Cardiac autonomic balance as a treatment target and indicator of treatment response following an exercise intervention among young adults with depression: Results from a secondary data analysis

By

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Written under the direction of Brandon L. Alderman

And approved by

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ABSTRACT OF THE DISSERTATION

Cardiac autonomic balance as a treatment target and indicator of treatment response following an exercise intervention among young adults with depression:

Results from a secondary data analysis

By ANTHONY J. BOCCHINE

Dissertation Director:
Brandon L. Alderman

Major depressive disorder (MDD) is a prevalent neuropsychiatric disorder and a leading cause of worldwide disability. Depression is associated with debilitating symptoms and significant impairments to quality of life and exacts a significant burden to society. Although there are available treatment options, including pharmacological and cognitive behavioral therapy, remission rates remain low and treatment response is considerably variable. Furthermore, low diagnostic success rates for depression could be due in part to a lack of knowledge or consideration of unique psychophysiological processes that contribute to depression. There has been increasing research attention devoted to alternative or adjunctive treatments that do not carry the same challenges or limitations to pharmacological (e.g., tolerance, side effect profiles) and cognitive behavioral therapies (e.g., cost, accessibility). Accumulating evidence supports the efficacy of aerobic exercise as an alternative monotherapy or adjunct to conventional treatments for depression. However, treatment response rates to aerobic exercise are also variable underscoring the need to
identify transdiagnostic intervention targets and predictors of treatment response to advance precision medicine approaches incorporating exercise for depression. One promising psychophysiological mechanism in depression can be captured by heart rate variability (HRV), or the variation between successive heart beats within the electrocardiogram. Dysregulation in sympathetic and parasympathetic branches of the autonomic nervous system (ANS), often indexed by alterations in HRV, has been examined within the context of major depression for decades. In the first aim, we examined resting levels of CAB before and following an 8-week aerobic exercise intervention among individuals with and without depression. Resting CAB was reduced in non-responders relative to responders of the aerobic exercise intervention. Secondary aims were to determine whether the magnitude of change in CAB from pre-to-post intervention was correlated with change in depressive symptoms and whether CAB at baseline could predict treatment response across 8 weeks of intervention with aerobic exercise or light stretching. No significant pre-to-post treatment changes were observed for any of the autonomic measures; however, pretreatment CAB was a marginally significant predictor of treatment response, net of baseline depressive symptoms, aerobic fitness, and body mass index. Collectively, these findings suggest that 8 weeks of aerobic exercise is effective for reducing depressive symptoms, although the observed symptom reductions are not accompanied by meaningful change in CAB, HF-HRV, or PEP. The marginally significant finding of baseline CAB as predictor of treatment response is noteworthy and potentially relevant for identifying patients most likely to benefit from exercise interventions.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ANS</td>
<td>Autonomic Nervous System</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<tr>
<td>BAI</td>
<td>Beck anxiety inventory</td>
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<td>BDI-II</td>
<td>Beck depression inventory, Second Edition</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>bpm</td>
<td>beats per minute</td>
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<td>CAB</td>
<td>Cardiac autonomic balance</td>
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<td>CAD</td>
<td>Coronary Heart Disease</td>
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<td>CAPS</td>
<td>Counseling, alcohol, and other drug assistance program &amp; psychiatric services</td>
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<td>CAR</td>
<td>Cardiac autonomic regulation</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CONSORT</td>
<td>Consolidated standards of reporting trials</td>
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<tr>
<td>DSM-III-R</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised</td>
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<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</td>
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<tr>
<td>DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition</td>
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<tr>
<td>ECI</td>
<td>Emotion context-insensitivity</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>FFT</td>
<td>Fast fourier transform</td>
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<td>GAD</td>
<td>Generalized anxiety disorder</td>
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<td>HAM-D</td>
<td>Hamilton rating scale for depression</td>
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<tr>
<td>HF</td>
<td>High-frequency</td>
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<tr>
<td>HIIE</td>
<td>High-intensity interval exercise</td>
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<td>HR</td>
<td>Heart rate</td>
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<td>HRR</td>
<td>Heart rate reserve</td>
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<td>HRV</td>
<td>Heart rate variability</td>
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<td>Hz</td>
<td>Hertz</td>
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<tr>
<td>IAPS</td>
<td>International Affective Picture System</td>
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<td>IBI</td>
<td>Interbeat interval</td>
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<td>IBM Corp.</td>
<td>International Business Machines Corporation</td>
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<tr>
<td>ICG</td>
<td>Impedance cardiography</td>
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<tr>
<td>ICD-10</td>
<td>International Classification of Diseases-10</td>
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<td>in.</td>
<td>inch</td>
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<td>IPAQ</td>
<td>International Physical Activity Questionnaire</td>
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<tr>
<td>kCal</td>
<td>kilocalorie</td>
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<td>kg</td>
<td>kilogram</td>
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<tr>
<td>LF</td>
<td>Low-frequency</td>
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<tr>
<td>LF/HF</td>
<td>Low-frequency to high frequency ratio</td>
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<td>LF-HRV</td>
<td>Low-frequency heart rate variability</td>
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<tr>
<td>ln</td>
<td>Natural-logged</td>
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<tr>
<td>m</td>
<td>meter</td>
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<tr>
<td>MCID</td>
<td>Minimally clinical important difference</td>
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</table>
MDD  Major depressive disorder
MET  Metabolic equivalent
min  minute
MINI  Mini-International Neuropsychiatric Interview
mL  milliliter
mph  miles per hour
ms  milliseconds
NA  Negative affect
NDRIs  Norepinephrine dopamine reuptake inhibitors
NIMH  National Institute of Mental Health
OR  Odds ratio
PAR-Q  Physical Activity Readiness Questionnaire
PEP  Pre-ejection period
rANOVA  Repeated measures analysis of variance
RDoC  Research Domain Criteria
RER  Respiratory exchange ratio
RPE  Rating of perceived exertion
RR  Respiratory rate
RT  Reaction time
s  second
SD  Standard deviation
SDNN  Standard deviation of normal-to-normal intervals
SNRIs  Serotonin norepinephrine reuptake inhibitors
SPSS  Statistical Package for the Social Sciences
<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>SSRIs</td>
<td>Selective serotonin reuptake inhibitors</td>
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<tr>
<td>STAR*D</td>
<td>Sequenced Treatment Alternatives to Relieve Depression</td>
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<tr>
<td>TCAs</td>
<td>Tricyclic antidepressants</td>
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<tr>
<td>VO₂ peak</td>
<td>Cardiorespiratory fitness</td>
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Introduction

Major depressive disorder (MDD) is a prevalent neuropsychiatric disorder and a leading cause of worldwide disability (Kessler & Bromet, 2013; WHO, 2017). Depression is associated with debilitating symptoms and significant impairments to quality of life and exacts a significant burden to society (Greenberg et al., 2015; Liu et al., 2020). Although there are available treatment options, including pharmacological and cognitive behavioral therapy, remission rates remain low and treatment response is considerably variable (Joyce & Paykel, 1989; Ritchey et al., 2011). Furthermore, low diagnostic success rates for depression could be due in part to a lack of knowledge or consideration of unique psychophysiological processes that contribute to depression (Lesnewich et al., 2019).

