EXAMINING NEURAL MEASURES AS TREATMENT TARGETS AND PREDICTORS OF CHANGE TO EXERCISE IN DEPRESSION

By

Christopher J. Brush

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Brandon L. Alderman

And approved by

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ABSTRACT OF THE DISSERTATION

Examining neural measures as treatment targets and predictors of change to exercise in depression

By CHRISTOPHER J. BRUSH

Dissertation Director:
Brandon L. Alderman

Major depressive disorder (MDD) is a common and economically burdensome neuropsychiatric disorder characterized by the two cardinal features of low mood and anhedonia. These symptoms coincide with a wide range of secondary symptoms, including significant weight loss or weight gain, fatigue, feelings of worthlessness, and diminished ability to concentrate. While MDD is often diagnosed as a single disorder, it is a highly heterogeneous disease with poor treatment outcomes. Due to high symptom variability, matching an individual to optimal treatments is difficult and is a barrier to precision medicine approaches for clinical practice. Thus, identifying clinical and neurophysiological markers associated with treatment response or that can be altered as depressive symptoms change with treatment is critical. Aerobic exercise has garnered considerable support as a robust behavioral treatment intervention for MDD; however, the underlying neurophysiological mechanisms of action are not well understood. In study 1, we examined whether the reward positivity (RewP) event-related brain potential (ERP) component could be used to index abnormal reward processing in MDD, and whether this neurophysiological measure was correlated with depressive symptom severity. RewP amplitudes were significantly reduced among individuals with MDD

relative to healthy, non-depressed controls, and this effect was moderated by depressive symptom severity, such that a smaller RewP was observed in individuals with greater depressive symptom severity. These findings demonstrate that individuals with MDD show impaired reward processing during the initial evaluation of a rewarding stimulus. In study 2, we examined two separate candidate neural markers of emotion, the RewP and late positive potential (LPP), following a single bout of moderate-intensity aerobic exercise in young adults with variable symptoms of depression. Acute exercise was shown to modify the LPP component, such that increased LPP amplitude to pleasantly-valenced content was found following exercise relative to seated rest. Regardless of symptom severity, acute exercise did not modify RewP amplitude. Findings from this study suggest that these emotional processes are modifiable through exercise, suggesting potential targets for future exercise interventions. Lastly, in study 3 we examined the effects of an 8-week moderate-intensity aerobic exercise intervention performed three days per week on reward processing and cognitive control, two candidate transdiagnostic mechanisms that are disrupted in MDD. Significant reductions in depressive symptoms were found following both treatment arms, but were larger following moderate-intensity aerobic exercise relative to a light-intensity stretching condition. Pre-to-post changes in cognitive control (i.e., smaller error-related negativity [ERN]) were correlated with pre-to-post changes in depressive symptoms. ERN was also a significant predictor of treatment response; larger pre-treatment ERN amplitude was associated with a greater antidepressant treatment response. Although exercise did not impact RewP, larger pre-treatment RewP amplitude was also associated with treatment response (≥ 50% pre-to-post treatment reduction in depressive symptoms). These findings highlight the use of

exercise as an antidepressant treatment option for MDD, and suggest that differential patterns of reward processing and cognitive control may have utility for selecting appropriate treatments for individuals with MDD.

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
A/D	Analog-to-digital
Ag-AgCl	Silver-Silver Chloride
ANOVA	Analysis of variance
BAI	Beck anxiety inventory
BDI-II	Beck depression inventory, Second Edition
BMI	Body mass index
BOLD	Blood-oxygen-level dependent
bpm	beats per minute
CBT	Cognitive behavioral therapy
CI	Confidence interval
cm	centimeter
CRN	Correct-related negativity
D	Decision
DASS	Depression anxiety and stress scales
DC	Direct current
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition- Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECI	Emotion context-insensitivity
EEG	Electroencephalography

EGI	Electrical Geodesics, Inc.
EOG	Electrooculogram
ERA	ERP Reliability Analysis
ERN	Error-related negativity
ERP	Event-related potential
FAS	Felt arousal scale
fMRI	Functional magnetic resonance imaging
FN	Feedback negativity
FS	Feeling scale
G	Generalizability
GAD	Generalized anxiety disorder
HEOG	Horizontal electrooculogram
HIIE	High-intensity interval exercise
HR	Heart rate
HRR	Heart rate reserve
Hz	Hertz
IAPS	International Affective Picture System
IBM Corp.	International Business Machines Corporation
ICA	Independent component analysis
ICC	Intraclass correlation coefficient
ICD-10	International Classification of Diseases-10
IIR	Infinite impulse response
in.	inch
IPAQ	International Physical Activity Questionnaire
kCal	kilocalorie

kg	kilogram
kΩ	kiloohms
LPP	Late positive potential
m	meter
MCID	Minimally clinical important difference
MDD	Major depressive disorder
MET	Metabolic equivalent
μV	Microvolts
min	minute
MINI	Mini-International Neuropsychiatric Interview
mL	milliliter
MLM	Multilevel modeling
mph	miles per hour
ms	milliseconds
NA	Negative affect
NIMH	National Institute of Mental Health
OCD	Obsessive compulsive disorder
OR	Odds ratio
PA	Positive affect
PANAS	Positive and negative affect schedule
PAR-Q	Physical Activity Readiness Questionnaire
PCA	Principal components analysis
PES	Post-error slowing
PFC	Prefrontal cortex
PIA	Post-error improvement in accuracy

POMS	Profile of mood states
rANOVA	Repeated measures analysis of variance
rANCOVA	Repeated measures analysis of covariance
RDoC	Research Domain Criteria
RER	Respiratory exchange ratio
RewP	Reward positivity
ROI	Region of interest
RPE	Rating of perceived exertion
RT	Reaction time
s	second
SAD	Social anxiety disorder
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
SSRI	Selective serotonin retake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
T1	Pretreatment
T2	Posttreatment
TF4SF1	Temporal factor 4 spatial factor 1
VEOG	Vertical electrooculogram
VO_2 peak	Cardiorespiratory fitness
ΔERN	Subtraction-based error-related negativity difference wave
ΔLPP	Subtraction-based late positive potential difference wave
ΔRewP	Subtraction-based reward positivity difference wave
$\Delta RewP_{resid}$	Residualized-based reward positivity difference wave

Chapter 1

Using multilevel modeling to examine blunted neural responses to reward in major depression

Christopher J. Brush, Peter J. Ehmann, Greg Hajcak, Edward A. Selby, & Brandon L. Alderman

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Introduction

Major depressive disorder (MDD) is a pernicious and often chronic affective disorder characterized by sustained negative affect and difficulties experiencing positive affect (Joormann & Stanton, 2016). MDD is a leading cause of global disability and disease (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015; Mathers, Fat, & Boerma, 2008; Murray & Lopez, 1996) and is associated with substantial economic burden (Kessler et al., 2003; Kessler & Bromet, 2013). Although surprisingly little is known about the neurobiology underlying depression, one promising area relates to reward dysfunction. Previous research has shown that individuals with MDD evidence decreased brain activation (Diekhof, Falkai, & Gruber, 2008) and grey matter volume (Pizzagalli et al., 2009; Wacker, Dillon, & Pizzagalli, 2009) in brain regions associated with reward

processing. Diekhof et al. (2008) highlighted functional magnetic resonance imaging (fMRI) evidence indicating decreased activation in reward-sensitive regions (ventral striatum, medial prefrontal cortex, amygdala) in response to monetary rewards and positively-valenced stimuli in depression. Pizzagalli et al. (2009) found decreased striatal grey matter volume and reduced caudate nucleus activation to unpredictable rewarding outcomes in MDD. These reward processing impairments often persist into remission and are predictive of relapse despite antidepressant treatment (Vrieze et al., 2013).

Event-related potentials (ERPs), which reflect voltage fluctuations in the ongoing electroencephalogram (EEG) time-locked to an event, have excellent temporal sensitivity and provide a direct measure of neural activity. ERPs have successfully been used to reveal reward-related and cognitive impairments in MDD (Erickson, Kappenman, & Luck, 2018; Klumpp & Shankman, 2018). The ERPs elicited by the presentation of feedback indicating rewards and losses are characterized by a relative positivity and negativity, respectively, that are maximal approximately 200-300 ms at frontocentral electrode sites (Walsh & Anderson, 2012). The feedback negativity (FN) refers to the *relative negativity* following losses, whereas the *relative positivity* in the ERP waveform, which is either reduced or absent in response to losses, is referred to as the reward positivity (RewP; Proudfit, 2015). Previous studies indicate that variability in the difference between the neural response to gains and losses is driven by the RewP (Bress & Hajcak, 2013; Carlson, Foti, Mujica-Parodi, Harmon-Jones, & Hajcak, 2011; Foti, Weinberg, Dien, & Hajcak, 2011; Holroyd, Pakzad-Vaezi, & Krigolson, 2008); thus, Levinson, Speed, Infantolino, and Hajcak (2017) recently referred to the difference between the RewP and FN as the ΔRewP. In this study, we adopt this nomenclature to

differentiate neural responses to rewards (RewP), losses (FN), and to the gain-loss difference (ΔRewP).

The RewP and FN demonstrate acceptable-to-excellent psychometric properties (Levinson et al., 2017) and relate to reward-related behavioral (Bress, Foti, Kotov, Klein, & Hajcak, 2013) and fMRI measures (Carlson et al., 2011; Foti, Carlson, Sauder, & Proudfit, 2014), making them ideal neural measures to examine reward dysfunction in MDD (Hajcak & Patrick, 2015). Indeed, previous studies have shown a smaller RewP and ΔRewP among depressed individuals relative to healthy controls (Foti et al., 2014; Foti & Hajcak, 2009; Liu et al., 2014). In terms of neural circuitry, the RewP may be generated by reward-related striatal activity (Becker, Nitsch, Miltner, & Straube, 2014; Carlson et al., 2011; Cohen, Cavanagh, & Slagter, 2011; Whitton et al., 2017), while some evidence suggests the FN may originate from the dorsal anterior cingulate (Foti, Weinberg, Bernat, & Proudfit, 2015; Gehring & Willoughby, 2002). Using a combined ERP and fMRI approach, Carlson et al. (2011) found that the ventral striatum, caudate, amygdala, medial prefrontal cortex, and orbitofrontal cortex were involved in generating the RewP, while Foti et al. (2015) used source localization techniques and observed increased reward-related activity in the basal ganglia. Further, a simultaneous ERP and fMRI study observed that trial-to-trial ERP variation to rewards predicted hemodynamic activity across the reward circuit (Becker et al., 2014). These brain structures are all implicated in the mesocorticolimbic dopamine system, an important system in reward circuitry (Delgado, 2007), suggesting that reward-related ERPs may be used to detect reward processing deficits in depression.

Typically, ERP studies average data across many trials of the same type to isolate a psychological process of interest and are traditionally analyzed using repeated measures analysis of variance (rANOVA) designs. Recently, Volpert-Esmond, Merkle, Levsen, Ito, and Bartholow (2017) noted that the underlying assumption of the averaging process is that neural activity does not vary across the course of an experiment. They provided two examples demonstrating how multilevel modeling (MLM) can be used to examine change in neurophysiological processes over the course of an experimental session, while accounting for unique sources of variance (e.g., individual- and trial-level variability).

MLM is particularly relevant for studying the neural response to rewards and losses in gambling paradigms, as well as the temporal dynamics of reward processing in depression. For instance, Heller et al. (2009) collected fMRI data during an emotion regulation paradigm to test whether depression reflects deficits in the ability to sustain activity in neural structures involved in reward, motivation, and positive affect over a 37-min scan session. Individuals with MDD were unable to sustain nucleus accumbens activity over time compared to controls, which was related to individual differences in self-reported positive affect. In a separate study, antidepressant treatment-induced change in the sustained engagement of prefrontal-striatal circuitry predicted improvements in the experience of positive emotion in daily life (Heller et al., 2013). In both studies, fMRI data were averaged from the first and second half of the experimental session to examine engagement over time. Incorporating MLM within ERP experiments allows for the detection of subtle changes in psychological processes that occur across a task or experiment. Nonetheless, these findings are provocative and suggest important temporal dynamics in reward processing that can be examined in a laboratory setting.

To date, no study has extended the previous findings of blunted reward processing in depression (Foti & Hajcak, 2009; Liu et al., 2014; Proudfit, 2015) using MLM to examine changes in reward processing over the course of an experiment. Understanding neural responses to reward across time may provide insight into mechanisms underlying MDD. Therefore, we examined individual and trial-level differences in the RewP, FN, and ΔRewP using MLM to track the trajectory of responses over successive reward and loss trials. We hypothesized an attenuated ΔRewP for individuals with MDD relative to healthy controls. Based on the findings of impaired striatal engagement in depression (Heller et al., 2009), individuals with MDD were expected to exhibit reduced RewP over time relative to control participants, as indicated by negative linear change across the task. Depression symptom severity was also examined as a moderator of RewP and FN, and was expected to be associated with reduced RewP over time. Lastly, we examined the psychometrics of these feedback-related ERPs using internal consistency measures to further establish their utility in psychopathology research (Klumpp & Shankman, 2018).

Methods

Participants

Individuals of all ethnic origins between 18 and 25 years of age (n = 101) were recruited from university counseling and psychiatric clinics and advertisements posted around the surrounding community. All participants were interviewed using the Mini International Neuropsychiatric Diagnostic Interview (MINI; Sheehan et al., 1998) and had normal or corrected-to-normal vision. Exclusion criteria included any history or presence of bipolar spectrum disorder, schizophrenia, self-injurious or suicidal ideation, or neurological disorders or injuries resulting in a loss of consciousness. One participant

was removed from the analyses due to poor EEG data quality, resulting in 100 participants (71 female; 52 MDD) being included in the analyses. The final sample composition was sufficiently powered to test the primary hypothesis and included 38 Asian, 29 White, 13 Hispanic, 12 African-American, and 8 individuals self-identifying as more than one race. Participants provided written informed consent and the study was approved by the university's Institutional Review Board.

Sample Size Calculation

We conducted an *a priori* power analysis according to recommendations by Larson and Carbine (Larson & Carbine, 2017) to detect differences in ΔRewP by depression status. Rather than using a 2 (group: MDD, controls) x 2 (feedback type: gain, loss) rANOVA, which cubes the familywise error rate (i.e, $1 - 0.95^3 = 0.143$), an independent-samples *t* test was assumed for the calculation. Using G*Power version 3.1.9.3 (Faul, Erdfelder, Lang, & Buchner, 2007), power estimates indicated 96 participants (48 per group) were needed to achieve 80% power to detect an effect size of $d = 0.58$ ($\Delta = 3.58$ μV, $\sigma_{pooled} = 6.14$ μV; Bress et al. (2013)).

MDD Diagnosis

The MINI is a brief, structured interview that is highly reliable (Sheehan et al., 1998) and widely used for evaluating diagnoses of psychiatric disorders according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth and Fifth Editions* (DSM-IV; DSM-5) and *International Classification of Diseases-10* (ICD-10). The MINI was used to screen for Axis-I disorders and presence of a current major depressive episode. All interviewers had previous experience in administering structured clinical interviews.

Depression Symptom Severity

The Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996), a 21-item self-report inventory, was used to assess depression symptom severity over the past two weeks. Each item is scored on a 4-point scale (0-3), with a range of 0-63. The BDI-II scores in this sample demonstrated high internal consistency (Cronbach's $\alpha = 0.92$).

The Doors Task

The doors task (Proudfit, 2015) was administered using E-Prime Professional version 2.0 software (Psychology Software Tools, Inc., Pittsburgh, PA, USA) and consisted of five blocks of 20 trials. On each trial, a fixation cross was presented at the center of the screen for 1,000 ms followed by the presentation of two doors, which remained on the screen until participants made a left or right button press corresponding to the left or right door using a Logitech® F310 response gamepad. Following stimulus offset, another fixation cross was presented for 2,000 ms before displaying the feedback stimulus for 2,000 ms. Feedback indicated whether the participant won $0.50 (reward trial) or lost $0.25 (loss trial), which was represented by a green upwards arrow and a red downwards arrow, respectively. After feedback, another fixation cross was presented for 1,500 ms, which was followed by a short break prior to the next trial. Fifty reward and 50 loss trials were presented on a monitor 70 cm centered to the nasion, with vertical and horizontal visual angles of 1.2° and 6.6°, respectively. Participants were compensated their winnings ($12.50) following the task.

ERP Processing and Measurement

Continuous EEG was recorded from a 33 electrode actiCap system (Brain Products, GmbH; Munich, Germany) arranged according to the 10/20 guidelines. The electrooculogram (EOG) activity was recorded from 2 electrodes placed 2 cm outside the

outer canthus of the left eye and 2 cm below the right eye. EEG was amplified using an Electrical Geodesics, Inc. (EGI; Eugene, OR, USA) system (20,000 nominal gain, bandpass of 0.10–100 Hz) and sampled at 500 Hz with a 24-bit A/D converter referenced to the vertex electrode (Cz) at acquisition. Impedances were kept below 20 kΩ throughout recording.

EEG data were exported to EEGLAB toolbox version 14.1.1 (Delorme & Makeig, 2004) in Matlab version R2016b (The Mathworks, Inc., Natick, MA, USA) for data preprocessing. Data were bandpass filtered using a 2nd order infinite impulse response Butterworth filter of 0.10-30 Hz and adjusted for DC offset. EEG data were visually inspected for artifacts or extreme offsets and segmented to create feedback-locked epochs for gain and loss trials separately using a -200 to 800 ms time window. Oculomotor artifacts were removed using ICA blink templates provided by ERP PCA toolkit version 2.63 (Dien, 2010) and generated from the current dataset. ICA components that correlated 0.9 or higher with scalp topographies of the blink template were removed. Trials were also rejected if there was a voltage difference of 100 μV between minimum and maximum values or if channels differed by more than 30 μV from the neighboring 6 closest channels marked bad. Trials with > 10% of channels marked as bad were also removed. Epochs were re-referenced to the mean of the two mastoids (TP9, TP10), averaged separately by rewards and losses, and baseline corrected using the 200 ms pre-stimulus interval.

Consistent with previous research (Foti & Hajcak, 2010; Krigolson, Hassall, & Handy, 2014; Levinson et al., 2017; Proudfit, 2015) and the maximal activity at frontocentral sites in the present study, the RewP (rewards) and FN (losses) were

assessed at FCz. Feedback-locked amplitudes were measured as the mean voltage in a time window 200-300 ms post-feedback onset and was determined by visual inspection of the grand average waveform collapsed across participants and feedback types to minimize bias (Luck, 2014). The gain-loss difference waveform (ΔRewP), defined as RewP (rewards) minus FN (losses), was derived to isolate reward-related activity (Proudfit, 2015). The regression-based residualized difference score ($\Delta RewP_{resid}$) was also calculated since recent research suggests that it may be slightly more reliable than subtraction-based differences scores (Levinson et al., 2017; Meyer, Lerner, De Los Reyes, Laird, & Hajcak, 2017). Internal consistency measures were quantified using classical test theory and generalizability (G) theory estimates of dependability (Clayson & Miller, 2017).

Cross-Sectional Psychometrics

Split-half reliability analyses were conducted to determine the reliability of RewP, FN, and ΔRewP, while G theory estimates were used to assess overall dependability of RewP and FN, since it accounts for multiple sources of error variance (Clayson & Miller, 2017). RewP and FN split-half reliability analyses were performed by correlating averages of odd- and even-numbered trials for gains and loss trials separately, while ΔRewP was calculated by correlating averaged ΔRewP for odd and even trials. For the split-half reliability analyses, the Spearman-Brown corrected formula was used: split-half reliability = $2 * r_{odd/even} /1 + r_{odd/even}$. Dependability estimates (i.e., reliability coefficients determined from a Decision [D] study; Clayson and Miller (2017) were also derived from formulas provided by Baldwin et al. (Baldwin, Larson, & Clayson, 2015) using ERP Reliability Analysis (ERA) Toolbox version 0.4.5 (Clayson & Miller, 2017) which uses

CmdStan version 2.16.0 to implement statistical models in Stan (Carpenter et al., 2016). See Clayson and Miller (2017) for an extended overview and breakdown of the formulas used to calculate the dependability estimates.

Statistical Analyses

All analyses were performed using SPSS version 24 (IBM Corp., Armonk, NY, USA). To minimize the influence of poor data quality, participants with fewer EEG trials than needed to obtain a dependability point estimate of 0.80 were removed. One participant was removed due to this criterion. All MDD and control participants had a minimum of 33 (range = 33-100) and 32 (range = 32-100) trials, respectively.

A 2 (feedback type: gain, loss) x 2 (group: MDD, controls) rANOVA was used to examine group-level effects in RewP and FN, while an independent-samples *t* test was conducted to test the primary hypothesis of differences in ΔRewP (and $\Delta RewP_{resid}$) by depression status. A two-tailed alpha level of .05 was used and follow-up tests were adjusted using the Bonferroni correction (p_{corr} = .05/2 = .025).

RewP and FN were analyzed using MLM. Due to the nested structure of the data, two level models were to examine slopes of RewP and FN across the doors task. MLM accounts for individual differences in baseline responses at the beginning of the experiment (trial #1; random intercept) and changes over time (slopes) in a way that cannot be modeled with traditional approaches. MLM also partitions unique sources of variance, where the predictor variables, such as current diagnosis and depressive severity, are used to predict individual-specific change. MLM was used to model variation in RewP and FN across doors task trials as well as the covariance of non-independence between repeated measures. These types of models are ideal for ERP data, since MLMs

are robust to occasional missing trial-level data (Goldstein, 2011; Volpert-Esmond et al., 2017).

For the current models, the dependent variable was within-subject RewP and FN amplitudes. At level 1 (during each trial), predictors were trial (continuous; represents task trial number and linear growth) and task feedback type (dichotomous; 0 = losses; 1 = gains). For level 2 (for each participant), separate models included diagnostic status (dichotomous; 0 = control; 1 = MDD) and depressive symptom severity (continuous; grand-mean centered BDI-II score) as predictors. Model 1 was constructed to determine the prediction of current depression status on RewP and FN. Cross-level interactions between depression status and trial were included to examine the moderating influence of depression status on RewP and FN changes from the beginning to the end of the experiment. Additionally, another cross-level interaction between depression status, feedback type, and trial was included in the model to examine whether depression status served as a moderator of feedback type on RewP and FN over time. Model 2 included the same parameters; however, depression symptom severity was substituted for diagnostic status to examine symptom severity rather than simple presence of a diagnosis. For both models, trial was shifted so that the first trial corresponded with the intercept (t=0). Thus, the 50 reward and 50 loss trials ranged from 0 to 49 in the MLM analyses. Dichotomous variables, such as depression status, cannot be included as a random effect in mixed models. While trial was retained as a random effect in both models, based on parsimony and the nonsignificant finding for depression severity as a random effect, we retained both diagnostic status and depression severity as fixed effects in the models. Finally, the

models used restricted maximum likelihood estimation and an unstructured covariance matrix.

