspected for any remaining artifacts, and data from individual channels containing artifacts were rejected on a trial-by-trial basis. Trials with incorrect behavioral responses were excluded from all analyses.

Consistent with previous ERP research (23, 74) and to reduce selection bias, *a priori* time windows for the ERP components were established. The N2 component was defined as the mean negative amplitudes within a 200-350 ms window post-stimulus onset, while the P3 component was defined as the mean amplitude within a 250-500 ms window post-stimulus onset. Although peak amplitudes are often used in the literature to define ERP components, Luck (18) suggests using mean amplitudes to better capture ERP components over an extended period of time, especially when the data collected may be biased by added noise due to muscular or bodily movements during exercise. Moreover, Luck (18) asserts that it is impossible to estimate the time course or peak latency of an underlying ERP component by looking at a single ERP waveform and this is especially true when two or more ERP components are being compared. Therefore, in the current study we limited our analysis to ERP component amplitudes.

Data Analysis

Descriptive statistics were first performed on participant demographic and fitness data. Repeated measures analyses of variance (rANOVA) were used for ERP and behavioral analyses with a 2-tailed alpha level of .05 for all statistical tests, and probability values

were adjusted when appropriate with the Greenhouse-Geisser epsilon correction for nonsphericity (137). To reduce the potential effect of outliers, trials with RTs beyond the individual mean ± 3 SD for each trial type were excluded. As a manipulation check of exercise intensity, a 3 (Condition: control, 40%, 60% VO_2 peak) x 3 (Time: Blocks 1-3) rANOVA was conducted to compare HR across conditions. This analysis was expected to reveal significant linear increases in HR from rest to 40% to 60% exercise conditions. Behavioral performance data (i.e., response time and accuracy) were submitted to a 3 (Condition: control, 40%, 60% VO_2 peak) x 3 (Time: Blocks 1-3) x 2 (Task Congruency: Congruent, Incongruent) rANOVA. Additionally, the total number of trials performed during each 6.5 min block were submitted to a 3 (Condition: control, 40%, 60% VO_2 peak) x 3 (Time: Blocks 1-3) rANOVA to determine potential differences in total trials attempted per block. The time blocks refer to when the cognitive task was administered during each condition, with each block representing 6.5 min of cognitive testing. Block 1 began at min 5, block 2 at min 15, and block 3 at min 25 following the start of each condition.

For the ERP data, statistical analyses for the N2 and P3 components were performed using 5 electrode sites across the midline (N2: Fz, FCz, and Cz; P3: Cz, CPz, and Pz). The anterior N2 is most robust and frequently examined at frontocentral midline electrode sites (23, 138). Thus, Fz, FCz, and Cz electrodes were used for N2 analyses. N2 data were submitted to a 3 (Condition: control, 40%, 60% VO_2 peak) x 3 (Time: Blocks 1-3) x 2 (Task Congruency: Congruent, Incongruent) x 3 (Site: Fz, FCz, Cz) rANOVA. To replicate the Pontifex and Hillman (2007) study and because the posterior P3 component is most prominent and commonly studied at centroparietal midline electrode

sites (139, 140), analyses for P3 included the Cz, CPz, and Pz electrode sites. P3 data were submitted to a 3 (Condition: control, 40%, 60% VO_2 peak) x 3 (Time: Blocks 1-3) x 2 (Task Congruency: Congruent, Incongruent) x 3 (Site: Cz, CPz, Pz) rANOVA.

RESULTS

Mean reaction time (RT), response accuracy, N2 and P3 amplitudes by condition are shown in Table 3. Preliminary analyses revealed no gender differences on behavioral performance variables or amplitude of the N2 and P3 components. As expected, males had higher VO_2 peak (48.2 ± 10.1 $mL*kg^{-1}* min^{-1}$ vs. 33.7 ± 7.9 $mL*kg^{-1}* min^{-1}$) values than females. Given no gender differences in cognitive performance, data were collapsed across gender for all subsequent analyses. As a manipulation check of exercise intensity, the 2-way rANOVA revealed a significant main effect of Condition, $F(2,25)=147.9$, $p<.001$, $\eta^2_p = .91$, with higher HR values elicited by the 40% and 60% VO_2 peak conditions compared to rest (see Figure 8). The two exercise conditions also significantly differed from one another, $p<.001$. The 2-way rANOVA on total trials revealed no significant main effect of Condition, $F(2,25)=.37$, $p>.05$, $\eta^2_p = .03$, or Time, $F(2,25)=.21$, $p>.05$, $\eta^2_p = .02$. There was also no significant Condition x Time interaction, $F(4,23)=1.4$, $p>.05$, $\eta^2_p = 0.2$). There were approximately 138 trials completed per 6.5 min block.

Behavioral Performance. The 3-way rANOVA for response accuracy revealed a main effect of Condition, $F(2,25)=6.8$, $p<.01$, $\eta^2_p = .31$, and Task Congruency, $F(1,26)=34.4$, $p<.001$, $\eta^2_p = .53$. However, these were superseded by a 2-way interaction of Condition x Task Congruency, $F(2,25)=8.2$, $p<.001$, $\eta^2_p = .35$. Post hoc Bonferroni corrected *t* tests of

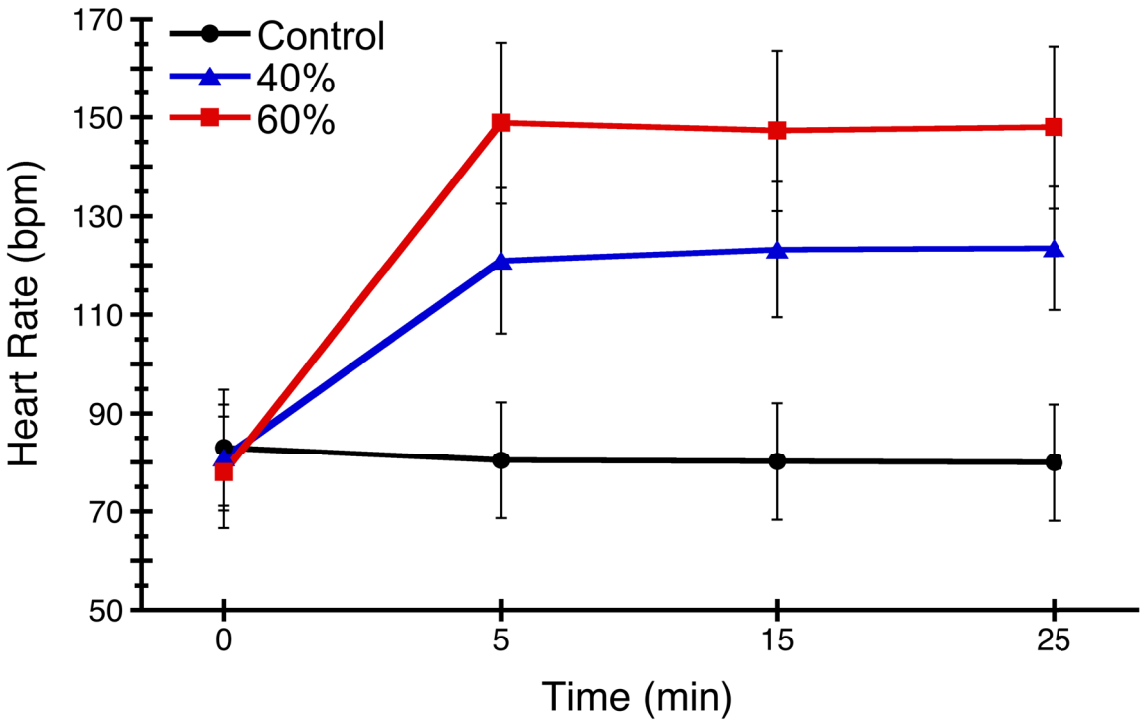

Figure 8. Average heart rate responses between experimental conditions. Heart rate values are averaged across 6.5 min trial blocks presented at 5, 15, and 25 min. As expected, participants displayed higher heart rates during 40% and 60% VO_2 peak conditions compared with rest, with the 60% condition displaying the highest values.

Task Congruency by Condition revealed a significant decrease in response accuracy for incongruent trials in 40%, $t(26)=2.7$, $p<.05$, and 60% VO_2 peak conditions, $t(26)=3.2$, $p<.01$, compared to rest. No significant differences were found between the two exercise conditions for the incongruent trials, $t(26)=.02$, $p>.05$ (see Figure 9). In addition, no significant differences were found between conditions for congruent trials, $p>.05$.The 3-way rANOVA for RT similarly revealed a main effect of Condition, $F(2,25)=9.1$, $p<.001$, $\eta^2_p = .38$, and Task Congruency, $F(1,26)=282.7$, $p<.001$, $\eta^2_p = .90$. As anticipated, shorter RT was found for congruent relative to incongruent trials. In terms of Condition, the 60%

VO_2 peak condition resulted in faster RT than rest or the 40% VO_2 peak condition. No significant difference was observed between rest and 40% VO_2 peak conditions. In addition, a significant Time main effect was also observed, $F(2,25)=13.3$, $p<.001$, $\eta^2_p = .47$. Post hoc Bonferroni *t* tests revealed that participants responded significantly faster across successive time blocks (Block 1: $M = 337.3$ ms, SE = 11.3; Block 2: $M = 327.9$ ms, SE = 11.6; Block 3: $M = 316.7$ ms, SE = 10.8), $p<.05$.

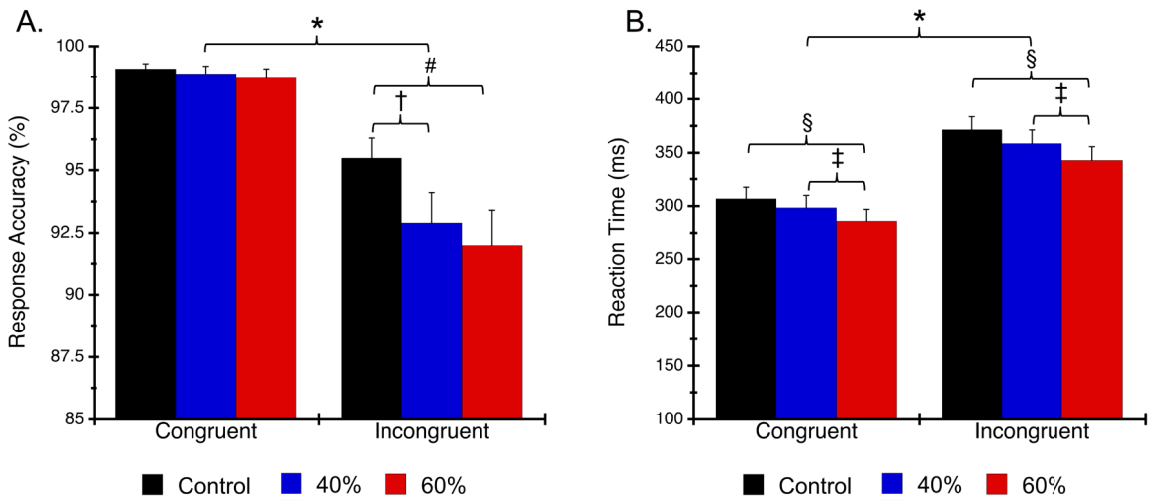

Figure 9. Mean (±) SE behavioral task performance for: A) response accuracy (%) and B) reaction time (ms) on the flanker task. *Congruency main effect: congruent trials significantly different from incongruent trials; #Condition × Task interaction: control condition significantly different from 60% for incongruent trials only; †Condition × Task interaction: control condition significantly different from 40% on incongruent trials only; §Condition main effect: 60% significantly different from control condition; ‡Condition main effect: 60% significantly different from 40% condition.

N2 Amplitude. Analyses revealed a significant main effect of Task Congruency, $F(1,26)=23.2$, $p<.001$, $\eta^2_p = .47$, which was superseded by Condition x Congruency, $F(2,25)=3.6$, $p<.05$, $\eta^2_p = .22$, and Congruency x Time, $F(2,25)=13.4$, $p<.001$, $\eta^2_p = .52$,

interactions. Post hoc Bonferroni corrected *t* tests of Congruency within each Condition revealed greater congruency effects in the exercise conditions (40%: 1.7μV and 60%: 1.4μV) compared to the rest condition (0.7μV), $p<.05$. For the Congruency x Time interaction, *t*-tests indicated more negative amplitudes over time for congruent conditions while amplitudes for incongruent conditions become more positive over time, $p<.05$. A Condition main effect approached significance at $p=.07$, with both exercise conditions displaying more negative amplitudes compared to the rest condition (Figure 10).

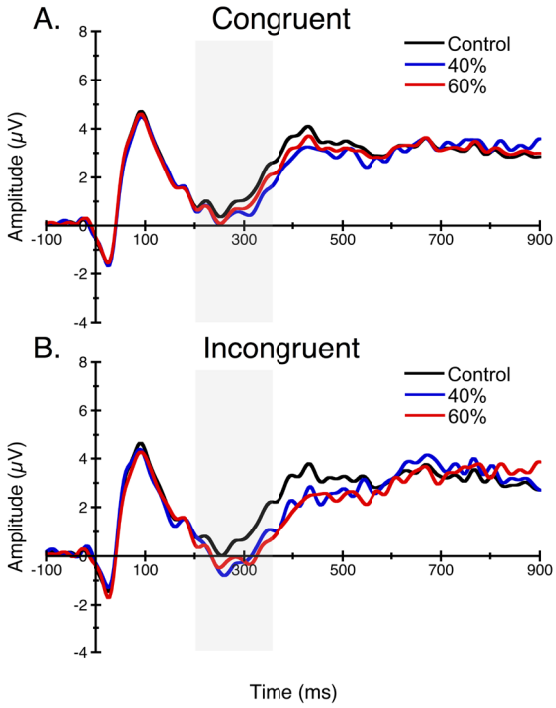

Figure 10. Stimulus-locked grand average ERP waveforms for N2 by condition for congruent (A) and incongruent (B) flanker conditions averaged across frontocentral midline electrode sites (Fz, FCz, and Cz). Shading highlights the N2 time window of 200–350 ms post-stimulus onset.

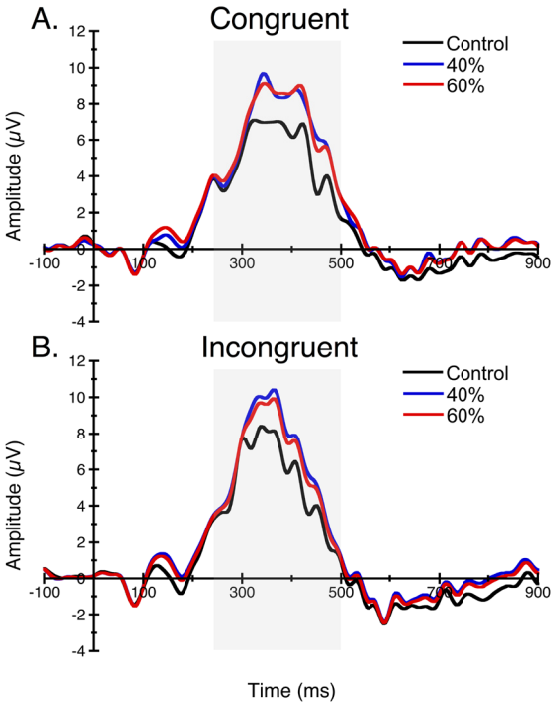

Figure 11. Stimulus-locked grand average ERP waveforms for P3 by condition for congruent (A) and incongruent (B) flanker conditions averaged across centroparietal midline electrode sites (Cz, CPz, and Pz). Shading highlights the P3 time window of 250–500 ms post-stimulus onset.

P3 Amplitude. Analyses revealed a significant main effect of Condition, $F(2,25)=10.5$, $p<.001$, $\eta^2_p = .46$, with both exercise conditions resulting in larger amplitudes compared to rest (see Figure 11). A Congruency main effect, $F(1,26)=9.8$, $p<.01$, $\eta^2_p = .27$, revealed smaller amplitudes for congruent trials compared to incongruent trials. A significant Time main effect, $F(2,25)=6.5$, $p<.01$, $\eta^2_p = .34$, showed reduced amplitudes over each time block (Figure 12), $p<.01$. Lastly, a Site main effect, $F(2,25)=123.7$, $p<.001$, $\eta^2_p = .31$, revealed larger amplitudes displayed at Pz (8.68µV) and CPz (8.50µV) electrode sites compared to Cz (8.25µV). No significant interactions were observed for P3 amplitude (Figure 13).

DISCUSSION

The aim of this study was to examine neurophysiological and behavioral correlates of cognitive control elicited by a modified flanker task while exercising at low (40% VO_2 peak) and moderate intensity (60% VO_2 peak) relative to a no-exercise seated control condition. A secondary aim was to examine cognitive control processes at several time points during a 31 min bout of acute exercise to determine whether cognition is selectively influenced by the duration of exercise.

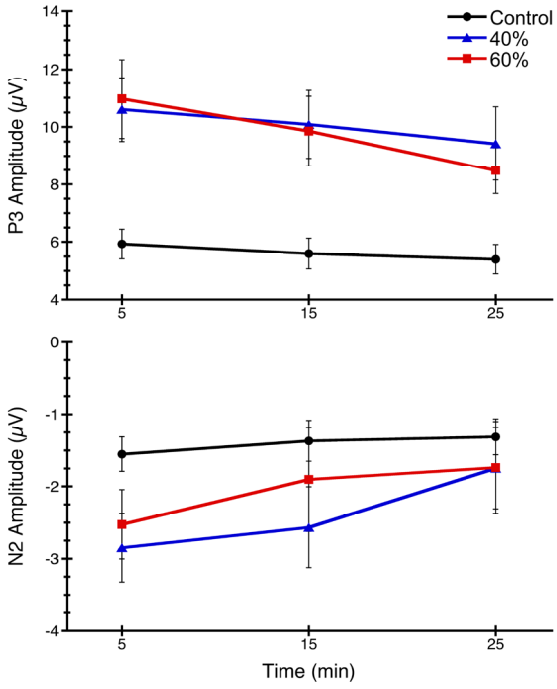

Figure 12. Amplitudes for P3 and N2 ERP components averaged across 6.5 min trial blocks presented at 5, 15, and 25 min during exercise.

Behavioral findings revealed impaired response accuracy for the flanker task during exercise, regardless of intensity. However, this decrease in accuracy during exercise only occurred for the more challenging incongruent flanker trials. In terms of RT, participants responded faster during the 60% VO_2 peak condition relative to the 40% VO_2 peak and resting conditions, which did not differ from one another. There was a trend, however, supporting a beneficial dose response effect of exercise intensity on RT. Neurophysiological findings revealed significantly increased N2 amplitudes (i.e., more negative) during both exercise conditions, which were particularly observed in response to the incongruent flanker task condition (i.e., the task condition requiring greater amounts of cognitive control). Increased P3 amplitude was also found during both exercise conditions, particularly at centroparietal electrode sites, although notably the amplitude of the P3 decreased across time for both exercise and rest conditions. Together, these findings suggest divergent effects of exercise on behavioral task responses accompanied by an upregulation of cognitive control during a 31 min bout of aerobic exercise.