There has been increasing research attention devoted to alternative or adjunctive treatments (e.g., Thachil et al., 2007) that do not carry the same challenges or limitations to pharmacological (e.g., tolerance, side effect profiles) and cognitive behavioral therapies (e.g., cost, accessibility). Accumulating evidence supports the efficacy of aerobic exercise as an alternative monotherapy or adjunct to conventional treatments for depression (Blumenthal et al., 1999; Ekkekakis, 2020; Rethorst & Trivedi, 2013). However, treatment response rates to aerobic exercise are also variable (Brush et al., 2020; Rahman et al., 2018; Suterwala et al., 2016), underscoring the need to identify transdiagnostic intervention targets and predictors of treatment response to advance precision medicine exercise interventions for depression (Akil et al., 2018; Trivedi, 2016).

One promising psychophysiological mechanism in depression can be captured by
heart rate variability (HRV), or the variation between successive heart beats within the electrocardiogram. Dysregulation in sympathetic and parasympathetic branches of the autonomic nervous system (ANS), often indexed by alterations in HRV, has been examined within the context of major depression for decades (e.g., Averill, 1969; Goldstein, 1965; Lehofer et al., 1997). For instance, Carney et al. (1998) found higher overall mean heart rate and lower HRV during 24-hour ambulatory ECG monitoring in depressed patients with coronary artery disease (CAD) relative to nondepressed CAD patients, independent of age, smoking status, and beta blocker use. Kemp et al. (2010) conducted a meta-analysis of 18 studies examining the impact of depression and antidepressant treatment on HRV in depressed patients without known cardiovascular disease and found that individuals with depression had lower HRV than nonpsychiatric healthy controls, and that depression symptom severity negatively correlated with HRV. Tricyclic medication use decreased HRV, although serotonin reuptake inhibitors, mirtazapine, and nefazodone had no significant impact on HRV. Several additional meta-analyses have provided further evidence that HRV is lower in MDD patients relative to healthy controls across all age groups (Brown et al., 2018; Kemp et al., 2010; Koch et al., 2019; Koenig et al., 2016; Rottenberg, 2007). Greater HRV has been interpreted as a psychophysiological index of behavioral flexibility and adaptability to environmental challenge (Bates & Buckman, 2013). Lower observed HRV in depression may reflect both a general autonomic imbalance and an overall lack of adaptability (Rottenberg, 2007).

HRV can be quantified using various time domain (e.g., the standard deviation of normal-to-normal intervals [SDNN]) or frequency-domain (e.g., high and low
frequency HRV) measures that correspond to multi-level influences on autonomic and cardiovascular functioning (Bates & Buckman, 2013; Malik, 1996; Shaffer et al., 2014; Shaffer & Ginsberg, 2017). In terms of the frequency domain, the high frequency (HF) component of HRV (.15-.40 Hz) is thought to reflect parasympathetic nervous system activity or vagal influence on the heart (Bates & Buckman, 2013; Malik, 1996; Shaffer et al., 2014; Shaffer & Ginsberg, 2017). Depressed individuals have lower resting HF-HRV compared to their non-depressed counterparts (e.g., Rottenberg, 2007; Sgoifo et al., 2015), although group-level effect size differences tend to be small-to-medium in magnitude (Kemp et al., 2010; Koenig et al., 2016; Rottenberg, 2007). The low frequency (LF) component of HRV (.04-.15 Hz) has been used in the literature as a measure of the sympathetic nervous system and the ratio of LF to HF has been proposed as an index of autonomic balance (Malliani et al., 1998). However, LF-HRV actually provides an index of modulation in both sympathetic and parasympathetic branches of the ANS and the LF/HF ratio has been largely discredited as an index of autonomic balance (Berntson, 2019; Berntson et al., 1997; Billman, 2013; Eckberg, 1997; Reyes del Paso et al., 2013; Sherwood et al., 1990).

In his 1966 presidential address to the Society for Psychophysiological Research (SPR), Marion Wenger presented a concept of autonomic balance based on a continuous bipolar distribution of sympathetic and parasympathetic control. Wenger (1966) presented data indicating lower overall autonomic balance in psychiatric patients relative to normative samples. Based on research indicating that the ANS does not function exclusively through reciprocal sympathetic and parasympathetic control, Berntson and colleagues (2008) advanced a conceptual model of cardiac
autonomic balance (CAB) and cardiac autonomic regulation (CAR) using HF-HRV as the measure of vagally-mediated cardiac control and pre-ejection period (PEP), the time between the onset of ventricular depolarization and the opening of the aortic valve, as an index of cardiac sympathetic activity (Ahmed et al., 1972; Berntson et al., 2004, 2008; Cacioppo et al., 1994; Harris et al., 1967; Larkin & Kasprowicz, 1986; Lozano et al., 2007; Newlin & Levenson, 1979; Schachinger et al., 2001). PEP reflects the time interval from the Q point of the electrocardiogram (ECG) to the B point of the impedance signal (dZ/dt) from the cardiac impedance (ICG) signal. Individual differences in PEP as a measure of sympathetic influence have been examined using the “gold standard” approach of pharmacological sympathetic blockade (Cacioppo et al. 1994). Theoretically, combining PEP with HF-HRV may allow for the examination of both ANS branches, including their potential independence or coactivation.

Investigations incorporating HF-HRV and PEP have revealed that a reciprocal or balanced model of autonomic control does not adequately capture the observed patterns of autonomic activity across a number of physical and mental health conditions, including depression (Berntson, 2019; Berntson et al., 2008; Christopher J. Brush et al., 2019; Bylsma et al., 2015). For example, Bylsma et al. (2015) examined changes in CAB in response to two psychological (unsolvable puzzle, sad film) and two physical (handgrip, and forehead cold pressor) challenges in youth with juvenile onset MDD. Youth without MDD showed reductions in CAB during the handgrip and unsolvable puzzle challenges, reflecting a shift from relative parasympathetic to sympathetic activation. In contrast, youth with juvenile onset
depression showed increased CAB from baseline during both tasks, suggesting abnormal autonomic regulation during these physical and psychological challenges. Brush et al. (2019) extended these findings by examining CAB as a predictor of current MDD. CAB significantly predicted current MDD (OR = 0.70, 95% CI [0.53, 0.93]), an effect that remained after controlling for body mass index and aerobic fitness, two health-related markers frequently associated with depression (Schuch et al., 2016; Stunkard et al., 2003). Together, these studies suggest that the composite index of CAB may provide a more comprehensive measure of autonomic functioning in depression (Stone et al., 2020).