MLM Specifications

The model equations used for the MLM analyses are presented below:

Model 1

Level 1 (during each trial): $(\text{RewP/FN amplitude})_{ij} = \beta_{0j} + \beta_{1j}(\text{Trial})_{ij} + \beta_{2j}(\text{Feedback Type})_{ij} + \beta_{3j}(\text{Trial})_{ij}(\text{FeedbackType})_{ij} + r_{1j} + e_{ij}$

Level 2 (individual): $\beta_{0j} = \gamma_{00} + \gamma_{01}(\text{Diagnostic status})_j + u_{0j}$

$\beta_{1j} = \gamma_{10} + \gamma_{11}(\text{Diagnostic status})_j$

$\beta_{2j} = \gamma_{20}$

$\beta_{3j} = \gamma_{30} + \gamma_{31}(\text{Diagnostic status})_j$

Model 2 was the same as model 1, except depression severity was substituted into the equation to replace diagnostic status.

Intraclass Correlation Coefficient (ICC)

The ICC provides a measure of correlation among observations within a cluster and is determined from the unconditional (intercept-only) model (i.e., a model without predictors). The ICC, often denoted by "ρ", ranges from 0 to 1 and indicates the overall clustering and dependence of the data. According to Hox, Moerbeek, and Van de Schoot (2017), an ICC of 0 means all observations are independent from one another, while a nonzero ICC means observations are dependent. For the present study, the ICC was calculated as the variance of the individuals (σ_u^2) and the variance of the feedback-related ERP amplitudes (σ_e^2) at level 1; thus, the ICC was calculated as: ICC (ρ) = $\sigma_u^2 / (\sigma_u^2 + \sigma_e^2)$.

Results

Demographic and clinical characteristics are shown in Table 1. Bivariate correlations between depressive symptoms and feedback-related ERP amplitudes revealed a significant relationship between depressive symptoms and ΔRewP, $r(98) = -0.25$, $p < .05$, as well as $\Delta RewP_{resid}$, $r(98) = -0.23$, $p < .05$. Table 2 displays the internal consistency measures.

Table 1
Demographic and clinical characteristics

	MDD (n = 52)	Controls (n = 48)	Test Statistic	*p*-value
Male, Number (%)	12 (23.6)	17 (35.4)	$\chi^2 = 1.8$	.17
Age, Years	20.0 (1.4)	20.0 (1.5)	$t = 0.27$	.79
BMI, kg/m^2	23.6 (3.6)	22.9 (3.6)	$t = -0.96$	.34
BDI-II Total Score	24.0 (8.8)	7.9 (5.9)	$t = 10.83$	<.001
BAI Total Score	11.0 (9.1)	8.4 (6.3)	$t = 1.65$	.10
Comorbidities, Number (%)	13 (25%)	N/A		
Medicated, Number (%)	5 (10%)	N/A		

Note. Values are mean (SD), unless otherwise indicated (%). BMI = body mass index; BDI-II = Beck Depression Inventory-II; BAI = Beck Anxiety Inventory.

Table 2
Psychometric properties of feedback-related ERPs

Measure	RewP	FN	ΔRewP
Minimum Number of Trials[#]			
Controls	9	9	-
MDD	7	8	-
Split-half reliability			
Controls	0.95	0.95	0.58
MDD	0.97	0.96	0.53
Dependability [95% CIs]			
Controls	0.95 [0.93, 0.97]	0.96 [0.93, 0.97]	-
MDD	0.97 [0.95, 0.98]	0.96 [0.95, 0.98]	-

Note. [#]denotes minimum number of trials to reach the minimum dependability point estimate of 0.80 or above; CIs = confidence intervals.

ERP Analyses

A significant electrode site main effect revealed that ERP amplitudes were largest at FCz relative to Fz and Cz sites, $F(2,198) = 111.59$, $p < .001$, $\eta^2_p = 0.53$. There was the expected main effect of feedback type, $F(1,98) = 109.00$, $p < .001$, $\eta^2_p = 0.53$, indicating more positive amplitude for reward (RewP = 11.87 ± 6.56 μV) relative to loss trials (FN = 8.85 ± 6.05 μV). A significant feedback type x group interaction was observed, $F(1,98) = 13.00$, $p < .001$, $\eta^2_p = 0.12$. Decomposition of the interaction revealed a trend towards a smaller RewP for individuals with MDD (RewP = 10.57 ± 6.43 μV) relative to controls (RewP = 13.28 ± 6.48 μV), $t(98) = 2.10$, $p_{corr} = .04$, $d = 0.42$. Conversely, FN amplitude did not differ between groups, $t(98) = 0.49$, $p_{corr} = .62$, $d = 0.10$. Individuals with MDD had a significantly smaller ΔRewP (2.01 ± 2.52 μV) than controls (4.13 ± 3.33 μV), $t(98) = 3.61$, $p < .001$, $d = 0.72$, which was also observed in the regression-based $\Delta RewP_{resid}$ (MDD = -1.80 ± 4.68 μV; controls = 1.95 ± 6.24 μV), $t(98) = 3.42$, $p < .01$, $d = 0.68$.

Given the early deviation of the ERP parent waveforms, we also extracted the P2 component using temporospatial PCA. Using TF4SF1, which explained 3.1% of the variance, the P2 was assessed as the mean amplitude in a time window of 131-181 ms following feedback onset at FCz. The time window was determined using a time window consistent with the temporal loading peak of 156 (± 25) ms.

The rANOVA on P2 TF4SF1 amplitude resulted in a significant main effect of feedback type, $F(1,98) = 24.17$, $p < .001$, $\eta^2_p = 0.20$, indicating a larger P2 for rewards (5.49 ± 4.53 μV) compared to losses (4.36 ± 4.43 μV). There was a nonsignificant feedback type x group interaction, $F(1,98) = 1.60$, $p = .21$, $\eta^2_p = 0.02$. This suggests that there are no differences in P2 by group. Grand averaged parent and difference waveforms depicting RewP, FN, and ΔRewP by group are presented in Figure 1.

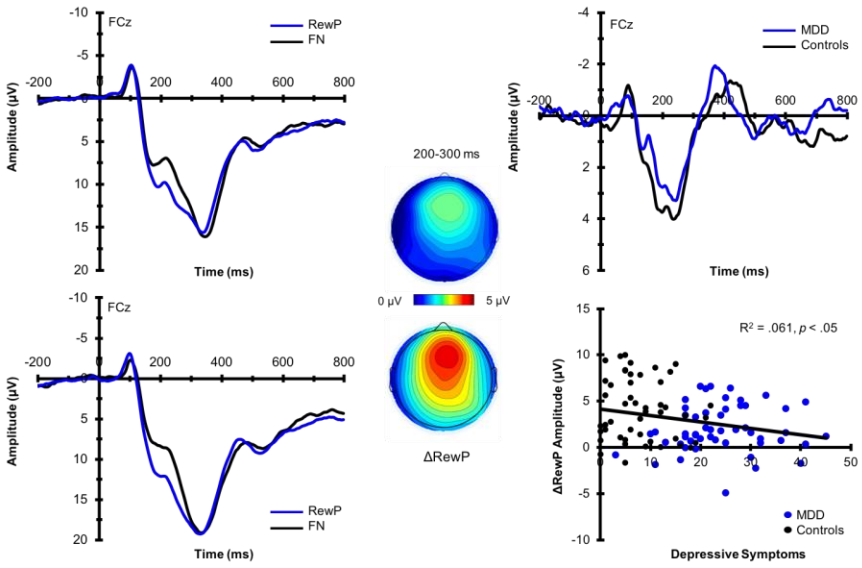

Figure 1. Feedback-locked grand averaged parent waveforms for individuals with MDD (top left) and control participants (bottom left) for RewP and FN. In the top right, the difference waveform (ΔRewP) is shown for individuals with MDD and controls, while

the negative association between ΔRewP and depressive symptoms is plotted on the bottom right. Topographic plots of the ΔRewP are presented in the center for MDD (top) and controls (bottom).

MLM Analyses

For the unconditional model, the mean intercept, b = 10.29, SE = 0.6, $t(99) = 16.9$, $p < .001$, and variance of the intercept across individuals b = 36.29, SE = 5.28, Wald = 6.87, $p < .001$, were significant. The ICC was 0.316, suggesting approximately 31.6% of the variance in feedback-related amplitude was accounted for by between-individual variability, while 68.4% was accounted for within individuals.

Model 1 assessed the moderating influence of diagnostic status on initial reward response and changes in RewP/FN amplitude over time. There was a significant main effect of feedback type, b = 2.59, SE = 0.35, $t(9039) = 7.32$, $p < .001$, indicating that RewP was 2.59 μV greater than FN amplitude. Although there was no significant main effect of trial, there was significant individual-level variability in RewP/FN amplitude across trials, b = 0.004, SE = 0.001, Wald = 3.65, $p < .001$. Additionally, there was a significant cross-level feedback type x trial interaction, b = 0.05, SE = 0.01, $t(9056) = 3.23$, $p < .001$, indicating positive linear growth for RewP across time, b = 0.03, $p < .01$, 95% CI [0.01, 0.05]. Current depression status failed to moderate initial (trial 1) RewP/FN amplitude, b = -1.20, SE = 1.26, $t(104) = -0.96$, $p = .34$. Lastly, there was a significant cross-level interaction between diagnostic status x feedback type x trial, b = -0.06, SE = 0.01, $t(9053) = -4.72$, $p < .001$. Follow-up simple slopes analysis revealed a significant increase in RewP amplitude only for controls, b = 0.04, $p < .05$, 95% CI [0.01, 0.07], while all other slopes were nonsignificant (see Figure 2).

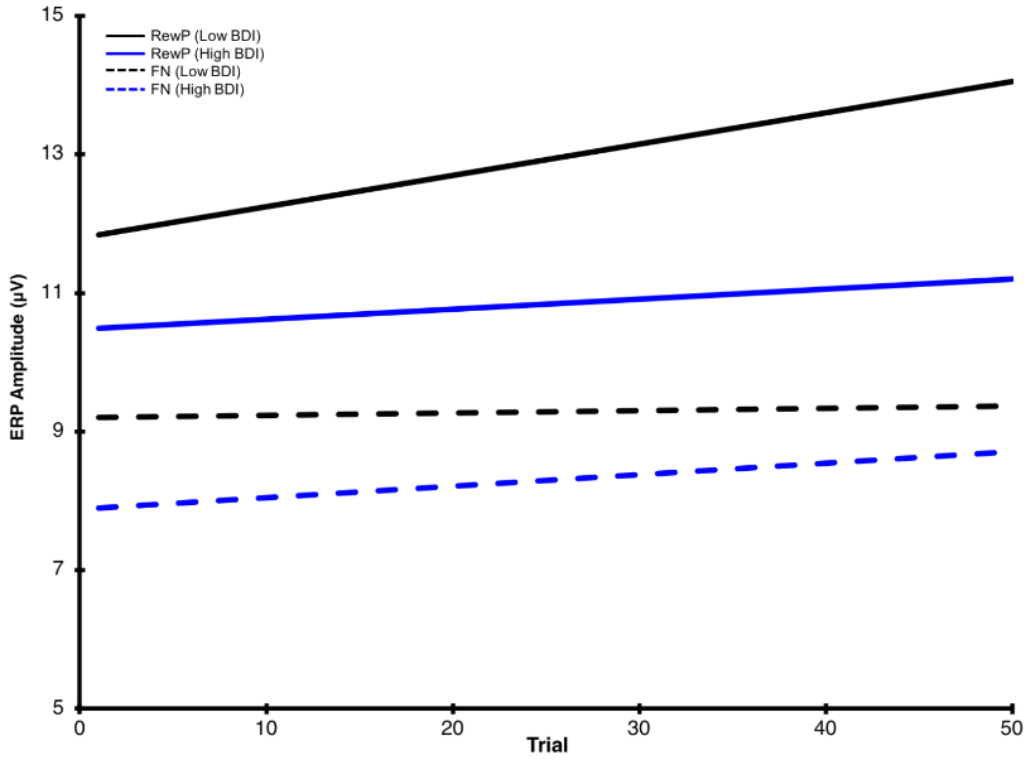

Figure 2. The slopes of ERP amplitudes to gain (RewP) and loss (FN) trials across the course of the doors task for individuals reporting lower versus higher symptoms of depression. Groups with low and high depressive symptoms were created by splitting the sample based on -1 (low) and +1 SD (high) from the sample BDI-II mean, respectively.

Model 2 examined the influence of depression severity on initial reward response and slope of change over time. Similar to model 1, model 2 findings indicated a significant feedback type main effect, b = 2.59, SE = 0.36, $t(9039) = 7.30$, $p < .001$, but no significant feedback type x trial interaction, b = 0.02, SE = 0.01, $t(9052) = 1.22$, $p = .23$. Although the main effect of trial was nonsignificant, there was significant individual-level variability in RewP/FN amplitude across trials, b = 0.004, SE = 0.001, Wald = 3.64, $p < .001$. Despite the intercept also varying significantly across individuals, depression

severity failed to moderate initial (trial #1) RewP/FN amplitude, b = -0.06, SE = 0.06, *t*(104) = -1.03, *p* = .30. Notably, a significant cross-level interaction of depression severity x feedback type x trial emerged, b = -0.002, SE = 0.001, *t*(9043) = -3.38, *p* < .01. Follow-up simple slopes analyses for RewP indicated a positive and significant slope coefficient at low levels of depression severity (1 SD below the BDI-II mean), b = 0.04, *p* < .05, 95% CI [0.01, 0.07], and average levels of depression (at the BDI-II mean), b = 0.03, *p* < .01, 95% CI [0.01, 0.05], such that there was a potentiated RewP over time for individuals with lower symptoms of depression (see Figure 3). In contrast, all other slopes were nonsignificant.

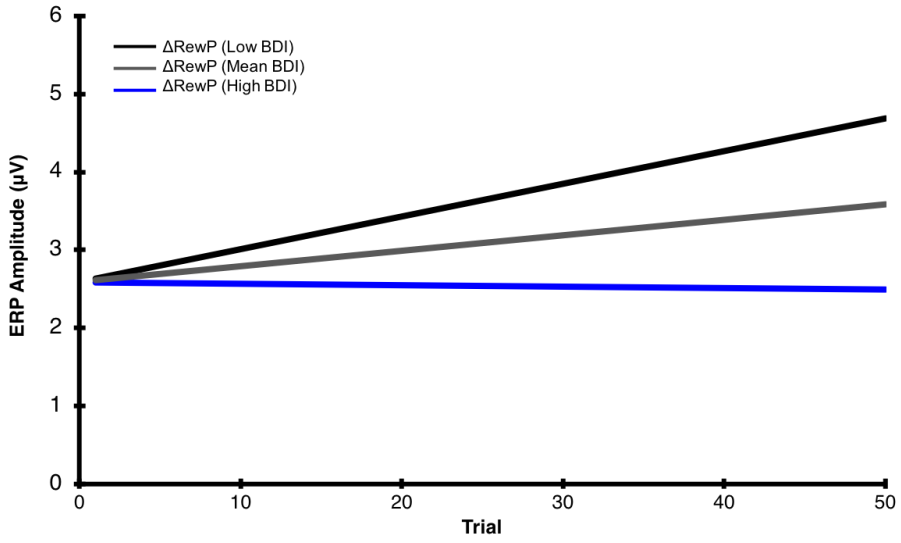

Figure 3. The trajectory of ΔRewP amplitude across the course of the doors task for individuals reporting low, average, and higher symptoms of depression. Groups with low, average, and high depressive symptoms were created by splitting the sample based on -1 SD (low), 0 SD (mean), and +1 SD (high) from the sample BDI-II mean, respectively.

A summary of findings for each model is displayed in Table 3. Findings from model 1 and 2 indicate no differences in initial reward sensitivity (intercept), while results from models 1 and 2 suggest that depression moderates RewP across trials (slope), with a potentiated response over time among individuals with lower symptoms of depression.

Table 3
Multilevel models of RewP and FN across time

	Amplitude				
Variable	b	SE	*t*	*df*	*p*
Model 1					
Intercept ***	9.16	.92	10.0	112.4	<.001
Trial	< -.001	.02	< -.1	171.2	.98
Feedback type ***	2.59	.35	7.3	9038.5	<.001
Feedback type x Trial ***	.05	.01	3.2	9056.3	<.001
Diagnostic status	-1.20	1.26	-1.0	103.9	.34
Diagnostic status x Trial	.02	.02	1.1	126.4	.27
Diagnostic status x Feedback type x Trial ***	-.06	.01	-4.7	9053.6	<.001
Model 2					
Intercept ***	8.54	.65	13.1	121.3	<.001
Trial	.01	.01	1.0	218.9	.33
Feedback type ***	2.59	.36	7.3	9038.6	<.001
Feedback type x Trial	.02	.01	1.2	9052.1	.23
Depression severity	-.06	.06	-1.0	103.7	.30
Depression severity x Trial	< .001	< .01	.7	124.4	.50
Depression severity x Feedback type x Trial **	-.002	.001	-3.4	9042.6	<.01

Note. $^{**}p < .01$; $^{***}p < .001$

Discussion

The goal of this study was to examine the neural response to reward and loss feedback in individuals with clinical depression relative to control participants and extend this line of research by examining individual and trial-level differences in RewP, FN, and ΔRewP over the course of the experiment using MLM. Similar to previous studies (Foti et al., 2014; Liu et al., 2014), a blunted ΔRewP was observed among individuals with MDD – an effect that was primarily driven by the neural response to rewards. Additionally, the feedback-related ERPs demonstrated acceptable-to-excellent psychometric properties, further supporting their utility in examining individual differences in psychopathology (Hajcak, Meyer, & Kotov, 2017). Although current MDD diagnosis and depression severity failed to moderate initial reward processing (i.e., intercept), both MDD diagnosis and depression symptom severity influenced the trajectory of neural responses over the course of the experiment (i.e., slope). Specifically, trial-level analyses indicated that a diagnosis of MDD and depressive symptom severity significantly moderated reward responses over time, with individuals with higher symptoms of depression demonstrating less sensitivity to rewards over time. These findings could not have been identified outside of the MLM framework, highlighting the potential of incorporating MLM in future ERP studies.

The current findings add to previous research indicating aberrant reward-related brain activity among individuals with MDD (Foti et al., 2014; Liu et al., 2014). Individuals with current MDD demonstrated a blunted ΔRewP that was primarily driven by an attenuated response to rewards relative to the neural response observed among healthy controls. Specifically, healthy controls showed positive linear growth in RewP

across time, a finding not found among individuals with MDD. The inclusion of symptom severity as a moderator revealed that individuals with lower symptoms of depression showed a potentiated response to gains as evidenced by a positive linear slope across the doors task. Such a trend was not observed among those reporting greater depression severity. These findings suggest that greater decreases in neural response to rewards in depressed individuals relative to controls suggests that a normal RewP response may be characterized by a slight increase over time, which is not characteristic of depressed individuals. This is the first study to examine trial-level differences in reward sensitivity across monetary reward or feedback paradigms, particularly among depressed individuals, and future studies are warranted to replicate these findings.

Individuals with MDD often display poorer modulation of behavior based on prior reward contingencies (Whitton, Treadway, & Pizzagalli, 2015), and the current findings of blunted RewP across time, relative to controls, may in part reflect this reward system dysfunction. Abnormalities in reward are central to many models of depression – and a blunted neural response to rewards has emerged as a prospective predictor of onset of depression (Nelson, Perlman, Klein, Kotov, & Hajcak, 2016). In a sample of 444 adolescents with no history of depression, Nelson and colleagues (2016) found that an attenuated ΔRewP at baseline was a significant predictor of first-onset depressive disorder and greater dysphoria 18 months later. Future prediction studies should include MLM-based analyses in the assessment of risk for depression. In addition, since a blunted ΔRewP represents a composite of reward- and loss-related activity, future research should incorporate time-frequency representations of reward (e.g., reward-related delta)

and loss (e.g., loss-related theta) to provide further insight into the underlying nature of reward-related network disruptions in depression (Foti et al., 2015; Webb et al., 2017).

The patterns of responding observed are consistent with the notion that depression is characterized by aberrant reward processing, possibly due to blunted phasic dopaminergic signaling (Whitton et al., 2017). Impaired mesocorticolimbic dopamine pathways (including ventral and dorsal striatal regions) have been hypothesized in MDD, and may be related to the decreased motivation and ability to experience reward. To the extent that the RewP indexes individual differences in reward sensitivity, the current data of suppressed reward response over time in individuals with high symptoms of depression is consistent with this hypothesis. In particular, it may shed light into conceptualizations of depression that highlight its core features of low positive affect and anhedonia (Pizzagalli, Jahn, & O'Shea, 2005; Shankman & Klein, 2003). Depressed individuals have displayed an inability to sustain nucleus accumbens and caudate activity during reward processing (Heller et al., 2009; Pizzagalli et al., 2009), which may be related to the impaired RewP across time.

Collectively, the current findings suggest that individuals with MDD are characterized by an attenuated response to reward. Additionally, individuals with lower depressive symptoms were increasingly responsive to rewards across the task while those reporting greater symptom severity demonstrated a relatively sustained RewP over time. These findings contribute to evidence suggesting that depression is associated with reward processing impairments and advance the investigation of individual differences and within-trial response patterns in reward sensitivity. As such, reward system

dysfunction may be a promising target for depression and examining changes in RewP over time may help to identify vulnerable individuals.

Chapter 2

Depression symptom severity does not moderate the effects of moderate-intensity aerobic exercise on reward sensitivity and emotional reactivity

Christopher J. Brush

Introduction

The question of whether or not exercise makes people feel better, often referred to in the scientific literature as affective responses to exercise, has been studied for well over half a century and is the longest continuous running line of inquiry in the field of exercise psychology (see Ekkekakis & Brand, 2018 for an overview). In general, the belief that exercise makes you feel better has been widely accepted among researchers across a number of diverse yet complementary fields, including kinesiology, clinical psychology, and affective neuroscience (Basso & Suzuki, 2017; Hogan, Mata, & Carstensen, 2013). This idea is also widely reported in the popular press and generally accepted by the public at large (e.g., Reynolds, 2011); however, as Ekkekakis and Brand (2018) have outlined, there are a number of critical issues that remain to be clarified and, importantly, despite the general acceptance of a "feel better" phenomenon of exercise, most individuals in advanced societies fail to meet the minimum recommended amounts of exercise or physical activity (Blair, 2009).

Despite the large number of studies indicating a general improvement in affective responses following a single bout of exercise (see Reed & Ones, 2006 for a meta-

analysis), the underlying mechanisms remain unknown. In most studies in this area, one or more self-report measures of affect or mood have been administered just prior to and again following an acute bout (one session) of exercise. However, these self-report measures may be sensitive to perceived or actual demand characteristics, and measurement of affect or emotion assumes that individuals can report on their feelings accurately and reliably (Hajcak, Weinberg, MacNamara, & Foti, 2011). To elucidate the psychobiological mechanisms associated with post-exercise affective responses, research has included select psychophysiological (e.g., blood pressure, heart rate variability) or neuroendocrine (e.g., cortisol) measures proximal to the self-report measures. However, these measures have relatively similar and comparatively poor temporal resolution, which is potentially problematic when attempting to capture in-the-moment changes in emotional or affective responses following an acute bout of exercise. Event-related potentials (ERPs) are an objective, direct measure of neural activity that can be used to isolate select psychological operations (e.g., sensory, cognitive, affective and motor-related processing) that are otherwise not observable through overt self-report or behavioral paradigms. ERPs are voltage fluctuations derived from the continuous electroencephalogram (EEG) that are time-locked to a specific stimulus or event. Due to their excellent temporal resolution, ERPs are ideally suited for examining the temporal dynamics of neural response to emotional stimuli (Hajcak et al., 2011). Two ERPs with utility in examining affective responses to exercise include the reward positivity (RewP) and late positive potential (LPP) components.