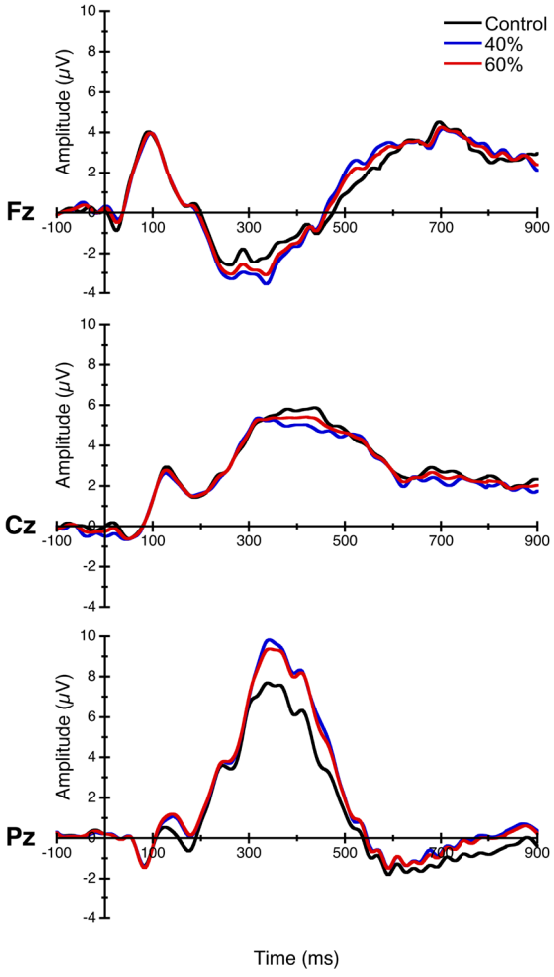

Figure 13. Stimulus-locked grand average ERP waveforms at Fz, Cz, and Pz electrode sites by condition.

Table 3. Behavioral and ERP results by condition and time.

	5-min	15-min	25-min
Response Accuracy (%)			
Congruent			
Control	99.3 ± 0.2	99.5 ± 0.2	98.5 ± 0.6
40%	98.9 ± 0.3	99.2 ± 0.3	98.6 ± 0.6
60%	98.5 ± 0.6	98.7 ± 0.4	98.8 ± 0.3
Incongruent			
Control	95.6 ± 1.0	95.9 ± 0.6	94.9 ± 1.0
40%	92.7 ± 1.3	92.8 ± 1.3	93.2 ± 1.2
60%	90.9 ± 1.7	92.5 ± 1.6	92.7 ± 1.2
Reaction Time (ms)			
Congruent			
Control	311.0 ± 11.9	308.3 ± 10.9	300.6 ± 11.1
40%	313.2 ± 11.7	296.9 ± 13.1	285.1 ± 10.9
60%	294.4 ± 12.0	284.2 ± 10.7	278.9 ± 11.1
Incongruent			
Control	378.9 ± 13.1	373.4 ± 12.2	361.8 ± 12.4
40%	373.3 ± 13.3	362.0 ± 14.6	340.2 ± 12.4
60%	353.0 ± 13.5	342.5 ± 12.9	333.3 ± 12.5
N2 Amplitude (μV)			
Congruent			
Control	-0.9 ± 0.3	-1.1 ± 0.3	-1.2 ± 0.4
40%	-0.8 ± 0.7	-1.9 ± 0.7	-2.6 ± 0.6
60%	-0.7 ± 0.5	-1.6 ± 0.8	-1.7 ± 0.7
Incongruent			
Control	-2.2 ± 0.2	-1.6 ± 0.2	-1.5 ± 0.3
40%	-3.5 ± 0.6	-3.3 ± 0.7	-3.1 ± 0.5
60%	-4.3 ± 0.5	-2.2 ± 1.2	-1.8 ± 0.8
P3 Amplitude (μV)			
Congruent			
Control	5.6 ± 0.6	5.4 ± 0.6	5.2 ± 0.5
40%	9.8 ± 1.4	9.7 ± 1.6	8.9 ± 1.4
60%	10.2 ± 1.7	9.3 ± 1.2	7.8 ± 0.8
Incongruent			
Control	6.3 ± 0.5	5.8 ± 0.6	5.6 ± 0.6
40%	11.4 ± 1.0	10.5 ± 1.1	10.0 ± 1.5
60%	11.8 ± 1.3	10.4 ± 1.3	9.1 ± 1.0

As expected and replicating a large body of evidence (see 23 for a review), findings indicated impaired accuracy and longer reaction times for trials with high levels

of conflict (incongruent trials) relative to trials with low levels of conflict (congruent trials). Further, impaired response accuracy was observed for the flanker task during both exercise conditions, but this decrease in accuracy only occurred for the more challenging incongruent flanker trials. No such effect was observed for congruent trials, suggesting that task conditions that elicit a higher level of conflict and require greater amounts of cognitive control are more selectively influenced by acute exercise. Using a shorter bout of exercise performed at an intensity approximating the 40% VO_2 peak condition in the current study, Pontifex and Hillman (124) similarly found disruptions in response accuracy only for the incongruent flanker task trials. Schmit et al. (128) had participants complete the flanker task while cycling at strenuous intensity until exhaustion and found a lower frequency of errors during rest than when exercising for the incongruent flanker trials but not for congruent trials. Yagi et al. (141) used moderate-to-vigorous intensity aerobic exercise (~65-75% HRmax) on a cycle ergometer to assess exercise-induced activation while performing a visual and auditory oddball task. Participants performed the oddball task during a 10 min rest period, a 10 min exercise bout, and a 10 min recovery period. Behavioral findings for the visual oddball task (auditory excluded) indicated similar reductions in response accuracy during exercise compared to rest or recovery, with nonsignificant increases in reaction time. Interestingly, others have shown no effect of moderate-to-vigorous intensity aerobic exercise on accuracy (e.g., 142). For instance, Davranche and McMorris (143) assessed behavioral performance measures during a 20 min steady-state cycling exercise at ventilatory threshold, i.e., the point at which ventilation begins to increase nonlinearly with increases in work rate (144).During exercise, participants completed a Simon task, which required participants to respond to

task-relevant features of a stimulus (color) while inhibiting the task-irrelevant features (spatial location). Although accuracy was unaffected by exercise, the congruency effect in the Simon task (i.e., Simon effect) appeared more pronounced during exercise compared to rest, suggesting that response inhibition is deteriorated during exercise. Collectively, these findings suggest a differential effect of acute exercise on select aspects of cognitive functioning. In 2007, Pontifex and Hillman called for increased research aimed at examining the effects of acute exercise on a variety of tasks that engage different cognitive control and executive functions. This suggestion remains understudied and warrants investigation.

In contrast to the findings on response accuracy, we observed a beneficial dose-response effect of exercise intensity on RT. Specifically, the 60% VO_2 peak condition resulted in faster response times relative to the 40% VO_2 peak and control conditions, although a nonsignificant trend supported a dose-dependent effect of exercise intensity on RT. Moreover, although there was no significant influence of exercise duration on RT, there was a nonsignificant trend for faster RT across time during exercise. These observed improvements in RT were not accompanied by a reduction in accuracy (i.e., no speed-accuracy tradeoff). Others have reported that increased physiological arousal during exercise results in faster speed of processing (142) and the limited effect of exercise intensity on accuracy may be due to the failure to select cognitive tasks that are sensitive enough to detect exercise-induced changes in performance accuracy. For instance, several authors (145-147) have argued that complex tasks are more likely to be affected by exercise than more simple tasks, particularly when cognition is assessed during exercise. The argument that complex tasks are more susceptible to acute exercise

of varying intensities is based on the interaction between central executive tasks, brain structure and function, and the physiological stress of exercise. Central executive tasks require greater prefrontal activation relative to other cognitive tasks (148) and the prefrontal cortex is particularly sensitive to stress (149-151). According to the transient hypofrontality theory proposed by Dietrich (145, 152, 153), the initiation and maintenance of exercise results in the signaling and activation of a number of peripheral and central physiological systems in order to meet the neuromuscular, autonomic, and metabolic demands of exercise (154). Given a limited attentional resource capacity, the activation of these pathways is predicted to result in a down regulation of metabolic resources to brain regions and circuits that are not essential for exercise (e.g., prefrontal activity). In this study we used a modified Eriksen flanker task, a commonly used measure of frontally-mediated cognitive control that incorporates both simple (congruent) and complex (incongruent) task types, to detect the influence of exercise intensity and duration on neurocognitive function. Our data support the notion that more complex cognitive tasks are sensitive to the subtle influences of acute exercise on RT. The effects of exercise on behavioral responses assessed post-exercise have been studied extensively (119, 120); however, research examining the effects of exercise on in-task behavioral measures is further warranted to illuminate these divergent effects of acute exercise on accuracy and RT. The current findings suggest that although response processes are faster during exercise, accuracy may be compromised.

In line with previous research (23, 25, 47), we observed a larger N2 amplitude for incongruent flanker trials relative to congruent trials. Given that the N2 is believed to be sensitive to the degree of conflict and the extent to which individuals attend to task-

irrelevant information (flanking arrows) compared to task-relevant information (target-stimulus; 24, 155, 156), our data adds to the extant literature suggesting a greater amount of cognitive control required to resolve the more difficult task condition. Exercise was also found to modulate N2 amplitude such that the 40% and 60% VO_2 peak conditions resulted in larger N2 amplitudes, particularly for incongruent task trials. Our data conflict with the findings from Pontifex and Hillman (124), who found decreases in N2 amplitude across frontal, central, and parietal electrode sites during a 6.5 min bout of cycling exercise at 60% of maximal HR. More recently, Vogt et al. (132) found that a short 5 min bout of cycling exercise did not have a measurable impact on N2 amplitudes. Unfortunately very little information was provided in their study to determine exercise intensity and participants completed the mental arithmetic problems while cycling in a virtual reality environment. Thus, important study design features may account for the discrepant findings. In the current study, we assessed cognitive control processes during a 31 min bout of steady-state exercise performed at 40% or 60% VO_2 peak. Although exercise was found to increase N2 amplitude overall, there was no influence of exercise duration on this component amplitude. Our data suggests that relative to the behavioral findings of impaired accuracy and faster RT, participants recruited greater cognitive control during task performance while exercising compared to rest. Functional magnetic resonance imaging (fMRI) and ERP studies suggest a critical role of the anterior cingulate cortex (ACC) in the N2 component, such that the ACC signals for increased recruitment of cognitive control from lateral prefrontal cortex (PFC) regions during the detection and evaluation of conflicts (25, 46, 47, 49). When viewed in light of the

behavioral findings, these results suggest that greater ACC-mediated conflict monitoring is required during exercise, particularly during the more demanding task condition.

Increased P3 amplitude was also observed across centroparietal electrode sites during exercise, suggesting an increase in the amount of attentional resources engaged during the dual-task performance (27). The increase in P3 amplitude during exercise supports the increase in N2, and suggests a greater upregulation of cognitive control and attentional resources necessary for successful task completion. Similar to our findings, Pontifex and Hillman (124) observed an increase in P3 amplitude over frontal and lateral electrode sites and interpreted this finding as a relative inefficiency of neuroelectric resources during exercise. Interestingly, and opposed to the current findings, Yagi and colleagues (141) showed reductions in P3 amplitude during exercise compared to rest and recovery periods. The authors suggest that their subjects treated exercise as a secondary task requiring the allocation of a limited resource (e.g., dual-task interference/distraction). However, it is important to note that half of the participants performed the rest, exercise, and recovery periods to the auditory oddball task first, immediately followed by the rest, exercise, and recovery periods to the visual oddball task. The other half completed the visual oddball task first. Potential residual effects of exercise may have influenced the second block of the procedure, thus washing out the initial period. Furthermore, data and results for standards (80% - Xs) and targets (20% - Os) were not discussed and exercise intensity was higher than the intensities used in the current study. Grego et al. (157) used a longer duration of moderate-intensity exercise (~66% VO_2 max for 180 min) to study the effects of fatigue on cognitive function (P3) in trained cyclists during an auditory oddball task. During the 1st and 2nd time points (mins 3 and 36) there was no difference in

P3 amplitude between rest and exercise; however, an increase in P3 amplitude emerged during the 3rd time point (min 72), peaked at the 4th time point (min 108), and was attenuated at the 5th and 6th time points (mins 144 and 180). The later changes (5th and 6th time points) occurred concomitantly with changes in insulin, cortisol, epinephrine, and norepinephrine. There were also significant increases in perceived exertion near the end of the exercise bout. The authors suggested that the improvement in cognitive function during exercise, as indexed by the increase in P3 amplitude between 60 to 120 min, may be affected (i.e., reduced) through the combined effects of arousal and central fatigue mechanisms during prolonged exercise. Results from previous studies focusing on acute physical fatigue and cognitive performance have been inconsistent (158, 159). Although we did not assess fatigue or exertion levels in this study, it is possible that cognitive performance may be altered by the duration of exercise due to activation of physiological processes during the progression to steady-state exercise. It is also possible that cardiorespiratory fitness may moderate the influence of fatigue on cognition such that higher fit individuals are less impacted by physical fatigue. We did not find a moderating influence of fitness in the current study, but we did not select participants with a wide range of fitness levels (i.e., individuals with very low vs. high levels of fitness). Future research aimed at examining concurrent cognitive, affective, and exertional responses during exercise among individuals varying widely in levels of aerobic fitness is needed.

In terms of theoretical support, the selective effect of exercise on cognitive task performance has been explained in terms of dual-task paradigms and the transient hypofrontality theory (152, 160, 161). Performing cognitive tasks while exercising may create a dual-task scenario whereby individuals' attention may be divided in an attempt to

successfully accomplish the cognitive task while maintaining appropriate metabolic, cardiovascular, and neuromuscular responses for exercise. In this study, participants completed the cognitive tasks while engaging in steady-state exercise. Our results for response accuracy and increased neurophysiological responses during exercise corroborate previous findings suggesting an inefficiency in the ability to inhibit conflicting responses during exercise (124). Similar flanker paradigms used in previous studies with healthy young adults have resulted in high levels of performance for both congruent and incongruent flanker trials (162, 163), thus a finding of impaired accuracy during exercise is meaningful. In line with the transient hypofrontality theory (145, 152, 153), it was initially hypothesized that response accuracy would be impaired during the exercise conditions due to reduced cortical resources for successful task completion. Although this theory has received some support in acute exercise contexts (123, 124), not all studies have found impaired executive functioning or cognitive control processing during exercise (128, 164). Although the accuracy and ERP data in our study provide support for this theory, the RT data do not. Clearly more work using both behavioral and neuroimaging techniques are warranted to test the tenets of this theory as it relates to acute exercise effects on prefrontally-mediated cognitive performance.

Limitations

There were several limitations in the current study. First, the design of our study may have led to adaptive and learning effects. Our behavioral and neuroelectric findings could, at least partially, be attributed to conflict adaptation over time or learning effects due to prolonged exposure to the flanker task. However, participants were

counterbalanced into each condition and were afforded a practice period prior to the initiation of each session. A second limitation relates to the impaired accuracy and ERP measures during exercise combined with the improved reaction time for the 60% VO_2 peak condition. Moreover, there was a nonsignificant trend for RT such that the 40% condition resulted in faster performance than the no-exercise control. These findings indicate the potential for a speed-accuracy tradeoff during moderate-intensity exercise, where accuracy is impaired (for incongruent trials only) yet reaction time is enhanced. Exercise increased response time efficiency during exercise but resulted in a more inefficient resolution of conflict, possibly due to increased physiological arousal. The speed-accuracy tradeoff in the present study conflicts with findings from McMorris and Hale (142) who concluded that speed of cognition is modified during exercise, while response accuracy remains relatively unaffected. More research is required to replicate our findings and further understand the nature of acute exercise and speed-accuracy tradeoffs at varying intensities. A third limitation is the restriction to low and moderate intensities of exercise only. Exercise intensities of 40% and 60% of VO_2 peak, which were characterized as low and moderate respectively, were compared to a no-exercise seated control to address dose-response effects on neurocognitive performance during exercise. Wang et al. (125) used a control and three exercise intensities at 30% HRR, 50% HRR, and 80% HRR, which represented low, moderate, and high intensities, respectively. They found impaired executive function performance on the WCST only for the high intensity condition. Due to the need for restricted movement for the EEG data collection in this study, the full range of exercise intensities were not studied. Future investigation with enhanced methodologies should include both light and vigorous

exercise intensities in addition to moderate intensities to more fully characterize the moderating influence of exercise intensity on cognition.

Conclusions

This study adds to the small body of literature that has examined changes in cognitive performance during steady-state exercise. The results further reinforce the complex relationship between acute exercise and neurocognitive performance. We observed impaired accuracy but faster response times during exercise, regardless of intensity. Neuroelectric measures indicated increased neurophysiological responses during exercise which were modulated by exercise intensity. There were no significant effects of exercise duration on behavioral or neurophysiological measures. In summary, these findings suggest divergent effects of exercise on behavioral performance measures accompanied by an upregulation of cognitive control during aerobic exercise.

CHAPTER 3: A randomized trial of aerobic exercise for improving neurocognitive function in major depressive disorder

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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 (165). 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 (166). 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 demonstrates that exercise is an effective treatment intervention for reducing depressive symptoms (167-169), which is noteworthy because it can be self-administered, cost-effective, and result in additional health benefits (e.g., cardiovascular and musculoskeletal health, improved quality of life). The evidence for the mental health benefits of exercise, although impressive for otherwise healthy individuals, is even stronger for clinical and psychiatric populations. Indeed, RCTs indicate that aerobic exercise is as effective as antidepressants (e.g., sertraline) in reducing depression (3), as well as in improving coronary heart disease (CHD) risk factors and reducing relapse rates (2, 170). However, the precise mechanisms

underlying the antidepressant effects of exercise remain unknown and comparatively understudied.

One proposed mechanism includes impaired neurocognitive function and/or cognitive deficits, which are frequently observed in MDD. For instance, depression has been linked to functional deficits in different areas of the prefrontal (PFC) and anterior cingulate cortices (ACC; 4, 171), regions implicated in attention, working memory, and cognitive control (172-174). In depressed individuals, deficits in structure and function of the PFC and ACC regions have been hypothesized to contribute specifically to sustained emotional and amygdalar processing (175, 176) and reductions in cognitive control processes that lead to an individual's inability to disengage from unwanted thoughts (31). Since cognitive control is critical for healthy affective functioning, impairments in these processes may be critically related to the persistence of other symptoms in depression, such as emotion dysregulation and rumination (92, 177). Moreover, deficits in cognitive control processes may also play a role in increasing individual vulnerability for rumination, a particularly maladaptive emotion regulation strategy that has been linked to risk for depression and other forms of psychopathology (31). As treatment efforts continue to revolutionize, it is important to consider their influence on potential neurocognitive targets in MDD.