HRV has also been examined as an intervention target for various physical (e.g., cardiovascular disease) and mental health (e.g., depression) conditions (Ahmed et al., 1972; Berntson et al., 2004; Cacioppo et al., 1994; Harris et al., 1967; Larkin & Kasprowicz, 1986; Lozano et al., 2007; Newlin & Levenson, 1979; Schachinger et al., 2001). For instance, Chambers and Allen (2002) examined vagal tone as a predictor of treatment response to 8-weeks of acupuncture treatment in 16 women with nonchronic major depression and found that women with a large change in vagal tone from pre-to-post treatment showed a large decrease in depression as measured by change in their Hamilton rating scale for depression (HAM-D) score (-14.8 points). Choi et al. (2019) found that change in the LF/HF ratio and pNN50 (a time-domain HRV measure sensitive to parasympathetic modulation) predicted successful treatment response (defined as a ≥ 50% reduction of HAM-D score) in depressed patients who received 12-weeks of standard antidepressant treatment with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors...
(SNRIs), norepinephrine dopamine reuptake inhibitors (NDRIs), and/or tricyclic antidepressants (TCAs). Although HRV measures may serve as treatment targets and indicators of change in depressive symptoms, no study to date has examined this possibility using CAB.

There is substantial evidence suggesting that aerobic exercise favorably influences a number of HRV metrics in both adults and children (Albinet et al., 2010; Carter et al., 2003; Jurca et al., 2004; Winsley, 2002). For instance, in a systematic review of 12 aerobic exercise intervention studies, Sandercock et al. (2005) reported that exercise training results in significant increases in HF-HRV. However, no research to date has examined the influence of aerobic exercise on CAB, and whether pre-to-post changes in CAB may correspond to reductions in symptoms of depression. This is important given the predictive utility of CAB in depression and the consideration of both parasympathetic and sympathetic contributions to autonomic control. Furthermore, as a measure of adaptability, it is possible that resting measures of CAB may serve as a successful psychophysiological index of treatment response. However, it is currently unknown whether pre-treatment measures of CAB or the underlying autonomic measures of HF-HRV and PEP can be used to characterize individualized treatment response (Bredt et al., 2015; Fabbri et al., 2013; Fu et al., 2013; Pizzagalli, 2011).

Therefore, this study has two aims. The first aim is to examine resting levels of CAB before and following an 8-week aerobic exercise intervention among individuals with and without depression. It was hypothesized that increased CAB would be observed from pre-to-post intervention and change in CAB will covary with
change in depressive symptoms. The second aim was to examine whether pre-intervention (baseline) CAB, as a measure of adaptability, would predict treatment response to the exercise intervention. As an exploratory follow-up, measures of HF-HRV and PEP were analyzed separately as predictors of treatment response.

Methods

This dissertation is a secondary data analysis of two separate previously published randomized controlled trials of aerobic exercise for major depressive disorder (Brush et al., 2020; Olson et al., 2017), each comprising a 2-month training intervention and two parallel intervention arms including moderate-intensity aerobic exercise (active intervention) and light stretching (control group or comparator). Clinical, behavioral, and psychophysiological measures were conducted at baseline (pre-intervention) and following the 8-week training intervention (post-intervention). Baseline psychological and psychophysiological data in depressed participants in comparison to healthy controls have been previously published (Brush et al., 2019; Lesnewich et al., 2020). Interested participants underwent an eligibility screening and were subsequently scheduled for an initial baseline assessment. Informed consent was obtained from all participants and the research protocols were approved by the Institutional Review Board at Rutgers, the State University of New Jersey (Protocol #’s 12-218M and 12-381M). Study recruitment procedures commenced in August 2014, and the study was completed in May 2018.

Participants

Participants were recruited through the use of advertisements, brochures posted at
Rutgers University Counseling, Alcohol and Other Drug Assistance Program & Psychiatric Services (CAPS) centers, and at information tabling sessions at university student centers between August 2014 and February 2018. The intervention commenced in October 2014 and ended in May 2018.

Eligibility criteria included men and women between the ages of 18 and 30 years who were not regularly physically active (defined as an energy expenditure of < 35 kcal/kg/day or < 3 days/week of physical activity for < 20 min/session over the month prior to the baseline assessment), and who were free from medical or physical contraindications to exercise. All participants were physically able to engage in exercise as indicated by the physical activity readiness questionnaire (PAR-Q; Shephard, Cox, & Simper, 1981). Additional inclusion criteria included normal or corrected-to-normal vision for neurocognitive testing and no concurrent psychological or pharmacological treatments for depression beyond stable (> 6 weeks at stable dose) antidepressant or mood stabilizer treatment. Any participant endorsing current or lifetime history of diagnosed bipolar or psychotic disorders, self-injurious or suicidal ideation, or any head injury that resulted in a loss of consciousness was also excluded from the study.

Randomization and Sample Size

These trials were initially powered to detect the effects of an 8-week moderate-intensity aerobic exercise intervention on cognitive control processes. Based on the observed effect size of $\eta^2_p = 0.13$ from Olson et al. (2017), a power analysis was conducted using an effect size of Cohen’s $f^2 = 0.38$. Using a two-sided $\alpha=0.05$ and a correlation among repeated measures of 0.4 in G*Power v. 3.1.9.2 (see Faul et al.,
2007), at least 10 participants with a MDD diagnosis (20 total) were anticipated to achieve power of > 0.80. MDD participants were randomized 1:1 to treatment arms in varying block sizes of 4 and 6 stratified by depressive symptom severity. A computer-generated list of random assignments was used (https://www.sealedenvelope.com).

**Intervention Arms**

The experimental conditions involved three 30-45-minute sessions of aerobic exercise (active) or light stretching (comparator) per week for 8 weeks performed at university recreation centers. Sessions were scheduled by convenience depending on participant availability and most sessions occurred on non-consecutive days of the week. During the exercise and stretching sessions, research study staff monitored participants at 10-minute time intervals. Heart rate (HR) and ratings of perceived exertion (RPE) were recorded at these intervals to monitor session intensity. Session adherence was also tracked across the duration of the 8-week interventions.