The RewP manifests as a frontocentral positivity in the ERP waveform that arises around 200-350 ms following the receipt of a reward relative to negative feedback (i.e.,

loss) during reward tasks (Proudfit, 2015). Historically, researchers referred to the RewP as the feedback negativity (FN), which was conceptualized as a negative deflection in the waveform elicited by unfavorable outcomes (Gehring & Willoughby, 2002; Miltner, Braun, & Coles, 1997); however, recent data suggests that the RewP reflects a relative positivity in the ERP waveform that is modulated by reward outcomes (Foti & Hajcak, 2009; Foti et al., 2011; Holroyd et al., 2008; Proudfit, 2015). Importantly, the RewP indexes the initial evaluation of reward outcomes and has been shown to be correlated with activity of brain structures implicated in the reward system, including ventral striatum, caudate, amygdala, medial prefrontal cortex, and orbitofrontal cortex (see Becker et al., 2014; Carlson et al., 2011). RewP amplitude is often elicited using simple gambling tasks, such as the doors task (Proudfit, 2015). In this task, participants are presented with two doors and on each trial, they are instructed to choose a door that hides a monetary reward or loss.

The LPP, on the other hand, is a broad positive deflection that is maximal at central, parietal, and occipital electrode sites around 300-800 ms and is thought to reflect enhanced (or sustained) attentional engagement and visual processing of emotional content (Bradley, 2009; Bradley, Codispoti, & Lang, 2006; Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000). LPP amplitude is often assessed using passive viewing paradigms of emotionally-valenced content (e.g., Foti & Hajcak, 2010; MacNamara, Kotov, & Hajcak, 2016) and is larger for emotional compared to neutral stimuli (Cuthbert et al., 2000; Hajcak, MacNamara, & Olvet, 2010). Evidence from combined ERP and fMRI recordings have shown that the LPP is correlated with emotion-related activation in the visual cortex and amygdala (Liu, Huang, McGinnis-Deweese, Keil, & Ding, 2012). A

large body of research indicates that LPP is positively associated with subjective ratings of arousal to emotional pictures and words, which provides support for LPP as a neural index of emotional engagement (Cuthbert et al., 2000). This modulation of LPP amplitudes reflects the dynamic allocation of attention to motivationally salient information, offering insight into the time course of emotional reactivity (Bradley et al., 2006; Hajcak, Dunning, & Foti, 2009; Schupp et al., 2000).

Only two published studies to date have examined the influence of acute exercise on RewP (Walsh et al., 2019) and LPP (Tartar, Salzmann, Pierreulus, & Antonio, 2018). Walsh and colleagues demonstrated that an 11-min bout of high intensity interval exercise (HIIE) diminished the RewP elicited by a probabilistic reward task completed approximately 10 min following exercise cessation. The authors concluded that mechanisms of reinforcement learning are down-regulated during the initial post-exercise recovery period, possibly due to heightened physiological arousal. In terms of LPP, Tartar and colleagues found that a 30 min bout of vigorous aerobic exercise (at 75-85% of an individual's estimated maximal HR) decreased the amplitude of the LPP to negative pictures among an unselected sample of undergraduates. This vigorous bout of exercise also significantly reduced total mood disturbance, as assessed by the profile of mood states (POMS); however, post-exercise LPP responses were not significantly associated with self-reported mood outcomes. This dose of exercise (i.e., intensity) in both of these studies may actually suppress rather than promote favorable affective responses during and immediately following exercise (Pronk, Crouse, & Rohack, 1995; Reed & Ones, 2006); nonetheless, this emerging evidence suggests a state-like property of the RewP and LPP, and that these components may be modulated by acute exercise.

A second limitation of previous research on affective responses to exercise is the lack of attention to the influence of personality traits and individual difference variables (Ekkekakis, Hargreaves, & Parfitt, 2013). For instance, although the effects of acute exercise have been studied among patients with major depressive disorder (MDD; Bartholomew, Morrison, & Ciccolo, 2005), symptoms of depression have not been examined as a moderating influence of affective responses to exercise. This is surprising considering that one of the primary motivators for the initial investigations of affective responses to exercise was to determine whether exercise could be used as an effective alternative or adjunctive treatment for improving mental health (Ekkekakis & Brand, 2018). In terms of neural measures, previous ERP research has revealed that depression is associated with deficits in reward processing and emotional engagement (Foti, Novak, Hill, & Oumeziane, 2018; Foti & Weinberg, 2018; Liu et al., 2014; Pizzagalli, 2014; Proudfit, 2015). Studies have consistently demonstrated a blunted RewP in depression (Foti et al., 2014; Liu et al., 2014; Proudfit, 2015) and that RewP amplitude is associated with depression symptom severity (Brush, Ehmann, Hajcak, Selby, & Alderman, 2018). In terms of LPP, early studies found reduced LPP amplitudes to both pleasant and unpleasant stimuli relative to neutral word stimuli in individuals with MDD (Blackburn, Roxborough, Muir, Glabus, & Blackwood, 1990), while a recent study showed that depression was related to blunted LPP amplitude to both pleasantly and unpleasantly-valenced images, but not neutral images (Hill, South, Egan, & Foti, 2019).

Examining the effects of an acute bout of exercise on RewP and LPP components may help advance understanding about the temporal dynamics of reward and emotional processing following a robust physiological stimulus. Furthermore, there is evidence

supporting the roles of the mesolimbic dopamine and ascending locus coeruleus-norepinephrine systems in modulating RewP and LPP amplitude (Heydari & Holroyd, 2016; Nieuwenhuis, Aston-Jones, & Cohen, 2005), respectively. Translational findings from human to basic animal studies indicate that acute exercise activates these same key neurotransmitter systems (Chaouloff, 1997; Chaouloff, Laude, & Elghozi, 1989; Dishman et al., 2006; Foley & Fleshner, 2008); therefore, the purpose of this study was to examine the effects of continuous moderate-intensity aerobic exercise on reward processing and emotional engagement, as indexed by RewP and LPP. Considering the large body of evidence supporting the effects of acute aerobic exercise on affective responses (e.g., Ekkekakis, Parfitt, & Petruzzello, 2011), we hypothesized that exercise would increase LPP amplitude to positive images and decrease LPP amplitude to negative images. Given evidence demonstrating the capacity of exercise to activate dopaminergic signaling pathways (Foley & Fleshner, 2008), we also hypothesized that aerobic exercise would increase RewP. These acute enhancements in RewP and LPP were hypothesized to be moderated by symptoms of depression, such that larger effects would be found among individuals reporting greater depressive symptom severity, considering that individuals with greater depression severity tend to exhibit blunted RewP and LPP amplitudes (Bress, Meyer, & Hajcak, 2015; Brush et al., 2018; Hill et al., 2019)

Methods

Participants

Individuals between the ages of 18 and 30 years were recruited from Rutgers University and the surrounding community using flyers and advertisements posted

around the campus. Participants were native English speakers and had normal or corrected-to-normal vision. Exclusion criteria consisted of the presence or history of any cardiovascular, neurological, or musculoskeletal problems contraindicated to exercise, as well as a history of any head injury with a loss of consciousness. All participants were physically able to engage in aerobic exercise as indicated by the physical activity readiness questionnaire (PAR-Q; Thomas, Reading, & Shephard, 1992). Participants provided written informed consent and the study was approved by the university's institutional review board.

Sample Size Determination

We conducted an *a priori* power analysis to detect acute exercise-related changes in RewP and LPP. Findings from Tartar et al. (2018) indicated that high-intensity aerobic exercise results in a moderate reduction (Cohen's $d = 0.48$ [assuming a correlation between groups of 0.4]) in LPP amplitude to negative stimuli. Given that no previous studies have examined the effects of acute exercise on both RewP and LPP, we used a more conservative, small-to-medium effect size estimate of Cohen's $f = 0.20$. Using G*Power version 3.1.9.2 (Faul, Erdfelder, Lang, & Buchner, 2014), power estimates indicated a total sample size of 62 participants was required to detect a medium-sized effect at 80% power with a correlation among repeated measures set at a conservative estimate of 0.4.

Procedures

Participants visited the laboratory on two separate days approximately 48-72 hours apart at the same time of day. During the initial session, participants were given a

description of the study, provided written informed consent, and completed a series of questionnaires that included demographics, health history, physical activity, and affect questionnaires. Participants then completed either the aerobic exercise or seated rest condition, which were counterbalanced across participants. Prior to each condition, participants were fitted with a Polar V800 heart rate monitor (V800, Polar Electro Oy, Kempele, Finland) to assess heart rate responses throughout the testing session. During the control condition, participants sat quietly at rest for 30 minutes on the cycle ergometer (Lode Corival, Lode B.V., Groningen, Netherlands). The exercise condition consisted of 30 minutes of continuous moderate-intensity aerobic exercise performed at a rating of perceived exertion (RPE; Borg, 1998) of 12-14 on a scale from 6 (low-intensity) to 20 (high-intensity). To enhance attention and motivation and to help minimize demand characteristics and boredom, participants were allowed to choose between a series of neutral films from *Wonders of the Universe* (Cooter, 2011) to watch during both experimental conditions (see Pontifex, Parks, Henning, & Kamijo, 2015 for a similar approach). Feeling (FS) and felt arousal scales (FAS) were administered prior to and following both conditions. Additionally, the Positive and Negative Affect Schedule (PANAS) was also administered before and after the experimental and control conditions. Immediately following each condition, a 33-electrode net was applied to assess electroencephalographic (EEG) activity during the IAPS and Doors tasks, which were administered in a counterbalanced order across participants and days. In order to account for the time taken to prepare the participant with the EEG electrode cap following each condition, the time elapsed from completion of the experimental condition to beginning of the EEG assessment was documented. At the conclusion of the final experimental

session, participants were compensated and briefed on the purpose of the study. See Figure 4 for an overview of the study flow.

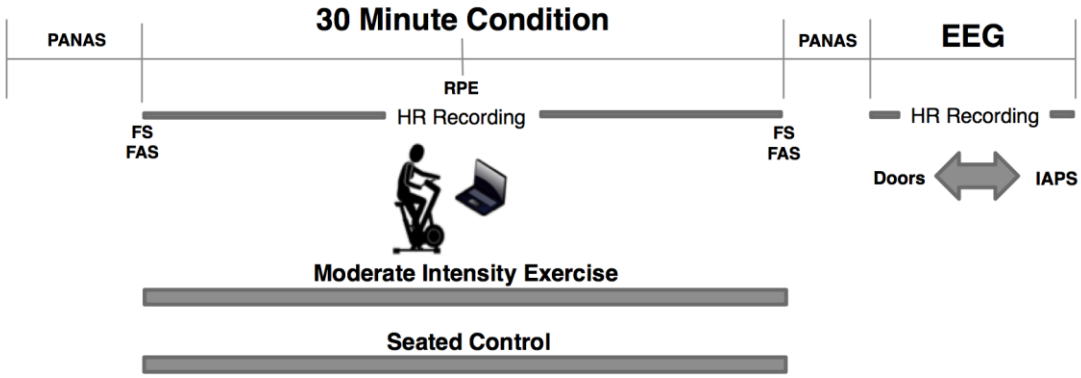

Figure 4. Study flow diagram.

Self-Report Measures

Clinical symptoms. The 21-item version of the Depression Anxiety Stress Scale (DASS-21; Lovibond & Lovibond, 1995) was used to assess the presence of symptoms of depression, anxiety, and psychological stress over the past week. There are three subscales of the DASS-21 that comprise 7 items each. Items on the DASS-21 were created to differentiate between internalizing psychopathology symptoms that often overlap, with the depression subscale conceptualized as low positive affect and anxiety conceptualized as physiological arousal. The stress subscale is conceptualized by items that reflect non-specific negative affect (e.g., difficulties in relaxing, nervous tension, irritability). The DASS-21 ranges from 0 to 42 for each subscale. The DASS-21 has excellent reliability and validity across clinical and non-clinical samples (Antony, Bieling, Cox, Enns, & Swinson, 1998; Henry & Crawford, 2005; Hill et al., 2019). In the

current sample, each of the three subscales demonstrated acceptable-to-good reliability (Depression subscale: α = 0.87; Anxiety subscale: α = 0.77; Stress subscale: α = 0.80).

Positive and negative affect. The Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988) was administered during each testing session to assess affective responses. Participants were asked to rate "how much you feel right now" on a scale from 1 ("very slightly or not at all") to 5 ("extremely") for each of 20 different adjectives. The positive affect (PA) subscale consists of ten positive adjectives (proud, excited, strong, enthusiastic, determined, attentive, inspired, alert, interested, and active) while the negative affect (NA) subscale consists of ten negative adjectives (distressed, upset, guilty, scared, hostile, irritable, ashamed, nervous, jittery, and afraid). Previous research demonstrates that the PANAS is a reliable and well-validated scale that indexes both positive and negative affect (Watson et al., 1988). In the present sample, the PA and NA subscales demonstrated good-to-excellent reliability (PA subscale: α = 0.90; NA subscale: α = 0.86), which was determined during the baseline assessment on the seated rest control day.

Feeling and felt arousal scales. Affective valence (pleasure-displeasure) was assessed using the Feeling Scale (FS; Hardy & Rejeski, 1989), while perceived activation was examined by the Felt Arousal Scale (FAS; Svebak & Murgatroyd, 1985). The FS is an 11-point, single-item bipolar rating scale used to assess affective responses to exercise. The scale ranges from -5 to 5 ("Very Good" to "Very Bad"). The FAS (arousal) is a 6-point, single-item rating instrument that ranges from 1 ("Low Arousal") to 6 ("High Arousal"). The FAS has been commonly used to index somatic arousal changes due to exercise (Ekkekakis, Hall, & Petruzzello, 2004).

Computerized Tasks and Stimulus Presentation Parameters

The administered tasks were programmed and presented using E-Prime Professional version 2.0 software (Psychology Software Tools, Inc. Pittsburgh, PA, USA). During the EEG assessment, participants sat approximately 28 in. from the monitor, which was centered to the nasion. For both tasks, participants viewed the stimuli at vertical and horizontal visual angles of angles of 1.2° and 6.6°, respectively.

The Doors task. The doors task consisted of three blocks of 20 trials. On each trial, a fixation cross was presented at the center of the screen for 1,000 ms followed by the presentation of two doors, which remained on the screen until participants made a left or right button press corresponding to the left or right door using a Logitech® F310 response gamepad. Following stimulus offset, another fixation cross was presented for 2,000 ms before displaying the feedback stimulus for 2,000 ms. Feedback indicated whether the participant won $0.50 (reward trial) or lost $0.25 (loss trial). Reward trials were indicated by a green upwards arrow, while a red downwards arrow was presented to indicate feedback for loss trials. After feedback, another fixation cross was presented for 1,500 ms, which was followed by a short break prior to the next trial. Across the entirety of the doors task, 30 reward and 30 loss trials were randomly presented. Following each experimental session, participants were compensated their total winnings of $7.50.

International Affective Picture System (IAPS) stimuli. The passive viewing stimuli were 42 pleasant (e.g., smiling faces, babies), 42 neutral (e.g., household objects, neutral faces), and 42 unpleasant (e.g., sad faces, violent scenes) pictures. Normative ratings of valence and arousal were assessed before the study among a sample of 17 volunteer undergraduate students from Rutgers University, who were similar to the

experimental participants in terms of age, gender, and sociocultural background. The three categories of images differed on normative ratings of valence, which were based on 9-point Likert scale with 1 being “maximally unpleasant” and 9 being “maximally pleasant” (pleasant: 5.90 ± 2.05; unpleasant: 3.69 ± 2.23; Neutral: 4.21 ± 1.86). The three image categories also differed on normative ratings of arousal (pleasant: 4.56 ± 2.38; unpleasant: 5.60 ± 1.73; neutral: 3.82 ± 2.54), which were based on a 9-point Likert scale with 1 being “maximally calm” and 9 being “maximally excited”. Six blocks of 21 images were displayed (126 pictures in total). Each stimulus was displayed in color for 2,000 ms with a random variable intertrial interval (1,700-2,300 ms) following the offset of each stimulus.

ERP Measurement and Processing

Continuous EEG was recorded from a 33-electrode actiCap system (Brain Products, GmbH; Munich, Germany) arranged according to International 10/20 guidelines. The electrooculogram (EOG) activity was recorded from 2 electrodes placed 2 cm outside the outer canthus of the left eye and 2 cm below the right eye. EEG was amplified using an Electrical Geodesics, Inc. (EGI; Eugene, OR, USA) system (20,000 nominal gain, bandpass of 0.10–100 Hz) and sampled at 500 Hz with a 24-bit A/D converter referenced to the vertex electrode (Cz) at acquisition. Impedances were kept at or below 20 kΩ throughout recording.

EEG data were exported to EEGLAB toolbox version 14.1.1 (Delorme & Makeig, 2004) in Matlab version R2018a (The Mathworks, Inc., Natick, MA, USA) for data preprocessing. Using ERPLAB toolbox version 7.0.0 (Lopez-Calderon & Luck, 2014), data were bandpass filtered using a 2nd order infinite impulse response Butterworth filter

of 0.1-30 Hz and adjusted for DC offset. Data were then downsampled from 500 Hz to 250 Hz. For the doors and IAPS tasks, EEG data were visually inspected for artifacts or extreme offsets and segmented to create time-locked epochs by trial type. For the doors task, reward and loss trials were segmented separately using a -200 to 800 ms time window, while EEG data for the IAPS task were segmented separately to create stimulus-locked epochs for pleasant, unpleasant, and neutral image types using a -500 to 2,000 ms time window. The ERP PCA toolkit version 2.75 (Dien, 2010) was used for artifact rejection and correction procedures. ICA blink templates provided by the toolkit author (J. Dien, author), as well as a blink template generated from the current datasets for each task were used to remove oculomotor artifacts. For both tasks, all epochs were re-referenced to the mean of the two mastoids (TP9, TP10). For the doors task, a prestimulus period of -200 to 0 ms was used for baseline correction, while a prestimulus period of -500 to 0 ms was used for baseline correction in the IAPS task.

Consistent with our previous study (see Brush et al., 2018) and a collapsed localizers approach (Luck & Gaspelin, 2017), RewP (rewards), FN (losses), and the subtraction-based difference waveform ΔRewP, defined as RewP minus FN amplitudes were assessed in a time window of 200-300 ms post-feedback. Per recommendations by Krigolson (2018) and a similar approach taken by Walsh and colleagues (2019), we also scored the ΔRewP using a peak interval technique that quantified mean amplitude (± 20 ms) encompassing the largest positive-going peak within the 200-300 ms time window post-feedback. The peak times were identified from the grand average difference waveforms as 224 ± 20 ms and 244 ± 20 ms for the exercise and control conditions, respectively. The RewP, FN, and ΔRewP was assessed at the Cz electrode site, where

activity was maximal. Since the task protocol in the present study was identical to the task procedure used by Foti, Hajcak, and Dien (2009) to elicit the LPP, we examined the LPP to pleasant, unpleasant, and neutral pictures, which was maximal at Pz. Similar to the Hill et al. (2019) study, the LPP was measured as the mean voltage in an *a priori* time window of 400-1,000 ms following stimulus presentation. The subtraction-based difference waveform (ΔLPP) for responses to pleasant and unpleasant pictures was defined as LPP to pleasant (or unpleasant) minus LPP to neutral pictures. Additionally, the ΔLPP to pleasant and the ΔLPP to unpleasant pictures was examined using the Pz electrode site and averaged activity in a time window of 400-1,000 ms.

Data Analyses

All statistical analyses were performed using SPSS version 25.0 (IBM Corporation, Armonk, NY, USA) with a two-tailed familywise error rate for all tests set at $p = .05$. Descriptive statistics were performed to examine demographics and as a manipulation check of exercise intensity, a repeated measures analysis of variance (rANOVA) was used to compare HR during each experimental condition and during the EEG assessment. Although the order of the experimental conditions and task manipulations were counterbalanced, rANOVA was performed to determine any potential influence of condition or task order on the ERP measures.

To test the primary hypotheses, repeated measures analyses of covariance (rANCOVAs) were conducted with experimental condition (control, aerobic exercise) and trial type as within-subject factors. For the doors task, feedback type (reward, loss) was a within-subjects factor, while for the IAPS task, picture type (unpleasant, neutral, pleasant) was a within-subjects factor. Depressive symptom severity (mean-centered

DASS-21 depression subscale score; continuous) served as a covariate in all analyses to examine its potential moderating role on the ERP measures. Changes in arousal (measured by FAS), pleasure-displeasure (measured by FS), and pleasant and unpleasant affect (measured by PANAS) by experimental condition were analyzed with 2 (time: baseline, post-condition) x 2 (condition: control, exercise) rANCOVAs. Bivariate Pearson correlations between changes in affect (ΔPA, ΔNA, ΔFS, ΔFAS) and the subtraction-based ERP difference waves (ΔRewP, ΔLPP to unpleasant pictures, ΔLPP to pleasant pictures) to determine if there was a relationship between exercise-related changes in affect and neural measures of reward processing and emotional engagement. Lastly, we conducted exploratory subgroup analyses by examining the effects of experimental condition on the ERP measures by creating a group based on individuals experiencing the presence of clinical depressive symptoms, ranging from mild-to-extremely severe symptoms. For all analyses, the Greenhouse-Geisser epsilon correction was applied in cases when the sphericity assumption was violated, and effect size estimates are presented as η^2_p and *d* as appropriate. Follow-up Bonferroni corrected *t* tests and simple slopes analyses were conducted to decompose significant main effects and interactions.

Results

In total, 73 participants completed both experimental conditions; however, data from seven participants were removed from the analyses due to unusable EEG data for the following reasons: problems during EEG recording that compromised data quality (n = 5) and experimenter error (i.e., administered tasks without recording EEG; n = 2). Therefore, the final sample included 66 individuals. The race breakdown was 41 White

individuals, 22 Asian individuals, 2 individuals self-identifying as more than one race, and 1 Black individual. Of the total sample, 11 individuals identified as Hispanic or Latino. Demographics and characteristics of the sample are shown in Table 4.