Over 40 years ago, Aaron Beck (1) proposed a cognitive model of depression, an empirically based framework for identifying and understanding factors that sustain depressive episodes. As motivated by Beck's cognitive model of depression and the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative for developing new ways of classifying mental health disorders based on behavioral

dimensions and neurobiological measures, there has been a recent increase in investigating risk factors and mechanisms, as well as identifying treatments that may specifically target neurocognitive impairments in MDD. Cognitive impairment is frequently observed in MDD and is a common residual symptom despite antidepressant treatment (178). For instance, in an examination of 428 responders (defined as a 50% or greater reduction in overall depressive symptoms, but failure to achieve symptomatic remission) from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, ~70% of patients reported difficulties in concentration and decision-making despite a positive clinical response to 12 weeks of citalopram treatment (179). Accordingly, current treatments should focus on reducing both symptoms and cognitive outcomes in MDD. Exercise may be a particularly important behavioral treatment for MDD, considering that a large body of empirical evidence supports the influence of exercise on neurocognitive function (16, 180). Despite the parallel lines of inquiry of exercise benefits for depression and cognitive function, few studies have specifically examined the efficacy of exercise in enhancing neurocognitive function in MDD.

In one of the few studies to date that have examined the effects of exercise on cognition in MDD, Greer et al. (178) evaluated the effectiveness of exercise as an augmentation strategy for patients who had previously undergone SSRI treatment and reported persistent cognitive deficits. In a 12-week RCT, participants completed either a high (16 kcal per kilogram of body weight per week [KKW]) or lower (4KKW) dose of exercise (see TREAD trial; 181). Although both groups improved on measures of psychomotor speed, visuospatial memory, and executive function, only the high dose exercise condition yielded improvements in spatial working memory. This study is an

important first step towards examining exercise as a neurobehavioral treatment strategy for MDD, and future studies that examine the influence of exercise on established neurocognitive deficits in MDD are warranted.

The majority of studies that have investigated the benefits of exercise on cognitive processes in MDD have relied heavily on the use of behavioral performance outcomes (e.g., response accuracy, reaction time) as outcome measures of neuropsychological or neurocognitive function. Although these measures have undoubtedly advanced our fundamental understanding of cognitive deficits experienced in MDD, these measures make it challenging to make conclusions about the subtle changes in neurocognitive processes that may occur since response accuracy and reaction time performance represent end-state processes. That is, measures of accuracy and reaction time represent the end product of a series of psychological events and cognitive processes, including the detection of an auditory or visual stimulus, recognition and comparison of the stimulus with information held in working memory, and the preparation for and execution of a manual response. Due to the relative difficulties in drawing conclusions based solely on behavioral measures, more precise neuroscientific techniques may be used to investigate covert cognitive processes that may change following a behavioral intervention. One such approach is through event-related potentials (ERPs). ERPs are voltage fluctuations in the ongoing electroencephalogram (EEG) that are time-locked to an event, such as the presentation of a visual stimulus or execution of a manual response (129). The ERP is comprised of numerous underlying components that are time-locked to specific stimuli or responses and represent specific aspects of information and cognitive processing. Specifically, the N2 component is a negative deflection in the stimulus-locked ERP with

a frontocentral scalp distribution peaking approximately 200-350 ms post-stimulus (19-23). The anterior N2 is implicated in the detection of conflict, mismatch of stimuli from a mental template, and cognitive control during response inhibition (23-25). We previously found reduced N2 amplitude elicited by a flanker task in 33 individuals with MDD compared with 36 non-depressed, otherwise healthy controls. Level of self-reported rumination among this sample was also correlated with N2 amplitude. Accordingly, the N2 may serve as a potential target in the development of neurobehavioral interventions aimed at enhancing cognitive control deficits.

Therefore, the primary aims of this study were twofold: the first was to determine the effects of an 8-week moderate-intensity aerobic exercise (AE) intervention on cognitive control and symptoms of depression and rumination in individuals with MDD. A secondary aim was exploratory to determine whether changes in depressive symptoms and rumination across an exercise intervention are mediated by changes in cognitive control. We hypothesized that participants assigned to the AE condition would display greater reductions in depressive symptoms and rumination from pre-to-post intervention relative to those assigned to a placebo exercise (PE) condition. Further, we hypothesized that these reductions would be mediated by cognitive control such that symptom reduction would be greatest for individuals demonstrating the greatest pre-to-post increases in cognitive control.

METHODS

Participants

Men and women with a diagnosis of nonpsychotic MDD confirmed by the Mini-International Neuropsychiatric Interview (MINI; 77) were recruited from university counseling and psychiatric clinics, physician referrals, and advertisements around the university. Inclusion criteria included: (1) men and women aged 18–30 years; (2) confirmed MDD diagnosis by the MINI; (3) no current psychological or pharmacological treatments for depression beyond stable (>6 weeks at stable dose) selective serotonin reuptake inhibitor (SSRI) 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 or less per 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 MINI; and/or (3) pregnancy or considering becoming pregnant in women.

Recruited participants were scheduled for study entry and baseline assessments by trained clinical research staff. After determining initial eligibility, the study coordinator scheduled a secondary screening appointment for the informed consent process and baseline assessments where they completed a structured diagnostic interview, neurocognitive testing, and a maximal aerobic fitness assessment (VO_2 peak). Participants who met all inclusion criteria and completed baseline testing were randomly assigned to 8 weeks of either an AE or PE condition. At the end of the 8-week intervention, participants were invited back to the laboratory to complete the same battery

of assessments, including clinical, neurocognitive, and fitness measures following the same protocol (see Figure 14 for study diagram).

Table 4. Baseline characteristics (M ± SD) by Condition (AE, PE).

Characteristic	AE (*n*=30)	PE (*n*=30)	*F*	*p*-value
Age (years)	21.0 ± 1.9	21.2 ± 2.2	0.07	0.79
Height (cm)	164.9 ± 11.5	161.1 ± 6.1	1.24	0.28
Weight (kg)	63.6 ± 16.8	61.4 ± 8.9	0.20	0.66
BMI ($kg * m^{-2}$)	23.3 ± 5.0	23.7 ± 3.2	0.07	0.80
VO_2 peak ($mL * kg^{-1} * min^{-1}$)	36.5 ± 8.3	35.7 ± 5.6	0.77	0.77
PA (MET $min * week^{-1}$)	2372.7 ± 2387.2	2385.7 ± 2331.9	0.99	0.99
Depressive Symptoms (BDI)	24.5 ± 11.5	24.3 ± 11.9	0.004	0.95
Rumination – Total (RRS)	56.8 ± 11.6	58.6 ± 14.9	0.14	0.71
Depressive	32.7 ± 6.6	32.8 ± 7.6	0.001	0.98
Brooding	12.9 ± 3.3	14.1 ± 4.2	0.67	0.42
Reflection	11.1 ± 3.4	11.7 ± 4.5	0.17	0.69
Anxiety (BAI)	12.9 ± 8.9	13.1 ± 8.6	0.007	0.93

Note. BMI = Body Mass Index; VO_2 peak = peak aerobic fitness; PA = physical activity; BDI = Beck Depression Inventory; RRS = Ruminative Responses Scale; BAI = Beck Anxiety Inventory

Fifty-two participants with a current diagnosis of MDD (40 female; age: 20.6 +/- 1.9 years) who met the inclusion criteria were initially enrolled and randomized. Thirty-four individuals initiated participation in their assigned intervention arm (~65% attrition

rate) and 30 individuals completed the 8-week intervention with complete baseline and post-intervention data (~88% retention rate). No significant differences at baseline were observed for any demographic, behavioral, or cognitive outcome between those who finished the intervention and those who did not, *p*s > 0.05. Prior to participation in this study, all participants provided written informed consent that was approved by the Institutional Review Board at Rutgers, The State University of New Jersey.

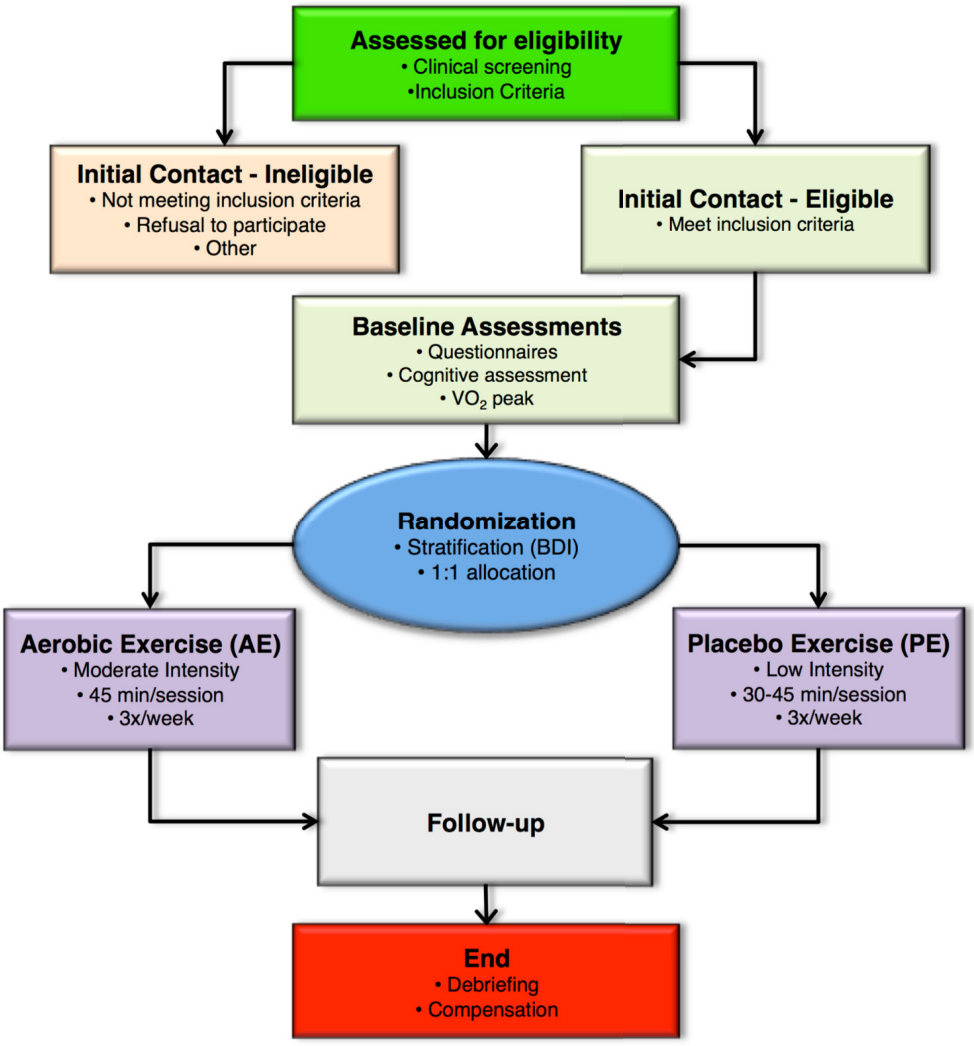

Figure 14. Study diagram. Subjects meeting inclusion criteria were randomly assigned to 8 weeks of either AE or PE.

Study Design and Randomization Procedures

The design for this study was a small-scale randomized controlled trial (RCT) of aerobic exercise on depressive symptoms, maladaptive rumination, and cognitive control that was powered to detect changes in N2 amplitude rather than other randomized treatment comparisons. Using G*Power version 3.1.9.2 (182), hypothesis testing at a two-sided $\alpha = 0.05$ and at least 12 participants finishing each condition would provide power of 0.80 to detect an effect size of 0.30 (Cohen's $d = 0.56$; see [26]). The study took place across three academic semesters from spring 2015 to spring 2016. Subjects were screened at the beginning of each semester, stratified based on current depressive symptoms, and randomly allocated in a 1:1 ratio into either AE or PE groups. Subjects were stratified according to BDI scores (Stratum A: BDI < 21; Stratum B: BDI ≥ 21) at the time of recruitment and randomly assigned to the treatment or control arms using a computer-generated number list (183). Stratification methods were used to control for between-subject variation in baseline depressive symptoms (184).

Interventions

For both treatment conditions, participants attended three 30-45 min sessions per week for 8-weeks. Depending on participant availability, most sessions occurred on non-consecutive days. Trained laboratory staff monitored participants during all sessions at 10-min intervals. Additionally, heart rate (HR) and ratings of perceived exertion (RPE) were recorded throughout each session and participants were encouraged to maintain the prescribed intensity. Adherence was also tracked and monitored across the duration of the study.

Aerobic Exercise (AE). AE consisted of 45 min of continuous steady-state exercise performed on a treadmill or cycle ergometer at a prescribed moderate-intensity corresponding to 40-65% of HR reserve (HRR), determined from HR recorded during the initial baseline fitness test. Participants were instructed and encouraged to maintain this intensity during all exercise sessions. This dose of exercise was selected based on increasing the likelihood of successful adherence and is consistent with public health recommendations (185, 186). A similar exercise regimen proved successful in a recent study of exercise as augmentation treatment for patients with MDD who had not successfully remitted with SSRI treatment (169).

Placebo Exercise (PE). PE consisted of 30-45 min of low-intensity stretching targeting major muscle groups, similar to the stretching protocol administered by Knubben and colleagues (183). Light stretching exercises were performed while seated and standing, with each muscle group being stretched for 20 sec for 3 sets, with a rest period of 40 sec between stretches. Participants were instructed on how to properly perform each stretch by trained research staff prior to each session. The PE condition was used to minimize potential demand characteristics inherent to behavioral interventions in general, and exercise interventions in particular (187). Relative to a waitlist control comparison condition, this treatment arm increased the safety of our protocol by allowing us to track adherence and monitor for any adverse events throughout the study.

General Medical History

A complete health and medical history was obtained using a self-reported medical history form designed to collect information about history and/or treatment of medical conditions, such as heart disease, high blood pressure, and diabetes. The form also assessed family history of disease, medical symptoms, past surgeries, tobacco/alcohol use, and prior and current medication use. Additionally, participants completed the Physical Activity Readiness Questionnaire (PAR-Q; 188) to ensure that it was safe to engage in the aerobic fitness assessment and subsequent exercise program.

MDD Diagnosis

The Mini Neuropsychiatric Diagnostic Interview (MINI; manic/hypomanic episodes, obsessive-compulsive disorder, substance and alcohol use disorders) was used to confirm clinical diagnosis of MDD. The MINI is a brief structured interview that has been used extensively to aid in making diagnoses of Diagnostic and Statistical Manual of Mental Disorders, Fourth and Fifth Editions (DSM-IV, V) and International Classification of Diseases-10 (ICD-10) psychiatric disorders. The reliability and validity of this instrument has been previously established (77, 82, 83). Important to the current study, it can be administered in a shorter period of time than other clinical interviews such as the SCID (Structured Clinical Interview for the DSM-IV; 77). All interviewers received supervised training in the use of the MINI and had previous experience in administering structured clinical interviews with psychiatric patients (see [26] for a similar protocol).

Depressive Symptoms

The Beck Depression Inventory-II (BDI-II; 80), a 21-item, self-report inventory of the severity of current depressive symptoms, was used to assess severity of depressive symptoms. Higher total scores reflect greater subjectively perceived depressive symptomatology. The BDI-II in this sample demonstrated good internal consistency (21 items; $\alpha = 0.91$) at baseline.

Ruminative Thought Patterns

The Ruminative Responses Scale (RRS; 189) was used to assess maladaptive ruminative thought patterns at baseline and post-intervention. The RRS is a 22-item, self-report questionnaire describing thoughts and responses that are self-focused, symptom-focused, and focused on the potential consequences and causes of their depressed mood. The scale includes three subscales, including depressive, brooding, and reflective ruminations (190). The total RRS score ranges from 22 to 88, with the depression subscale ranging from 12 to 48 and the brooding and reflection subscales ranging from 5 to 20. In the present study, the RRS scale demonstrated appropriate internal consistency (22 items; $\alpha = 0.90$) at baseline.

Cardiorespiratory Fitness and Physical Activity

Cardiorespiratory fitness (VO_2 peak) was assessed using a modified Bruce protocol on a motor-driven treadmill (191). VO_2 peak reflects the maximum capacity of an individual to transport and utilize oxygen during exercise of progressively increasing intensity (achieving or approaching maximal effort) and has been shown to improve following similar exercise interventions in a clinically depressed population (169). During this test,

participants began walking on a treadmill while the speed and incline were gradually increased every 2 min until volitional exhaustion or VO_2 peak criteria were met. A Polar heart rate (HR) monitor (Polar Electro, Finland) was used to monitor HR throughout the test. Participants' ratings of perceived exertion (RPE; 192) were taken 1 min into each stage using the RPE scale, which ranges from 6 (minimal) to 20 (maximal) and correlates with HR during exercise (193). RPE measures perceived physical effort during exercise. Relative VO_2 peak ($mL*kg^{-1}* min^{-1}$) was determined using indirect calorimetry and was established as the maximal average oxygen consumption when at least three of the following four criteria were met: (1) a plateau in VO_2 despite an increase in workload, (2) heart rate (HR) within 10 beats per min (bpm) of age-predicted maximum (220 bpm minus age in years), (3) respiratory exchange ratio (RER) greater than 1.10, or (4) RPE greater than or equal to 17. Oxygen consumption was measured through indirect calorimetry using a ParvoMedics True Max 2400 Metabolic Measurement Cart (ParvoMedics, Inc., Sandy, UT) and averaged over 15 sec intervals. Following completion of the test, a 3-5 min cool-down was performed at 2.5 mph and 0% grade to ensure participants returned to near baseline cardiovascular values. HR was recorded during the fitness assessment and later used to define individual training zones during the intervention. Fitness was re-assessed upon completion of the 8-week intervention using the same procedures.

In addition to aerobic fitness, physical activity levels were assessed using the International Physical Activity Questionnaire (IPAQ; 194). The IPAQ is the most commonly used subjective measure of PA (195) and was used to evaluate changes in PA

levels across the intervention. PA level is represented as MET mins/week, an index that reflects the metabolic cost of PA.

Cognitive control task

A modified flanker task (84) was presented using E-Prime Professional, version 2.0 software (Psychology Software Tools, Inc., Pittsburgh, PA). Participants were presented with five arrows aligned horizontally on the center of the screen and instructed to press a button as quickly and accurately as possible depending on the direction of the centrally located target arrow. The flanker task was composed of congruent trials, with arrows pointing in the same direction (e.g., <<<<<), and incongruent trials, where the target arrow is flanked by arrows pointing in the opposing direction (e.g., <<><<). Trials began with a white fixation cross (+) in the center of a black screen for 500 ms, followed by 1.5 cm tall x 8 cm long white arrows centered focally on a black background for 100 ms with a response window of 1500 ms. A random inter-stimulus time interval of 900, 1100, or 1300 ms was used between each visual fixation cross and the stimulus in order to minimize anticipatory responses. Following verbal and on-screen instructions, participants completed 20 practice trials where performance feedback was provided and any remaining questions were resolved to ensure sufficient familiarization and understanding of the task. After the practice session, participants completed two blocks of 120 equiprobable, randomly selected congruent and incongruent trials with a 2 min rest period between blocks. The stimuli were presented on a monitor at an average distance of 70 cm centered to the nasion, with the vertical and horizontal visual angles measuring 1.2° and 6.6°, respectively. Behavioral performance measures of response accuracy (%

correct) and reaction time (ms) were derived from this task. In addition to behavioral measures, EEG data were simultaneously collected to derive N2 ERP amplitudes.