**Active condition**

The active treatment consisted of 45 minutes of continuous steady-state exercise performed on a motor-driven treadmill or cycle ergometer at an intensity corresponding to 40-65% of participant’s HR reserve (HRR), which was determined during the initial graded exercise test at baseline. The choice of exercising on a treadmill or cycle ergometer was used to increase autonomy and adherence across the 8-week period. Participants received encouragement to maintain their prescribed exercise intensity throughout all exercise sessions at each 10-min assessment to maintain the prescribed exercise intensity. This dose of moderate-intensity exercise is consistent with public health recommendations, and has been recommended for
individuals with depression (e.g., Dunn et al., 2005; Rethorst & Trivedi, 2013).

**Control condition**

The control or comparator arm consisted of 30-45 minutes of stretching aimed at targeting major muscle groups, and was similar to the stretching protocol administered by Knubben et al. (2007). The stretching-based exercises were performed while sitting and standing, with the stretch being held for each muscle group for approximately 20 seconds in sets of 3 with a 40 second rest period between each stretch. Trained research staff instructed participants on the proper form for each stretch prior to and during each session. The control condition was used to minimize potential demand characteristics commonly reported in the exercise psychology literature (Morgan, 1997). Similar light-intensity stretch exercise protocols have been implemented in exercise trials for depression (J. Krogh et al., 2012).

**Measures**

*General medical history*

General health and medical history was collected using a self-reported health history questionnaire. This form assessed family medical history, cardiovascular health and risk factors, current and past medical diagnoses, past surgeries, tobacco/alcohol use, as well as prior and current medication and supplementation use. In addition, the Physical Activity Readiness Questionnaire (Shephard et al., 1981) was used to ensure participants could safely engage in exercise.

*Mini-International neuropsychiatric interview (MINI)*

The MINI is a short, structured diagnostic interview that is designed to make diagnoses of psychiatric disorders according to the Diagnostic and Statistical Manual
of Mental Disorders, Fourth and Fifth Editions (DSM-IV; 5) and International Classification of Diseases-10 (ICD-10). It has excellent inter-rater and test-retest reliability and good concordance with the Structured Interview for DSM-III-R (Sheehan, 1997; Sheehan et al., 1998). All interviews were conducted by graduate students who were trained and supervised by clinical psychology faculty (E. Selby) at Rutgers University.

Clinical symptom severity

The 21-item Beck Depression Inventory-II (BDI-II; Beck, 1996) and 21-item Beck Anxiety Inventory (Beck et al., 1988) were used to assess clinical symptom severity of depression and anxiety over the past two weeks, respectively. Briefly, each item is scored on a 4-point scale (0-3), with scores ranging from 0-63. A higher total score reflects greater subjective symptomatology. Both BDI-II and BAI scales are well validated and have demonstrated high internal consistency estimates in previous studies, including from our laboratory (Brush et al., 2020; Brush et al., 2019; Olson et al., 2017).

Cardiorespiratory fitness

Cardiorespiratory fitness (VO₂ peak) was assessed using a modified Bruce protocol, which involved increasing the speed and grade of the treadmill every two min until volitional exhaustion was reached. A Polar heart rate (HR) monitor was used to record HR throughout the test. VO₂ 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) and averaged across 15 s intervals. VO₂ peak was defined as the maximal rate of oxygen
consumption per kg of body weight at the point when at least three of the following four criteria were met: (1) a plateau in oxygen consumption corresponding to an increase of less than 150 mL in oxygen uptake despite a progressive increase in workload, (2) HR within 10 beats per min (bpm) of age-predicted maximal values (220 bpm - age in years), (3) a respiratory exchange ratio greater than 1.10, or (4) a RPE greater than or equal to 17 on the original 6-20 scale. Upon completion of the graded exercise protocol, a five min cool down was performed at 2.5 mph and 0% grade.

Electrocardiogram recording

ECG signals were acquired according to recommendations by (Jennings et al., 1981) using a modified limb lead II configuration with Ag/AgCl disposable snap electrodes placed on the left and right lowest floating ribs and right clavicular bone. Impedance cardiograph (ICG) signals were recorded according to established guidelines by Sherwood et al. (1990). The ECG and ICG signals were sampled at 500 Hz and filtered through a MindWare BioNex system and acquired through BioLab software. The ICG ($Z_0$) thoracic impedance signal was recorded to derive respiratory rate (RR), since RSA is influenced by RR (Ernst et al., 1999). Spectral analyses were used to identify variation in the $Z_0$ signal caused by respiration and yields scores highly comparable to spirometric respiration measures (de Geus et al., 1995; Ernst et al., 1999; Houtven et al., 2006). Cardiovascular data were recorded throughout the protocol during rest, resonance breathing, and reactivity to separate blocks of positive and negative images. See Figure 2 for a depiction of study procedures for the autonomic cardiovascular data collection.
HF-HRV was derived from the ECG using MindWare HRV version 3.0.17 software (MindWare Technologies, Ltd., Gahanna, OH, USA). The cardiovascular data were screened for artifacts by visual inspection by a blinded assessor. Epochs of the ECG were averaged once data were cleaned by manually correcting software-identified inappropriately placed R peaks, according to the IBI Min/Max and the MAD/MED artifact detection algorithms (Berntson et al., 1990). From the ECG, the R-R interbeat interval (IBI) series was converted into time series data with a 4 Hz resolution (with interpolation), linearly detrended and end tapered using a Hamming windowing function and submitted to a fast Fourier transform (FFT). HF-HRV was computed as the natural-logged (ln) spectral power value in the high-frequency bandwidth (0.15-0.40 Hz) (Berntson et al., 1997). Following extraction from the software, HRV values were scanned for the presence of outliers, which were first identified as 3 SDs above or below the mean and subsequently removed.

PEP was derived from the ICG signal using MindWare IMP version 3.0.17 software (MindWare Technologies) and was quantified from the dZ/dt signal. Specifically, the time interval (in milliseconds) from the onset of the ECG Q wave (onset of ventricular depolarization) to the B point (opening of the aortic valve) of the dZ/dt wave was used to derive PEP (Sherwood et al., 1990). The max slope method was used to automatically place the B point, which was later manually adjusted based on visual inspection similar to previous recommendations (see Lozano et al., 2007).

Using RSA and PEP as measures of parasympathetic and sympathetic cardiac control, an index of CAB is derived as the difference between RSA and PEP. In order to combine the different measurement scales of RSA and PEP into a single index of
CAB, each variable was normalized by transforming the raw values to z scores. Given that greater sympathetic activity is associated with shorter PEP values, PEP was multiplied by −1 for ease in interpreting values (i.e., higher −zPEP values indicate more sympathetic activation, just as higher zRSA values indicate more parasympathetic activation; Berntson et al., 2008). CAB was calculated using the formula $\text{CAB} = \text{zRSA} - (-\text{zPEP})$, with higher CAB values reflecting reciprocal parasympathetic control and lower CAB values reflecting reciprocal sympathetic control.