Table 4
Sample characteristics (M ± SD) overall and by gender

	Female	Male	Overall
Sample size (n)	34	32	66
Age (years)	20.7 ± 2.2	20.5 ± 2.3	20.6 ± 2.2
BMI (kg/m^2)	24.7 ± 5.6	24.2 ± 3.1	24.5 ± 4.6
IPAQ (MET-min/wk)	4,039.3 ± 4,123.7	5,818.5 ± 4,517.0	4,902.0 ± 4,378.0
DASS Score Range	0-68	0-52	0-68
Depression	0-30	0-22	0-30
Anxiety	0-11	0-16	0-16
Stress	0-28	0-30	0-30

Note. BMI = body mass index; IPAQ = International Physical Activity Questionnaire; DASS = Depression Anxiety Stress Scale

EEG assessments began approximately 21.6 ± 9.6 min following the cessation of the experimental conditions. There were no significant differences by condition for transition time from end of each condition to the commencement of the EEG assessment (exercise: 20.8 ± 12.3 min; control: 22.4 ± 11.3 min), $t(65) = 0.9$, $p = .36$, $d = 0.12$. There was a significant condition x time interaction for average HR, $F(1,65) = 325.9$, $p < .001$, $\eta^2_p = 0.83$, such that HR was elevated during exercise (120.7 ± 13.9 bpm) relative to the seated rest condition (81.0 ± 11.9 bpm), $t(65) = 20.6$, $p < .001$, $d = 2.55$. Additionally, average HR remained slightly elevated during the EEG assessment following exercise (77.8 ± 10.7 bpm) compared to seated rest (71.2 ± 10.6 bpm), $t(65) = 6.6$, $p < .001$, $d = 0.81$. No significant influence of condition order or task order was found for any of the ERP parent or difference waveforms, ps > .05.

ERP Analyses

Reward-related ERPs.

Electrode site analysis. When collapsed across feedback type and condition, a significant electrode site main effect emerged, $F(2,64) = 54.1$, $p < .001$, $\eta^2_p = 0.45$, such that RewP/FN amplitudes were largest at Cz (8.7 ± 6.3 μV) relative to FCz (8.4 ± 6.4 μV), $t(65) = 3.4$, $p < .01$, $d = 0.33$, and Fz (6.2 ± 6.3 μV), $t(66) = 7.4$, $p < .001$, $d = 1.06$. Therefore, all ERP analyses for the doors task used the Cz electrode site.

As anticipated, a significant main effect of feedback type, $F(1,64) = 37.0$, $p < .001$, $\eta^2_p = 0.37$, indicated more positive amplitude on gain trials (RewP: 9.7 ± 6.5 μV) relative to loss trials (FN: 7.7 ± 6.5 μV). There was also a significant feedback type x depressive symptom interaction, $F(1,64) = 7.2$, $p < .01$, $\eta^2_p = 0.10$. Follow-up simple slopes analyses revealed a trend towards larger RewP amplitude for individuals reporting no depressive symptoms (DASS-21 depression subscale score = 0), $b = 2.8$, $p = .06$, 95% CI [-0.1, 5.7]. No other significant main effect, interactions, or significant slopes emerged, ps > .05. Significant relationships were found between depressive symptoms and ΔRewP, $r(64) = -0.31$, $p < .05$; self-reported stress and RewP, $r(64) = -0.29$, $p < .05$, and ΔRewP, $r(64) = -0.26$, $p < .05$; and total internalizing symptoms (i.e., the sum of the three DASS subscales) and ΔRewP, $r(64) = -0.32$, $p < .05$. No other relationships between symptom scores and ERP measures were observed.

Experimental condition effects. For the subtraction-based ΔRewP difference wave in the 200-300 ms time window, there was no significant difference by condition (ΔRewP for exercise: 1.9 ± 3.5 μV; ΔRewP for control: 2.1 ± 3.6 μV), $F(1,64) = 0.7$, $p =$

.40, $\eta^2_p = 0.01$. Additionally, the condition x depressive symptom interaction was also nonsignificant, $F(1,64) = 0.5$, $p = .48$, $\eta^2_p = 0.01$.

Using the peak interval measurement method (i.e., defined as ± 20 ms around the most positive-going peak in a time window of 200-300 ms) to examine ΔRewP, there was also no significant main effect for condition (ΔRewP for exercise: 2.8 ± 4.1 μV; ΔRewP for control: 2.6 ± 4.3 μV), $F(1,64) = 0.3$, $p = .62$, $\eta^2_p = 0.004$, nor a condition x depressive symptom interaction, $F(1,64) = 1.8$, $p = .18$, $\eta^2_p = 0.03$. The ΔRewP quantified as mean amplitude using the traditional time-windowed approach was significantly correlated with the peak interval measurement of ΔRewP for both exercise, $r(64) = 0.90$, $p < .001$, and control, $r(64) = 0.96$, $p < .001$. See Figure 5 for grand averaged parent and difference waveforms depicting RewP, FN, and ΔRewP by condition.

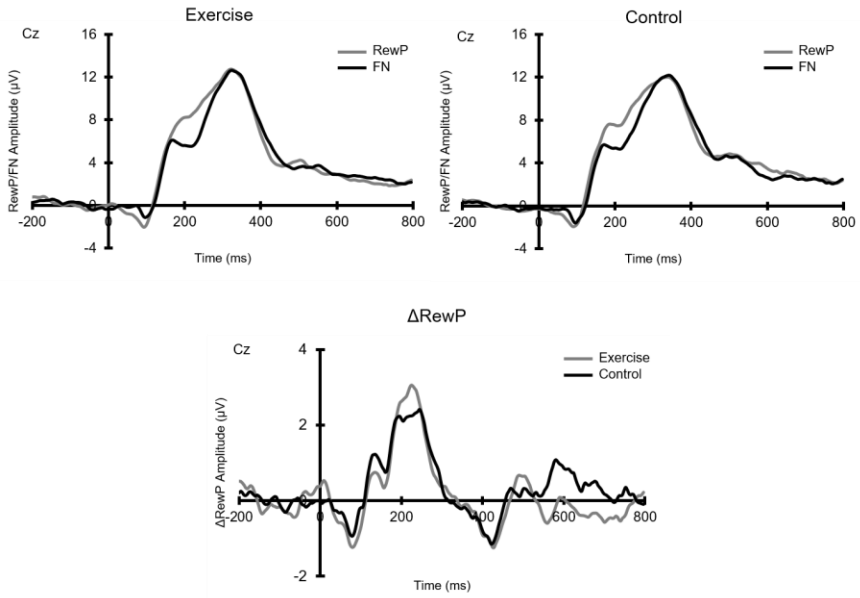

Figure 5. Feedback-locked grand averaged parent and difference ERP waveforms for RewP, FN, and the subtraction-based difference waveform (ΔRewP) by condition. The parent ERP waveforms for exercise are shown on the top left panel, while the parent ERP

waveforms for the control condition are shown on the top right panel. The difference waveform (ΔRewP) is shown on the bottom.

Emotional engagement-related ERPs.

Electrode site analysis. When collapsed across picture type and condition, a significant electrode site main effect emerged, $F(3,63) = 44.8$, $p < .001$, $\eta^2_p = 0.41$, with larger LPP amplitude at Pz (2.0 ± 3.8 μV) relative to Cz (-0.95 ± 3.7 μV), $t(65) = 6.8$, $p < .001$, $d = 0.91$, CP1 (0.9 ± 3.3 μV), $t(65) = 5.0$, $p < .001$, $d = 0.60$, and CP2 (1.1 ± 3.3 μV), $t(65) = 4.2$, $p < .001$, $d = 0.48$; therefore, all ERP analyses for the IAPS task were assessed at the Pz electrode site.

Experimental condition effects. As anticipated, there was a significant main effect of picture type, $F(2,63) = 51.4$, $p < .001$, $\eta^2_p = 0.45$, but no main effect of condition, $F(1,64) = 0.1$, $p = .70$, $\eta^2_p = 0.002$. Relative to neutral pictures (0.4 ± 3.0 μV), the picture type main effect indicated increased LPP amplitudes to unpleasant (2.9 ± 4.4 μV), $t(65) = 8.4$, $p < .001$, $d = 1.06$, and pleasant pictures (2.8 ± 4.3 μV), $t(65) = 8.3$, $p < .001$, $d = 1.05$. This main effect was superseded by a picture type x depressive symptom interaction, $F(2,63) = 5.0$, $p < .05$, $\eta^2_p = 0.14$. Follow-up simple slopes analysis revealed that LPP amplitudes to both unpleasant and pleasant pictures relative to neutral pictures were largest for individuals reporting no depressive symptoms, $b = 2.8$, $p < .001$, 95% CI [1.3, 4.4], followed by those participants with average levels, $b = 2.4$, $p < .001$, 95% CI [1.2, 3.6], and high levels of depressive symptoms, $b = 1.9$, $p < .05$, 95% CI [0.2, 3.6]. Lastly, there was a significant condition x picture type interaction, $F(2,63) = 3.6$, $p < .05$, $\eta^2_p = 0.10$. Decomposition of the interaction with Bonferroni corrected t tests ($\alpha_{corr} = .05/2 = .025$) indicated an increased LPP to pleasant pictures following exercise (3.2 ±

4.8 μV) relative to seated rest (2.3 ± 4.6 μV), $t(65) = 2.1$, $p = .04$, $d = 0.24$. Although LPP amplitude to negative pictures was larger following exercise (3.1 ± 5.0 μV) relative to seated rest (2.8 ± 4.7 μV), this difference was not statistically significant, $t(65) = 0.6$, $p = .57$, $d = 0.07$.

For the subtraction-based ΔLPP difference waves, there was a significant condition x picture type interaction, $F(1,64) = 3.9$, $p = .05$, $\eta^2_p = 0.06$. Decomposition of the interaction with Bonferroni corrected *t* tests ($\alpha_{corr} = .05/2 = .025$) suggested that there was a significant increase in ΔLPP to pleasant pictures following exercise (2.9 ± 3.0 μV) compared to seated rest (1.8 ± 2.6 μV), $t(65) = 2.6$, $p < .025$, $d = 0.33$. There was no significant difference in ΔLPP to negative pictures following exercise (2.7 ± 2.6 μV) relative to seated rest (2.3 ± 2.9 μV), $t(65) = 1.0$, $p = .34$, $d = 0.12$. No other significant main effects or interactions were observed, *p*s > .05. See Figure 6 for grand averaged parent and difference waveforms depicting LPP and ΔLPP to pleasant, unpleasant, and neutral pictures by condition. See Figure 6 for grand averaged parent and difference waveforms depicting LPP and ΔLPP by condition.

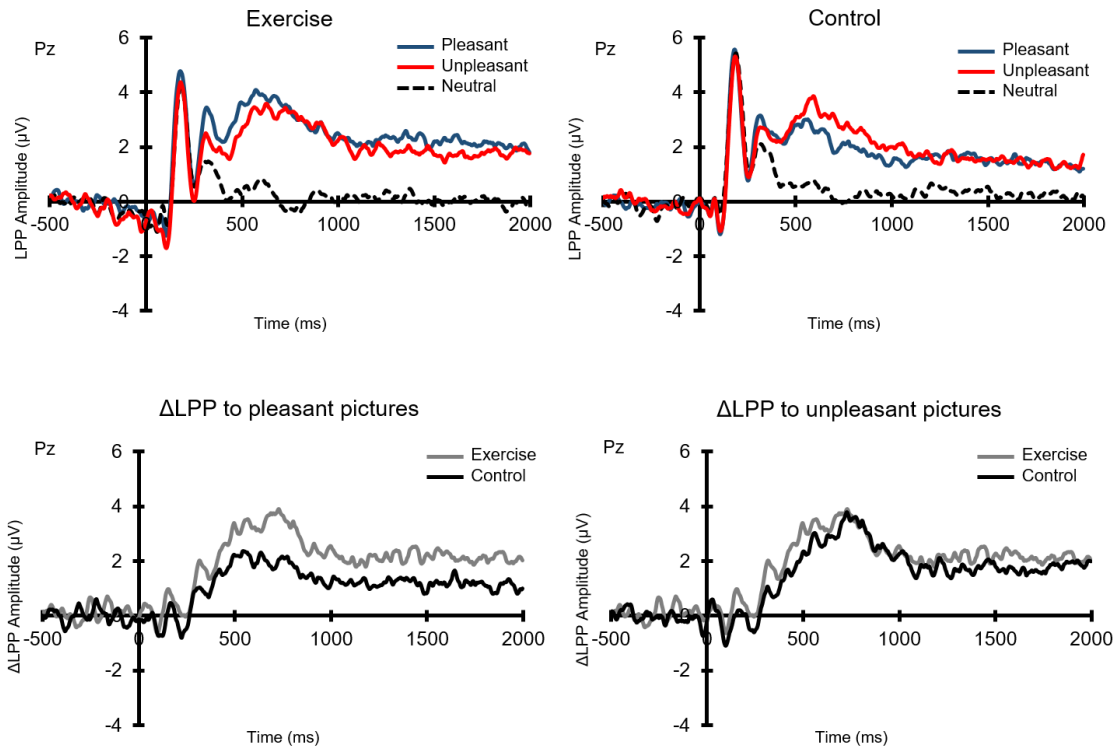

Figure 6. Stimulus-locked grand averaged parent and difference ERP waveforms for LPP and the subtraction-based difference waveform (ΔLPP) by condition. LPP parent waveforms are shown for exercise (top left panel) relative to a seated rest control (top right panel). The ΔLPP difference waveform to pleasant pictures (bottom left) and to unpleasant pictures (bottom right) is shown by condition.

Affective Responses

For PA, a significant main effect of condition, $F(1,64) = 5.0$, $p < .05$, $\eta^2_p = 0.07$, and a significant main effect of time, $F(1,64) = 15.2$, $p < .001$, $\eta^2_p = 0.19$, was observed, which was superseded by a significant condition x time interaction, $F(1,64) = 6.8$, $p < .05$, $\eta^2_p = 0.10$. Decomposition of the interaction with Bonferroni corrected ($\alpha_{corr} = 0.05/4 = 0.0125$) *t* tests revealed greater PA following exercise (PA score: 28.7 ± 9.7) relative to

seated rest (PA score: 24.7 ± 10.0), $t(65) = 3.4$, $p < .01$, $d = 0.42$. There was also a significant reduction in PA following seated rest relative to the pre-condition baseline period (PA score: 28.7 ± 8.3), $t(65) = 5.0$, $p < .001$, $d = 0.64$. PA was not significantly different by condition at baseline, $t(65) = 0.04$, $p = .97$, $d = 0.01$, while there was a maintenance of PA from the baseline period before exercise (PA score: 28.8 ± 10.7) to following exercise, $t(65) = 0.1$, $p = 0.91$, $d = 0.01$. No other significant main effects or interactions emerged for PA.

For NA, a significant main effect of time, $F(1,64) = 12.9$, $p < .01$, $\eta^2_p = 0.17$, but not condition, $F(1,64) = 3.5$, $p = .07$, $\eta^2_p = 0.05$, was observed, indicating less NA following the experimental conditions (NA score: 13.8 ± 4.6) relative to baseline (NA score: 16.8 ± 5.9). This was superseded by a condition x time x depressive symptom interaction, $F(1,64) = 6.6$, $p < .05$, $\eta^2_p = 0.09$. Follow-up simple slopes analyses revealed significantly lower NA following exercise relative to baseline for those with no depressive symptoms (DASS-21 depression subscale score = 0), $b = -2.6$, $p < .05$, 95% CI [-5.0, -0.1], average (at the DASS-21 depression subscale score mean), $b = -2.7$, $p < .01$, 95% CI [-4.5, -0.8], and high levels of depressive symptoms (1 SD below the DASS-21 depression subscale score mean), $b = -2.7$, $p < .05$, 95% CI [-5.4, -0.1]. There was also significantly lower NA following seated rest for those with average, $b = -3.3$, $p < .001$, 95% CI [-5.2, -1.4], and high depressive symptoms, $b = -5.5$, $p < .001$, 95% CI [-8.2, -2.9]. A nonsignificant slope was observed for individuals reporting no depressive symptoms, $p > .05$.

Affective valence (pleasure-displeasure) and perceived activation (arousal) were assessed using the FS and FAS, respectively. For affective valence (from the FS), there

was a significant main effect of condition, $F(1,64) = 4.6$, $p < .05$, $\eta^2_p = 0.07$, with increased pleasure for exercise (affective valence score: 2.6 ± 1.4) compared to the seated rest control (affective valence score: 2.3 ± 1.7). No other significant main effects of interactions emerged for affective valence, *p*s > .05.

For perceived activation (from the FAS), there was a significant main effect of condition, $F(1,64) = 25.4$, $p < .001$, $\eta^2_p = 0.28$, with increased arousal following exercise (3.6 ± 1.1) relative to the seated rest control (2.8 ± 1.3). This was superseded by a significant condition x time interaction, $F(1,64) = 10.6$, $p < .01$, $\eta^2_p = 0.14$. Decomposition of the interaction with Bonferroni corrected ($\alpha_{corr} = 0.05/4 = 0.0125$) paired-sample *t*-tests indicated that exercise elicited higher arousal (4.0 ± 1.2) compared to baseline (3.1 ± 1.4), $t(65) = 6.0$, $p < .001$, $d = 0.76$. There was a significant difference in arousal following conditions, $t(65) = 7.2$, $p < .001$, $d = 0.92$, such that exercise elicited higher arousal compared to the seated rest condition (2.6 ± 1.4). There was significantly lower arousal from baseline (perceived activation score: 3.0 ± 1.4) to after the seated rest condition (perceived activation score: 2.6 ± 1.4), $t(65) = 7.2$, $p < .001$, $d = 0.37$.

Correlations

Bivariate Pearson correlations between changes in affect (ΔPA, ΔNA, ΔFS, ΔFAS) and the subtraction-based ERP difference waves (ΔRewP, ΔLPP to unpleasant pictures, ΔLPP to pleasant pictures) are displayed in Table 5. A relationship between ΔRewP and ΔLPP to pleasant pictures following exercise was observed, $r(64) = 0.24$, $p = .058$, with larger ΔRewP and ΔLPP amplitudes observed following exercise. There was no relationship between ΔRewP and ΔLPP to unpleasant pictures following exercise, *p* > .05. Lastly, there were significant relationships between ΔNA and ΔLPP to pleasant

pictures, $r(64) = 0.28$, $p < .05$, and ΔFS and ΔLPP to unpleasant pictures following exercise, $r(64) = -0.30$, $p < .05$.

Table 5
Correlations between exercise-related changes in affect and ERP difference waves

	ΔRewP	$\Delta LPP_{unpleasant}$	$\Delta LPP_{pleasant}$
ΔPA	0.21	-0.11	-0.001
ΔNA	-0.07	0.22	0.28*
ΔFS	0.02	-0.30*	-0.22
ΔFAS	0.02	0.08	0.03

Note. ΔPA = change in positive affect; ΔNA = change in negative affect; ΔFS = change in feeling scale; ΔFAS = change in felt arousal scale; ΔRewP = reward positivity difference wave (calculated as RewP to rewards minus FN to losses); $\Delta LPP_{unpleasant}$ = late positive potential difference wave (calculated as LPP to unpleasant pictures minus LPP to neutral pictures); $\Delta LPP_{pleasant}$ = late positive potential difference wave (calculated as LPP to pleasant pictures minus LPP to neutral pictures).* $p < .05$.

Subgroup Analyses

Subgroup analyses were performed to determine whether individuals with mild-to-extremely severe depressive symptoms exhibited differences in any of the ERP measures by condition. Thirteen individuals (DASS-21 depression subscale score = 15.8 ± 6.7; range = 10-30) met the symptom cutoff score of 10 or greater, which indicates the presence of at least mild depressive symptoms according to guidelines by Lovibond and Lovibond (1995). There was no significant condition main effect or condition x feedback

type interaction for the RewP/FN parent and difference waves, *p*s > .05. Similarly, no significant condition or condition x picture type interactions were observed for the LPP parent and difference waves, *p*s > .05. A breakdown of the subgroup analyses is presented in Table 6.

Table 6
ERP measures (in μV) in a sample of individuals with mild-to-extremely severe levels of depressive symptoms by experimental condition (M ± SD)

	Exercise	**Control**	**Test Statistic**	***p*-value**
Reward-related ERPs				
RewP	9.1 ± 6.9	8.3 ± 7.6	$t(12) = 0.8$	0.42
FN	8.8 ± 9.0	7.4 ± 7.4	$t(12) = 1.6$	0.14
ΔRewP	0.2 ± 3.4	0.9 ± 4.0	$t(12) = -0.6$	0.54
Emotional reactivity ERPs				
$LPP_{pleasant}$	2.5 ± 3.9	2.1 ± 3.0	$t(12) = 0.3$	0.75
$LPP_{unpleasant}$	3.1 ± 3.5	2.9 ± 3.4	$t(12) = 0.2$	0.88
$LPP_{neutral}$	0.8 ± 2.9	0.8 ± 2.0	$t(12) < 0.1$	0.97
$\Delta LPP_{pleasant}$	1.7 ± 3.3	1.3 ± 1.7	$t(12) = 0.3$	0.75
$\Delta LPP_{unpleasant}$	2.3 ± 2.1	2.1 ± 2.1	$t(12) = 0.2$	0.85

Discussion

Depression has been linked to hypersensitivity to negative stimuli and blunted reward-related responsiveness (Webb et al., 2017). However, whether neural indices of reward processing (RewP) and emotional engagement (LPP) are modifiable through treatment (state-like) or are stable vulnerability markers (trait-like) remains unknown. The purpose of this study was to examine the effects of a single bout of continuous moderate-intensity aerobic exercise on RewP and LPP. A secondary purpose was to examine the association between changes in these neural measures and self-reported affective responses to exercise, and whether these effects were moderated by depressive symptoms. In line with previous research, it was hypothesized that exercise would

increase RewP and LPP amplitude to positive images, while decreasing LPP amplitude to negative images. The findings revealed that a single bout of moderate-intensity aerobic exercise did not influence RewP, FN, or ΔRewP amplitudes; however, larger LPP parent and difference waves (ΔLPP) to pleasant pictures were observed following exercise. That is, exercise selectively bolstered emotional reactivity to pleasant stimuli. The hypothesis that post-exercise changes in neural responses would be moderated by depressive symptom severity was not supported. Overall, these findings contribute to the extant evidence of affective responses to exercise (Ekkekakis et al., 2013), and suggest that exercise enhances neural activity to positively-valenced content regardless of current depressive symptomatology.

A novel contribution of the present study was the finding of increased LPP to positive pictures following exercise. The LPP, a neural measure of motivated attention and emotional engagement, is related to activation in lateral occipital, inferior temporal, and medial parietal cortex (Sabatinelli, Lang, Keil, & Bradley, 2007) and the temporal parietal junction and lateral prefrontal cortex (Nieuwenhuis et al., 2005). Previous research has demonstrated that LPP amplitude may be influenced by acute manipulations (Gable & Harmon-Jones, 2013; Tartar et al., 2018) and top-down regulatory processes (e.g., cognitive control processes; Hajcak et al., 2009). For instance, Gable and Harmon-Jones (2013) used a stationary cycling protocol to manipulate physiological arousal and found that elevated HR in the cycling condition was positively related to greater left frontal LPP amplitudes to pleasant pictures that were administered during the activity, a finding that was not observed following a no-pedaling control condition. Notably, HR in the cycling condition only resulted in a 10 bpm increase above resting values. Tartar et al.