Event-Related Potentials

Continuous EEG activity was recorded from 32 scalp sites using a BrainVision actiCap with active electrodes (Brain Products GmbH; Munich, Germany) arranged in accordance with an extended international 10-20 system (196) and an Electrical Geodesics, Inc. (EGI; Eugene, OR, USA) amplifier system (20 K nominal gain, bandpass = .1-100 Hz). Electrooculogram (EOG) activity was recorded from electrodes placed above and below (VEOG), and to the side (HEOG) of each eye. Continuous data were visualized in NetStation 4.0, initially referenced to the vertex electrode (Cz), and digitized continuously at 500 Hz with a 24-bit analog-to-digital converter. Impedances were maintained below 10 kΩ throughout the duration of the experiment.

Data were exported from NetStation 4.0 to the ERP PCA toolkit (197) and bandpass filtered with a low-pass frequency of 30 Hz and high-pass frequency of 0.1 Hz. Data were then adjusted for DC offset and manually inspected for periods with large movement-related artifacts (e.g., eye-blinks, eye movement, and muscle activity), which were subsequently removed. Stimulus-locked epochs were then created using a 100 ms pre-stimulus to 1,000 ms post-stimulus period. Remaining eye blinks were removed from epoched data using ICA blink templates in the ERP PCA Toolkit, with one generated from the current dataset of all subjects and one provided by the author. ICA components that correlated at 0.9 with scalp topographies of either blink template were removed. Trials with a difference of 100 μV between minimum and maximum values in that trial or

channels differing in the epoch by more than 30 μV from the neighboring 6 closest channels were marked bad. Trials with >10% of channels marked as bad were also removed. Remaining bad channels were corrected through interpolation obtained from "good" channels of the scalp voltage field within each segment. Lastly, epochs were re-referenced to the left and right mastoids (90, 91), averaged by flanker trial type, and baseline corrected using the 100 ms pre-stimulus period. Correct trials were averaged to determine N2 ERP amplitudes.

Consistent with previous ERP research (23, 74, 198-200) and due to the scalp distribution reflecting the component of interest, amplitude measures of both grand averaged ERP and temporal-spatial factors (TFSFs) were assessed at frontocentral (Fz, FCz, and Cz) electrode sites for the N2 component. A mean amplitude approach with an *a priori* time window for the N2 grand averaged ERP was used to reduce selection bias (18) and defined as the mean amplitude within a 200-350 ms window post-stimulus onset (21-23). Individual mean amplitudes at each electrode site pre- and post-intervention were calculated and exported for analyses.

ERP PCA Toolkit was used to extract ERP components through temporospatial Principal Components Analysis (PCA; 197, 201). PCA took place on all subject trial averages in two steps: (1) temporal PCA with Promax rotation on all time points from single subject averages as variables, with subjects and electrodes as observations and (2) spatial PCA with Infomax rotation on electrode sites as variables, with subjects and temporal factors as observations. Scree plots employing the parallel test were used to determine the number of factors prior to each step (202). PCA was conducted separately for pre- and post-intervention files to avoid assuming equal scalp locations and

component latencies, thus variable TFSFs were produced. Step (1) produced 12 temporal factors (TFs) pre-intervention and 15 TFs post-intervention, while step (2) produced 4 spatial factors (SFs) pre-intervention and 4 SFs post-intervention. The scalp distribution and timing of the N2 component was most closely represented by TF9SF1 pre-intervention and TF7FS1 post-intervention (Figure 17). Based on visual inspection of TFSFs, individual mean amplitudes within a 260-450 time window post-stimulus onset were calculated for each electrode site pre- and post-intervention and exported for analyses.

Data Analysis

Descriptive statistics were first performed on participant demographic, clinical, neurocognitive, and fitness data. Group differences in baseline measures and symptom scores were evaluated by separate independent samples *t* tests or Chi-square tests for categorical data. All cognitive outcomes were assessed for normality prior to conducting analyses. Separate repeated measures analyses of variance (RM ANOVA) were conducted with Condition (AE, PE) as the between subjects variable and Time (Pre, Post) as the within subjects variable to test the effects on depressive symptoms, rumination, and aerobic fitness. For behavioral measures of response accuracy and reaction time, 3-way RM ANOVAs were conducted with Condition as a between subjects variable while Time and Congruency (Congruent, Incongruent) served as within subjects variables. For N2 grand average and TFSF amplitudes, separate four way RM ANOVAs were conducted with Condition as a between-subjects variable while Time, Congruency, and Site (Fz, FCz, Cz) served as within subjects variables. Trials with accuracy, reaction

times, or amplitudes beyond the individual mean ± 3 SD for each trial type were excluded to reduce the effect of outliers. The anterior N2 is most robust and frequently examined at frontocentral midline electrode sites (23, 138); thus, statistical analyses were performed using Fz, FCz, and Cz electrodes. Planned comparisons were conducted using Bonferroni corrected *t* tests. The family-wise alpha level for all tests was set at $p = 0.05$ prior to Bonferroni correction and probability values were adjusted when appropriate with the Greenhouse-Geisser epsilon correction for non-sphericity (203). Previous research indicates that comorbid anxiety-related disorders and psychotropic medications may influence neural activation patterns and psychomotor speed (95, 96, 204), thus we reanalyzed outcomes while excluding those participants with comorbid diagnoses or current psychotropic medication use. Partial eta squared (η^2_p) values were reported to demonstrate the magnitude of effect sizes (ES) following ANOVAs, with 0.01–0.059 representing a small effect, 0.06–0.139 a medium effect, and >0.14 a large effect (98). ES for any pairwise comparisons were presented using Hedges' g statistic (99). A critical alpha level of $p < 0.05$ was adopted for all significance tests.

Lastly, bivariate correlations were conducted to examine the relationship between change scores in N2 amplitudes, depressive symptoms, and rumination. Exploratory mediation analyses were also conducted to further explore these relationships. The mediation model postulated that the exercise intervention would predict the mediating variable, i.e. change in N2 amplitude, which in turn would predict lower depressive symptom scores at post-intervention (205). Separate mediation analyses were conducted using PROCESS software for SPSS (v2.15; 206) to determine whether changes in N2 grand average amplitude or N2 TFSF amplitude mediated the relationship between

treatment condition and reductions in post-intervention depressive symptoms. For both analyses, regression was conducted for path a (predictor → mediator), path b (mediator → outcome), path c (predictor → outcome), and path c' (true indirect effect). To determine the significance of the mediation (true indirect effect), bootstrapped 95% confidence intervals were constructed based on 5000 bootstrapped resamples (206). Statistical significance of the mediation was achieved if the estimated 95% confidence interval for the indirect effect (paths c-c') did not overlap with zero.

RESULTS

No significant between group differences were found for any of the demographic, clinical, neurocognitive, or fitness measures at baseline (*p*s > 0.28; see Table 4). In line with higher rates of MDD among women (207, 208), more females than males were eligible for inclusion in this study (24 females, 6 males). Preliminary analyses revealed no significant gender differences in depressive symptoms, rumination, or baseline neurocognitive measures; however, as expected, males had higher VO_2 peak values than females (42.2 ± 4.2 $mL*kg^{-1}* min^{-1}$ vs. 34.6 ± 6.7 $mL*kg^{-1}* min^{-1}$). Data were therefore collapsed across gender for all subsequent analyses. As expected, our manipulation check of intensity found significant differences by Condition, such that the AE group displayed higher average HR (147.8 bpm) and RPE (12.6) values compared to PE (HR = 86.1 bpm, RPE = 8.1).

Depressive symptoms and rumination

The two way RM ANOVA on depressive symptoms (BDI-II score) revealed a significant main effect of Time, $F(1,28) = 22.1$, $p < 0.001$, $\eta^2_p = 0.44$, which was superseded by a significant Time x Condition interaction, $F(1,28) = 4.54$, $p = 0.04$, $\eta^2_p = 0.14$. Follow-up Bonferroni corrected *t* tests of the Time x Condition interaction revealed greater pre-to-post reductions in depressive symptoms for the AE (ES = 0.569; 58% decrease) relative to PE group (ES = 0.243; 22% decrease), see Figure 15. For rumination (RRS score), there was a significant Time main effect, $F(1,28) = 6.85$, $p = 0.014$, $\eta^2_p = 0.20$, indicating an overall decrease in rumination following both interventions (12.6% reduction). The depressive and brooding subscales of the RRS showed similar Time main effects, *p*s < 0.01, whereas no pre-to-post effects were found for the reflection subscale, $p = 0.53$. Although the AE group displayed a 19% reduction (ES = 0.333) in total rumination compared to a 6% reduction (ES = 0.064) in the PE group, the Time x Condition interaction failed to reach significance, $F(1,28) = 1.68$, $p = 0.21$, $\eta^2_p = 0.06$.

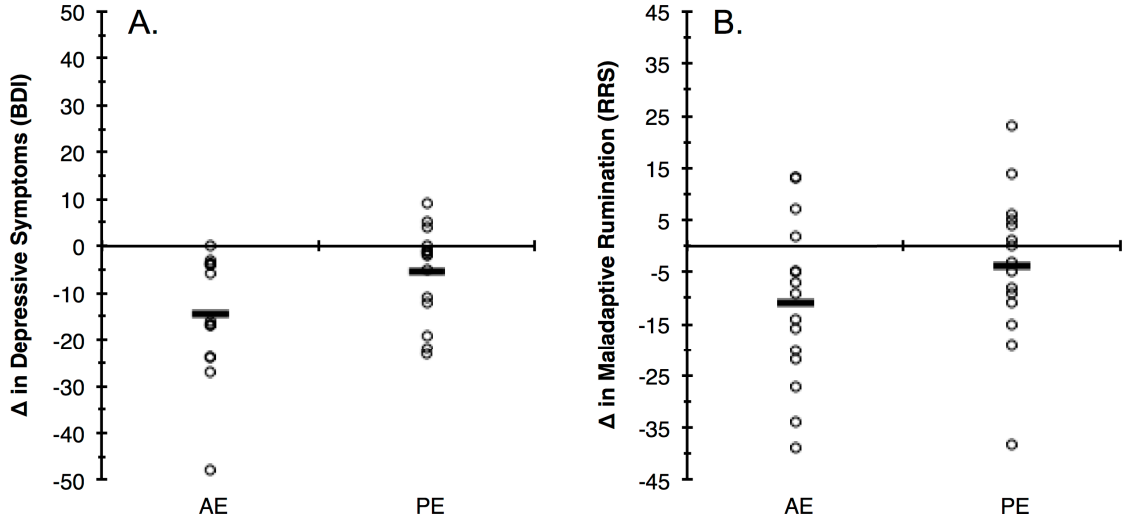

Figure 15. Change in depressive symptoms (A.) and rumination levels (B.) for AE and PE. The AE group displayed a significantly larger change in depressive symptoms compared to the PE group.

Cardiorespiratory Fitness (VO_2 peak) and Physical Activity

No significant Time main effect, $F(1,28) = 1.96$, $p = 0.17$, $\eta^2_p = 0.07$, or Time x Condition interaction, $F(1,28) = 1.42$, $p = 0.24$, $\eta^2_p = 0.05$, was found for VO_2 peak, indicating no significant changes in aerobic fitness following either intervention group. These results also indicate the AE group (E= 0.195; +5.7%) did not significantly increase their aerobic fitness compared to the PE group (ES = 0.002, +0.5%). However, analysis of self-reported PA levels (IPAQ) revealed a significant Time x Condition interaction, $F(1,28) = 4.34$, $p = 0.046$, $\eta^2_p = 0.13$, such that individuals in the AE group reported a large increase in PA (ES = 0.345; +2,807.5 MET min/week) relative to reduction in PA in the PE group (ES = 0.00;-68.76 MET min/week). No other significant main effects or interactions were found.

Flanker accuracy and RT

For response accuracy, there was a significant main effect of Congruency, $F(1,28) = 4.50$, $p = 0.043$, $\eta^2_p = 0.14$, indicating better performance for congruent (93.3%) relative to incongruent (89.9%) flanker trials. A Time x Condition interaction approached significance, $F(1,28) = 3.13$, $p = 0.088$, $\eta^2_p = 0.10$, with a 1.4% increase in the AE group relative to a 2.0% decrease in the PE group. No further main effects or interactions were found, $ps > 0.05$. Similar to response accuracy, the analysis for RT revealed a significant main effect of Congruency, $F(1,28) = 37.18$, $p < 0.001$, $\eta^2_p = 0.57$, indicating increased response latency for incongruent (694.4 ms) relative to congruent (576.5 ms) trials. This analysis also revealed significant Time x Congruency, $F(1,28) = 4.33$, $p = 0.047$, $\eta^2_p = 0.13$, and Time x Condition, $F(1,28) = 4.34$, $p = 0.047$, $\eta^2_p = 0.13$, interactions. Post hoc

Bonferroni corrected *t* tests of the Time x Congruency interaction revealed significant reductions in the RT congruency effect (incongruent RT – congruent RT) from pre-post intervention (Pre: 145.97 ms, Post: 89.73 ms). This effect was driven by a 57.97 ms reduction for incongruent trials compared to a 1.73 ms reduction for congruent trials. Decomposition of the Time x Condition interaction revealed a significant 73.45 ms reduction in RT for the AE group relative to a 13.76 ms increase in the PE group (Figure 16). No other significant main effects or interactions were found, *p*s > 0.05.

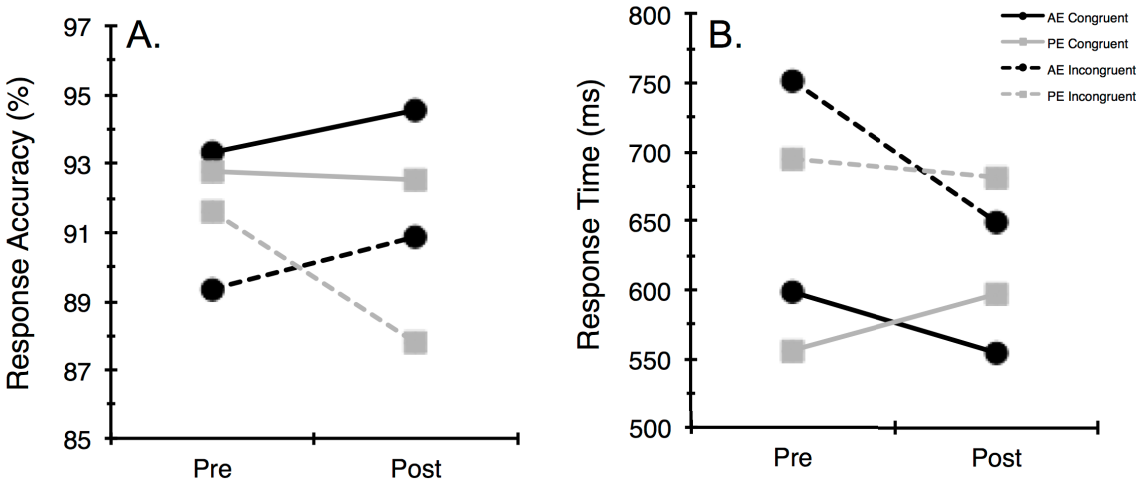

Figure 16. Pre-to-post response accuracy (A.) and reaction time (B.) scores for congruent and incongruent trials of the flanker task. The AE group displayed significantly faster reaction times compared to the PE group following the 8-week intervention.

N2 amplitude

The mixed model two-way ANOVA for the grand averaged N2 amplitude revealed significant Congruency, $F(1,28) = 3.97$, $p = 0.05$, $\eta^2_p = 0.12$, and Site main effects, $F(2,27) = 15.39$, $p < 0.001$, $\eta^2_p = 0.53$. Follow-up Bonferroni corrected *t* tests for

congruency revealed more negative N2 amplitudes for incongruent (4.20 μV) compared to congruent task trials (4.75 μV). Follow-up tests of the Site main effect revealed more negative amplitudes from frontal to central electrode sites (Fz: 3.72 μV; FCz: 4.48 μV; Cz: 5.22 μV). No additional significant main effects or interactions were observed, *p*s > 0.05 (Figure 18).

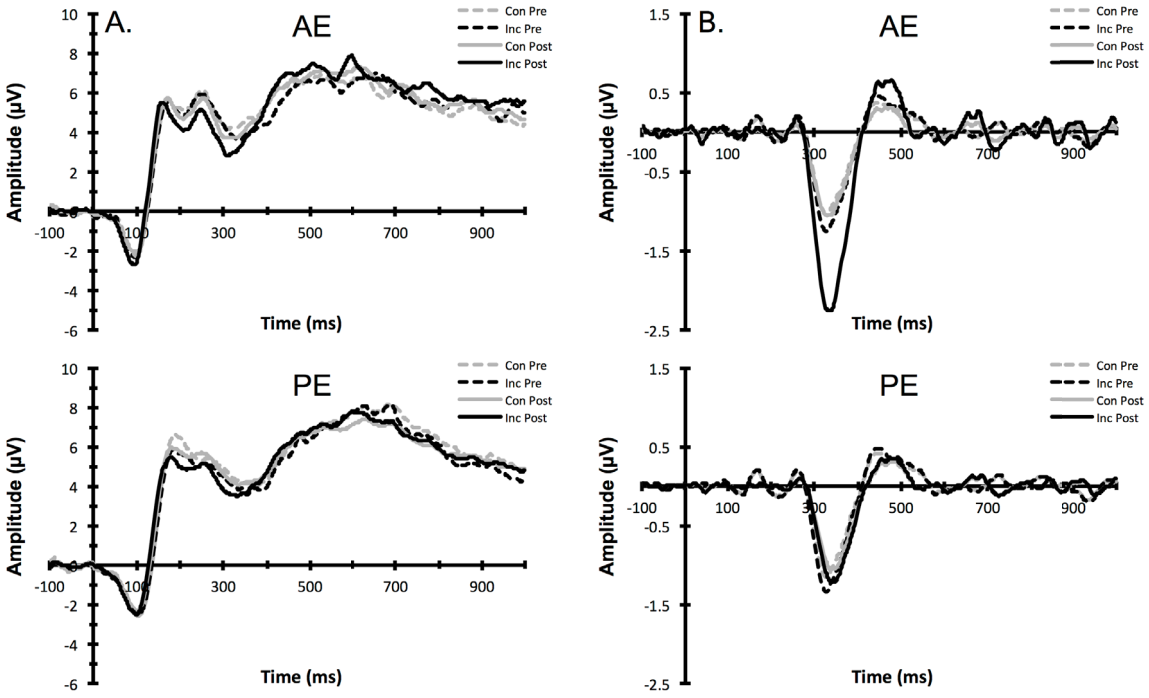

Figure 17. Stimulus-locked grand average ERP waveforms for the N2 component (A.) and N2 TFSF (B.) across frontocentral electrode sites (Fz, FCz, Cz) for AE (top panels) and SE (bottom panels). N2 TFSF amplitude increased for incongruent trials following 8 weeks of AE relative to PE.