**Vanilla baseline**

Participants were fitted with disposable snap electrodes for ECG and ICG recordings and were instructed to relax for five min in a seated position. Following this five-minute relaxation period, a “vanilla” task (Jennings et al., 1992) was presented on a 17” Dell laptop using E-Prime Professional version 2.0 software (Psychology Software Tools, Pittsburgh, PA, USA), with the center of the laptop screen being situated approximately 60 cm from the participant’s head at eye level. During the task, participants passively viewed slides of rectangles that changed color every five seconds. Participants were instructed to silently count the number of blue rectangles they saw during the five-minute stimulus presentation and were subsequently asked at the end of the task to recall how many blue rectangles they counted.

The vanilla task is a minimally demanding cognitive task that has been validated as a reliable method for assessing resting cardiovascular function that helps to standardize resting cognitive activity both within and across participants (Jennings et
al., 1992). Participants also completed a 5-min course of resonance paced breathing (Bates et al., 2019; Vaschillo et al., 2011) as well as 5-min of passive viewing of emotionally-valenced images from the International Affective Picture System (IAPS; Lang, 1997). However, these data are not included here.

**Data Analyses**

All statistical analyses were performed using SPSS v. 27 (IBM Corp., Armonk, NY, USA) with a familywise alpha level of 0.05. All outcomes were assessed for normality prior to conducting analyses. Descriptive statistics were conducted for demographic, clinical, and cardiovascular data at pre-intervention (Pre), including potential group differences in psychophysiological measures and symptom scores by sex using an independent-samples t-test. Bivariate Pearson correlations were conducted to examine relationships between depressive symptoms, HF-HRV, PEP, and CAB at baseline.

Repeated measures analyses of variance (rANOVAs) were used to test whether there were any pre-to-post treatment changes in depressive symptoms and cardiorespiratory fitness. Separate rANOVA was also used to test the initial hypothesis that increased CAB will be observed from pre-intervention (Pre) to post-intervention (Post), as well as any pre-to-post treatment changes in HF-HRV and PEP. Treatment condition (exercise, stretching) served as a between-subjects factor and time (Pre, Post) was used as a within-subjects factor in the analysis. Follow-up comparisons were conducted using Bonferroni corrected t tests and the Greenhouse-Geisser epsilon correction was used when sphericity was violated (Jennings & Wood, 1976). For rANOVAs, effect size estimates were presented as partial eta squared ($\eta^2_p$)
values, while Cohen’s $d$ is presented for $t$ tests. Bivariate Pearson correlations between changes in CAB, HF-HRV, and PEP measures and changes in depressive symptoms (BDI-II score) were performed. As a further test to determine whether any treatment-related changes in autonomic function may accompany symptom reduction, a rANOVA was conducted on Pre-to-Post changes in CAB, HF-HRV, and PEP by treatment responder status. Similar to the Sequenced Treatment Alternative to Relieve Depression (STAR*D) study that examined treatment response following antidepressant therapy (McClintock et al., 2011), treatment response was examined as a dichotomous outcome, based on whether or not a $\geq 50\%$ treatment reduction in depressive symptoms was met (treatment response).

For the secondary aim, i.e., to determine whether CAB, HF-HRV, and PEP at pre-intervention baseline predict change in depressive symptoms, separate multiple linear regression analyses controlling for gender (0 = male; 1 = female) and baseline (T1) depressive symptoms were conducted. Age, BMI, and $V_{O_2}$peak were retained as control variables in the regression models if they were significantly correlated with the outcomes. In these regression analyses, baseline (pre-intervention) depressive symptoms and treatment condition (active, control) were entered at step 1 and at step 2, the 2-way interaction between $\Delta$CAB (centered) and treatment condition were entered.

The same model was conducted for HF-HRV and PEP, except $\Delta$HF-HRV and $\Delta$PEP (centered) were substituted in place of $\Delta$CAB.; separate binary logistic regression analyses with the same predictors used in the multiple linear regression analyses were used, except the dependent variable was coded as 0 = nonresponder
and 1 = responder based on treatment response. For the linear and logistic regression analyses, there were 17 responders and 13 non-responders.

Results

Study Demographics and Clinical Characteristics

Overall, 32 participants completed both experimental conditions and had HF-HRV and PEP data collected at pre and post-intervention. Data from two participants were unusable due to problems during recording that compromised data quality. Therefore, data from 30 participants were included in this secondary data analysis.

Demographics and characteristics of the study sample are shown in Table 1.

| Table 1. Baseline characteristics by treatment condition (Active, Control). M ± SD. |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| Characteristic                          | Active (n=15) | Control (n=15) | p-value         |
| Age (years)                             | 20.9 ± 1.8     | 21.1 ± 2.2      | 0.79            |
| BMI (kg/m²)                             | 23.5 ± 3.8     | 24.2 ± 2.6      | 0.57            |
| VO₂ peak (mL·kg⁻¹·min⁻¹)               | 35.1 ± 6.1     | 37.6 ± 6.7      | 0.30            |
| Depressive Symptoms (BDI-II)            | 24.2 ± 10.7    | 19.9 ± 11.1     | 0.29            |
| Anxiety Symptoms (BAI)                  | 11.3 ± 8.5     | 14.8 ± 8.1      | 0.27            |

Note. Active = moderate-intensity aerobic exercise; Control = light-intensity stretching; VO₂ peak = peak aerobic fitness; BDI-II = Beck Depression Inventory-II; BAI = Beck Anxiety Inventory

No significant differences by treatment condition were found for any of the demographic, clinical, fitness, or autonomic measures at baseline, ps > .27. No significant gender differences in depressive symptoms, anxiety symptoms, baseline health outcomes or HRV measures were found; however, BMI was higher among females (BMI: 24.0 ± 2.7 kg/m²) compared to males (BMI: 23.5 ± 3.8 kg/m²), while VO₂ peak was lower
among females (VO_2 peak: 35.7 ± 6.8 mL/kg/min) relative to males (VO_2 peak: 37.0 ± 6.9 mL/kg/min). There was no significant difference between groups in the male to female ratio composition, \( \chi^2(1, N = 30) = 0.13, p > 0.05 \). Bivariate Pearson correlations between depressive symptoms and autonomic measures revealed a marginally significant relationship between pre-treatment depressive symptom severity and PEP, \( r(30) = 0.31, p = .096 \); depressive symptoms were not associated with HF-HRV, \( p = 0.29 \).