(2018) examined the influence of an acute bout of exercise on LPP elicited by negative stimuli. The exercise session consisted of a 30 min bout of vigorous aerobic exercise (i.e., running on a treadmill at 75-85% max HR) and LPP amplitude to negative and neutral stimuli were assessed between 30-60 min post-exercise among a small unselected sample of undergraduates. LPP amplitude to negative pictures was increased following exercise relative to the seated rest condition. This vigorous bout of exercise also significantly reduced total mood disturbance, as assessed by the POMS; however, self-reported mood outcomes following exercise were not associated with LPP amplitudes. Notably, nearly opposite effects on the LPP were found in the current study. One plausible explanation for these divergent findings is the dose of exercise used. Tartar et al. used an intense bout of running on a treadmill, which may have resulted in a suppressing effect on post-exercise affective responses. This is particularly the case since evidence indicates that affective responses become progressively more negative beyond the ventilatory threshold (i.e., transition from aerobic to anaerobic metabolism; Ekkekakis et al., 2004; Ekkekakis, Hall, & Petruzzello, 2008; Hall, Ekkekakis, & Petruzzello, 2002). In the current study, participants were encouraged to exercise at a moderate intensity according to a rating of perceived exertion, which may have resulted in an overall positive net effect on post-exercise affective responses.

Consistent with the depression and ΔRewP literature (Bress et al., 2013; Brush et al., 2018; Proudfit, 2015), we observed a significant association between blunted ΔRewP and depressive symptom severity in the present sample. Numerous findings have found a blunted RewP in depression (Bress et al., 2013; Brush et al., 2018; Foti & Hajcak, 2009; Proudfit, 2015) and data also suggests that RewP can prospectively predict increases in

depressive symptoms and onset of MDD (Nelson, Perlman, et al., 2016). Both ERP and fMRI studies have demonstrated that acute stress or unpredictability can modulate neural circuits of reward processing (Nelson, Kessel, Jackson, & Hajcak, 2016; Porcelli, Lewis, & Delgado, 2012). However, only one published study has examined the acute effects of exercise on RewP. Walsh and colleagues (2019) demonstrated that an 11-min bout of HIIE diminished the RewP elicited by a probabilistic reward task completed approximately 10 min following exercise cessation. The authors concluded that mechanisms of reinforcement learning are downregulated during the initial post-exercise recovery period, possibly due to the heightened physiological arousal from the HIIE bout. In the current study, the longer duration bout of continuous moderate-intensity exercise did not significantly influence RewP relative to the seated rest condition. However, while the condition effect of exercise on RewP was not significant, we observed a relationship between ΔRewP and ΔLPP to pleasant pictures post-exercise, suggesting that individuals experiencing a larger ΔLPP to pleasant content also experienced a larger ΔRewP following exercise. These findings suggest that rather than a selective effect of exercise on reward sensitivity and emotional engagement, exercise may increase reactivity to appetitive (or rewarding) stimuli more generally. This suggestion warrants future research attention incorporating temporally-sensitive neurophysiological measures such as ERPs.

In terms of affective responses, positive affect was significantly higher immediately following exercise relative to the control condition; however, this was mainly due to a suppression of positive affect during the seated rest condition. Negative affect was reduced following both experimental conditions. Additionally, greater pleasure

and higher self-reported arousal were observed following exercise relative to the seated rest. This finding is consistent with the Reed and Ones (2006) meta-analysis indicating that acute exercise has a moderate effect on positive activated affect (d = 0.47), which reflects a combination of positive valence (increased pleasure) and increased activation (high arousal), or what Russell (2003) describes as core affect. Interestingly, although positive affect, as measured by the PANAS, was sustained from pre-to-post exercise, there was an increase in positive activated affect post-exercise, as reflected by greater pleasure and higher self-reported arousal rating. The divergent findings in exercise-associated changes in positive affect reflect a long standing issue in the field of exercise and affect research, which has been highlighted by Ekkekakis in several publications (Ekkekakis, 2013; Ekkekakis & Brand, 2018; Ekkekakis & Zenko, 2016) and is the focus of his 2013 book, *The Measurement of Affect, Mood, and Emotion: A Guide for Health-Behavioral Research*. That is, most measures employed in studies on the exercise-affect relation have been chosen without considering a proposed theoretical framework or the psychometric problems associated with the chosen affective measures in relation to exercise. In order to resolve discrepancies and advance understanding in this area, future research should align with Ekkekakis and Zenko's (2016) recommendations for selecting appropriate measures that correspond to a desired construct and theoretical framework. In their three-step approach, Ekkekakis and Zenko suggest researchers select measures that not only demonstrate sound psychometric properties (e.g., high internal consistency) related to a proposed construct, but that also captures the psychological process of interest (i.e., affect, mood, or emotion). The findings from the current study add to the growing literature of exercise and affect and collectively, and indicate that exercise

results in a more favorable pattern of affective responding, but that the selection and use of valid and reliable measures of affect is important.

Depressive symptom severity failed to moderate any of the effects of exercise on the ERP measures in the current study. All participants, regardless of depressive symptom severity, reported lower negative affect following exercise, although only those individuals with average and high depressive symptoms reported lower negative affect following the control session of seated rest. Lastly, despite the lack of moderation on any of the neural outcomes by depressive symptoms, we also performed subgroup analyses to determine whether individuals with mild-to-extremely severe depressive symptoms exhibited differences in any of the ERP measures by condition. Although no significant differences were observed, only about ~20% of the sample exhibited clinical symptoms of depression, which limits generalizability of the findings to clinical populations; therefore, future work should target the inclusion of both nonclinical and clinical populations in order to better understand the well documented “feel better” effects of exercise.

According to the emotion context-insensitivity (ECI) hypothesis, individuals with depression exhibit diminished emotional reactivity to positively-valenced emotional stimuli and attenuated reactivity to negatively-valenced emotional stimuli. In a broader context, the ECI hypothesis postulates that depression is characterized by emotional disengagement from the environment (Klinger, 1975; Nesse, 2000; Rottenberg, Gross, & Gotlib, 2005). A meta-analysis of 19 studies (n = 917 individuals) supported a diminished emotional reactivity to both positively- and negatively-valenced content in individuals with MDD (Bylsma, Morris, & Rottenberg, 2008). Although the review included studies

using multiple units of analysis (i.e., self-report, behavioral, and peripheral psychophysiology), neural measures of emotional reactivity were not included in the authors' analysis. To this end, several neuroimaging studies using fMRI have demonstrated attenuated reactivity to emotional stimuli; thus, bolstering support for the ECI hypothesis in depression (Moses-Kolko et al., 2010; Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011). Moreover, a recent study by Hill et al. (2019) found that a blunted LPP amplitude was observed to both pleasantly- and unpleasantly-valenced images, but not to neutral images, providing further support for the ECI hypothesis. Although a nonsignificant relationship between depressive symptoms and LPP was observed on the non-exercise control day, exercise was shown to boost emotional reactivity to both positively- and negatively-valenced pictures, although the effects were only significant for the positively-valenced content. Thus, a single bout of exercise may have the potential to modulate reactivity to positively-valenced components of the environment, which may help to resolve the blunted emotional reactivity to positive stimuli in depression. It is also possible that the post-exercise increase in LPP to positive stimuli represents an important neurophysiological mechanism of the affective and mood-enhancing benefits of exercise.

Limitations and Future Directions

Despite its strengths, this study had several limitations. First, participants did not completely return to baseline cardiovascular levels following exercise before the EEG assessment commenced. Although there were no significant relationships between measures related to physical arousal (i.e., HR and FAS responses) and any of the ERP measures, the findings related to increased LPP amplitude may be related to increased

arousal via catecholamine signaling (Basso & Suzuki, 2017; Cooper, 1973; Gable & Harmon-Jones, 2013). Future studies should investigate potential dose-response effects of exercise on emotion processing and standardize the post-exercise recovery time to minimize the influence of physiological-induced arousal during the emotion assessment. Second, although we documented the time of the EEG assessment following cessation of exercise, the temporal dynamics of emotional and affective responding following exercise remains relatively unexplored (e.g., Bixby, Spalding, & Hatfield, 2001). Future studies should include a precise timing of the post-exercise assessments to determine the precise nature and persistence of post-exercise-related benefits (Pontifex et al., 2019). Responses to a single bout of moderate-intensity exercise were examined in this study, which limits comparisons to affective and neural responses following different exercise doses (e.g., short duration, high-intensity interval exercise used in the Walsh et al. (2019) study). Additionally, participants were only allowed to cycle, rather than perform other modes of exercise (e.g., running, swimming), and preference for type of exercise may influence post-exercise affective responses (Miller, Bartholomew, & Springer, 2005; Parfitt & Gledhill, 2004). Lastly, we did not include individuals with a current diagnosis of MDD, but rather recruited individuals with varying levels of self-reported depressive and internalizing psychopathology symptoms. Future work should attempt to replicate the findings of this study using clinical samples.

Conclusions

In conclusion, using well validated neural indicators of reward sensitivity and emotional reactivity, this study examined the effects of acute, continuous moderate-intensity aerobic exercise on affective responses and reward sensitivity (i.e., RewP) and

emotional engagement (i.e., LPP), with a specific focus on the moderating influence of depressive symptoms on these responses. The study incorporated multiple units of analysis (i.e., ERPs from affective neuroscience and self-report methods) to assess exercise-associated changes. Relative to seated rest, acute moderate-intensity aerobic exercise resulted in increased pleasure, greater positive affect, and an increase in LPP amplitude to positively-valenced content. Although depressive symptoms were related to ΔRewP on the non-exercise control day, depressive symptom severity did not significantly moderate the effects of exercise on RewP or LPP. Overall, these findings suggest that acute aerobic exercise increases emotional engagement to pleasant stimuli, which may have implications for protecting against the development of anhedonia (i.e., the second cardinal symptom of MDD) or resolving the blunted emotional reactivity to positive stimuli in depression. Future research should incorporate ERPs to further examine the temporal dynamics of emotional and cognitive responding following acute exercise.

Chapter 3

Neural responsiveness to reward and cognitive control following a randomized trial of aerobic exercise in major depression

Christopher J. Brush

Introduction

Major depressive disorder (MDD) is a pernicious and chronic affective disorder that affects over 300 million individuals worldwide (Greenberg et al., 2015; World Health Organization, 2017). Despite available treatments for psychiatric management (e.g., pharmacotherapy and depression-focused psychotherapy), remission rates remain low and unpredictable (Akil et al., 2018; Trivedi, 2016). This variability in treatment response presents a challenge to clinical care and may be a product of the heterogeneity of depression. That is, compared with many other medical conditions, little is known about the pathophysiology of depression and approximately 681 possible combinations of symptoms can result in a MDD diagnosis (Akil et al., 2018). Identifying underlying or transdiagnostic mechanisms in depression, along with modifiable risk factors and predictors of treatment response all have the potential to advance precision medicine approaches for depression (Akil et al., 2018; Williams et al., 2016).

Reward processing and cognitive control deficits have been proposed as candidate transdiagnostic mechanisms of depression, proposals that are directly in line with the National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC)

initiative (Cuthbert & Insel, 2010). A cardinal feature of depression is anhedonia, or the inability to derive pleasure from normally enjoyable activities. Considering that depression is characterized by sustained negative affect and an inability to modulate behavior as a function of rewards (Burkhouse et al., 2016; Joormann & Stanton, 2016), impairments in reward processing have been examined as neural mechanisms in depression using electroencephalography (EEG) and event-related brain potentials (ERPs). Specifically, the reward positivity (RewP) and feedback negativity (FN) components reflect neural activity at frontocentral electrode sites approximately 200-350 ms following the receipt of rewards or positive feedback versus losses or negative feedback (Proudfit, 2015). There is growing evidence that the RewP is a valid measure of individual differences in initial reward responsiveness (Bress et al., 2013; Brush et al., 2018; Burkhouse et al., 2016), and is correlated with blood-oxygen-level dependent (BOLD) activation across the mesocorticolimbic dopaminergic reward circuitry, particularly in the ventral striatum and medial prefrontal cortex (Becker et al., 2014; Carlson et al., 2011). Notably, depression has consistently been associated with reduced RewP amplitude (Bress et al., 2013; Liu et al., 2014; Nelson, Perlman, et al., 2016) although it is uncertain whether RewP represents a trait-like vulnerability factor or is a modifiable biomarker of depression (Proudfit, 2015).

A second putative transdiagnostic mechanism of depression involves cognitive impairment, which is frequently observed in MDD patients and is a common residual symptom even following treatment with antidepressants (Greer, Grannemann, Chansard, Karim, & Trivedi, 2015). For example, approximately 70% of the 428 responders from the Sequenced Treatment Alternative to Relieve Depression (STAR*D) study who

achieved a clinically meaningful reduction in depressive symptoms (≥ 50% pre-to-post treatment reduction in depressive symptoms) reported difficulties in concentrating and decision-making (McClintock et al., 2011). Cognitive impairment has also been associated with poor treatment response (Potter, Kittinger, Wagner, Steffens, & Krishnan, 2004; Roiser, Elliott, & Sahakian, 2012; Story, Potter, Attix, Welsh-Bohmer, & Steffens, 2008). Brain regions associated with cognitive impairment in depression include prefrontal (PFC) and anterior cingulate cortices (ACC; Davidson, Putnam, & Larson, 2000; Holroyd & Coles, 2002; Ladouceur et al., 2018; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007) structures largely implicated in cognitive control. Cognitive control refers to the mental processes involved in goal-directed behavior; thus, it is critical in helping individuals to resist temptations and distractions to maintain focus on more goal-directed behavior (Inzlicht, Bartholow, & Hirsh, 2015). Deficits in cognitive control have been linked with emotion dysregulation and may serve as both a vulnerability risk factor for and mechanism underlying MDD (Joormann & Tanovic, 2015). Importantly, the error-related negativity (ERN) is a neural measure of cognitive control that has received substantial attention since its discovery in the early 1990s (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993).

The ERN, an index of error detection and response monitoring processes, is a neural response elicited approximately 50-100 ms following an error in speeded reaction time tasks at frontocentral electrode sites (Gehring et al., 1993). The ERN manifests as a negative deflection in the ERP waveform, with previous research demonstrating that it signals the need to adjust behavior and increase cognitive control to improve future

performance (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Holroyd & Coles, 2002). In terms of neural generators, prevailing neuroscientific evidence indicates that the ERN reflects activity of early error processing that occurs in the ACC, which has been borne out by source localization (Holroyd, Dien, & Coles, 1998; Van Veen & Carter, 2002), magnetoencephalography (Miltner et al., 2003), and intracerebral recording (Brázdil, Roman, Daniel, & Rektor, 2005) studies. Consistent with the notion of negative biasing of information in depression, Holmes and Pizzagalli (2008) found that individuals with depression exhibited a larger ERN following error commission on the Stroop task compared to healthy controls. Chiu and Deldin (2007) similarly observed a larger ERN in individuals with depression relative to healthy controls. Notably, the larger ERN was only observed for neutral and punishment conditions of the flanker task, but not for the rewarding task condition, suggesting increased sensitivity to negative rather than favorable outcomes (Chiu & Deldin, 2007; Elliott, Sahakian, Michael, Paykel, & Dolan, 1998). However, previous findings of ERN in depression are mixed, as some evidence suggests that ERN is blunted in MDD (Ladouceur et al., 2012; Schoenberg, 2014; Schrijvers et al., 2008; Weinberg, Kotov, & Proudfit, 2015) and other studies finding similar ERN amplitudes between MDD and healthy controls (Olvet, Klein, & Hajcak, 2010; Ruchsow et al., 2004; Weinberg, Klein, & Hajcak, 2012; Weinberg, Riesel, & Proudfit, 2014). Weinberg, Dieterich, and Riesel (2015) contend that the discrepant nature of findings may be due to subtle differences in tasks employed and sample composition (i.e., diagnostic heterogeneity) across the literature. For instance, Weinberg, Liu, and Shankman (2016) found that individuals with a melancholic presentation of depression exhibited a blunted ERN, while ERN amplitude was not significantly different

between individuals with other subtypes of depression and healthy controls. Despite current inconsistencies in the literature (Weinberg, Dieterich, et al., 2015), the ERN is a well-established and reliable index of ACC activity (Baldwin et al., 2015; Riesel, Weinberg, Endrass, Meyer, & Hajcak, 2013) and ACC function has been suggested to play a vital role in the antidepressant treatment response (Pizzagalli, 2011). It is therefore important to further examine the relationship between ERN and depressive symptomatology and determine whether the ERN is modifiable or predictive of treatment response through interventions.

One promising approach for influencing impairments in reward processing reward-related and cognitive control in depression is aerobic exercise. Aerobic exercise has previously demonstrated similar efficacy to first-line antidepressant treatments (e.g., sertraline and escitalopram) in reducing depressive symptomatology (Babyak et al., 2000; Blumenthal et al., 1999; Sherwood et al., 2016) and has been shown to influence activity in mesolimbic reward neurocircuitry and prefrontal and parietal cortical regions. Although exercise has demonstrated effectiveness in reducing depression (Kvam, Kleppe, Nordhus, & Hovland, 2016; Schuch et al., 2016), there are gaps in our knowledge of biomarkers that may predict response to exercise treatment and specific neurobiological mechanisms underlying the antidepressant response to aerobic exercise. As previously mentioned, there is large heterogeneity in treatment response to first-line treatments for depression (Carter et al., 2012), with as a many as 20-30% patients failing to respond to two rounds of antidepressant medications. Aerobic exercise as an antidepressant treatment is likely no different. For example, previous studies Dimeo, Bauer, Varahram, Proest, and Halter (2001) and Knubben et al. (2007) found that only 48-65% of the

depressed sample responded to an aerobic exercise intervention, leaving considerable numbers who failed to respond. In order to improve overall effectiveness in response rates to aerobic exercise interventions and ultimately guide behavioral interventions, efforts must be shifted from the current 'trial-and-error' approach of treatment prescription to identifying predictive biomarkers or biosignatures of treatment response (Herzog, Beckmann, Lieb, Ryu, & Muller, 2018). Since exercise has been shown to increase dopamine signaling in the brain, especially within the ACC (Kitaoka et al., 2010; Sutoo & Akiyama, 2003), and given the involvement of the dopaminergic system in both reward processing (Delgado, 2007) and error detection processes (Holroyd & Coles, 2002), the RewP and ERN represent suitable candidate neurobiological markers that may potentially account for treatment-related response to an exercise intervention.

To date, little is known about the efficacy of exercise to modify reward and error-related neural responses in depression, and no research to date has examined whether variability in reward processing and cognitive control can be used to appropriately identify who benefits from an exercise intervention. Therefore, the purpose of this study was threefold. The first aim was to replicate previous studies demonstrating a negative relationship between RewP and depressive symptomatology among patients at baseline (Bress et al., 2013; Brush et al., 2018; Proudfit, 2015). The relationship between ERN and depressive symptomatology among patients was also assessed at baseline. The second aim was to examine pre (T1) to post (T2) intervention changes in RewP and ERN following an 8-week program of exercise in a sample of individuals with MDD. We also evaluated whether pretreatment (T1) to posttreatment (T2) change in RewP and ERN would track changes in depressive symptoms. Changes in RewP and ERN were

hypothesized to correlate with the change in depressive symptoms following 8 weeks of aerobic exercise. Lastly, given the emphasis on neural predictors of treatment response in depression and psychopathology research in general (Ball, Stein, & Paulus, 2014; Ball, Stein, Ramsawh, Campbell-Sills, & Paulus, 2014), individual differences in pretreatment (T1) RewP and ERN were examined as predictors of treatment response following the treatment interventions. No previous studies have examined the utility of ERPs in predicting treatment response to exercise; therefore, there are no directional hypotheses related to the final aim.

Methods

Participants

Individuals were recruited using advertisements, university counseling and psychiatric clinics, and information tabling sessions at university student centers. Eligible participants included men and women between the ages of 18 and 35 years, no regular exercise program (defined as energy expenditure of < 35 kCal/kg/day or < 3 days/week for < 20 min/session over the month prior to the baseline assessment), and must have been free of physical limitations or contraindications to exercise. Additionally, participants had normal or corrected-to-normal vision and were not currently engaged in psychological or pharmacological treatments for depression beyond stable (> 6 weeks at stable dose) antidepressant or mood stabilizer treatment. Exclusion criteria included current or previous history of bipolar spectrum disorder, schizophrenia, self-injurious or suicidal ideation, or head injuries that result in a loss of consciousness. Clinical research staff trained in all study methods scheduled participants for study entry if they were deemed eligible following initial screening. All participants were physically able to

engage in aerobic exercise as indicated by the physical activity readiness questionnaire (PAR-Q) and were provided monetary compensation for their participation following the completion of the study. Informed consent was obtained prior to participation and the university's Institutional Review Board approved the research protocol. Study recruitment procedures commenced in January 2016, and the study was completed in December 2018.

Randomization and Sample Size

The present study compared the effects of an 8-week moderate-intensity aerobic exercise intervention to an 8-week light-intensity stretching on reward processing and cognitive control. 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 (using https://www.sealedenvelope.com/). Participants were assigned to groups once they were deemed eligible to participate in the study and had provided informed consent.

Based on the observed effect size of $\eta^2_p = 0.13$ from Olson et al. (Olson, Brush, Ehmann, & Alderman, 2017), an *a priori* power analysis was conducted using an effect size of Cohen's $f^2 = 0.38$. Using a two-sided $\alpha=0.05$ and a conservative estimate of 0.5 for correlation among repeated measures in G*Power version 3.1.9.2 (Faul et al., 2014) and power of ≥ 0.95, a total of 26 participants (13 in each arm) were required to power the present study.

Intervention Arms

The treatment conditions involved three 30-45 min sessions of aerobic exercise or light stretching per week for 8 weeks at the university recreation centers. Sessions were

scheduled by convenience depending on participant availability. Most sessions occurred on non-consecutive days. Research study staff monitored participants during sessions at 10 min intervals. Heart rate (HR) and ratings of perceived exertion (RPE) were recorded at these intervals to monitor exercise intensity. Session adherence was tracked across the duration of the study. See Figure 7 for a CONSORT study flow diagram.

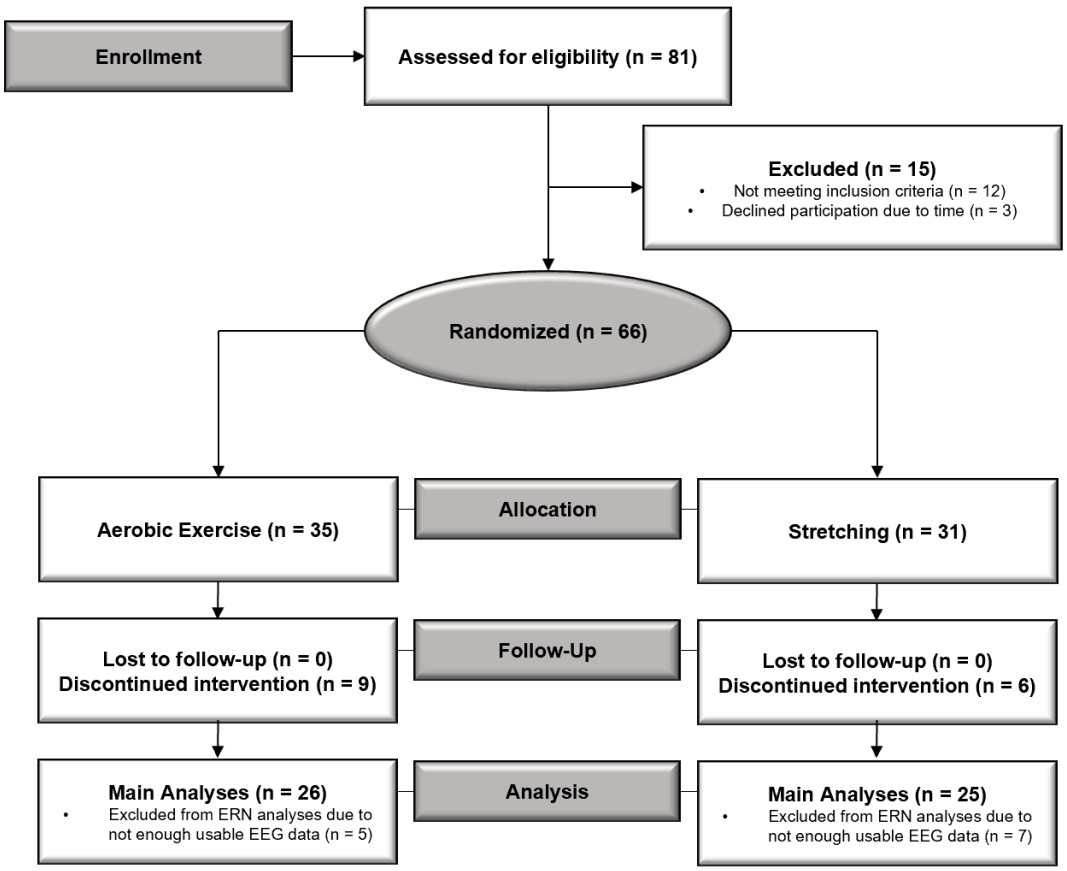

Figure 7. Study flow diagram. Individuals meeting study inclusion criteria were randomly assigned to either 8 weeks of moderate-intensity aerobic exercise or light-intensity stretching.