For the N2 TFSF, the RM ANOVA revealed significant Congruency, $F(1,28) = 11.48$, $p = 0.002$, $\eta^2_p = 0.29$, and Site main effects, $F(2,27) = 11.70$, $p < 0.001$, $\eta^2_p = 0.46$. Follow-up *t* tests of the Congruency main effect found more negative amplitudes for incongruent (-0.84 μV) relative to congruent (-0.50 μV) task trials. The follow-up *t* tests

of the Site main effect showed more negative N2 amplitudes at frontal relative to central electrode sites (Fz: -0.73 μV; FCz: -0.67 μV; Cz: -0.64 μV). These main effects were superseded by a significant Time x Congruency x Condition interaction, $F(1,28) = 4.21$, $p = 0.05$, $\eta^2_p = 0.13$. Decomposition of the three-way interaction revealed significant increases in the congruency effect (incongruent N2 amplitude – congruent N2 amplitude) for the AE group (0.679 μV) compared to the PE group (0.005 μV). A 0.677 μV increase in N2 amplitude on incongruent trials in the AE group was found compared to a 0.008 μV increase in the PE group (see Table 5). No further significant main effects or interactions were observed, *p*s > 0.05.

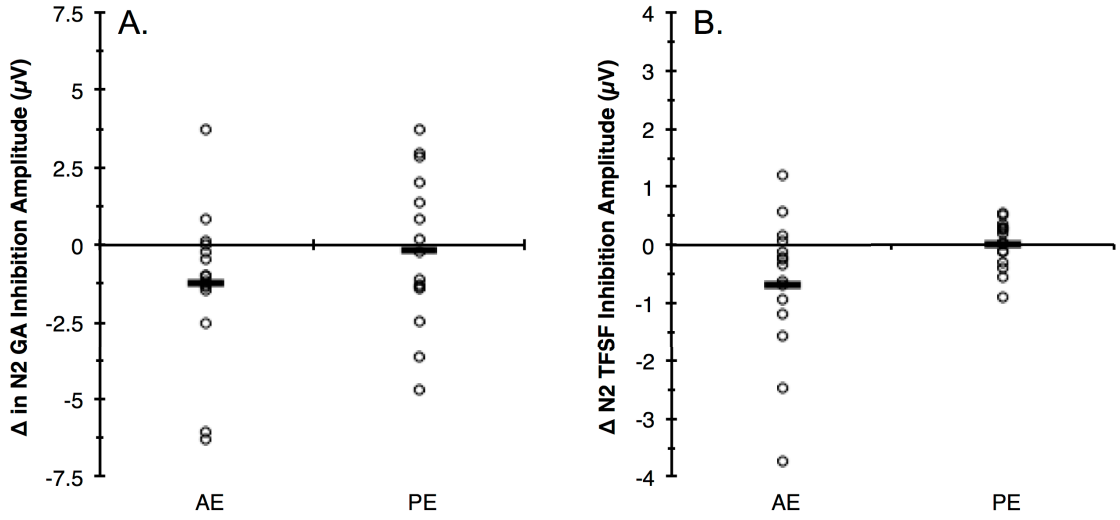

Figure 18. Change in N2 grand average inhibition (A.) and N2 TFSF (B.) amplitudes for AE and PE. N2 TFSF inhibition amplitude increased following 8 weeks of AE relative to PE.

Correlation and Mediation Analyses

Bivariate correlations were conducted between change scores in N2 grand average and N2 TFSF amplitudes and change scores in depressive symptoms and rumination to assess

whether change in depressive symptoms and ruminative thought patterns were related to change in N2 amplitude. Change in depressive symptoms, $r(28) = 0.51$, $p = 0.004$, and rumination, $r(28) = 0.58$, $p = 0.001$, were significantly correlated with change in N2 TFSF amplitude; however, these relationships were not significantly correlated with grand average N2 amplitude, ps > 0.05. Additionally, condition (AE and PE) was significantly associated with change in depressive symptoms, $r(28) = 0.36$, $p = 0.05$, and change in N2 TFSF amplitude, $r(28) = 0.37$, $p = 0.04$, suggesting the possibility of mediation.

Table 5. Mean (95% CI) values for behavioral performance and neurocognitive measures pre- and post-intervention.

	AE (n = 30)		PE (n = 30)	
	Pre	Post	Pre	Post
Behavioral Performance				
Response Accuracy (%)				
Congruent	93.3 ± 4.4	94.6 ± 5.4	92.8 ± 7.2	92.5 ± 6.8
Incongruent	89.4 ± 15.5	90.9 ± 11.8	91.6 ± 8.2	87.8 ± 13.5
Reaction Time (ms)				
Congruent	598.5 ± 124.0	554.5 ± 141.2	556.4 ± 138.1	596.9 ± 248.2
Incongruent	752.1 ± 219.9	649.2 ± 177.1	694.6 ± 277.8	681.7 ± 324.6
N2 Amplitude (μV)				
Grand Average				
Congruent	5.01 ± 3.49	4.07 ± 3.42	5.05 ± 3.49	4.88 ± 3.43
Incongruent	4.80 ± 3.52	2.66 ± 3.83	4.82 ± 3.52	4.51 ± 3.83
TFSF				
Congruent	-0.50 ± 1.06	-0.50 ± 0.89	-0.51 ± 1.06	-0.50 ± 0.89
Incongruent	-0.67 ± 1.06	-1.35 ± 1.28	-0.67 ± 1.06	-0.66 ± 1.28

Note. % = percentage; ms = milliseconds; μV = microvolts

The exploratory mediation analysis using changes in N2 TFSF amplitudes from pre-post intervention are reported along with unstandardized regression coefficients, standard errors of the mean, and 95% confidence intervals in Table 6. For the mediation model using changes in N2 TFSF amplitude as the mediating variable, paths a, b, and c reached significance. Furthermore, when changes in N2 TFSF amplitudes were controlled, treatment condition had no effect on changes in depressive symptoms (path c'). Finally, the true indirect effect for the model (c – c') was nonsignificant after using 5000 bootstrapped bias-corrected resamples of the data [95% CI: -0.85, 12.19], suggesting that changes in N2 TFSF amplitude did not account for the relationship between the condition and changes in depressive symptoms, although paths a, b, and c were all significant. Thus, the exploratory mediation analysis was nonsignificant.

Table 6. Mediation of change in N2 TFSF amplitude on change in depressive symptoms.

			95% CI	
Path/effect	*b*	SE	LL	UL
Mediation model: C → N2 TFSF → BDI				
a (C → N2 TFSF)	-0.68	0.33	-1.37	-0.01*
b (N2 TFSF → BDI)	5.44	2.18	0.96	9.91*
c (C → BDI)	-8.93	4.19	-17.53	-0.34*
c'	-5.21	4.13	-13.69	3.26
c – c'	-3.72	3.23	-12.02	0.91

Note. *b* = unstandardized regression coefficient; SE = standard error of the mean; 95% CI = 95% confidence interval; LL = lower limit; UL = upper limit; C = treatment condition; N2 TFSF= changes in N2 TFSF amplitude; BDI = changes in depressive symptoms

*Zero is not in the 95% confidence interval.

DISCUSSION

The aim of this study was to determine the effects of an 8-week moderate-intensity aerobic exercise intervention on cognitive control, symptoms of depression, and ruminative thought patterns in individuals with MDD. A secondary aim was to determine whether changes in depressive symptoms and rumination following the AE intervention were mediated by changes in cognitive control. We found significant reductions in depressive symptoms following 8 weeks of AE compared to PE. Reductions in ruminative thought patterns were observed after the intervention, with no significant differences observed between the two groups. For cognitive control, although there were no changes found for response accuracy on the flanker task, there was a significant pre-to-post reduction in RT for the AE group, primarily driven by faster response times to incongruent trials. A significant increase (i.e., more negative) in N2 amplitude to incongruent trials was also found following 8 weeks of AE, suggesting an increase in conflict monitoring processes. However, this increase in cognitive control was not shown to significantly mediate change in symptom outcomes. Taken together, these findings suggest that 8 weeks of AE results in decreased symptoms of depression and improvements in conflict monitoring processes in individuals with MDD.

In line with a large number of systematic reviews and meta-analyses indicating that exercise has similar effects as antidepressant medication and psychotherapy (167, 186, 209, 210), we found a significant and clinically meaningful reduction in depressive symptoms after 8 weeks of moderate-intensity AE. This amounted to a 58% (i.e., 14.3 pt) reduction in the AE group relative to a 22% (i.e., 5.4 pt) reduction in the PE condition. The AE intervention resulted in a reduction that meets the minimal clinically important difference (MCID) for the BDI-II (i.e., 17.5%; 211). While the 22% reduction in depressive symptoms also meets the MCID for the BDI, the duration that individuals were coping with depression was not assessed in this study. It is suggested that a MCID reduction of 32% is required for individuals dealing with depression for longer periods of time and who fail to respond to antidepressants. Understanding the difference in clinically meaningful treatment effects will further allows us to make informed decisions about the timing of treatment benefits and may aid in the development of patient-centered treatments that include AE. These findings are comparable with several other controlled studies. For instance, in a multicenter trial involving 2322 stable patients treated for heart failure, Blumenthal and colleagues (212) randomized patients to either supervised AE for 3 months followed by home-based AE for 9 months (12 months total) or to an education and care-as-usual (CAU) condition. After 3 months of supervised exercise, patients in the AE group experienced a 1.75-point reduction in BDI-II scores compared to a 0.98-point reduction for the CAU control group. This effect was even larger within a subset of patients displaying clinically significant depressive symptoms (BDI-II score $\geq$ 14). Reductions in depressive symptoms were also maintained in the AE group in months 4 through 12, with a 2.2 reduction from baseline compared to a 1.3 points reduction in the

CAU condition. While the difference between the AE and CAU groups is small, the authors were unclear if this difference carried any clinical significance. Additionally, it was noted that the difference in BDI scores between AE and CAU for subjects reporting higher levels of depression was comparable with numerous placebo-control trials. More recently, Hallgren et al. (213) randomized 946 patients diagnosed with mild to moderate depression to one of three 12-week interventions: exercise, internet-based cognitive–behavioral therapy (ICBT), or a treatment as usual (TAU) condition. All three interventions resulted in improvements in depressive symptoms at follow-up; however, the mean reduction in severity of depressive symptoms as measured by the Montgomery–Äsberg Depression Rating Scale (MADRS) were significantly larger in the exercise and ICBT groups compared with TAU. Our study adds to these trials to support the efficacy of AE for reducing symptoms of depression among young adults with MDD.

Currently, there is much debate regarding the most appropriate comparison group in exercise and mental health trials. In this study, we chose to implement a PE condition that consisted of light-intensity stretching and flexibility exercises performed for a similar duration as the AE group to control for demand characteristics, such as attention and expectancy effects, and to avoid ethical concerns related to depriving individuals with MDD from active monitoring of their depression levels and safety. Participants assigned to the PE intervention did not show the same changes in depressive symptomatology or cognitive control relative to those in the AE condition, which is important in ruling out a placebo effect and a variety of behavioral artifacts that are often uncontrolled in exercise intervention studies (214). However, it should be noted that early studies by Egil Martinsen (215) indicate similar reductions in depressive symptoms following 8 weeks of

aerobic exercise compared to a nonaerobic (i.e., stretching) comparison condition in ninety-nine inpatients who met criteria for MDD. Subjects in this study were randomly assigned and performed one hour of training three days per week. Despite a significant increase in aerobic capacity for the aerobic exercise group, both conditions displayed reductions in depressive symptoms. Interestingly, the change in fitness showed little correlation with change in depressive symptoms, suggesting the antidepressive effects of associated with exercise may be independent of changes in cardiorespiratory fitness. The 22% reduction in BDI-II scores in our study complement these early findings by Martinsen and suggest that low-intensity exercise programs may result in a slight improvement in depressive symptoms, although whether this constitutes a lasting and clinically meaningful reduction remains unknown.

In addition to the mode of exercise and optimal comparison groups, additional considerations must be considered when prescribing exercise for depressive symptoms. For the DOSE trial, Dunn et al. (185) randomized individuals with MDD to one of five doses of exercise: low dose (LD; 7.0 kcal/kg/week) at 3 days/week and 5 days/week, public health dose (PHD; 17.5 kcal/kg/week) at 3 days/week and 5 days/week, or exercise placebo control group (stretching and flexibility) at 3 days/week. Following 12 weeks, the reduction in the 17-item Hamilton Rating Scale for Depression (HRSD) was significant for the PHD and LD performed for 3 or 5 days/week, and the exercise placebo control groups. However, the PHD condition was found to be significantly more effective than the LD and control conditions in reducing weekly HRSD scores, with the LD showing no difference from the control condition. Additionally, the 3 days/week and 5 days/week conditions were not significantly different from one another. They suggested

that the prescription of aerobic exercise needs to be consistent with public health recommendations (i.e., 17.5-kcal/kg/week dose) in order to be efficacious in treating depression. In the current study, we chose a minimum dose of exercise that has been shown to result in reductions in depression but that would also result in optimizing behavioral adherence (186). Future studies are warranted to further explore dose-dependent effects of exercise on depression and how the relation impacts upon neurobiological mechanisms and individual response variation.

With respect to mechanisms, there are many potential candidates. Recently, prefrontal-dependent cognitive control has been proposed as a neurobiological underpinning of symptomatology in MDD (216). Specifically, a systematic review of 59 functional neuroimaging studies demonstrated that under-engagement of cognitive control is associated with indecisiveness, negative automatic thoughts, poor concentration, and distorted cognitive processing. In the current study, we used the ERP technique to examine a direct measure of neural transmission related to cognitive control. We found that N2 amplitude can be modified through 8 weeks of moderate-intensity aerobic exercise, especially for trials requiring the greatest levels of conflict monitoring (i.e., incongruent trials). However, this was only observed when analyzing the N2 TFSF data, which suggests that common analyses of ERPs (e.g., peak, adaptive, and mean amplitude) may be less sensitive at revealing small changes that occur following behavioral interventions. Techniques like PCA and independent component analysis were developed to help identify the constituent components of the ERP, provide dependent measures of these components, and help improve the localization of ERP sources (197). Together, these methods may prove to be especially useful for populations where data

may be especially contaminated with artifact or for populations displaying neuropsychological dysfunction.

Studies examining the influence of exercise on cognitive function have been mixed. Hoffman et al. (217) did not find benefits of either supervised or home-based exercise compared to placebo following 4-months of treatment in depressed patients, although exercise was superior to the selective serotonin reuptake inhibitor (SSRI), sertraline, on tests of executive function. In persons with major depressive disorder who reported cognitive impairment and had only a partial response to their initial SSRI treatment, high dose exercise yielded improvements in spatial working memory, and both doses improved certain aspects of cognitive function across several domains. Both doses showed similar reductions in symptom severity with both clinician-rated and self-report symptom severity measures; however, changes in cognitive performance were not correlated with changes in depressive symptom severity, suggesting they were independent of improvements in mood. This is consistent with several recent reports that have found cognitive improvements in depressed patients that are independent of reductions in symptom severity (218-220). These findings support that the impact of depression on cognition does not fully correspond to depressive symptomatology and suggest that targeted treatments, such as exercise, are needed for cognitive impairments observed with depression.

The findings presented herein suggest that AE may be viewed as an effective "neurobehavioral therapy" in that it may impact biological mechanisms believed to underlie psychological disorders, in the same sense that pharmacological and surgical treatments address such mechanisms. Yet, they use behavioral methods to do so.

Neurobehavioral therapies are readily evaluated on dimensions rather than symptoms. The efficacy of these trials is dependent on whether a change in a specifically targeted aspect of brain function is achieved, thus they may better serve to explain the underlying mechanisms. Many have started to use forms of neurobehavioral therapy for treating clinical populations, including those with depression. For example, Calkins and colleagues (221) implemented a 2-week computer based Cognitive Control Training (CCT) program with the aim of strengthening cognitive and emotional function. Previously, it was found that CCT reduced negative affect and rumination, as well as improved concentration in individuals with MDD (13). Forty-eight subjects reporting high levels of depressive symptoms (indexed by the BDI-II) were randomized to CCT or a comparison condition (Peripheral Vision Training; PVT). Larger effect sizes favoring CCT over PVT were found on the BDI-II, suggesting CCT was effective at reducing negative mood. Results from this study support the notion that a neurobehavioral therapy can alter mood; however, these changes may be specific to select mood dimensions.

Limitations

We acknowledge several limitations in the present study. First, the sample is small, which results in insufficient power for the exploratory mediation analysis. The trial was initially powered to detect changes in depressive symptoms, so the lack of significant mediation of N2 on clinical outcomes should be viewed with caution. Second, the intervention was relatively short in duration (i.e., two months) and it is unclear whether continued improvements in neurocognitive function and clinical symptoms would be found with a longer intervention. Despite the nonsignificant mediation of cognitive control, we are

optimistic that significant and clinically meaningful reductions in depressive symptoms and increases in cognitive control were found in as few as 8 weeks. However, future clinical trials of exercise should attempt to determine clinical cutpoints and how long these benefits remain by assessing the same symptoms at several follow-up time points.

Another limitation of the study was related to the comparison group. Since the results demonstrate that AE is more effective at reducing depressive symptoms and enhancing cognitive control processes relative to PE, we can conclude that AE is an effective treatment for treating depression; however, future research with a pragmatic primary objective (e.g., aimed at policy decisions relating to prescribed treatments for MDD) should incorporate standard-of-care or CAU control groups to determine if AE is at least as effective or superior to conventional therapies for MDD (e.g., SSRI, CBT).

Conclusion

Findings from the current study indicate that AE is an effective intervention for symptoms of depression and cognitive control impairments in MDD. Considering the frequent report of cognitive impairments in MDD and the failure of these symptoms to subside despite antidepressant treatment, the use of exercise as a stand-alone or adjunctive treatment for MDD is recommended. Exercise may be particularly useful for depressed individuals with impaired cognitive control. It remains to be determined whether exercise further enhances cognitive outcomes in patients undergoing antidepressant medication, and whether the improvements in cognitive function may mediate other important outcomes besides depressive symptoms and rumination (e.g., fatigue, medication adherence). Given the recent calls for a precision medicine approach

and established treatments for neurocognitive deficits in MDD, these findings are supportive of exercise as a potential neurobehavioral therapy and suggest the need for additional research in this area.