**Depressive Symptoms and Cardiorespiratory Fitness: Response to Treatment**

The rANOVA on depressive symptoms (BDI-II score) revealed a significant main effect of time, \( F_{1,28} = 17.27, p < .05, \eta^2_p = 0.38 \), which was superseded by a significant time x condition interaction, \( F_{1,28} = 6.86, p < .05, \eta^2_p = 0.20 \). This interaction indicated a greater Pre-to-Post treatment reduction in depressive symptoms following exercise relative to the stretching control. Although there were no significant differences in depressive symptoms between treatment conditions at Pre-treatment baseline, follow-up Bonferroni corrected \( t \) tests for the time x condition interaction confirmed lower depressive symptoms at Post-treatment following the active exercise condition (9.8 ± 9.9) relative to the stretching control (16.6 ± 15.3), \( t(28) = 4.8, p < .01, d = 0.76 \). For cardiorespiratory fitness, there was no significant time main effect, \( F_{1,28} = 1.06, p = 0.312, \eta^2_p = 0.04 \) nor a time x condition interaction, \( F_{1,28} = 0.00, p = 0.98, \eta^2_p = 0.00 \).

Figure 2 shows changes in depressive symptoms and VO_2 peak from Pre-to-Post treatment.
Figure 1. Pre-to-post changes in depressive symptoms (A) and (B) aerobic fitness by condition. There was a significant pre-to-post treatment reduction in depressive symptoms in the active (aerobic exercise) versus control (light stretching) condition. No significant changes in aerobic fitness were found by treatment condition.

Autonomic Measures: Response to Treatment

The rANOVA for CAB revealed no significant main effect of time, $F_{1,28} = 0.00$, $p = 1.00$, $\eta^2_p = 0.00$. In addition, no significant time main effects were observed for either of the constituent autonomic measures of HF-HRV, $F_{1,28} = 0.392$, $p = 0.536$, $\eta^2_p = 0.014$, or PEP, $F_{1,28} = 1.241$, $p = 0.275$, $\eta^2_p = 0.042$. No significant interactions were found for CAB, HF-HRV, or PEP, $ps > 0.17$. See Table 2 for values of all cardiovascular autonomic measures at Pre- and Post-treatment for the active exercise and stretching control conditions.
Table 2. Pre-Post autonomic measures by treatment condition (Active, Control). $M \pm SD$.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Moderate-Intensity Exercise (Active)</th>
<th>Light-Intensity Stretching (Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre $(n=15)$</td>
<td>Post $(n=15)$</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>$76.4 \pm 7.1$</td>
<td>$78.9 \pm 7.7$</td>
</tr>
<tr>
<td>HF-HRV (ms²)</td>
<td>$6.7 \pm 0.7$</td>
<td>$6.7 \pm 0.7$</td>
</tr>
<tr>
<td>PEP (ms)</td>
<td>$103.3 \pm 13.9$</td>
<td>$104.3 \pm 5.9$</td>
</tr>
<tr>
<td>CAB</td>
<td>$0.1 \pm 0.7$</td>
<td>$0.2 \pm 1.0$</td>
</tr>
<tr>
<td>CAR</td>
<td>$-0.2 \pm 1.5$</td>
<td>$0.1 \pm 1.1$</td>
</tr>
</tbody>
</table>

Note. CAB = cardiac autonomic balance; CAR = cardiac autonomic regulation; HR = heart rate; LF/HF = low frequency/high frequency ratio; PEP = pre-ejection period; RSA = respiratory sinus arrhythmia.

**Figure 2.** Individual participant Pre-to-Post changes in HF-HRV for exercise (A), control (B), and both groups (C).
When examining relationships between change in depressive symptoms (BDI-II) and autonomic measures from Pre-to-Post treatment, the association between change in depressive symptoms and CAB approached significance, \( r(30) = -0.34, p = 0.068 \). Change in depressive symptoms was not associated with change in PEP, \( r(30) = -0.25, p = 0.192 \). Figures 3 displays associations between change in resting CAB and change in depressive symptoms.

![Graph showing association between change in CAB and change in depressive symptoms](image)

**Figure 3.** Relationship between change in resting CAB and change in depressive symptoms from pre-to-post intervention.

**Was there a pre-to-post treatment change in autonomic function by responder status?** The rANOVA on Pre-to-Post changes in CAB, HF-HRV, and PEP by responder status indicated no significant main effect of time for CAB, \( F_{1,28} = 0.004, p = 0.947, \eta^2_p = 0.000 \), HF-HRV, \( F_{1,28} = 0.354, p = 0.56, \eta^2_p = 0.012 \), or PEP, \( F_{1,28} = 1.473, p \)
= 0.24, $\eta^2_p = 0.050$. There were also no significant interactions of condition x time for any of the variables, $p > 0.05$. Table 3 displays changes in autonomic variables from Pre-to-Post treatment by responder status.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Responders</th>
<th>Non-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre (n=17)</td>
<td>Post (n=13)</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>75.4 ± 7.6</td>
<td>76.0 ± 8.5</td>
</tr>
<tr>
<td>HF-HRV (ms²)</td>
<td>6.8 ± 0.8</td>
<td>6.7 ± 0.7</td>
</tr>
<tr>
<td>PEP (ms)</td>
<td>103.0 ± 14.0</td>
<td>104.1 ± 5.6</td>
</tr>
<tr>
<td>CAB</td>
<td>0.22 ± 0.7</td>
<td>0.09 ± 1.1</td>
</tr>
<tr>
<td>CAR</td>
<td>-0.05 ± 1.6</td>
<td>0.05 ± 1.0</td>
</tr>
</tbody>
</table>

**Table 3.** Pre-Post autonomic measures by responder status (Responder, Non-Responders). $M \pm SD$.

*Note:* CAB = cardiac autonomic balance; CAR = cardiac autonomic regulation; HF = heart rate; LF/HF = low frequency/high frequency ratio; PEP = pre-ejection period; RSA = respiratory sinus arrhythmia

**Do resting autonomic measures predict treatment response?** Three separate multiple linear regression analyses (CAB, HF-HRV, PEP) revealed no significant associations between HF-HRV and PEP measures and Pre-to-Post change in depressive symptoms. However, after controlling for gender and baseline depressive symptoms, Pre-treatment CAB was a marginally significant predictor of Post-treatment depressive symptoms, $\beta = -0.31$, $t = 1.90$, $p = .068$. See Figure 4 for baseline levels of CAB (and cardiac autonomic regulation; CAR) between responders and non-responders. See Table 4 as a reference for all linear regression models and their respective model values.
We also explored treatment outcome as a dichotomous variable (nonresponder = 0, responder = 1) across both conditions. After controlling for gender and Pre-treatment depressive symptoms, CAB emerged as a marginally significant predictor of responder status, $\beta = 1.12$, Wald = 3.20, $p = .074$, $OR = 3.05$, 95% CI = [0.90, 10.34]. That is, for every single unit increase in CAB, the odds of responding to the intervention increased by a factor of 3.05.