Moderate-intensity aerobic exercise. The moderate-intensity aerobic exercise condition consisted of 45 min 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 baseline fitness test. Participants received encouragement to maintain their prescribed exercise intensity throughout all exercise sessions. This dose of moderate-intensity exercise is consistent with public health recommendations, has been recommended for depression (Dunn, Trivedi, Kampert, Clark, & Chambliss, 2005; Rethorst & Trivedi, 2013), and was recently shown to improve cognitive control processes in MDD (Olson et al., 2017).

Light-intensity stretching. The light-intensity stretching protocol consisted of 30-45 minutes of stretching that targeted 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 20 s in sets of 3 with a 40 s rest period between each stretch. Trained research study staff instructed participants on proper form of each stretch prior to and during each session. The stretching condition was used to minimize potential demand characteristics commonly reported in the exercise literature (Morgan, 1997). Similar light-intensity stretch exercise protocols have been implemented in exercise trials for depression (Krogh, Videbech, Thomsen, Gluud, & Nordentoft, 2012).

Measures

General medical history. General health and medical history was collected using a self-reported medical 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 supplementation and medication use. In addition, the Physical Activity Readiness Questionnaire (PAR-Q; Shephard, Cox, & Simper, 1981) was administered to ensure participants could safely engage in an exercise program.

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 et al., 1998). All interviewers were trained under the supervision of experienced clinical staff and had previous experience in administering structured clinical interviews with psychiatric patients.

Clinical symptom severity. The 21-item Beck Depression Inventory-II, or BDI-II, (Beck et al., 1996) and 21-item Beck Anxiety Inventory, or BAI (Beck, Epstein, Brown, & Steer, 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 been shown to demonstrate high internal consistency in similar samples (Alderman, Olson, Brush, & Shors, 2016; Brush et al., 2018; Olson et al., 2017). In the current study, the clinical symptom scales demonstrated good-to-excellent internal consistency at both assessment points (BDI-II at T1: $\alpha = 0.80$; BDI-II at T2: $\alpha = 0.88$; BAI at T1: $\alpha = 0.89$; BAI at T2: $\alpha = 0.94$).

Cardiorespiratory fitness. Cardiorespiratory fitness (VO_2 peak) was assessed using a modified Bruce protocol (American College of Sports Medicine, 2013), which involved increasing the speed and grade of the treadmill every two min until volitional exhaustion was reached. A Polar HR monitor was used to record heart rate throughout the test. VO_2 peak (mL/kg/min) 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. VO_2 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 (RER) greater than 1.10, or (4) a RPE greater than or equal to 17. Upon completion of the assessment, a five min cool-down was performed at 2.5 mph and 0% grade.

Computerized Tasks

Individuals were given 10 practice trials on both tasks to ensure that they understood how to perform the tasks. Tasks were presented using E-Prime Professional version 2.0 software (Psychology Software Tools, Inc. Pittsburgh, PA) and individuals used a Logitech® F310 game gamepad (Logitech, Lausanne, Switzerland) to make responses. The 17 in. computer monitor was positioned 28 in. from participants, centered to the nasion, with vertical and horizontal visual angles of 1.2° and 6.6°.

Doors guessing task. The task consisted of five blocks of 20 trials, with each trial beginning with the presentation of two side-by-side doors. Participants selected either the

left or right door by making a left or right button press, respectively. Participants were told that they could either win $0.50 or lose $0.25 on each trial, values that are often used to equate the subjective value of gains and losses (Proudfit, 2015; Tversky & Kahneman, 1981, 1992). At the start of each trial, a fixation cross was presented at the center of the screen for 1,000 ms followed by the presentation of two doors, which stayed on the screen until the participant executed a button press. Following a button press and stimulus offset, another fixation cross was presented for 2,000 ms before the feedback stimulus was presented for 2,000 ms. Feedback indicated whether the participant won $0.50 (reward trial) or lost $0.25 (loss trial), and were represented by a green up arrow and a red down arrow, respectively. After feedback presentation, another fixation cross was presented for 1,500 ms, which was followed by a short break prior to the next trial. The task consisted of 50 reward and 50 loss trials presented randomly across the duration of the task. Participants were compensated for their respective winnings ($12.50) upon task conclusion. Outcome measures derived from the doors task include the RewP, FN, and ΔRewP.

Flanker task. Participants were presented with five arrows aligned horizontally on the center of the screen and were instructed to execute a manual left or right button press that corresponded to the direction of the central arrow. Participants were instructed to respond as quickly and as accurately as possible. The task consisted of congruent and incongruent trials, with the central target arrow pointing in the same direction as the flanking arrows for congruent trials (<<<<<), while the target arrow pointed in the opposite direction of the arrow flankers for incongruent trials (<<><<). Each trial began with a white fixation cross (+) presented for 500 ms on a black computer screen and was

followed by 1.5 x 8 cm white arrows centered focally for 100 ms. After stimulus offset, participants were given a 1,500 ms response window, which was followed by a variable intertrial interval of 900-1,300 ms. The task consisted of 2 blocks of 120 equiprobable congruent and incongruent trials with a timed, two min rest period between blocks. Behavioral outcome measures included reaction time (ms), response accuracy (%), post-error improvement in accuracy (PIA; %), and post-error slowing (PES; ms). Additionally, the CRN, ERN, and ΔERN served as ERP outcome measures from the flanker task.

EEG Data Acquisition and Reduction

Electroencephalogram (EEG) data were recorded from a 33 electrode actiCap using active, sintered Ag-AgCl electrodes (Brain Products, GmbH; Munich, Germany) that was arranged according to the 10/20 system. The electrooculogram (EOG) activity was recorded from 2 electrodes that were placed approximately 2 cm outside the outer canthus of the left eye (HEOG) and approximately 2 cm below the right eye (VEOG). Data were recorded using an Electrical Geodesics, Inc. (EGI; Eugene, OR, USA) amplifier system (20,000 gain, nominal bandpass = 0.10–100 Hz) and were online referenced to the vertex electrode (Cz). Data were digitized continuously at 500 Hz with a 24-bit analog-to-digital converter and were visualized in NetStation 4.0. Impedances were ≤ 20 kΩ throughout recording.

All EEG data were exported to EEGLAB toolbox version 14.1.1 (Delorme & Makeig, 2004) in Matlab version R2018a (The Mathworks, Inc., Natick, MA, USA) for preprocessing analyses. Data were bandpass filtered using a 2nd order infinite impulse response (IIR) Butterworth filter of 0.10-30 Hz and adjusted for DC offset. All continuous EEG activity was visually inspected to identify and remove any segments

containing large muscle-related artifacts or extreme offsets of activity. The data were then referenced offline to the average of the left and right mastoids (TP9, TP10). Separate epochs were extracted to derive the ERP components from the flanker and doors tasks.

For the doors task, feedback-locked epochs were extracted with a duration of 1,000 ms, while response-locked epochs were extracted with a duration of 1,200 ms for the flanker task. Oculomotor and eye blink artifacts were then removed from the segmented waveforms using ICA blink templates that were provided both by the author of the ERP PCA toolkit version 2.66 (Dien, 2010) and were generated from the already epoched data. ICA components that correlated 0.9 or higher with scalp topographies of the blink templates provided were removed during this step. Trials were also rejected if there was a voltage difference of 100 μV within a segment, or if channels differed by more than 50 μV, which was measured from the neighboring 6 closest channels. Trials with > 15 % of channels marked as bad were removed. The remaining bad channels were corrected through interpolation obtained from "good" channels of the scalp voltage field within each segment of data. Lastly, epochs were averaged separately by trial type for each task (flanker: correct, error; doors: reward, loss) and baseline corrected using the -200 to 0 ms pre-feedback interval for the doors task and the -400 to -200 ms pre-response interval for the flanker task.

For ERP amplitude measurement, previous work suggests averaging across electrodes to provide increased reliability (Baldwin et al., 2015); therefore, we averaged mean electrical activity across Fz, FC1, FCz, FC2, and Cz electrode sites for all ERP analyses. In line with recommendations (Luck & Gaspelin, 2017), we used a collapsed localizers approach to address the problem of multiple implicit comparisons inherent in

ERP research. Briefly, we averaged all the waveforms across conditions for the doors and flanker tasks, separately. We then selected the time window that demonstrated the largest negative deflections at the general time frame of interest. The RewP (to reward trials), FN (to loss trials), and ΔRewP (reward trials minus loss trials) were measured in a time window of 200 to 300 ms locked to the feedback stimulus (Brush et al., 2018), while the ERN (to error trials), CRN (to correct trials), and ΔERN (error trials minus correct trials) were assessed in a time window of 0 to 100 ms locked to the response (Olvet & Hajcak, 2008). Amplitudes were measured as the mean electrical activity for each individual within the time windows mentioned above for each ERP component.

Data Analyses

All statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA) with a family-wise alpha level of 0.05. Descriptive statistics were performed on demographic, clinical, behavioral, and ERP data. All outcomes were assessed for normality prior to conducting analyses and trial-level data on the flanker and doors tasks that were beyond ± 3 *SD* from an individual's mean were excluded. We also conducted bivariate Pearson correlations to examine the relationship between depressive symptoms and the pre-treatment (T1) ERP measures.

To assess mean-level changes from pre (T1) to post (T2) treatment, repeated measures analyses of variance (rANOVAs) were used. The between-subjects factor used for all analyses was condition (exercise, stretching) and time (T1, T2) was the within-subjects factor. For ERP outcomes, there was an added factor of task trial type. For the doors task, feedback type (reward, loss) was the within-subjects factor, while for the flanker task, accuracy (correct, error) was the within-subjects factor. For all rANOVAs,

sphericity was assessed and the Greenhouse-Geisser epsilon correction was used to adjust for cases when sphericity was violated. All planned comparisons were conducted using Bonferroni corrected *t* tests and the effect size estimates are presented, when appropriate, for all analyses. To examine stability of the ERP measures, we conducted bivariate Pearson correlations of the ERP measures from T1 to T2.

We were also interested in determining whether T1 to T2 change in the ERP measures tracked changes in symptomatology across the intervention; therefore, we conducted bivariate Pearson correlations between changes in ERP measures and changes in depressive symptoms (BDI-II score). Additionally, to determine whether any of the ERP measures at T1 predicted change in depressive symptoms, separate multiple linear regression analyses controlling for gender (0 = male; 1 = female), baseline (T1) depressive symptoms, and baseline (T1) ERP amplitude were conducted. Age, BMI, and VO_2 peak were not associated with any of the outcomes in the regression models, so they were not retained as control variables in the regression models. The same model was used for all ERP measures (RewP, FN, ΔRewP; CRN, ERN, ΔERN). Lastly, similar to the Sequenced Treatment Alternative to Relieve Depression (STAR*D) study that examined treatment response following antidepressant therapy (McClintock et al., 2011) and the Burkhouse et al. (2016) study that found RewP as a predictor of treatment response to CBT in depression, we also examined treatment response as a dichotomous outcome, based on whether or not a ≥ 50% treatment reduction in depressive symptoms was met (treatment response); therefore, we also conducted separate binary logistic regression analyses with the same predictors used in the multiple linear regression analyses, except the dependent variable was categorical and coded as 0 = nonresponder and 1 = responder.

For all the baseline (T1) ERP binary logistic regression analyses, there were 28 nonresponders and 23 responders for the RewP analyses, while the ERN analyses included 20 nonresponders and 20 responders.

Results

Demographic and Clinical Characteristics

No significant differences by condition were found for any of the demographic, clinical, fitness, behavioral performance, or ERP measures at baseline, *p*s > .27. In line with higher rates of MDD among women (Kessler et al., 2003; Kessler et al., 2005), a greater number of females were enrolled in (50 females, 17 males) and completed the intervention (38 females, 13 males). No significant gender differences in depressive symptoms, anxiety symptoms, baseline cognitive outcomes (flanker accuracy and RT), or ERP measures were found; however, BMI was higher among females (BMI: 24.2 ± 4.8 kg/m^2) compared to males (BMI: 22.3 ± 2.1 kg/m^2), while VO_2 peak was lower among females (VO_2 peak: 35.3 ± 8.1 mL/kg/min) relative to males (VO_2 peak: 47.0 ± 10.5 mL/kg/min).

Across the sample, no significant relationships between depressive symptoms and anxiety symptoms were observed with any of the behavioral performance outcomes or ERP measures, *p*s > .05. There were also no significant relationships between VO_2 peak and any of the demographic or ERP measures, *p*s > .05. As expected, the manipulation check of intensity revealed significant differences by condition, such that the exercise condition elicited higher HR (147.2 bpm) and RPE (13.3) values relative to the stretching condition (HR: 88.2 bpm; RPE: 7.8). Previous evidence indicates that comorbid depression and anxiety, as well as psychotropic medications, may impact neural activity

as well as psychomotor speed (Gehring & Knight, 2000; Hajcak, Franklin, Foa, & Simons, 2008); therefore, we also reanalyzed the data after excluding individuals with comorbid diagnoses or current psychotropic medication use. Since the outcomes did not change and there were low rates of antidepressant use (~10%) or the presence of comorbid anxiety and depression (~18%), the findings are reported below without exception. Sample characteristics are presented in Table 7.

Table 7

Baseline sample characteristics of participants with complete ERP data at T1 and T2

Measure	**RewP Analyses**			**ERN Analyses**		
	Exercise (n = 26)	Stretching (n = 25)	*P*-value	Exercise (n = 21)	Stretching (n =18)	*P*-value
Male/Female (n)	8/18	5/20	$p = .38$	5/16	4/14	$p = .16$
Race						
White (n)	8	8	$p = .54$	6	6	$p = .34$
Asian (n)	8	11		5	7	
Other (n)	10	6		10	5	
Age, Years	20.4 (3.2)	20.0 (1.7)	$p = .34$	19.7 (1.3)	20.1 (1.8)	$p = .42$
BMI (kg/m^2)	24.0 (4.7)	23.4 (4.8)	$p = .67$	23.7 (4.2)	23.8 (5.0)	$p = .94$
VO_2 peak (mL/kg/min)	37.4 (10.2)	39.8 (10.2)	$p = .39$	38.8 (10.5)	37.8 (10.5)	$p = .74$
Depressive Symptoms (BDI-II Score)	21.9 (8.2)	20.3 (7.3)	$p = .46$	22.3 (7.7)	19.8 (8.0)	$p = .24$
Anxiety Symptoms (BAI Score)	13.6 (11.1)	13.9 (8.1)	$p = .34$	13.7(9.7)	12.5 (8.7)	$p = .65$
T1 ERP amplitude measures (μV)						
RewP	9.9 (6.5)	8.3 (5.5)	$p = .37$			
FN	7.1 (5.3)	6.1 (5.5)	$p = .50$			
ΔRewP	2.8 (2.9)	2.2 (3.1)	$p = .54$			
CRN				0.1 (3.8)	0.8 (4.3)	$p = .52$
ERN				-2.2 (3.9)	-2.8 (3.7)	$p = .55$
ΔERN				-2.3 (3.1)	-3.6 (3.9)	$p = .16$

Note. All values are presented as M (SD), unless denoted otherwise. T1 = pre-treatment assessment; T2 = post-treatment assessment; BMI = body mass index; VO_2 peak = cardiorespiratory fitness; BDI-II = Beck Depression Inventory, Second Edition; BAI = Beck Anxiety Inventory; ERP = event-related potential; RewP = reward positivity; FN = feedback negativity; ΔRewP = reward positivity difference wave, calculated as RewP (to rewards) minus FN (to losses); CRN = correct-related negativity; ERN = error-related negativity; ΔERN = error-related negativity difference wave, calculated as ERN (to error trials) minus CRN (to correct trials).

Attrition Rate and Drop-Out Analyses

For the whole intervention, the attrition rate was 77.3%, since a total of 16 individuals (9 exercise; 7 stretching) dropped out of the intervention and completed a range of 1-17 sessions. A total of 3 individuals completed 1 session, 5 individuals completed 2 sessions, 3 individuals completed 4-7 sessions, 4 individuals completed 10-11 sessions, while 1 individual finished 17 sessions. In terms of characterizing drop-outs, baseline differences between the 16 drop-outs and the 51 individuals who completed the intervention were examined. Independent samples *t* tests revealed no significant differences in age, BMI, VO_2 peak, physical activity, BDI-II score, and BAI score, all *p*s > .05. Although there were no differences in demographic variables, there was a marginally significant difference in baseline ΔRewP, $t(65) = -1.8$, $p = .083$, $d = 0.54$, such that drop-outs had a smaller baseline ΔRewP (ΔRewP: 1.1 ± 2.3 μV) relative to individuals who completed the intervention (ΔRewP: 2.5 ± 3.0 μV). There were no other significant between group differences for any of the other ERP components (RewP, FN, CRN, ERN, ΔERN) or behavioral performance measures (flanker accuracy and RT) at baseline, *p*s > .05.

Change in Clinical Symptoms

The rANOVA on depressive symptoms (BDI-II score) revealed a significant main effect of time, $F(1,49) = 87.6$, $p < .001$, $\eta^2_p = 0.64$, which was superseded by a significant time x condition interaction, $F(1,49) = 9.8$, $p < .01$, $\eta^2_p = 0.17$. This interaction indicated a greater T1-to-T2 reduction in depressive symptoms for the exercise condition (66% reduction) relative to the stretching condition (36% reduction). Although there were no significant differences in baseline depressive symptoms between conditions, Bonferroni

corrected *t* tests of the time x condition interaction confirmed less depressive symptoms at T2 for the exercise condition (BDI-II score: 7.4 ± 6.8) relative to the stretching condition (BDI-II score: 13.1 ± 5.5), $t(49) = -3.3$, $p < .01$, $d = 0.92$. The rANOVA on anxiety symptoms (BAI score) revealed a significant main effect of time, $F(1,48) = 4.6$, $p < .05$, $\eta^2_p = 0.09$, such that there was an overall decrease in anxiety symptoms from T1 (BAI score: 13.7 ± 9.7) to T2 (BAI score: 10.8 ± 10.6). No significant time x condition interaction was observed, $p > .05$.

Change in Cardiorespiratory Fitness and Physical Activity

A significant main effect of time, $F(1,49) = 7.9$, $p < .01$, $\eta^2_p = 0.14$, was observed for cardiorespiratory fitness, indicating an overall increase in cardiorespiratory fitness from T1 (VO_2 peak: 38.6 ± 10.2 mL/kg/min) to T2 (VO_2 peak: 40.0 ± 9.4 mL/kg/min) across both conditions. There was a nonsignificant time x condition interaction, $F(1,49) = 2.3$, $p = .13$, $\eta^2_p = 0.05$, indicating no significant changes in VO_2 peak from T1-to-T2 for either intervention group. For physical activity derived from the IPAQ, the rANOVA revealed no significant time main effect or time x condition interaction, *p*s > .05. Refer to Figure 8 for T1-to-T2 changes in depressive symptoms, VO_2 peak, and physical activity by condition (exercise, stretching).

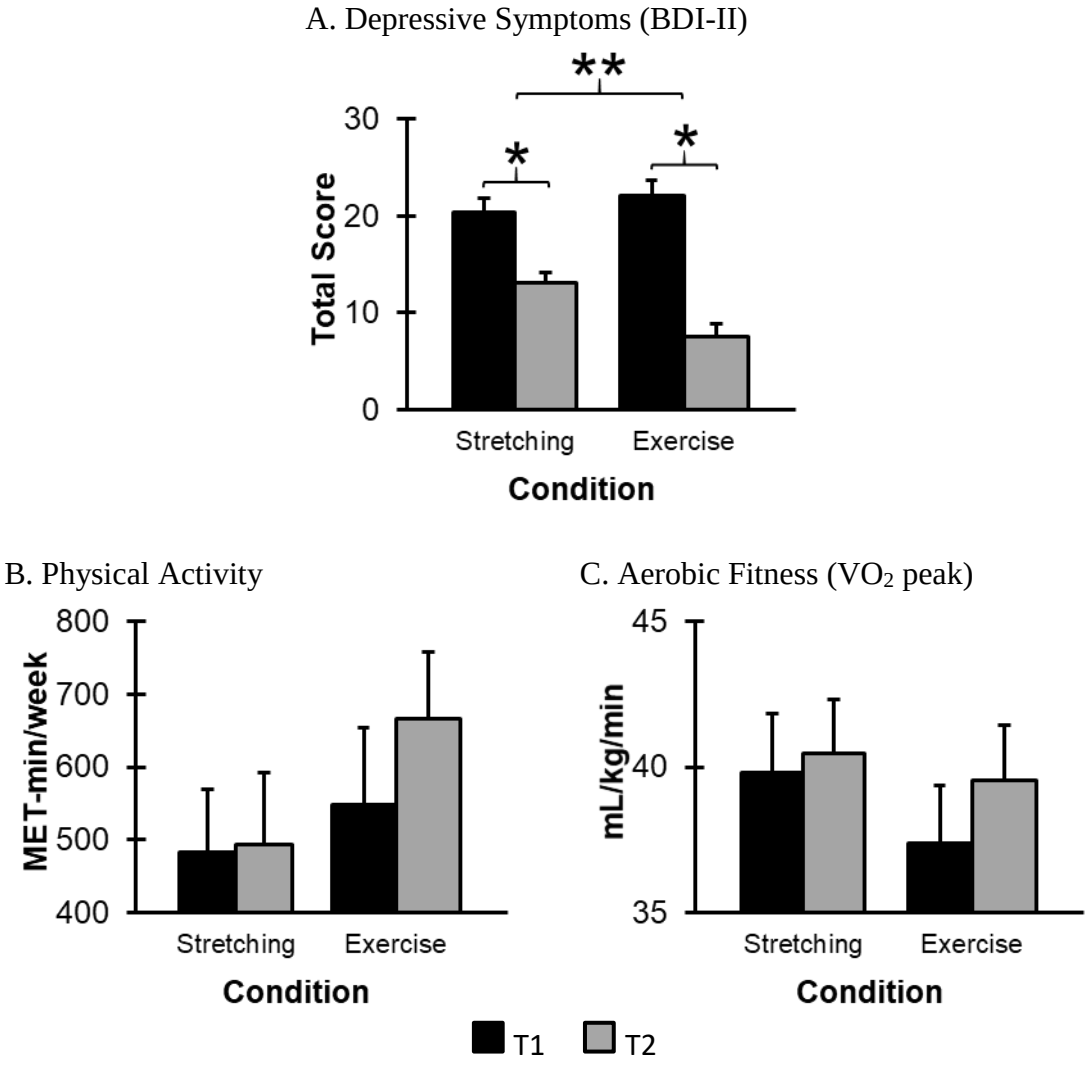

Figure 8. Pre-to-post changes in depressive symptoms (A), physical activity (B), and aerobic fitness (C) by condition. Individuals in the exercise condition experienced a significantly larger reduction in depressive symptoms relative to individuals in the stretching condition. No significant changes in physical activity or aerobic fitness by condition.