GENERAL DISCUSSION

Summary

Chapter 1 set out to determine relationships between ruminative thought patterns and cognitive control processes in individuals diagnosed with MDD compared to age- and sex-matched healthy control participants. We hypothesized that individuals with a current diagnosis of depression would display deficits in cognitive control processes, as indexed by reductions in N2 and P3 amplitudes, as well as impaired behavioral task performance outcomes. Individual differences in rumination were also predicted to covary with both ERP and behavioral performance measures elicited by the flanker task. This latter finding would suggest that there is an association between cognitive control and the ability to inhibit or "gate out" unwanted thought patterns that are often associated with depression. The results revealed decreased (i.e., less negative) N2 amplitudes during the flanker task in individuals with MDD compared to their non-depressed counterparts. This finding was observed despite a lack of significant group differences in behavioral task performance measures of reaction time and accuracy. Notably, reductions in N2 among individuals with MDD occurred for trials requiring greater conflict monitoring (i.e., the more challenging incongruent trials), suggesting less recruitment of cognitive control in depression. Relative to the second hypothesis, we also found that individuals who reported higher levels of rumination displayed reduced flanker N2 amplitudes. Thus, our hypotheses were partly supported such that we were able to establish a relationship between ruminative thought patterns and cognitive control in MDD. Importantly, in

Study 1 we were able to identify neurocognitive deficits in MDD that may potentially serve as an effective target for neurobehavioral therapies (e.g., exercise intervention).

Chapter 2 was designed to assess whether ERP components of cognitive control (i.e., N2 and P3 components) are state-dependent and altered by exercise. In the larger field of Psychophysiology, it remains unknown whether many of the established ERP components are trait like and relatively immutable, or whether they are state like and modifiable through behavioral activation. Demonstrating state-dependent changes in ERP indices of cognitive control, particularly through acute exercise, could provide evidence that neural targets associated with rumination and depressive symptoms in MDD can be improved through a chronic exercise intervention. A secondary purpose was to examine cognitive control processes during an acute bout of aerobic exercise performed at 40% (low-intensity) and 60% (moderate-intensity) of peak aerobic fitness (VO_2 peak) at 5, 15, and 25 min time points during steady-state exercise. We hypothesized that N2 and P3 would be sensitive to acute exercise such that they would be enhanced (i.e., larger) compared with the control condition. Based on previous findings in the acute exercise and cognition literature, we also expected greater cognitive control required when assessed at 25-min following exercise onset relative to earlier assessment times (5- and 15-min). The results from Chapter 2 showed impaired response accuracy for incongruent trials of the flanker task during low- and moderate-intensity aerobic exercise relative to a no-exercise control in healthy individuals. This reduction in accuracy was accompanied by faster reaction times in the moderate-intensity exercise condition compared to low-intensity and control conditions, suggesting a possible speed-accuracy tradeoff associated with exercise. Relative to the neurophysiological measures, more negative N2 and more

positive P3 amplitudes were found during both exercise conditions and were most prominent for incongruent flanker task trials. The primary finding from Study 2 was that acute exercise altered neurophysiological indices of cognitive control processes in an otherwise healthy population. In light of the impairments in accuracy observed during exercise (although concomitant with an increase in reaction time), the increase in N2 and P3 amplitudes are believed to reflect an increased need for cognitive control during exercise. Thus, in otherwise healthy individuals who do not typically engage in these novel types of cognitive control tasks during exercise, this dual-task scenario requires a greater upregulation of cognitive control in order to successfully meet task demands. As it relates to Chapter 1, changes in these ERP components through acute exercise, particularly N2, provide initial support for the impact of exercise on healthy brain functioning. We anticipate that combined acute bouts of aerobic exercise (i.e., chronic exercise) may lead to long-term changes potentially impacting ruminative thought patterns and depressive symptoms found in MDD. Relative to Chapter 3, findings from this study contribute additional support to a growing body of literature demonstrating the beneficial effects of low- to moderate-intensity exercise on cognition. As such, this intensity of exercise may serve as an optimal dose for a chronic exercise program aimed at ameliorating cognitive deficits in MDD.

Chapter 3 was designed to determine the effects of an 8-week moderate-intensity aerobic exercise intervention on cognitive control and symptoms of depression and rumination in individuals with MDD. We hypothesized that 8 weeks of moderate-intensity exercise would significantly restore impaired cognitive control processes (N2 amplitude), while reducing depressive symptoms and ruminative thoughts in individuals

with MDD. Lastly, although this randomized trial was not specifically powered for mediation, we expected changes in cognitive control to mediate reductions in depressive symptoms and rumination from pre-to-post intervention. The results from Chapter 3 revealed that at baseline, depressed individuals displayed similar flanker N2 amplitudes as those from MDD participants in Chapter 1. That is, no significant flanker congruency effect was found between congruent and incongruent trials. Importantly, we found that 8 weeks of moderate-intensity aerobic exercise resulted in significantly faster reaction time performance, increases in N2 amplitude during incongruent trials, and reduced depressive symptoms in individuals with MDD relative to individuals assigned to a placebo exercise condition. Interestingly, these changes occurred without a change in aerobic fitness (VO_2 peak) from pre-to-post intervention, suggesting that aerobic exercise improves conflict monitoring and cognitive control processes in MDD despite marginal changes in cardiorespiratory fitness. Previous studies have suggested that 8-12 weeks of exercise performed at moderate (30 min per day, 5 days per week, 150 total min per week) to vigorous (20 min per day, 3 days per week, 75 total min per week) intensity is necessary to raise cardiorespiratory fitness levels in a young, otherwise healthy population (222). The study population in this trial consisted of young, college-aged individuals with MDD; however, some findings indicate that a longer period of time or more vigorous exercise, depending on initial conditioning levels, would be needed to statistically and meaningfully improve aerobic fitness levels (223). Although we anticipated significant mediation of symptom change from change in cognitive control, the indirect effect in the meditational model was nonsignificant and suggested that although aerobic exercise significantly enhances cognitive control and reduces symptoms of depression, the

changes in cognitive control do not mediate symptom improvements. This study is an important initial step in identifying potential neural mechanisms of action for the antidepressant effects of exercise that should be targeted in future randomized exercise trials for depression. Future trials should also be statistically powered to test for mediation effects.

Taken together, these results support previous research showing that chronic aerobic exercise may be used as an alternative or augmentative treatment therapy for individuals with MDD. Specifically, findings from this dissertation suggest appropriate neural targets in MDD, that these are state-like and modifiable, and that changes in depression and depressive symptoms may be associated with changes in neurocognitive processes, especially those related to conflict monitoring and cognitive control.

General limitations and future directions

There are several limitations to consider when interpreting our results. First, the sample sizes were small and consisted of a relatively homogeneous group of students in regard to a number or demographic and health characteristics including age, education level, body-mass index, cardiorespiratory fitness, and primary diagnosis. Despite separate power analyses supporting the sample sizes, generalizability of these findings may be limited to young adults with MDD. Second, although participants in Studies 1 and 3 received a baseline clinical assessment for depression, the primary outcome measure (symptoms of depression) was assessed through the BDI-II, which assesses a wide-range of unrelated symptoms that may limit the capacity to characterize the extent of remission following the intervention. Recent clinical trials have used BDI-II scores as a primary

outcome measure (224, 225) and it has been suggested that reductions in BDI-II values correspond to clinical and diagnostic changes in depression. In order to improve clinical interpretation and allow for comparison between studies, future trials of exercise on cognitive function in MDD should assess pre-to-post changes in clinical levels of depression through structured interviews and/or the HRSD.

Third, this dissertation implemented the ERP technique to document changes in cognitive control processes, but a number of limiting factors must be considered. In particular, MDD is associated with cognitive deficits stemming from a number of brain regions including the hippocampus, amygdala, and prefrontal and anterior cingulate cortices. Despite converging evidence identifying the ACC and DLPFC as neural generators of the N2 component through source localization and fMRI methods, ERPs are poorly suited for addressing questions focused on neuroanatomical specificity. That is, ERPs represent a direct measure of neurotransmission and would be better suited investigating the timing of psychological processes. Due to the alignment of cortical pyramidal neurons and the process of neurotransmission (i.e., from the brain, through the dura layers, through the skull layers, through the scalp, and to the electrode), the signal becomes spatially smeared, rendering spatial analyses ineffective unless a dense array (>128 channels) EEG system is used. Additionally, individual ERP component amplitudes are not especially useful and the polarity of the component provides little information on the type of neurotransmitters (i.e., excitatory or inhibitory) that may be affected in MDD and modifiable by intervention. As it currently stands, the ERP technique cannot be used in the diagnosis of mental health disorders, yet the advantages of this system far outweigh the disadvantages in that it is cost-effective, minimally

invasive, and temporally superior to alternative neuroimaging techniques. Future research incorporating multiple imaging approaches simultaneously (e.g., fMRI and ERPs) may help to source localize neural deficits in MDD.

Lastly, the temporal relationship between cognitive and affective changes following an exercise intervention remains unknown. That is, it is possible that changes in affect and symptoms of depression improve during the initial phases of an exercise intervention trial, and these changes in affect might mediate alterations in cognitive control processes. The integration of affect/emotion and cognition has received recent attention (226) and future studies should attempt to evaluate the integration and temporal nature of emotion and cognition changes in MDD using temporally-sensitive measures such as ERPs.

Future exercise studies should also examine the time-course of integrated neurobiological processes in MDD (i.e., rumination, depressive symptoms, neurocognitive function) to determine whether changes in symptoms precede ERP changes or vice versa. Additionally, any improvements in psychobiological outcome measures should be monitored several weeks post-intervention to determine the long-term effects of exercise on neurocognitive and psychological resilience (227). Studies examining potential moderators and mediators of change are also warranted to partially address individual differences and the heterogeneity of MDD. Specifically, MDD is clinically diagnosed by responding to a series of questions related to symptoms or symptom clusters. Many of these symptoms (e.g., sleep disturbances, feeling of guilt, weight fluctuations) could affect behavioral and neurocognitive measures, thus focusing on specific subtypes of depression or smaller symptom clusters will allow us to better

understand this complex disease from a transdiagnostic perspective. Finally, research efforts should focus on characterizing responders and non-responders to traditional and more novel neurobehavioral treatments. For instance, understanding whether individuals who fail to respond to exercise might respond to CBT or antidepressants (and vice versa) would be an important next step in identifying biological mechanisms and tailoring interventions in depression. In addition, change in cognitions and an increase in suicidal thoughts are well known side effects of antidepressants. It is possible that exercise can be used as an adjunctive therapy with antidepressants to reduce these treatment-related side effects. This may also allow us to develop and advance a precision-based medicine approach for exercise and more conventional treatments that addresses the important role of individual variability.

General conclusion

Overall, our results indicate that individuals with MDD display impaired neurocognitive function, especially in tasks requiring greater amounts of cognitive control. These neurocognitive impairments were shown to be modifiable by acute low-to-moderate-intensity aerobic exercise. Finally, we showed that neurocognitive deficits in MDD are amenable to change through a chronic exercise intervention and that there was a larger, clinical effect on depressive symptoms following the AE intervention compared an attention controlled PE condition. Together, these findings are supportive of exercise as an effective neurobehavioral therapy for the treatment of depression in young adults.

REFERENCES

1 Beck, A. T. (1967). *Depression: Clinical, Experimental, and Theoretical Aspects*. University of Pennsylvania Press.

2 Babyak, M., Blumenthal, J. A., Herman, S., Khatri, P., Doraiswamy, M., Moore, K., et al. (2000). Exercise treatment for major depression: Maintenance of therapeutic benefit at 10 months. *Psychosomatic Medicine, 62*, 633-638.

3 Blumenthal, J. A., Babyak, M. A., Moore, K. A., Craighead, W. E., Herman, S., Khatri, P., et al. (1999). Effects of exercise training on older patients with major depression. *Archives of Internal Medicine, 159*, 2349-2356.

4 Davidson, R. J., Pizzagalli, D., Nitschke, J. B., & Putnam, K. (2002). Depression: Perspectives from affective neuroscience. *Annual Review of Psychology, 53*, 545-574.

5 Fava, M., Graves, L. M., Benazzi, F., Scalia, M. J., Iosifescu, D. V., Alpert, J. E., et al. (2006). A cross-sectional study of the prevalence of cognitive and physical symptoms during long-term antidepressant treatment. *The Journal of Clinical Psychiatry, 67*, 1754-1759.

6 Lee, R. S., Hermens, D. F., Porter, M. A., & Redoblado-Hodge, M. A. (2012). A meta-analysis of cognitive deficits in first-episode major depressive disorder. *Journal of Affective Disorders, 140*, 113-124.

7 Murrough, J. W., Iacoviello, B., Neumeister, A., Charney, D. S., & Iosifescu, D. V. (2011). Cognitive dysfunction in depression: Neurocircuitry and new therapeutic strategies. *Neurobiology of Learning and Memory, 96*, 553-563.

8 Millan, M. J., Agid, Y., Brune, M., Bullmore, E. T., Carter, C. S., Clayton, N. S., et al. (2012). Cognitive dysfunction in psychiatric disorders: Characteristics, causes and the quest for improved therapy. *Nature Reviews Drug Discovery, 11*, 141-168.

9 Wagner, S., Doering, B., Helmreich, I., Lieb, K., & Tadic, A. (2012). A meta-analysis of executive dysfunctions in unipolar major depressive disorder without psychotic symptoms and their changes during antidepressant treatment. *Acta Psychiatrica Scandinavica, 125*, 281-292.

10 Jaeger, J., Berns, S., Uzelac, S., & Davis-Conway, S. (2006). Neurocognitive deficits and disability in major depressive disorder. *Psychiatry Research, 145*, 39-48.

11 McCall, W. V., & Dunn, A. G. (2003). Cognitive deficits are associated with functional impairment in severely depressed patients. *Psychiatry Research, 121*, 179-184.

12 Naismith, S. L., Longley, W. A., Scott, E. M., & Hickie, I. B. (2007). Disability in major depression related to self-rated and objectively-measured cognitive deficits: A preliminary study. *BMC Psychiatry, 7*, 32.

13 Siegle, G. J., Ghinassi, F., & Thase, M. E. (2007). Neurobehavioral therapies in the 21st century: Summary of an emerging field and an extended example of cognitive control training for depression. *Cognitive Therapy and Research, 31*, 235-262.

14 Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience, 24*, 167-202.

15 Etnier, J. L., Salazar, W., Landers, D. M., Petruzzello, S. J., Han, M., & Nowell, P. (1997). The influence of physical fitness and exercise upon cognitive functioning: A meta-analysis. *Journal of Sport & Exercise Psychology, 19*, 249-277.

16 Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychological Science, 14*, 125-130.

17 Diamond, A. (2013). Executive functions. *Annual Review of Psychology, 64*, 135-168.

18 Luck, S. J. (2014). *An Introduction to the Event-Related Potential Technique*. Cambridge, MA: The MIT Press.

19 Botvinick, M. M., Cohen, J. D., & Carter, C. S. (2004). Conflict monitoring and anterior cingulate cortex: An update. *Trends in Cognitive Sciences, 8*, 539-546.

20 Clawson, A., Clayson, P. E., & Larson, M. J. (2013). Cognitive control adjustments and conflict adaptation in major depressive disorder. *Psychophysiology, 50*, 711-721.

21 Olson, R. L., Chang, Y. K., Brush, C. J., Kwok, A. N., Gordon, V. X., & Alderman, B. L. (2016). Neurophysiological and behavioral correlates of cognitive control during low and moderate intensity exercise. *NeuroImage, 131*, 171-180.

22 Alderman, B. L., Olson, R. L., Bates, M. E., Selby, E. A., Buckman, J. F., Brush, C. J., et al. (2015). Rumination in major depressive disorder is associated with impaired neural activation during conflict monitoring. *Frontiers in Human Neuroscience, 9*, 269.

23 Folstein, J. R., & Van Petten, C. (2008). Influence of cognitive control and mismatch on the N2 component of the ERP: A review. *Psychophysiology, 45*, 152-170.

24 Larson, M. J., Clayson, P. E., & Clawson, A. (2014). Making sense of all the conflict: A theoretical review and critique of conflict-related ERPs. *International Journal of Psychophysiology, 93*, 283-297.

25 Van Veen, V., & Carter, C. S. (2002). The timing of action-monitoring processes in the anterior cingulate cortex. *Journal of Cognitive Neuroscience, 14*, 593-602.

26 Alderman, B. L., Olson, R. L., Brush, C. J., & Shors, T. J. (2016). Mental and Physical (MAP) Training: Combining meditation and aerobic exercise reduces depression and rumination while enhancing synchronized brain activity. *Translational Psychiatry, 6*, e726.

27 Polich, J. (2012). Neuropsychology of P300. In Kappenman, E. S. & Luck, S. J. (Eds.), *The Oxford Handbook of Event-Related Potential Components*. New York, NY: Oxford University Press.

28 Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*, 593-602.

29 Mathers, C. D., Fat, D. M., & Boerma, J. (2008). *The Global Burden of Disease: 2004 Update*. World Health Organization.

30 American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association.

31 Gotlib, I. H., & Joormann, J. (2010). Cognition and depression: Current status and future directions. *Annual Review of Clinical Psychology, 6*, 285-312.

32 Hammar, A., & Ardal, G. (2009). Cognitive functioning in major depression-a summary. *Frontiers in Human Neuroscience, 3*, 26.

33 Holmes, A. J., & Pizzagalli, D. A. (2008). Response conflict and frontocingulate dysfunction in unmedicated participants with major depression. *Neuropsychologia, 46*, 2904-2913.

34 McLaughlin, K. A., Borkovec, T. D., & Sibrava, N. J. (2007). The effects of worry and rumination on affect states and cognitive activity. *Behavior Therapy, 38*, 23-38.

35 Nolen-Hoeksema, S., Larson, J., & Grayson, C. (1999). Explaining the gender difference in depressive symptoms. *Journal of Personality and Social Psychology, 77*, 1061-1072.

36 Nolen-Hoeksema, S., Wisco, B. E., & Lyubomirsky, S. (2008). Rethinking rumination. *Perspectives on Psychological Science, 3*, 400-424.

37 Lemelin, S., Baruch, P., Vincent, A., Everett, J., & Vincent, P. (1997). Distractibility and processing resource deficit in major depression. Evidence for two deficient attentional processing models. *The Journal of Nervous and Mental Disease, 185*, 542-548.

38 Vanderhasselt, M. A., De Raedt, R., Dillon, D. G., Dutra, S. J., Brooks, N., & Pizzagalli, D. A. (2012). Decreased cognitive control in response to negative information in patients with remitted depression: An event-related potential study. *Journal of Psychiatry & Neuroscience, 37*, 250-258.

39 Aron, A. R. (2007). The neural basis of inhibition in cognitive control. *The Neuroscientist, 13*, 214-228.

40 Miller, E. K. (2000). The prefontral cortex and cognitive control. *Nature Reviews Neuroscience, 1*, 59-65.

41 Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience, 24*, 167-202.