Table 4. Linear regression analyses predicting post-intervention depressive symptoms from baseline measures

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model Fit Indices</th>
<th>Model Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>$F$</td>
</tr>
<tr>
<td>Model 1: CAB x BDI x VO2</td>
<td>0.28</td>
<td>3.46</td>
</tr>
<tr>
<td>(Intercept)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAB</td>
<td>-4.32</td>
<td>-1.66</td>
</tr>
<tr>
<td>BDI-II Pre</td>
<td>0.61</td>
<td>2.97</td>
</tr>
<tr>
<td>VO2 peak</td>
<td>0.20</td>
<td>0.57</td>
</tr>
<tr>
<td>Model 2: CAB x BDI x BMI</td>
<td>0.28</td>
<td>3.38</td>
</tr>
<tr>
<td>(Intercept)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAB</td>
<td>-4.11</td>
<td>-1.58</td>
</tr>
<tr>
<td>BDI-II Pre</td>
<td>0.61</td>
<td>2.88</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.27</td>
<td>-0.38</td>
</tr>
<tr>
<td>Model 3: CAB x BDI x Gender</td>
<td>0.33</td>
<td>4.27</td>
</tr>
<tr>
<td>(Intercept)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAB</td>
<td>-4.85</td>
<td>-1.99</td>
</tr>
<tr>
<td>BDI-II Pre</td>
<td>0.64</td>
<td>3.24</td>
</tr>
<tr>
<td>Gender</td>
<td>-6.18</td>
<td>-1.44</td>
</tr>
</tbody>
</table>

*Note. The $R^2$ value presented is the coefficient of determination. BDI-II = Beck Depression Inventory, VO2 = peak oxygen consumption, BMI = body mass index, CAB = Cardiac autonomic balance.*
Figure 4. CAB and CAR in responders and non-responders. Data points illustrate means and standard errors of CAR and CAB by responder status (responder, non-responder). Compared to the responders, non-responders had lower CAB scores, indicating lower reflective of predominant sympathetic balance, but were not deviant on CAR.

**Does pre-intervention resting HF-HRV and PEP predict treatment response?** For the exploratory aim, three separate multiple linear regression analyses revealed no significant associations between HF-HRV and PEP measures and Pre-to-Post treatment change in depressive symptoms. We also explored treatment outcome as a dichotomous variable across both conditions, and both HF-HRV and PEP were nonsignificant predictors.
Discussion

The current study examined the effects of an 8-week aerobic exercise intervention on cardiac autonomic balance (CAB), the independent psychophysiological measures of sympathetic (PEP) and parasympathetic (HF-HRV) cardiac control, and symptoms of depression in individuals with MDD. Secondary aims were to determine whether the magnitude of change in CAB from pre-to-post intervention was correlated with change in depressive symptoms and whether CAB at baseline could predict treatment response across 8 weeks of intervention with aerobic exercise or light stretching. Similar to the previous trials that served as the foundation for this secondary analysis (Olson et al., 2017; Brush et al., 2020), significant reductions in depressive symptoms were observed in this sample following both the active treatment and control interventions, although greater symptom reductions occurred following aerobic exercise compared to stretching. No significant pre-to-post treatment changes were observed for any of the autonomic measures; however, pretreatment CAB was a marginally significant predictor of treatment response, net of baseline depressive symptoms, aerobic fitness, and body mass index. Collectively, these findings suggest that 8 weeks of aerobic exercise is effective for reducing depressive symptoms, although the observed symptom reductions are not accompanied by meaningful change in CAB, HF-HRV, or PEP. The marginally significant finding of baseline CAB as predictor of treatment response is noteworthy and potentially relevant for identifying patients most likely to benefit from exercise interventions.

There was a significant and clinically meaningful reduction in depressive symptoms after 8 weeks of aerobic exercise relative to the smaller reduction for
individuals assigned to the stretching condition. These results are consistent with findings from systematic reviews and meta-analyses indicating that aerobic exercise has similar antidepressant effects as traditional, first-line treatments (e.g., pharmacotherapy) treatments for depression (Blumenthal et al., 2012; Ekkekakis & Murri, 2017; Schuch et al., 2016). Importantly, the reduction in depressive symptoms following aerobic exercise reached the minimally clinical important difference (MCID) cut-off score (i.e., 17.5% treatment-related reduction in BDI-II score) that was previously established by Button and colleagues (Button et al., 2015). That is, individuals in the aerobic exercise condition, as well as those assigned to the 8-week stretching condition, both met MCID criteria. Reduced depressive symptoms following light stretching echo the early findings by Martinsen, Hoffart, and Solberg (1989), who reported depression symptom reductions among 99 patients with major depression following 8 weeks of aerobic exercise or a comparator consisting of light stretching and relaxation exercise. Future research should incorporate assessments of exercise preference (e.g., low intensity versus more moderate-to-vigorous intensity exercise) to document individual-level change in response to exercise interventions that vary in intensity (Ekkekakis et al., 2005). This is particularly important considering that depression may influence affected person’s preferred type and intensity of exercise (Busch et al., 2016).

It was initially hypothesized that changes in CAB would be observed following 8 weeks of aerobic exercise training, and that changes in CAB would covary with reductions in depressive symptoms. CAB has been positively correlated with parasympathetic control (HF-HRV) and inversely correlated with sympathetic control (-PEP) (Berntson et al., 2008); therefore, it was also expected that these normalized
autonomic indices could change following 8 weeks of intervention. Chambers and Allen (2002) previously examined whether increases in vagal tone were associated with successful treatment response following 8-weeks of acupuncture treatment in 16 women with nonchronic major depression. At baseline and following treatment, the Hamilton Rating Scale for Depression (HAM-D) was administered followed by ECG recording. Those women with little change in vagal tone from before to after treatment showed minimal reduction in HAM-D score (-4.8) while those with a larger change in vagal tone showed a large decrease in HAM-D (-14.8). Increases in HRV have also been observed following successful treatment of depression with electroconvulsive therapy (Agelink et al., 2002; Nahshoni et al., 2001) although not all studies are in agreement (Schultz et al., 1997). In the present analysis, no significant pre-to-post treatment changes were observed for CAB, HF-HRV, or PEP. In contrast, Jurca et al. (2004) reported that 8 weeks of moderate-intensity exercise performed at an intensity of ~50% VO2 max increased HRV among previously sedentary postmenopausal women. In the SEEDS trial, Toni et al. (2016) examined the effects of a common antidepressant (sertraline) plus structured, tailored group physical exercise (S + EX) versus sertraline alone (S) for 24 weeks among older adults (65-85 years) with major depression. Participants displayed significant improvements in HRV over time, irrespective of group assignment. However, patients in the S + EX group displayed greater increases across several HRV indices (RR, pNN50, RMSSD, SDHR, SDNN, HF, and LF) compared with those in the S group.