Note: *p<.001; **p<.01; MET=metabolic equivalent; mL=milliliter; kg=kilogram.

Reward Sensitivity ERPs

Bivariate Pearson correlations were used to examine the stability of the reward-related ERPs from T1-to-T2 across the entire sample. The Pearson correlation coefficients revealed poor to moderately high stability for each of the ERPs (RewP: $r(49) = 0.56$, $p < .001$; FN: $r(49) = 0.67$, $p < .001$; ΔRewP: $r(49) = 0.38$, $p < .01$).

Reward positivity: Response to treatment. A significant main effect of feedback type, $F(1,49) = 51.2$, $p < .001$, $\eta^2_p = 0.51$, was observed indicating larger ERP amplitude to win (RewP: 8.7 ± 5.4 μV) relative to loss (FN: 6.3 ± 5.2 μV) trials. There were no other significant main effects or interactions with condition or time (lowest $p = .36$). Refer to Figures 9 and 10 for the RewP/FN ERP parent and ΔRewP difference waveforms.

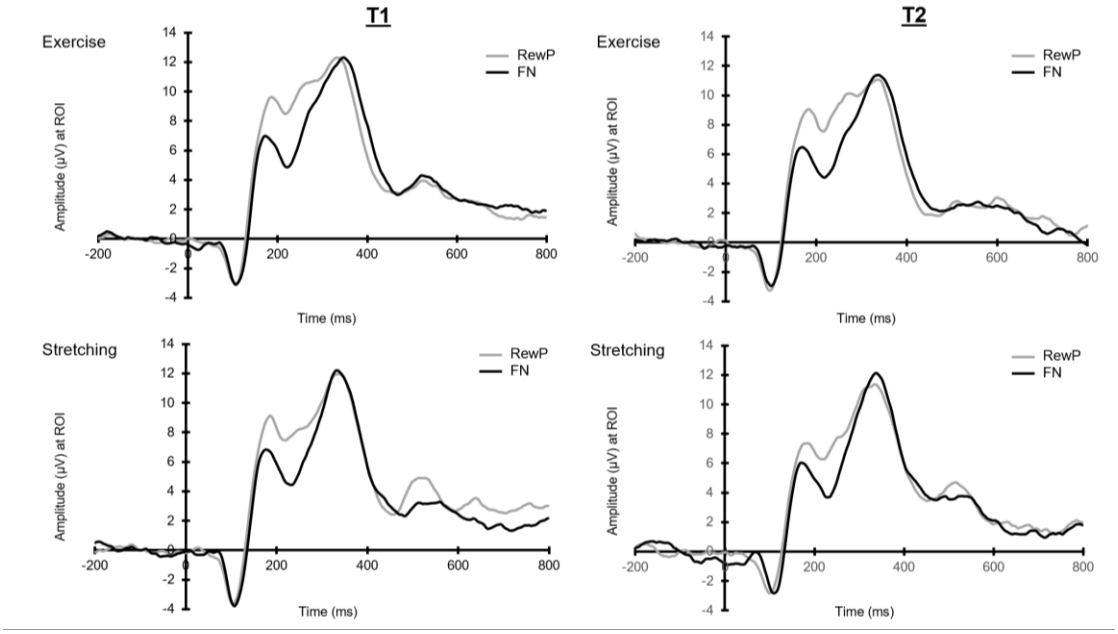

Figure 9. Feedback-locked grand averaged ERP waveforms for the RewP and FN components across a frontocentral region of interest (ROI) at Fz, FC1, FCz, FC2, and Cz electrode sites for exercise (top panels) and stretching (bottom panels)

across the intervention. There were no changes from pretreatment (T1) to posttreatment (T2) for RewP or FN.

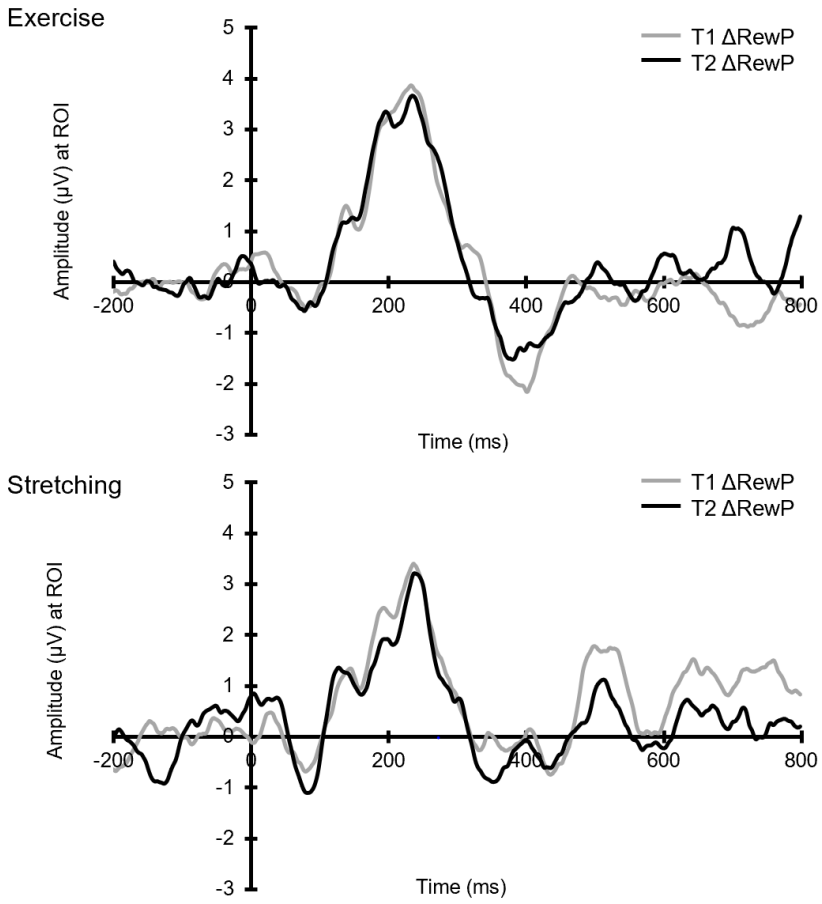

Figure 10. Subtraction-based (ΔRewP) difference waveforms for exercise (top panel) and stretching (bottom panel) from pretreatment (T1) to posttreatment (T2). ΔRewP remained stable across both treatment conditions.

Does change in ERP response to reward or loss track change in depressive symptoms? Across the entire sample, no significant correlations between T1-to-T2 change in RewP, FN, or ΔRewP and T1-to-T2 changes in depressive symptoms were found, *p*s > .05. No significant correlations were found between change in neural measures and change in depressive symptoms among individuals in the exercise condition only, *p*s > .05.

Do pretreatment reward or loss responses predict treatment outcome? Three separate multiple linear regression analyses revealed no significant associations between any of the T1 ERP measures (RewP, FN, or ΔRewP) measures and T1-to-T2 change in depressive symptoms.

We also explored treatment outcome as a dichotomous variable (nonresponder = 0; responder = 1) across both conditions. After controlling for gender and baseline depressive symptoms, ΔRewP at baseline was a marginally significant predictor, b = .22, Wald = 3.29, $p = .07$, OR = 1.24 [0.98, 1.57]. That is, for every one-unit increase in ΔRewP, the odds of responding to the intervention increased by a factor of 1.24. RewP and FN were nonsignificant predictors.

Cognitive Control Analyses

Flanker behavioral performance. For response accuracy, there was a significant main effect of congruency, $F(1,49) = 5.3$, $p < .05$, $\eta^2_p = 0.10$, indicating better performance for congruent (89.1 ± 13.6%) relative to incongruent flanker trials (86.2 ± 14.3%). Although the condition x time x congruency interaction approached significance, $F(1,49) = 3.9$, $p = .054$, $\eta^2_p = 0.07$, which was being driven by a larger T1-to-T2 improvement in response accuracy for the stretching (5.9% increase in accuracy)

compared to the exercise condition (1.4% increase in accuracy), all other main effects and interactions were nonsignificant, *p*s > .05. For RT, there was a significant main effect of congruency, $F(1,49) = 86.9$, $p < .001$, $\eta^2_p = 0.64$, indicating faster RTs on congruent (602.6 ± 136.9 ms) relative to incongruent trials (666.5 ± 156.3 ms). All other main effects and interactions were nonsignificant, *p*s > .05. See Figure 11 for a display of response accuracy and RT by condition across the intervention.

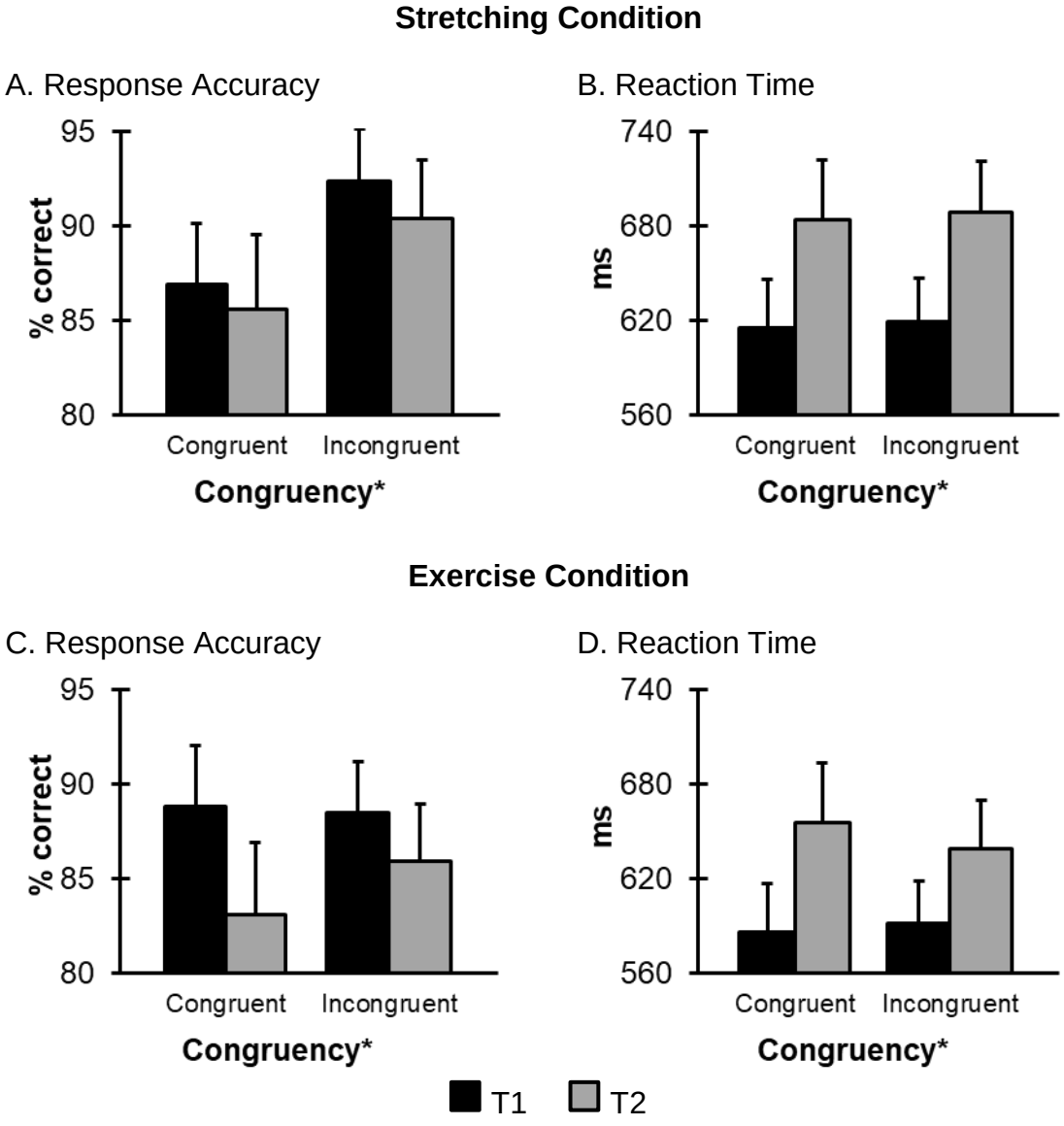

Figure 11. Mean (± SE) behavioral task performance for response accuracy (% correct; see A and C) and reaction time (ms; right panels; see B and D) on the flanker task from pretreatment (T1) to posttreatment (T2) for the stretching (top panel) and exercise conditions (bottom panel).

Note: *p<.001 = congruency main effect; ms=millisecond.

Given the importance of understanding post-error behavioral adjustments following the commission of an error, we also examined post-error improvement in accuracy (PIA) and post-error slowing responses. For PIA, there was a significant main effect of time, $F(1,49) = 7.2$, $p < .05$, $\eta^2_p = 0.13$, such that post-error accuracy was better at T1 (11.0 ± 8.4%) compared to T2 (7.7 ± 9.8%). There were no other significant main effects or interactions for PIA and PES, ps > .05.

Cognitive control ERPs. Due to the presence of noisy data and commission of fewer than six errors at T1 (Meyer, Riesel, & Hajcak Proudfit, 2013; Olvet & Hajcak, 2009), 12 participants (5 exercise; 7 stretching) were excluded from the ERN analyses. Of the remaining 39 participants with usable T1/T2 ERP data, bivariate Pearson correlations were used to examine the stability of the cognitive control ERPs from T1 to T2 across the entire sample. The Pearson correlation coefficients revealed poor-to-moderate stability for each of the ERPs (CRN: $r(37) = 0.49$, $p < .01$; ERN: $r(37) = 0.56$, $p < .001$; ΔERN: $r(37) = 0.48$, $p < .01$).

Error-related negativity: Response to treatment. A significant main effect of accuracy, $F(1,37) = 36.8$, $p < .001$, $\eta^2_p = 0.50$, revealed more negative ERP amplitudes for error (ERN: -2.4 ± 4.4 μV) compared to correct (CRN: 1.7 ± 4.9 μV) trials. A main

effect of time, $F(1,37) = 3.1$, $p = .087$, $\eta^2_p = 0.08$, and a time x accuracy interaction, $F(1,37) = 3.8$, $p = .06$, $\eta^2_p = 0.09$, both approached significance, indicating that ΔERN increased from T1 (ΔERN: -3.3 ± 3.8 μV) to T2 (ΔERN: -5.0 ± 6.1 μV). There were no other significant main effects or interactions by condition (lowest $p = .24$). See Figures 12 and 13 for the parent and difference ERP waveforms.

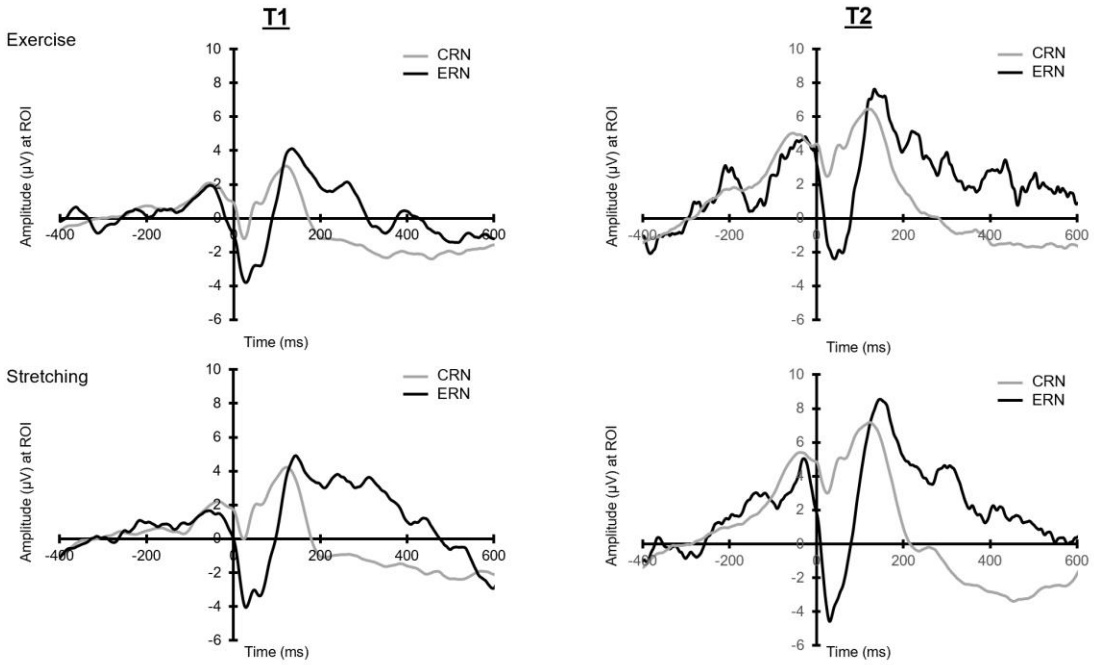

Figure 12. Response-locked grand averaged ERP waveforms for the ERN and CRN components across a frontocentral region of interest (ROI) at Fz, FC1, FCz, FC2, and Cz electrode sites for exercise (top panels) and stretching (bottom panels) across the intervention.

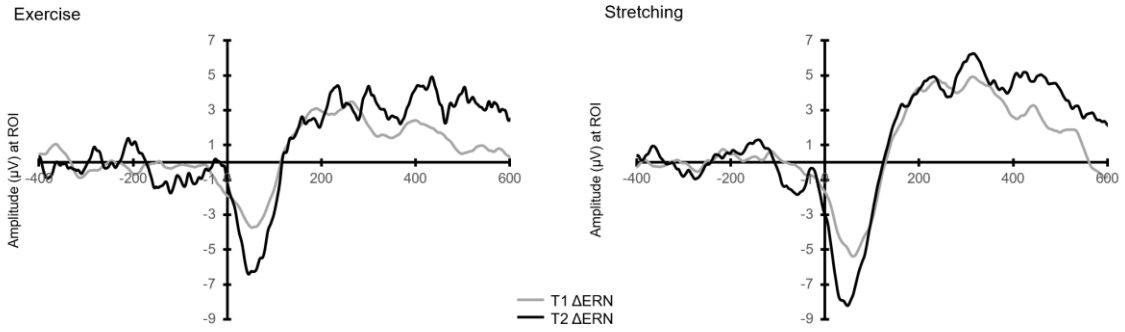

Figure 13. Pretreatment (T1) and posttreatment (T2) subtraction-based (ΔERN) difference waveforms for exercise (left) and stretching (right).

Does change in ERP response to error or correct trials relate to change in depressive symptoms? Across the entire sample, there were no significant correlations between T1-to-T2 change in CRN or ΔERN and change in depressive symptoms, *p*s > .05; however, there was a significant relationship between T1-to-T2 change in ERN and T1-to-T2 change in depressive symptoms, $r(37) = -0.41$, $p < .01$. That is, a larger T1-to-T2 reduction in depressive symptoms was associated with a smaller ERN (i.e., less negative ERN; Figure 14). No significant relationships were observed when only assessing these relationships for participants in the exercise condition, *p*s > .05.

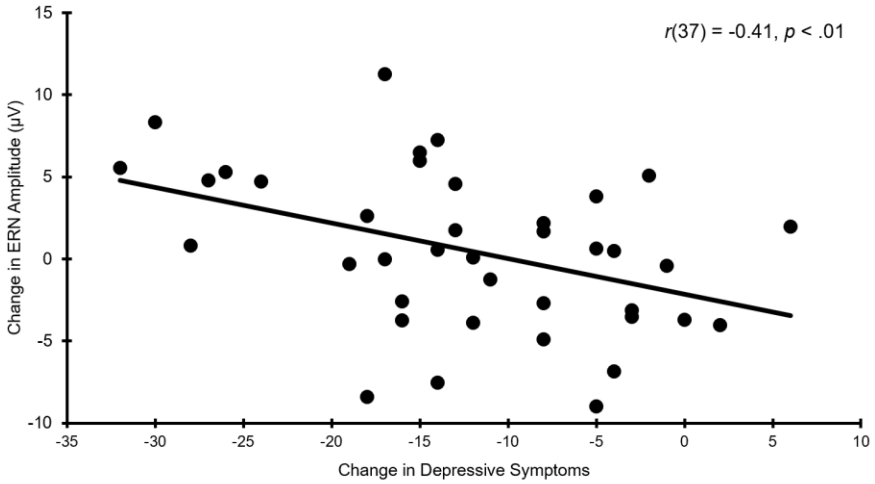

Figure 14. Association between change in depressive symptoms and change in the ERN parent difference wave. The graph depicts the relationship between ERN at the frontocentral ROI (Fz, FC1, Cz, FC2, and Cz) and change in depressive symptoms. The change in ERN is the difference between posttreatment (T2) response to errors minus pretreatment (T1) response to errors. The change in depressive symptoms is the difference between posttreatment (T2) and pretreatment (T1) depressive symptom scores.

Do baseline ERP responses to error or correct trials predict treatment outcome?

The results from three separate multiple linear regression analyses revealed no significant associations between any of the T1 ERP (CRN, ERN, or ΔERN) measures and depressive symptom change. In the binary logistic regression analyses, after accounting for gender and baseline depressive symptoms, baseline ERN was a significant predictor of change, b = -.24, Wald = 3.87, $p < .05$, OR = 0.79 [0.62, 1.00]. For ease of interpretation, we inverted the OR to reflect an OR > 1 and found that for every one-unit decrease in ERN (i.e., larger ERN), the odds of successful response increased by a factor of 1.27. CRN and ΔERN were both nonsignificant predictors. See Figure 15 for baseline (T1) ERP responses that predict treatment outcome by responder status.