42 Joormann, J., Dkane, M., & Gotlib, I. H. (2006). Adaptive and maladaptive components of rumination? Diagnostic specificity and relation to depressive biases. *Behavior Therapy, 37*, 269-280.

43 Whitmer, A. J., & Banich, M. T. (2007). Inhibition versus switching deficits in different forms of rumination. *Psychological Science, 18*, 546-553.

44 Wagner, G., Sinsel, E., Sobanski, T., Kohler, S., Marinou, V., Mentzel, H. J., et al. (2006). Cortical inefficiency in patients with unipolar depression: An event-related fMRI study with the Stroop task. *Biological Psychiatry, 59*, 958-965.

45 van Veen, V., & Carter, C. S. (2002). The anterior cingulate as a conflict monitor: fMRI and ERP studies. *Physiology & Behavior, 77*, 477-482.

46 Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review, 108*, 624-652.

47 Yeung, N., Botvinick, M. M., & Cohen, J. D. (2004). The neural basis of error detection: Conflict monitoring and the error-related negativity. *Psychological Review, 111*, 931-959.

48 Pizzagalli, D. A. (2011). Frontocingulate dysfunction in depression: Toward biomarkers of treatment response. *Neuropsychopharmacology, 36*, 183-206.

49 Botvinick, M., Nystrom, L. E., Fissell, K., Carter, C. S., & Cohen, J. D. (1999). Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature, 402*, 179-181.

50 Tillman, C. M., & Wiens, S. (2011). Behavioral and ERP indices of response conflict in Stroop and flanker tasks. *Psychophysiology, 48*, 1405-1411.

51 Bruder, G. E., Kayser, J., & Tenke, C. E. (2012). Event-related brain potentials in depression: Clinical, cognitive, and neurophysiologic implications. In Luck, S. J. & Kappenman, E. S. (Eds.), *The Oxford Handbook of Event-Related Potential Components*. New York, NY: Oxford University Press.

52 Kaiser, S., Unger, J., Kiefer, M., Markela, J., Mundt, C., & Weisbrod, M. (2003). Executive control deficit in depression: Event-related potentials in a Go/Nogo task. *Psychiatry Research, 122*, 169-184.

53 Ruchsow, M., Groen, G., Kiefer, M., Buchheim, A., Walter, H., Martius, P., et al. (2008). Response inhibition in borderline personality disorder: Event-related potentials in a Go/Nogo task. *Journal of Neural Transmission, 115*, 127-133.

54 Lyche, P., Jonassen, R., Stiles, T., Ulleberg, P., & Landrø, N. (2011). Attentional functions in major depressive disorders with and without comorbid anxiety. *Archives of Clinical Neuropsychology, 26*, 38-47.

55 Ravnkilde, B., Videbech, P., Clemmensen, K., Egander, A., Rasmussen, N. A., & Rosenberg, R. (2002). Cognitive deficits in major depression. *Scandinavian Journal of Psychology, 43*, 239-251.

56 Cohen, R., Lohr, I., Paul, R., & Boland, R. (2001). Impairments of attention and effort among patients with major affective disorders. *The Journal of Neuropsychiatry and Clinical Neurosciences, 13*, 385-395.

57 Hammar, A., Lund, A., & Hugdahl, K. (2003). Selective impairment in effortful information processing in major depression. *Journal of the International Neuropsychological Society, 9*, 954-959.

58 Ottowitz, W. E., Dougherty, D. D., & Savage, C. R. (2002). The neural network basis for abnormalities of attention and executive function in major depressive disorder: Implications for application of the medical disease model to psychiatric disorders. *Harvard Review of Psychiatry, 10*, 86-99.

59 Donaldson, C., Lam, D., & Mathews, A. (2007). Rumination and attention in major depression. *Behaviour Research and Therapy, 45*, 2664-2678.

60 Raymond, J. E., Shapiro, K. L., & Arnell, K. M. (1992). Temporary suppression of visual processing in an RSVP task: An attentional blink? *Journal of Experimental Psychology. Human Perception and Performance, 18*, 849-860.

61 Broadbent, D. E., & Broadbent, M. H. (1987). From detection to identification: Response to multiple targets in rapid serial visual presentation. *Perception & Psychophysics, 42*, 105-113.

62 Dux, P. E., & Marois, R. (2009). The attentional blink: A review of data and theory. *Attention, Perception, & Psychophysics, 71*, 1683-1700.

63 Luck, S. J., Vogel, E. K., & Shapiro, K. L. (1996). Word meanings can be accessed but not reported during the attentional blink. *Nature, 383*, 616-618.

64 Martens, S., Wolters, G., & van Raamsdonk, M. (2002). Blinks of the mind: Memory effects of attentional processes. *Journal of Experimental Psychology. Human Perception and Performance, 28*, 1275-1287.

65 Husain, M., & Rorden, C. (2003). Non-spatially lateralized mechanisms in hemispatial neglect. *Nature Reviews Neuroscience, 4*, 26-36.

66 Husain, M., Shapiro, K., Martin, J., & Kennard, C. (1997). Abnormal temporal dynamics of visual attention in spatial neglect patients. *Nature, 385*, 154-156.

67 Lahar, C. J., Isaak, M. I., & McArthur, A. D. (2001). Age differences in the magnitude of the attentional blink. *Aging, Neuropsychology, and Cognition, 8*, 149-159.

68 Maciokas, J. B., & Crognale, M. A. (2003). Cognitive and attentional changes with age: Evidence from attentional blink deficits. *Experimental Aging Research, 29*, 137-153.

69 Hollingsworth, D. E., McAuliffe, S. P., & Knowlton, B. J. (2001). Temporal allocation of visual attention in adult attention deficit hyperactivity disorder. *Journal of Cognitive Neuroscience, 13*, 298-305.

70 Li, C. S., Lin, W. H., Chang, H. L., & Hung, Y. W. (2004). A psychophysical measure of attention deficit in children with attention-deficit/hyperactivity disorder. *Journal of Abnormal Psychology, 113*, 228-236.

71 Hommel, B., Kessler, K., Schmitz, F., Gross, J., Akyürek, E., Shapiro, K., et al. (2006). How the brain blinks: Towards a neurocognitive model of the attentional blink. *Psychological Research, 70*, 425-435.

72 Marois, R., & Ivanoff, J. (2005). Capacity limits of information processing in the brain. *Trends in Cognitive Sciences, 9*, 296-305.

73 Donchin, E., & Coles, M. G. (1988). Is the P300 component a manifestation of context updating? *Behavioral and Brain Sciences, 11*, 357-374.

74 Polich, J. (2007). Updating P300: An integrative theory of P3a and P3b. *Clinical Neurophysiology, 118*, 2128-2148.

75 Luck, S. J., Woodman, G. F., & Vogel, E. K. (2000). Event-related potential studies of attention. *Trends in Cognitive Sciences, 4*, 432-440.

76 American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association.

77 Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The Mini-International Neuropsychiatric Interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry, 59*, 22-33.

78 First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (1995). The Structured Clinical Interview for DSM-III-R personality disorders (SCID-II). *Journal of Personality Disorders, 9*, 83-91.

79 Jones, J. E., Hermann, B. P., Barry, J. J., Gilliam, F., Kanner, A. M., & Meador, K. J. (2005). Clinical assessment of Axis I psychiatric morbidity in chronic epilepsy: A multicenter investigation. *The Journal of Neuropsychiatry and Clinical Neurosciences, 17*, 172-179.

80 Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation.

81 Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*, 561-571.

82 Lecrubier, Y., Sheehan, D., Weiller, E., Amorim, P., Bonora, I., Harnett Sheehan, K., et al. (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. *European Psychiatry, 12*, 224-231.

83 Sheehan, D., Lecrubier, Y., Harnett Sheehan, K., Janavs, J., Weiller, E., Keskiner, A., et al. (1997). The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *European Psychiatry, 12*, 232-241.

84 Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Attention, Perception, & Psychophysics, 16*, 143-149.

85 Slagter, H. A., Lutz, A., Greischar, L. L., Francis, A. D., Nieuwenhuis, S., Davis, J. M., et al. (2007). Mental training affects distribution of limited brain resources. *PLOS Biology, 5*, e138.

86 Martens, S., & Wyble, B. (2010). The attentional blink: Past, present, and future of a blind spot in perceptual awareness. *Neuroscience and Biobehavioral Reviews, 34*, 947-957.

87 Chatrian, G. E., Lettich, E., & Nelson, P. L. (1988). Modified nomenclature for the "10%" electrode system. *Journal of Clinical Neurophysiology, 5*, 183-186.

88 Ferree, T. C., Luu, P., Russell, G. S., & Tucker, D. M. (2001). Scalp electrode impedance, infection risk, and EEG data quality. *Clinical Neurophysiology, 112*, 536-544.

89 Keil, A., Debener, S., Gratton, G., Junghofer, M., Kappenman, E. S., Luck, S. J., et al. (2014). Committee report: Publication guidelines and recommendations for studies using electroencephalography and magnetoencephalography. *Psychophysiology, 51*, 1-21.

90 Bertrand, O., Perrin, F., & Pernier, J. (1985). A theoretical justification of the average reference in topographic evoked potential studies. *Electroencephalography and Clinical Neurophysiology, 62*, 462-464.

91 Tucker, D. M., Liotti, M., Potts, G. F., Russell, G. S., & Posner, M. I. (1994). Spatiotemporal analysis of brain electrical fields. *Human Brain Mapping, 1*, 134-152.

92 Krompinger, J. W., & Simons, R. F. (2011). Cognitive inefficiency in depressive undergraduates: Stroop processing and ERPs. *Biological Psychology, 86*, 239-246.

93 Dickter, C. L., & Bartholow, B. D. (2010). Ingroup categorization and response conflict: Interactive effects of target race, flanker compatibility, and infrequency on N2 amplitude. *Psychophysiology, 47*, 596-601.

94 Clayson, P. E., Baldwin, S. A., & Larson, M. J. (2013). How does noise affect amplitude and latency measurement of event-related potentials (ERPs)? A methodological critique and simulation study. *Psychophysiology, 50*, 174-186.

95 de Bruijn, E. R., Sabbe, B. G., Hulstijn, W., Ruigt, G. S., & Verkes, R. J. (2006). Effects of antipsychotic and antidepressant drugs on action monitoring in healthy volunteers. *Brain Research, 1105*, 122-129.

96 Gehring, W. J., Himle, J., & Nisenson, L. G. (2000). Action-monitoring dysfunction in obsessive-compulsive disorder. *Psychological Science, 11*, 1-6.

97 Hajcak, G., Franklin, M. E., Foa, E. B., & Simons, R. F. (2008). Increased error-related brain activity in pediatric obsessive-compulsive disorder before and after treatment. *The American Journal of Psychiatry, 165*, 116-123.

98 Cohen, J. (1973). Eta-squared and partial eta-squared in fixed factor ANOVA designs. *Educational and Psychological Measurement, 33*, 107-112.

99 Hedges, L. V. (1981). Distribution theory for Glass's estimator of effect size and related estimators. *Journal of Educational Statistics, 6*, 107-128.

100 Austin, M. P., Mitchell, P., & Goodwin, G. M. (2001). Cognitive deficits in depression: Possible implications for functional neuropathology. *The British Journal of Psychiatry, 178*, 200-206.

101 Veiel, H. O. (1997). A preliminary profile of neuropsychological deficits associated with major depression. *Journal of Clinical and Experimental Neuropsychology, 19*, 587-603.

102 Zakzanis, K. K., Leach, L., & Kaplan, E. (1998). On the nature and pattern of neurocognitive function in major depressive disorder. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 11*, 111-119.

103 Mao, W., Wang, Y., & Wang, D. (2005). Cognitive impairment in major depressive disorder revealed by event-related potential N270. *Clinical EEG and Neuroscience, 36*, 9-14.

104 McNeely, H. E., Lau, M. A., Christensen, B. K., & Alain, C. (2008). Neurophysiological evidence of cognitive inhibition anomalies in persons with major depressive disorder. *Clinical Neurophysiology, 119*, 1578-1589.

105 Mitterschiffthaler, M. T., Fu, C. H., Dalton, J. A., Andrew, C. M., & Williams, S. C. (2007). A functional MRI study of happy and sad affective states induced by classical music. *Human Brain Mapping, 28*, 1150-1162.

106 Katz, R., De Sanctis, P., Mahoney, J. R., Sehatpour, P., Murphy, C. F., Gomez-Ramirez, M., et al. (2010). Cognitive control in late-life depression: Response inhibition deficits and dysfunction of the anterior cingulate cortex. *The American Journal of Geriatric Psychiatry, 18*, 1017-1025.

107 Troy, A. S., Wilhelm, F. H., Shallcross, A. J., & Mauss, I. B. (2010). Seeing the silver lining: Cognitive reappraisal ability moderates the relationship between stress and depressive symptoms. *Emotion, 10*, 783-795.

108 Goeleven, E., De Raedt, R., Baert, S., & Koster, E. H. (2006). Deficient inhibition of emotional information in depression. *Journal of Affective Disorders, 93*, 149-157.

109 Lau, M. A., Christensen, B. K., Hawley, L. L., Gemar, M. S., & Segal, Z. V. (2007). Inhibitory deficits for negative information in persons with major depressive disorder. *Psychological Medicine, 37*, 1249-1259.

110 Joormann, J. (2004). Attentional bias in dysphoria: The role of inhibitory processes. *Cognition & Emotion, 18*, 125-147.

111 Joormann, J., & Gotlib, I. H. (2007). Selective attention to emotional faces following recovery from depression. *Journal of Abnormal Psychology, 116*, 80-85.

112 Goodkind, M., Eickhoff, S. B., Oathes, D. J., Jiang, Y., Chang, A., Jones-Hagata, L. B., et al. (2015). Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry*.

113 Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: A meta-analysis and review. *Psychological Bulletin, 139*, 81.

114 Martens, S., Munneke, J., Smid, H., & Johnson, A. (2006). Quick minds don't blink: Electrophysiological correlates of individual differences in attentional selection. *Journal of Cognitive Neuroscience, 18*, 1423-1438.

115 Wu, C. T., & Hillman, C. H. (2013). Aerobic fitness and the attentional blink in preadolescent children. *Neuropsychology, 27*, 642-653.

116 Clayson, P. E., & Larson, M. J. (2011). Effects of repetition priming on electrophysiological and behavioral indices of conflict adaptation and cognitive control. *Psychophysiology, 48*, 1621-1630.

117 Yeung, N., & Nieuwenhuis, S. (2009). Dissociating response conflict and error likelihood in anterior cingulate cortex. *The Journal of Neuroscience, 29*, 14506-14510.

118 Brisswalter, J., Collardeau, M., & Rene, A. (2002). Effects of acute physical exercise characteristics on cognitive performance. *Sports Medicine, 32*, 555-566.

119 Chang, Y. K., Labban, J. D., Gapin, J. I., & Etnier, J. L. (2012). The effects of acute exercise on cognitive performance: A meta-analysis. *Brain Research, 1453*, 87-101.

120 Lambourne, K., & Tomporowski, P. (2010). The effect of exercise-induced arousal on cognitive task performance: A meta-regression analysis. *Brain Research, 1341*, 12-24.

121 McMorris, T., Sproule, J., Turner, A., & Hale, B. J. (2011). Acute, intermediate intensity exercise, and speed and accuracy in working memory tasks: A meta-analytical comparison of effects. *Physiology & Behavior, 102*, 421-428.

122 Tomporowski, P. D. (2003). Effects of acute bouts of exercise on cognition. *Acta Psychologica, 112*, 297-324.

123 Dietrich, A., & Sparling, P. B. (2004). Endurance exercise selectively impairs prefrontal-dependent cognition. *Brain and Cognition, 55*, 516-524.

124 Pontifex, M. B., & Hillman, C. H. (2007). Neuroelectric and behavioral indices of interference control during acute cycling. *Clinical Neurophysiology, 118*, 570-580.

125 Wang, C. C., Chu, C. H., Chu, I. H., Chan, K. H., & Chang, Y. K. (2013). Executive function during acute exercise: The role of exercise intensity. *Journal of Sport and Exercise Psychology, 35*, 358-367.

126 Norman, D. A., & Shallice, T. (1986). Attention to action: Willed and automatic control of behavior. In Davidson, R. J., Schwartz, G. E. & Shapiro, D. (Eds.), *Consciousness and Self-Regulation* (Vol. 4, pp. 1-18). New York, NY: Plenum Press.

127 Rogers, R. D., & Monsell, S. (1995). Costs of a predictible switch between simple cognitive tasks. *Journal of Experimental Psychology: General, 124*, 207-231.

128 Schmit, C., Davranche, K., Easthope, C. S., Colson, S. S., Brisswalter, J., & Radel, R. (2015). Pushing to the limits: The dynamics of cognitive control during exhausting exercise. *Neuropsychologia, 68*, 71-81.

129 Kappenman, E. S., & Luck, S. J. (2011). ERP components: The ups and downs of brainwave recordings. In Luck, S. J. & Kappenman, E. S. (Eds.), *The Oxford Handbook of Event-Related Potential Components* (pp. 3-30). New York, NY: Oxford University Press.

130 Chang, Y. K., Pesce, C., Chiang, Y. T., Kuo, C. Y., & Fong, D. Y. (2015). Antecedent acute cycling exercise affects attention control: An ERP study using attention network test. *Frontiers in Human Neuroscience, 9*, 156.

131 Drollette, E. S., Scudder, M. R., Raine, L. B., Moore, R. D., Saliba, B. J., Pontifex, M. B., et al. (2014). Acute exercise facilitates brain function and cognition in children who need it most: An ERP study of individual differences in inhibitory control capacity. *Developmental Cognitive Neuroscience, 7*, 53-64.

132 Vogt, T., Herpers, R., Scherfgen, D., Struder, H. K., & Schneider, S. (2015). Neuroelectric adaptations to cognitive processing in virtual environments: an exercise-related approach. *Experimental Brain Research, 233*, 1321-1329.

133 Pontifex, M. B., & Hillman, C. H. (2008). Neuroelectric measurement of cognition during aerobic exercise. *Methods, 45*, 271-278.

134 Leonard, C. J., Kaiser, S. T., Robinson, B. M., Kappenman, E. S., Hahn, B., Gold, J. M., et al. (2012). Toward the neural mechanisms of reduced working memory capacity in schizophrenia. *Cerebral Cortex, 23*, 1582-1592.

135 Clayson, P. E., & Larson, M. J. (2013). Psychometric properties of conflict monitoring and conflict adaptation indices: Response time and conflict N2 event-related potentials. *Psychophysiology, 50*, 1209-1219.

136 Millner, A. J., Jaroszewski, A. C., Chamarthi, H., & Pizzagalli, D. A. (2012). Behavioral and electrophysiological correlates of training-induced cognitive control improvements. *NeuroImage, 63*, 742-753.