The participants in the current study included young adults with MDD, who may be characterized by autonomic systems that are relatively stable and less influenced by short behavioral interventions (e.g., exercise). Previous studies that have shown an
influence of exercise on HRV, particularly within the context of depression, have predominantly been conducted with older adults (e.g., Toni et al., 2016). Relative to the physiological reserve hypothesis (Morris et al., 2006; Sundgren et al., 2015) various humoral, neural, and neurobehavioral modulators of cardiac chronotropic control are likely to be impaired with aging. Accordingly, age-related changes in cardiac autonomic control may help to explain why measures of HRV have shown to be more amenable to short-term behavioral and/or pharmacological intervention in older versus younger adults. It is also possible that more vigorous intensities of exercise, or a longer duration of intervention, is necessary before observable changes in CAB may be demonstrated among younger adults.

Baseline CAB predicted, albeit only marginally significantly, treatment responders using both linear and logistic regression analyses. Early notions of autonomic balance assumed a reciprocal control of sympathetic and parasympathetic autonomic branches (e.g. Eppinger & Hess, 1915; Wenger, 1966). However, the two autonomic branches are not invariably reciprocally controlled and may be coactivated or independently activated depending on circumstances, psychological states, and neurophysiological substrates (Berntson et al., 2008). Heart rate variability has been suggested as a potential psychophysiological index of health, resilience, and adaptability (Bates & Buckman, 2013; Leyro, Buckman, & Bates, 2019; Rottenberg, 2007; Thayer & Lane, 2009). In line with this suggestion, CAB may serve as an informative psychophysiological index not only of cardiac autonomic balance, but also the capacity to adapt and deal with challenging demands. Although previous studies have demonstrated lower CAB and HRV in young adults with depression (Brush et al., 2019; Lesnewich et
al., 2020), the current findings suggest that young adults with MDD who are characterized by greater autonomic flexibility (i.e., higher CAB) may be more likely to benefit from an individualized exercise program. The mechanisms underlying this possibility are currently unknown and warrant future investigation.

The specific dose of exercise used in the trials that constituted this secondary analysis did not result in a meaningful change in cardiorespiratory fitness. This finding, although not specifically related to the primary aims of this study, warrant consideration. Previous studies have considered the cardiorespiratory fitness hypothesis of exercise and depression (Krogh et al., 2014; McCann & Holmes, 1984; Rahman et al., 2018) and this idea features prominently in the popular press. This hypothesis is based on the notion that one of the mechanisms through which exercise results in decreases in depressive symptoms is through increased cardiorespiratory fitness and the associated improvements in oxygen delivery through blood (e.g., improved cardiac output) and removal of waste byproducts (e.g., lowered peripheral resistance). Furthermore, increases in cardiorespiratory fitness as a result of exercise would undoubtedly influence the autonomic metrics assessed in this study. However, the findings herein suggest that light and moderate-intensity exercise programs result in an antidepressant response without a change in aerobic fitness. Collectively, the reduction in depressive symptoms following both treatment conditions complement the findings of Martinsen et al. (1989) and Imboden et al., (2020), and indicate that light-intensity exercise programs, which are less likely to impact cardiorespiratory fitness, may also result in meaningful reductions in depressive symptoms. Whether the antidepressant effects of such interventions persist beyond the duration of the exercise program currently remains unknown.
Limitations

These findings should be interpreted in the context of several limitations. The control condition used in this study, i.e., light-intensity stretching, may not be the most appropriate comparison condition. The most appropriate control conditions for exercise intervention studies have been a longstanding debate in the area of exercise and mental health (Lindheimer et al., 2015, 2020) in part because the psychobiological mechanisms instantiated by moderated-intensity exercise may also be activated by light stretching. The light-intensity stretching condition was chosen to control for potential demand characteristics, including attention and expectancy effects (Morgan, 1997). Future research should compare the effects of exercise on autonomic function in MDD to more traditional forms of treatment, including pharmacological and CBT approaches (e.g., Blumenthal et al., 1999). The duration of the intervention was relatively short in these trials, which makes it possible that the intervention and/or exercise dose was insufficient to modify autonomic functioning. We also did not control for time of day of assessment or previous night’s sleep on cardiac autonomic function. Lastly, these trials were powered to detect pre-to-post treatment changes in event-related potential measures of cognition. Therefore, these findings, although intriguing, should be examined in future exercise and behavioral intervention studies for depression. Future research should also incorporate a follow-up assessment to understand the lasting effects of exercise on depressive symptoms and whether individuals achieve or maintain remission following 8-weeks of exercise participation.

Conclusions

In summary, the findings of this study make a novel and clinically relevant
contribution to the literature on exercise and depression by demonstrating that pre-
treatment CAB may serve as a psychophysiological predictor of depressive symptom
change following a short, 8-week light and moderate-intensity exercise intervention.
These findings are particularly novel given that they are in young adults, who may be
characterized by greater physiological reserve in the autonomic nervous system. This also
has clinical relevance as decreased HRV has been shown in previous studies to be a
clinical risk factor for a variety of health outcomes and lower resilience. Future
interventions incorporating cardiac autonomic measures as predictors of response and
mechanistically-based targets may help to advance precision medicine approaches to
physical exercise intervention.
Postscript: General Remarks

Each of the aims of this dissertation came to fruition based on various opportunities that were afforded to me over the course of my Ph.D. work. The original plan for my dissertation was to conduct studies that extended previous work in acute exercise and emotion as well as work that examined respiratory sinus arrhythmia among individuals with variable levels of depressive symptoms. As the plan to execute these studies went forward, COVID-19 and the global pandemic started, shutting down lab research operations.

In the first 3 years of my Ph.D., our lab group worked on collecting EEG and HRV data through an 8-week exercise intervention trial in collaboration with the Cardiac Neuroscience lab of Dr. Marsha Bates and Dr. Jennifer Buckman. The HRV data was collected at pre and post intervention across the years 2015-2018, providing a nice subset of cardiovascular autonomic data. After publishing baseline CAB data that demonstrated predictive utility with current MDD, a next step involved examining whether CAB changed within an exercise intervention and if it held the same predictive utility in terms of treatment responders to the exercise intervention. I felt my experience in the Exercise Psychophysiology Lab as well as the potential questions that could be answered by this secondary data analysis aligned well with my research interests, which led to this project as my Ph.D. dissertation.
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