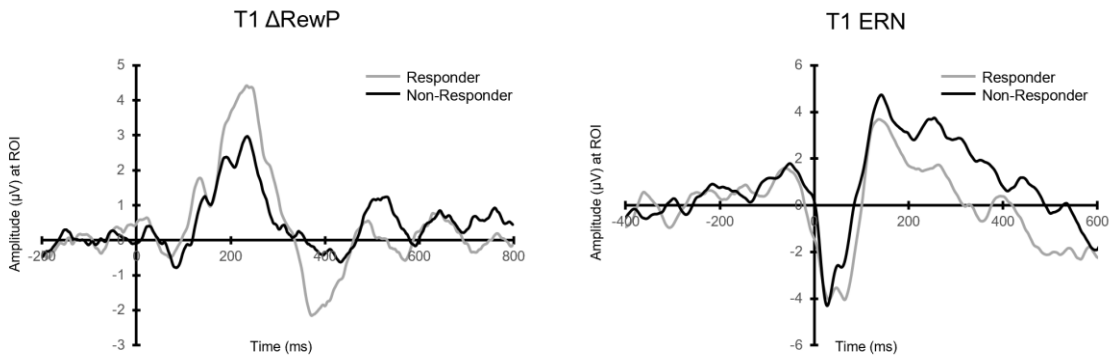

Figure 15. Pretreatment (T1) ΔRewP (left) and ERN (right) amplitude by antidepressant treatment response. The ERP waveforms are averaged across a frontocentral ROI (Fz, FC1, FCz, FC2, and Cz electrode sites). Individuals are grouped by responder status, as defined by a change in depressive symptoms that is ≥ 50% reduction from pretreatment to posttreatment. Larger ΔRewP (left) and larger ERN (right) are associated with a greater likelihood of an antidepressant response.

Discussion

The current study examined the effects of an 8-week aerobic exercise intervention on reward processing, cognitive control, and symptoms of depression in individuals with MDD. Secondary aims were to determine whether the magnitude of T1-to-T2 change in RewP or ERN was correlated with the magnitude of change in depressive symptoms and whether RewP or ERN assessed at baseline could predict the antidepressant response associated with aerobic exercise. Significant reductions in depressive symptoms were observed following both treatment arms, although greater reductions in symptoms occurred following aerobic exercise compared to stretching. For reward processing, there were no mean-level changes in RewP by condition; however, a larger ΔRewP was a marginally significant predictor of treatment response. In terms of cognitive control, the

magnitude of change in ERN was associated with change in depressive symptoms across the intervention, such that a reduction in ERN amplitude (i.e., less negative) was associated with a larger antidepressant response. Notably, ERN amplitude, not CRN or ΔERN, was a significant predictor of treatment response, even after controlling for individual difference characteristics, such as gender. That is, individuals with a larger T1 ERN (i.e., more negative) amplitude had a greater likelihood of responding to the exercise intervention. Collectively, these findings suggest that 8 weeks of aerobic exercise reduce depressive symptoms, while a smaller ERN amplitude across the intervention was related to the magnitude of the antidepressant response. The significant finding of larger ERN and marginally significant finding of ΔRewP amplitude as predictors of treatment response are particularly noteworthy and relevant for improving precision medicine approaches in depression.

There was a significant and clinically meaningful reduction in depressive symptoms after 8 weeks of aerobic exercise (66%) relative to the smaller reduction (36%) for individuals assigned to the stretching condition. This finding is comparable to the effects (58% reduction following aerobic exercise; 22% reduction following stretching) observed in a previous study that used the same protocol (Olson et al., 2017). These results are also 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 (Cooney et al., 2013; Rethorst & Trivedi, 2013; Rethorst, Wipfli, & Landers, 2009; Rimer et al., 2012). 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. Although the stretching condition was designed to serve as an active comparator, the finding of a MCID in depressive symptoms following 8 weeks of stretching echo early findings by Martinsen and colleagues (Martinsen, Hoffart, & Solberg, 1989) who observed similar reductions in depressive symptoms among MDD inpatients allocated to either 8 weeks of intensive aerobic exercise or a non-aerobic intervention consisting of muscular strength, flexibility stretches, and relaxation. The study, which was performed at the *Modum Bad Nervesanatorium*, a voluntary inpatient psychiatric clinic located in Norway that specialized in the treatment of severe neuroses and psychiatric disorders, demonstrated that the 47 individuals in the non-aerobic exercise condition experienced a similar reduction in depressive symptoms as the 40 patients completing the aerobic exercise condition. Interestingly, Martinsen and colleagues found that the antidepressant response was associated with an increase in cardiorespiratory fitness. In the current study, change in cardiorespiratory fitness was not related to pre-to-post intervention reduction in depressive symptoms, which suggests that low and moderate-intensity exercise programs may result in an antidepressant response without a change in aerobic fitness. This finding is consistent with a previous study that used the same study design among a similar sample demonstrating no changes in cardiorespiratory fitness following an 8 week aerobic exercise intervention (Olson et al., 2017). Collectively, the reduction in depressive symptoms following both conditions complement the findings of Martinsen et al. and Olson et al. indicate that light-intensity exercise programs may also result in

meaningful reductions in depressive symptoms; however, whether the antidepressant effects of such interventions persist currently remains unknown.

Previous research has shown that RewP is reduced in depression (Bress et al., 2013; Brush et al., 2018; Foti et al., 2014; Liu et al., 2014) and also serves as a vulnerability marker for the development of depression (Bress et al., 2013; Nelson, Perlman, et al., 2016). Contrary to our hypothesis, there was no impact of 8 weeks of exercise on RewP, which suggests that RewP may reflect more of a trait-like marker that remains stable across time and intervention. Indeed, Burkhouse et al. (2018) found no changes in ΔRewP across 12 weeks of CBT or SSRI treatment among adults with a primary DSM-5 anxiety or depressive disorder, but found a reduced ΔRewP at baseline predicted a greater reduction in depressive symptoms following SSRI treatment. In the current study, a larger ΔRewP amplitude was related to an increased probability of an antidepressant response to exercise, which contrasts with the findings from Burkhouse et al. who found that a more attenuated RewP at baseline predicted a greater reduction in depressive symptoms following treatment with SSRIs, but not after CBT. However, differences in patient populations (e.g., anxiety disorders) and types of treatments may help to explain the differential findings related to ΔRewP as a predictor of treatment response. The current sample included a relatively pure sample with MDD, and it is possible that individuals with a larger ΔRewP at baseline may be more likely to benefit from an aerobic exercise intervention either as an alternative or adjunctive therapy, while individuals with blunted ΔRewP amplitudes may benefit more from other antidepressant treatment options, such as SSRIs (Burkhouse et al., 2018) and CBT (Burkhouse et al., 2016). Given the role of the mesocorticolimbic dopamine pathway (Carlson et al., 2011;

Delgado, 2007) and brain structures (e.g., basal ganglia) involved in generating the RewP (Becker et al., 2014; Foti et al., 2014), it is possible that individuals who benefit from exercise exhibit greater dopaminergic activity at baseline, and that the integrity of the reward system helps to bolster an antidepressant response from exercise. Indeed, exercise has been shown to activate dopaminergic signaling pathways (Foley & Fleshner, 2008). Preliminary evidence from this study suggests that individual differences in reward processing may be used to identify individuals with depression most likely to benefit from an exercise program. Although parallels can be drawn between our study and the Burkhouse et al. studies (Burkhouse et al., 2018; Burkhouse et al., 2016), future research is warranted to examine RewP as a predictor of treatment response across treatment options, including combined treatments (McGrath et al., 2013).

In terms of cognitive control, ERN did not change with treatment, though larger ERN at baseline significantly predicted a greater likelihood of response to the intervention. This finding is consistent with previous findings from Gorka et al. (2018) who observed an association between larger baseline ERN with greater reductions in fear-based anxiety symptoms among individuals with comorbid anxiety disorders receiving CBT, but not SSRI treatment. However, not all studies are in agreement. Hajcak et al. (2008) failed to find a relationship between baseline ERN and symptomatic outcomes in a sample of patients with OCD. Interestingly, in the present study, T1-to-T2 reductions in ERN (i.e., more positive ERN) were significantly associated with a reduction in depressive symptoms. Together, these findings suggest ERN may be more state-like in MDD, since it is modulated by exercise and reflects a potential treatment target, whereas the stability of RewP indicates that it may be more of a trait-like marker.

Although no previous studies have examined treatment-related changes in ERN in depression, a study by Kujawa et al. (2016) found no treatment effects on ERN in patients with social anxiety disorder (SAD) relative to patients with generalized anxiety disorder (GAD) and healthy controls. A larger sustained ERN was found in SAD patients before and after CBT or SSRI treatment compared to GAD and healthy controls, while Hajcak et al. (2008) found a larger ERN before and after CBT in patients with OCD. Additionally, Gorka et al. (2018) found an increased ERN among anxiety disorder patients after 12 weeks of SSRIs, but not 12 weeks of CBT. With evidence suggesting that ERN may be malleable to treatment, it is possible that exercise, along with other available treatment options for depression, may be used to target the ERN to reduce depressive symptoms. In order to better understand whether the ERN holds promise as an objective neural marker for a precision medicine approach for treatment, future research should incorporate multiple treatment options within the same study to better identify predictors of treatment response to available treatments.

The RewP and ERN have different neural generators. The RewP is believed to reflect broad activity across the reward circuitry (Carlson et al., 2011; Foti et al., 2011), which is commonly altered in depression, while the ERN has been source localized to the ACC, and is often referenced in relation to cognitive control (Brázdil et al., 2005; Miltner et al., 2003). Differences in neural generators may partially account for the divergent findings in RewP and ERN across the intervention. A previous study assessed cognitive control before and after an 8 week aerobic exercise intervention among individuals with MDD (Olson et al., 2017). A larger stimulus-locked N2 amplitude to the more challenging incongruent trials of the flanker task (i.e., greater cognitive control) was

found following 8 weeks of exercise, suggesting an influence on cognitive control using the same dose of exercise used in the present study. However, despite the beneficial effects of aerobic exercise on cognitive control, changes in N2 failed to mediate the antidepressant effects of exercise. Similar to ERN, the stimulus-locked N2 is associated with the detection of conflict and cognitive control during response inhibition (Folstein & Van Petten, 2008) and has been found to be reduced in individuals with MDD relative to nondepressed, age- and sex-matched healthy controls (Alderman et al., 2015). The present findings add to the literature and suggest that exercise may resolve cognitive control deficits through changes in the response-locked ERN. A number of previous randomized trials of aerobic exercise or physical activity have shown alterations in cognitive control (Davis et al., 2011; Drollette et al., 2018; Hillman et al., 2014; Olson et al., 2017). Future work is needed to clarify associations across levels of analysis and determine the mechanisms whereby exercise exerts its benefits on these aspects of brain and cognitive function.

Currently, there is no way to match individuals to a particular treatment. In an attempt to advance this goal, former NIMH director Thomas R. Insel argued that “we need precision medicine for mental disorders” (p. 152; Insel, 2015). In the present study, larger ERN and larger ΔRewP at baseline were associated with a greater likelihood of successful antidepressant response to an exercise intervention. Although the investigation of clinical and biological predictors of treatment outcome in depression has begun (Rethorst, South, Rush, Greer, & Trivedi, 2017; Suterwala et al., 2016), this is the first study to use ERP measures as predictors of treatment response to exercise among individuals with depression. Interestingly, there was no association between ERN and

ΔRewP amplitudes at baseline, suggesting heterogeneity and separable success in classifying treatment response among baseline ERP markers. In order to advance our understanding of treatment prediction, future research should specifically target individuals with specific subtypes of clinical depression to understand whether the effects of exercise are global or specific to certain MDD subtypes.

Limitations

These findings should be interpreted in the context of several limitations. The comparator including active, light-intensity stretching which may not be the most appropriate comparison condition. This issue has been a longstanding debate in the area of exercise and mental health because the psychobiological mechanisms that are activated by exercise may also be influenced by light activity such as stretching. The light-intensity stretching condition was chosen as a comparator for this study to control for potential demand characteristics, such as attention and expectancy effects, and has been used successfully in previous exercise trials (Knubben et al., 2007). Future research should compare the effects of exercise to more traditional forms of treatment for MDD, including pharmacological and CBT approaches (Blumenthal et al., 1999). The duration of the intervention was relatively short, which makes it possible that the intervention and/or exercise dose was not sufficient to modify reward processing and cognitive control processes. Although changes in ERN amplitude across both treatment interventions tracked changes in depressive symptoms, no condition-level changes were found for reward and cognitive control processes. Lastly, only pre and post 8-week assessments were conducted. Therefore, the extent to which reductions in depressive symptoms are maintained following this exercise program remains unknown. Future research should

incorporate a follow-up assessment to understand the lasting effects of exercise on depressive symptoms and whether individuals achieve or maintain remission following an 8-week intervention of exercise.

Conclusions

In summary, these findings highlight the ERN and RewP as neural predictors of depressive symptom change following a short, 8-week light and moderate-intensity exercise intervention and ERN as a potential target of treatment and mechanism of antidepressant treatment response to exercise. This study is the first study to examine these responses to an exercise intervention trial using ERPs. Future interventions incorporating ERPs as predictors of response and mechanistically based targets may help to advance precision medicine approaches to behavioral intervention trials incorporating exercise.

General Discussion

Summary

The aims in Chapter 1 were to determine relationships between depressive symptom severity and reward processing in individuals with MDD relative to age- and gender-matched nondepressed, healthy controls. We hypothesized that individuals with a current diagnosis of MDD would exhibit deficits in reward processing, as indexed by blunted ΔRewP (i.e., differences in neural responses to reward [RewP] and loss [FN] feedback) amplitude. Individual differences in depressive symptom severity were also examined and hypothesized to moderate neural responses to monetary reward and loss feedback during a simple gambling task (i.e., doors task), such that individuals with greater depression symptom severity were predicted to exhibit a reduced RewP across the task relative to participants with lower depressive symptoms. This finding would be particularly novel given that no previous study to date has examined reward processing across time using an advanced MLM statistical approach, which may suggest important mechanisms related to striatal activity in depression. The results showed reduced ΔRewP amplitude during a simple gambling task in individuals with MDD relative to nondepressed, healthy controls. This finding was being driven by a smaller RewP amplitude to rewards in individuals with MDD relative to healthy controls, while FN amplitude was similar among the two groups. Relative to the second hypothesis, greater depressive symptom severity was related to blunted ΔRewP amplitude and was found to moderate reward responding over the course of the task. That is, individuals with greater depressive symptom severity exhibited less sensitivity to rewards (i.e., reduced RewP

amplitude) over time, relative to individuals with lower depressive symptoms who were increasingly sensitive to rewards (i.e., potentiated or larger RewP amplitude) over time. Thus, the hypotheses were supported and indicated that the RewP may be a viable biomarker of MDD and may serve a potential treatment target of engagement for intervention.

The aims of Chapter 2 were to determine whether emotion-related ERP components (i.e., RewP and LPP components) are state-dependent and can be used to capture the "feel better" effects associated with an acute bout (or single session) of aerobic exercise. Although the beneficial effects of exercise on affective responses is well documented, most studies have relied on self-report measures of affect, which often are confounded by demand characteristics (e.g., introspective ability, response bias) and measurement error. In this study, the RewP and LPP ERPs were used as objective and well-validated neural indicators of emotional processing. Specifically, the primary purpose was to assess whether acute exercise could modify RewP and LPP, which reflect reward sensitivity and emotional engagement psychological processes, respectively. Additionally, a second question that remains in the larger field of clinical neuroscience is whether well-known and validated ERP measures are even modifiable by brief laboratory manipulations, such as aerobic exercise. If the RewP and LPP components are modifiable through acute aerobic exercise, this could provide initial support that RewP and LPP may serve as treatment targets of engagement that can be improved through behavioral intervention. In line with the evidence base of the affective benefits of exercise (Ekkekakis et al., 2013), we hypothesized that acute exercise would increase LPP amplitude to pleasant images, while decreasing LPP amplitude to unpleasant images. We

also hypothesized that exercise would increase RewP amplitude. Given previous research demonstrating blunted RewP and attenuated LPP components in depression (Brush et al., 2018; Hill et al., 2019; Proudfit, 2015), we also predicted that the effects of exercise on RewP and LPP would be moderated by depression symptom severity, such that larger effects would be observed among individuals with greater depressive symptom severity. The results indicated that acute exercise boosted LPP amplitude to pleasant stimuli with no effects on LPP amplitude to unpleasant stimuli. There was also no exercise effect on RewP, indicating that the effects of exercise were specific to LPP, which is an index of emotional engagement to salient environmental stimuli. Interestingly, there was also no moderating influence of depressive symptom severity on LPP or RewP following exercise, indicating that the effects are generalizable to individuals with variable depressive symptom profiles. Related to Chapter 1, these findings provide preliminary support for exercise as an intervention to improve affective functioning in clinical and nonclinical populations. Relative to Chapter 3, we expect that these acute changes in affective function may, over time, help to resolve neural deficits in reward processing in MDD.

Chapter 3 was designed to investigate the effects of an 8-week moderate-intensity aerobic exercise intervention on reward processing impairments in depression. Additionally, given that cognitive impairment is also a core symptom of depression, we also were interested in assessing the effects of the intervention on cognitive control processes, as indexed by the error-related negativity (ERN). Although the antidepressant effects of exercise are well established (Meyer & Schuch, 2018), there is still a large proportion of individuals who fail to experience a significant reduction in depressive

symptoms following an exercise intervention (e.g., 11% to 41% of depressive symptom reduction remissions rates; Dunn et al., 2005), which may be due to the heterogeneity and various symptom profiles of depression (Schuch & de Almeida Fleck, 2013). Therefore, we examined reward processing and cognitive impairments in response to an exercise intervention in order to determine whether these two common symptoms of depression could capture different depressive phenotypes that may selectively benefit -- or fail to benefit -- from an exercise intervention. We hypothesized that an 8-week moderate-intensity aerobic exercise intervention would modify RewP and ERN, such that pre-to-post change in RewP and ERN would correlate with change in depressive symptoms following the intervention. Additionally, we examined whether these objective neural markers at T1 could be used to identify individuals most likely to derive an antidepressant effect from a chronic exercise intervention. Given that no studies to date have used ERPs to predict an antidepressant response to exercise, we had no specific a priori hypotheses related to this aim. The results from Chapter 3 revealed no significant effects of exercise on the ΔRewP difference waveforms. In addition, there were no significant correlations between RewP, FN, or ΔRewP and changes in depressive symptoms from pre to post-treatment. There were also no mean-level changes in ERN across the intervention. Interestingly, there was a significant relationship between change in ERN and change in depressive symptoms, such that a larger treatment-related reduction in depressive symptoms was associated with a smaller ERN at post-treatment (T2). When examining RewP and ERN as objective neural markers of treatment response using binary logistic regression analyses, baseline (T1) ΔRewP and ERN were significant predictors of successful antidepressant response (i.e., define here) even after accounting

for gender and baseline depressive symptoms. Similar to other exercise trials for depression (Martinsen et al., 1989; Olson et al., 2017), these findings were observed without a change in cardiorespiratory fitness, which suggests that the antidepressant effects of exercise occur without a necessary change in aerobic fitness. The findings from this study are important towards establishing potential objective neural markers in depression that may be modulated by aerobic exercise. Future research should be conducted to explore and identify additional targets of engagement that are modifiable by chronic exercise programs. In sum, the findings from this dissertation indicate potential neural treatment targets of engagement in depression that may either be state- and trait-related, and that several ERP components are modifiable through behavioral intervention with exercise. Lastly, exercise-related reductions in depressive symptoms may be associated with change in cognitive control processes, as indexed by ERN. This possibility needs to be further explored and replicated in future work.

General Remarks

Each of the three chapters of this dissertation came to fruition based on various opportunities that were afforded to me over the course of my doctoral work. I am extremely thankful and grateful for the number of opportunities and collaborations I have established throughout my graduate career, and wanted to conclude this dissertation with a brief overview of how these three chapters came about.

In the beginning of graduate school, in the Fall 2014 semester, I was involved in one of my first studies that examined the effects of a combined meditation and aerobic exercise training program, which we referred to as MAP training, on cognitive control processes in MDD. We found that 8-weeks of MAP training improved cognitive control

processes, as indexed by a treatment-related increase in stimulus-locked N2 amplitudes to the flanker task. These findings were published in *Translational Psychiatry* in 2016 and then led us to question which specific aspect of MAP training (meditation and/or exercise) may have resulted in the changes in cognitive control we observed following the combined 8-week MAP training program. As a result, in January 2015, we designed an exercise intervention as a stand-alone intervention to begin to disentangle the effects of MAP training on cognitive control. This inspired what ultimately became Chapter 3 of my dissertation.

In terms of Chapter 1, I had the pleasure of being accepted to attend the 2016 ERP Boot Camp funded by the NIMH at University of California, Davis. This boot camp was led by Drs. Steve Luck and Emily Kappenman, who are widely considered some of the top experts on the ERP methodological approach. This experience further inspired me to pursue and conduct methodologically sound ERP research. It was at this bootcamp that the idea of Chapter 1 was conceptualized. During a conversation with Dr. Greg Hajcak, who is known for his work on RewP in depression, he mentioned that he was excited to see if some of the data I had recently collected replicate previous findings from his laboratory. He also recommended examining trial-level response patterns across the doors task to track what is occurring with the RewP over time. Specifically, he suggested that I apply multilevel modeling (MLM) to the data to see if any interesting relationships may emerge in terms of understanding how reward processing unfolds over time, and how trial-by-trial fluctuations in RewP may provide insight into the brain's reward system response over time. Although I did not know how to perform this statistical approach at the time, I wrote this down in my notebook as a follow-up study. After the

boot camp concluded, I returned to campus at Rutgers with the goal of learning how to conduct MLM analyses with ERP data. Fortunately, the following academic year Dr. Edward Selby from the Department of Psychology at Rutgers taught a class on MLM and structural equation modeling. This class was extremely timely and afforded me the opportunity to learn MLM and apply it to my ERP dataset. The meeting with Greg Hajcak, along with the opportunity to take Ed Selby's class, allowed me to complete Chapter 1 that was published in *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. Notably, this publication was among the first ERP studies in the literature to apply MLM to ERP data, and in this case, on RewP data in a clinical MDD sample. After I began my work on the RewP in depression, I was also curious about the potential for brief laboratory manipulations to "move" or influence the RewP. That is, I wondered if a single session of aerobic exercise could modify RewP amplitude. I was also interested in using ERPs to test the neurotransmitter hypothesis of exercise, which typically is only assessed using animal models. That is, there remains a chasm between human and animal research related to the acute or immediate responses following exercise. Most research in humans has focused on the subjective "feel better" effects of exercise, without documenting objective neurophysiological indicators of emotion. In animals that cannot provide subjective feeling states following exercise, most research studies have examined neurophysiological measures such as post-exercise changes in dopaminergic, serotonergic, and noradrenergic systems. Considering that the RewP and LPP have been previously associated with engagement of mesolimbic dopaminergic and locus-coeruleus norepinephrine systems, using these ERP components may provide for

an indirect test of the neurophysiological basis for the “feel better” effects of exercise. These ideas formed the basis of Chapter 2.

In sum, the way in which each of these studies came about was an exciting endeavor, and ultimately formed the basis of the scientific process for my dissertation. Chapter 1 originated from collaborations across experts in clinical neuroscience, kinesiology, and statisticians. Chapter 2 was developed based on reading and identifying gaps in the literature and understanding how to design a study that may advance what is known in the exercise and affective responses literature. Chapter 3 stemmed from an early program of research as a part of Brandon’s work, and has offered new insight into not only pursuing the age-old question of how exercise reduces depression, but also has established a foundation for understanding which individuals are most likely to experience a successful antidepressant response to exercise. This is an important area of inquiry that I hope to continue throughout my professional journey.

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