137 Jennings, J. R., & Wood, C. C. (1976). Letter: The epsilon-adjustment procedure for repeated-measures analyses of variance. *Psychophysiology, 13*, 277-278.

138 Gehring, W. J., Gratton, G., Coles, M. G. H., & Donchin, E. (1992). Probability effects on stimulus evaluation and response processes. *Journal of Experimental Psychology: Human Perception & Performance, 18*, 198-216.

139 Donchin, E. (1981). Presidential address, 1980. Surprise!...Surprise? *Psychophysiology, 18*, 493-513.

140 Johnson, R. (1993). On the neural generators of the P300 component of the event-related potential. *Psychophysiology, 30*, 90-97.

141 Yagi, Y., Coburn, K. L., Estes, K. M., & Arruda, J. E. (1999). Effects of aerobic exercise and gender on visual and auditory P300, reaction time, and accuracy. *European Journal of Applied Physiology, 80*, 402-408.

142 McMorris, T., & Hale, B. J. (2012). Differential effects of differing intensities of acute exercise on speed and accuracy of cognition: A meta-analytical investigation. *Brain and Cognition, 80*, 338-351.

143 Davranche, K., & McMorris, T. (2009). Specific effects of acute moderate exercise on cognitive control. *Brain and Cognition, 69*, 565-570.

144 Brooks, G. A., Fahey, T. D., & Baldwin, K. M. (2005). *Exercise Physiology: Human Bioenergetics and its Applications*. 4th ed. New York, NY: McGraw-Hill.

145 Dietrich, A. (2003). Functional neuroanatomy of altered states of consciousness: The transient hypofrontality hypothesis. *Consciousness and Cognition, 12*, 231-256.

146 Luft, C. D., Takase, E., & Darby, D. (2009). Heart rate variability and cognitive function: Effects of physical effort. *Biological Psychology, 82*, 164-168.

147 McMorris, T., & Graydon, J. (2000). The effect of incremental exercise on cognitive performance. *International Journal of Sport Psychology, 31*, 66-81.

148 Leh, S. E., Petrides, M., & Strafella, A. P. (2010). The neural circuitry of executive functions in healthy subjects and Parkinson's disease. *Neuropsychopharmacology, 35*, 70-85.

149 Arnsten, A. F. T. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience, 10*, 410-422.

150 McEwen, B. S., Nasca, C., & Gray, J. D. (2016). Stress effects on neuronal structure: Hippocampus, amygdala, and prefrontal cortex. *Neuropsychopharmacology, 41*, 3-23.

151 Ramos, B. P., & Arnsten, A. F. (2007). Adrenergic pharmacology and cognition: Focus on the prefrontal cortex. *Pharmacology & Therapeutics, 113*, 523-536.

152 Dietrich, A. (2009). The transient hypofrontality theory and its implications for emotion and cognition. In McMorris, T., Tomporowski, P. D. & Audiffren, M. (Eds.), *Exercise and Cognitive Function*. Chichester, U.K.: John Wiley & Sons, Ltd.

153 Dietrich, A., & Audiffren, M. (2011). The reticular-activating hypofrontality (RAH) model of acute exercise. *Neuroscience and Biobehavioral Reviews, 35*, 1305-1325.

154 Secher, N. H., Seifer, T., Nielson, H. B., & Quistorff, B. (2009). Blood glucose and brain metabolism in exercise. In McMorris, T., Tomporowski, P. D. & Audiffren, M. (Eds.), *Exercise and Cognitive Function*. Chichester, U.K.: John Wiley & Sons, Ltd.

155 Yeung, N., & Cohen, J. D. (2006). The impact of cognitive deficits on conflict monitoring: Predictable dissociations between the error-related negativity and N2. *Psychological Science, 17*, 164-171.

156 Yeung, N., Nystrom, L. E., Aronson, J. A., & Cohen, J. D. (2006). Between-task competition and cognitive control in task switching. *The Journal of Neuroscience, 26*, 1429-1438.

157 Grego, F., Vallier, J. M., Collardeau, M., Bermon, S., Ferrari, P., Candito, M., et al. (2004). Effects of long duration exercise on cognitive function, blood glucose, and counterregulatory hormones in male cyclists. *Neuroscience Letters, 364*, 76-80.

158 McEwen, B. S. (2012). Brain on stress: How the social environment gets under the skin. *Proceedings of the National Academy of Sciences, 109*, 17180-17185.

159 Moore, R. D., Romine, M. W., O'Connor, P. J., & Tomporowski, P. D. (2012). The influence of exercise-induced fatigue on cognitive function. *Journal of Sports Sciences, 30*, 841-850.

160 Audiffren, M., Tomporowski, P. D., & Zagrodnik, J. (2009). Acute aerobic exercise and information processing: Modulation of executive control in a random number generation task. *Acta Psychologica, 132*, 85-95.

161 Pesce, C. (2009). An integrated approach to the effect of acute and chronic exercise on cognition: The linked role of individual and task constraints. In McMorris, T., Tomporowski, P. D. & Audiffren, M. (Eds.), *Exercise and Cognitive Function*. Chichester, U.K.: John Wiley & Sons, Ltd.

162 Alderman, B. L., & Olson, R. L. (2014). The relation of aerobic fitness to cognitive control and heart rate variability: A neurovisceral integration study. *Biological Psychology, 99*, 26-33.

163 Alderman, B. L., Olson, R. L., & Mattina, D. M. (2014). Cognitive function during low-intensity walking: A test of the treadmill workstation. *Journal of Physical Activity and Health, 11*, 752-758.

164 Davranche, K., Brisswalter, J., & Radel, R. (2015). Where are the limits of the effects of exercise intensity on cognitive control? *Journal of Sport and Health Science, 4*, 56-63.

165 Kessler, R. C., & Bromet, E. J. (2013). The epidemiology of depression across cultures. *Annual Review of Public Health, 34*, 119-138.

166 Thase, M. E. (2016). Adjunctive therapy with second-generation antipsychotics: The new standard for treatment-resistant depression? *Focus, 14*, 180-183.

167 Rethorst, C. D., Wipfli, B. M., & Landers, D. M. (2009). The antidepressive effects of exercise: A meta-analysis of randomized trials. *Sports Medicine, 39*, 491-511.

168 Rimer, J., Dwan, K., Lawlor, D. A., Greig, C. A., McMurdo, M., Morley, W., et al. (2012). Exercise for depression. *Cochrane Database of Systematic Reviews,* CD004366.

169 Trivedi, M. H., Greer, T. L., Church, T. S., Carmody, T. J., Grannemann, B. D., Galper, D. I., et al. (2011). Exercise as an augmentation treatment for nonremitted major depressive disorder: A randomized, parallel dose comparison. *The Journal of Clinical Psychiatry, 72*, 677-684.

170 Sherwood, A., Blumenthal, J. A., Smith, P. J., Watkins, L. L., Hoffman, B. M., & Hinderliter, A. L. (2016). Effects of exercise and sertraline on measures of coronary heart disease risk in patients with major depression: Results from the SMILE-II randomized clinical trial. *Psychosomatic Medicine, 78*, 602-609.

171 Siegle, G. J., Thompson, W., Carter, C. S., Steinhauer, S. R., & Thase, M. E. (2007). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: Related and independent features. *Biological Psychiatry, 61*, 198-209.

172 Cohen, J. D., Botvinick, M., & Carter, C. S. (2000). Anterior cingulate and prefrontal cortex: Who's in control? *Nature Neuroscience, 3*, 421-423.

173 Kane, M. J., & Engle, R. W. (2002). The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: An individual-differences perspective. *Psychonomic Bulletin and Review, 9*, 637-671.

174 Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., & Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. *Science, 306*, 443-447.

175 Siegle, G. J., Steinhauer, S. R., Carter, C. S., Ramel, W., & Thase, M. E. (2003). Do the seconds turn into hours? Relationships between sustained pupil dilation in response to emotional information and self-reported rumination. *Cognitive Therapy and Research, 27*, 365-382.

176 Siegle, G. J., Steinhauer, S. R., Thase, M. E., Stenger, V. A., & Carter, C. S. (2002). Can't shake that feeling: Event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biological Psychiatry, 51*, 693-707.

177 Levens, S. M., Muhtadie, L., & Gotlib, I. H. (2009). Rumination and impaired resource allocation in depression. *Journal of Abnormal Psychology, 118*, 757-766.

178 Greer, T. L., Grannemann, B. D., Chansard, M., Karim, A. I., & Trivedi, M. H. (2015). Dose-dependent changes in cognitive function with exercise augmentation for major depression: Results from the TREAD study. *European Neuropsychopharmacology, 25*, 248-256.

179 McClintock, S. M., Husain, M. M., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Trivedi, M. H., et al. (2011). Residual symptoms in depressed outpatients who respond by 50% but do not remit to antidepressant medication. *Journal of Clinical Psychopharmacology, 31*, 180-186.

180 Smith, P. J., Blumenthal, J. A., Hoffman, B. M., Cooper, H., Strauman, T. A., Welsh-Bohmer, K., et al. (2010). Aerobic exercise and neurocognitive performance: A meta-analytic review of randomized controlled trials. *Psychosomatic Medicine, 72*, 239-252.

181 Trivedi, M. H., Greer, T. L., Grannemann, B. D., Church, T. S., Galper, D. I., Sunderajan, P., et al. (2006). TREAD: TReatment with Exercise Augmentation for Depression: Study rationale and design. *Clinical Trials, 3*, 291-305.

182 Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*, 175-191.

183 Knubben, K., Reischies, F. M., Adli, M., Schlattmann, P., Bauer, M., & Dimeo, F. (2007). A randomised, controlled study on the effects of a short-term endurance training programme in patients with major depression. *British Journal of Sports Medicine, 41*, 29-33.

184 Friedman, L. M., Furberg, C., DeMets, D. L., Reboussin, D. M., & Granger, C. B. (2010). *Fundamentals of Clinical Trials*. Vol. 4. New York, NY: Springer.

185 Dunn, A. L., Trivedi, M. H., Kampert, J. B., Clark, C. G., & Chambliss, H. O. (2005). Exercise treatment for depression: Efficacy and dose response. *American Journal of Preventive Medicine, 28*, 1-8.

186 Rethorst, C. D., & Trivedi, M. H. (2013). Evidence-based recommendations for the prescription of exercise for major depressive disorder. *Journal of Psychiatric Practice, 19*, 204-212.

187 Dunn, L. B., Lindamer, L. A., Palmer, B. W., Golshan, S., Schneiderman, L. J., & Jeste, D. V. (2002). Improving understanding of research consent in middle-aged and elderly patients with psychotic disorders. *The American Journal of Geriatric Psychiatry, 10*, 142-150.

188 Shephard, R. J., Cox, M. H., & Simper, K. (1981). An analysis of "Par-Q" responses in an office population. *Canadian Journal of Public Health, 72*, 37-40.

189 Nolen-Hoeksema, S., & Davis, C. G. (1999). "Thanks for sharing that": Ruminators and their social support networks. *Journal of Personality and Social Psychology, 77*, 801-814.

190 Treynor, W., Gonzalez, R., & Nolen-Hoeksema, S. (2003). Rumination reconsidered: A psychometric analysis. *Cognitive Therapy and Research, 27*, 247-259.

191 American College of Sports Medicine. (2013). *ACSM's Guidelines for Exercise Testing and Prescription*. 9 ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins.

192 Borg, G. (1970). Perceived exertion as an indicator of somatic stress. *Scandinavian Journal of Rehabilitation Medicine, 2*, 92-98.

193 Borg, G. A. (1998). *Borg's Perceived Exertion and Pain Scales*. Champaign, IL: Human Kinetics.

194 Booth, M. (2000). Assessment of physical activity: An international perspective. *Research Quarterly for Exercise and Sport, 71*, S114-120.

195 van Poppel, M. N., Chinapaw, M. J., Mokkink, L. B., van Mechelen, W., & Terwee, C. B. (2010). Physical activity questionnaires for adults: A systematic review of measurement properties. *Sports Medicine, 40*, 565-600.

196 Oostenveld, R., & Praamstra, P. (2001). The five percent electrode system for high-resolution EEG and ERP measurements. *Clinical Neurophysiology, 112*, 713-719.

197 Dien, J. (2010). The ERP PCA Toolkit: An open source program for advanced statistical analysis of event-related potential data. *Journal of Neuroscience Methods, 187*, 138-145.

198 Falkenstein, M., Hoormann, J., Christ, S., & Hohnsbein, J. (2000). ERP components on reaction errors and their functional significance: A tutorial. *Biological Psychology, 51*, 87-107.

199 Gehring, W. J., Goss, B., Coles, M. G., Meyer, D. E., & Donchin, E. (1993). A neural system for error detection and compensation. *Psychological Science, 4*, 385-390.

200 Overbeek, T. J., Nieuwenhuis, S., & Ridderinkhof, K. R. (2005). Dissociable components of error processing: On the functional significance of the Pe vis-à-vis the ERN/Ne. *Journal of Psychophysiology, 19*, 319-329.

201 Foti, D., Weinberg, A., Dien, J., & Hajcak, G. (2011). Event-related potential activity in the basal ganglia differentiates rewards from nonrewards: Temporospatial principal components analysis and source localization of the feedback negativity. *Human Brain Mapping, 32*, 2207-2216.

202 Horn, J. L. (1965). A rationale and test for the number of factors in factor analysis. *Psychometrika, 30*, 179-185.

203 Jennings, J. R., & Wood, C. C. (1976). The e-adjustment procedure for repeated-measures analyses of variance. *Psychophysiology*.

204 Hajcak, G., Franklin, M. E., Foa, E. B., & Simons, R. F. (2008). Increased error-related brain activity in pediatric obsessive-compulsive disorder before and after treatment. *The American Journal of Psychiatry, 165*, 116-123.

205 Fairchild, A. J., & MacKinnon, D. P. (2014). Using mediation and moderation analyses to enhance prevention research. In *Defining Prevention Science* (pp. 537-555). New York, NY: Springer.

206 Hayes, A. F. (2013). *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach*. Guilford Press.

207 Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., et al. (2003). The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). *The Journal of the American Medical Association, 289*, 3095-3105.

208 Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*, 617-627.

209 Josefsson, T., Lindwall, M., & Archer, T. (2014). Physical exercise intervention in depressive disorders: Meta-analysis and systematic review. *Scandinavian Journal of Medicine & Science in Sports, 24*, 259-272.

210 Silveira, H., Moraes, H., Oliveira, N., Coutinho, E. S., Laks, J., & Deslandes, A. (2013). Physical exercise and clinically depressed patients: A systematic review and meta-analysis. *Neuropsychobiology, 67*, 61-68.

211 Button, K. S., Kounali, D., Thomas, L., Wiles, N. J., Peters, T. J., Welton, N. J., et al. (2015). Minimal clinically important difference on the Beck Depression Inventory-II according to the patient's perspective. *Psychological Medicine, 45*, 3269-3279.

212 Blumenthal, J. A., Sherwood, A., Babyak, M. A., Watkins, L. L., Smith, P. J., Hoffman, B. M., et al. (2012). Exercise and pharmacological treatment of depressive symptoms in patients with coronary heart disease: Results from the UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) study. *Journal of the American College of Cardiology, 60*, 1053-1063.

213 Hallgren, M., Kraepelien, M., Ojehagen, A., Lindefors, N., Zeebari, Z., Kaldo, V., et al. (2015). Physical exercise and internet-based cognitive-behavioural therapy in the treatment of depression: Randomised controlled trial. *The British Journal of Psychiatry, 207*, 227-234.

214 Morgan, W. P. (1997). Methodological considerations. *Physical Activity and Mental Health,* 3-32.

215 Martinsen, E. W., Hoffart, A., & Solberg, O. (1989). Comparing aerobic with nonaerobic forms of exercise in the treatment of clinical depression: A randomized trial. *Comprehensive Psychiatry, 30*, 324-331.

216 Rayner, G., Jackson, G., & Wilson, S. (2015). Cognition-related brain networks underpin the symptoms of unipolar depression: Evidence from a systematic review. *Neuroscience and Biobehavioral Reviews*.

217 Hoffman, B. M., Blumenthal, J. A., Babyak, M. A., Smith, P. J., Rogers, S. D., Doraiswamy, P. M., et al. (2008). Exercise fails to improve neurocognition in depressed middle-aged and older adults. *Medicine & Science in Sports & Exercise, 40*, 1344-1352.

218 Greer, T. L., Sunderajan, P., Grannemann, B. D., Kurian, B. T., & Trivedi, M. H. (2014). Does duloxetine improve cognitive function independently of its antidepressant effect in patients with major depressive disorder and subjective reports of cognitive dysfunction? *Depression Research and Treatment, 2014*.

219 Herrera-Guzman, I., Gudayol-Ferre, E., Herrera-Abarca, J. E., Herrera-Guzman, D., Montelongo-Pedraza, P., Padros Blazquez, F., et al. (2010). Major depressive disorder in recovery and neuropsychological functioning: Effects of selective serotonin reuptake inhibitor and dual inhibitor depression treatments on residual cognitive deficits in patients with major depressive disorder in recovery. *Journal of Affective Disorders, 123*, 341-350.

220 McClintock, S. M., Husain, M. M., Greer, T. L., & Cullum, C. M. (2010). Association between depression severity and neurocognitive function in major depressive disorder: A review and synthesis. *Neuropsychology, 24*, 9-34.

221 Calkins, A. W., McMorran, K. E., Siegle, G. J., & Otto, M. W. (2015). The effects of computerized cognitive control training on community adults with depressed mood. *Behavioural and Cognitive Psychotherapy, 43*, 578-589.

222 Garber, C. E., Blissmer, B., Deschenes, M. R., Franklin, B. A., Lamonte, M. J., Lee, I. M., et al. (2011). American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Medicine & Science in Sports & Exercise, 43*, 1334-1359.

223 Swain, D. P. (2005). Moderate or vigorous intensity exercise: Which is better for improving aerobic fitness? *Preventive Cardiology, 8*, 55-58.

224 Carney, R. M., Freedland, K. E., Steinmeyer, B., Rubin, E. H., Mann, D. L., & Rich, M. W. (2016). Cardiac risk markers and response to depression treatment in patients with coronary heart disease. *Psychosomatic Medicine, 78*, 49-59.

225 Freedland, K. E., Carney, R. M., Rich, M. W., Steinmeyer, B. C., & Rubin, E. H. (2015). Cognitive behavior therapy for depression and self-care in heart failure patients: A randomized clinical trial. *JAMA Internal Medicine, 175*, 1773-1782.

226 Shackman, A. J., Salomons, T. V., Slagter, H. A., Fox, A. S., Winter, J. J., & Davidson, R. J. (2011). The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nature Reviews Neuroscience, 12*, 154-167.

227 Charney, D. S. (2004). Psychobiological mechanisms of resilience and vulnerability: Implications for successful adaptation to extreme stress. *American Journal of Psychiatry, 161*, 195-216.