

## Original Article

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# A randomized trial of aerobic exercise for major depression: examining neural indicators of reward and cognitive control as predictors and treatment targets

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**Abstract**

**Background.** Aerobic exercise has demonstrated antidepressant efficacy among adults with major depression. There is a poor understanding of the neural mechanisms associated with these effects. Deficits in reward processing and cognitive control may be two candidate targets and predictors of treatment outcome to exercise in depression.

**Methods.** Sixty-six young adults aged 20.23 years (s.d. = 2.39) with major depression were randomized to 8 weeks of moderate-intensity aerobic exercise ( $n = 35$ ) or light stretching ( $n = 31$ ). Depressive symptoms were assessed across the intervention to track symptom reduction. Reward processing [reward positivity (RewP)] and cognitive control [error-related negativity (ERN)] were assessed before and after the intervention using event-related brain potentials.

**Results.** Compared to stretching, aerobic exercise resulted in greater symptom reduction ( $g_s = 0.66$ ). Aerobic exercise had no impact on the RewP ( $g_{av} = 0.08$ ) or ERN ( $g_{av} = 0.21$ ). In the aerobic exercise group, individuals with a larger pre-treatment RewP [odds ratio (OR) = 1.45] and increased baseline depressive symptom severity (OR = 1.18) were more likely to respond to an aerobic exercise program. Pre-treatment ERN did not predict response (OR = 0.74).

**Conclusions.** Aerobic exercise is effective in alleviating depressive symptoms in adults with major depression, particularly for those with increased depressive symptom severity and a larger RewP at baseline. Although aerobic exercise did not modify the RewP or ERN, there is preliminary support for the utility of the RewP in predicting who is most likely to respond to exercise as a treatment for depression.

**Introduction**

Major depression significantly contributes to the global burden of disease (World Health Organization, 2020). Despite available evidence-based treatments, many individuals fail to respond to treatment, with low remission (40–50%; Papakostas & Fava, 2010; Trivedi et al. 2006) and high recurrence (54% within 2 years; Vittengl, Clark, Dunn, & Jarrett, 2007). This poor success poses a challenge to clinical practice and may be a product of the heterogeneity of depression (Akil et al., 2018). Identifying treatment targets and predictors of treatment response may improve clinical outcomes (Cohen & DeRubeis, 2018).

Cardinal features of depression, most notably anhedonia, are thought to reflect alterations in reward processing (Keren et al., 2018; Pizzagalli, 2014). Deficits in the reward circuitry have been measured using the reward positivity (RewP), an event-related potential (ERP) indexing reward processing. The RewP is a positive-going component that arises 200–350 ms following positive relative to negative feedback (e.g. monetary rewards *v.* losses; Proudfit, 2015). Growing evidence indicates that the RewP is a reliable measure of individual differences in initial reward evaluation (Bress, Meyer, & Proudfit, 2015; Levinson, Speed, Infantolino, & Hajcak, 2017) and correlates positively with activation of the mesolimbic reward circuit (Becker, Nitsch, Miltner, & Straube, 2014; Carlson, Foti, Mujica-Parodi, Harmon-Jones, & Hajcak, 2011). Research supports a robust association between a blunted RewP and depression (Brush, Ehmann, Hajcak, Selby, & Alderman, 2018; Foti, Carlson, Sauder, & Proudfit, 2014; Klawohn, Burani, Bruchnak, Santopetro, & Hajcak, 2020a), indicating that the RewP is a promising biomarker that can be targeted by treatment.

Cognitive impairment is frequently observed in depression and is often a residual symptom following successful antidepressant treatment (Greer, Grannemann, Chansard, Karim, & Trivedi, 2015). For example, after 12 weeks of selective serotonin reuptake inhibitor (SSRI) treatment, ~70% of the 428 responders from the Sequenced Treatment Alternative to Relieve Depression study who achieved a meaningful reduction in depressive symptoms reported difficulties in concentration and decision making (McClintock *et al.*, 2011). Cognitive impairment is also associated with poor treatment response (Roiser, Elliott, & Sahakian, 2012) and is a risk factor for relapse (Porter, Bowie, Jordan, & Malhi, 2013). Among cognitive domains, cognitive control is most closely linked with treatment outcomes (Goodkind *et al.*, 2015). Cognitive control has been measured using the error-related negativity (ERN), a negative-going ERP component that arises within 100 ms following errors during speeded response tasks (Meyer & Hajcak, 2019; Meyer, Riesel, & Proudfit, 2013). Source localization (e.g. van Veen & Carter, 2002), magnetoencephalography (e.g. Miltner *et al.*, 2003), and intracerebral recording (e.g. Brázdil, Roman, Daniel, & Rektor, 2005) studies indicate that the ERN reflects early error processing activity involving the anterior cingulate cortex (ACC).

The relationship between ERN and depression is mixed. Relative to healthy controls, individuals with depression have shown a larger (Chiu & Deldin, 2007; Holmes & Pizzagalli, 2010; Tang *et al.*, 2013) or smaller (Ladouceur *et al.*, 2012; Schoenberg, 2014; Schrijvers *et al.*, 2008) ERN, while other studies have shown no differences (Klawohn, Santopetro, Meyer, & Hajcak, 2020b; Ruchow *et al.*, 2004). Weinberg, Dieterich, and Riesel (2015) contend that these discrepancies may be explained by task differences (e.g. flankers, go/no-go, or Stroop tasks), sample compositions, or diagnostic heterogeneity across studies. Despite these inconsistencies, the ERN is a well-established and reliable index of ACC activity (Baldwin, Larson, & Clayson, 2015; Riesel, Weinberg, Endrass, Meyer, & Hajcak, 2013) underlying cognitive control – and may be an important predictor of treatment response in depression (Pizzagalli, 2011).

Aerobic exercise has demonstrated efficacy in alleviating depression (e.g. Ekkekakis, 2015; Schuch *et al.*, 2015), with similar effects as pharmacologic and psychological interventions (Babyak *et al.*, 2000; Blumenthal *et al.*, 1999); however, the neural mechanisms underlying the antidepressant effects of exercise are poorly understood. Reward processing and cognitive control represent promising treatment targets for exercise interventions. Exercise has been shown to modulate activity of the reward circuitry (e.g. via upregulation of D2 receptors within the striatum; MacRae, Spirduso, Walters, Farrar, & Wilcox, 1987), while tolerability and hedonic response to exercise has also been linked with the reward system (Flack, Pankey, Uffholz, Johnson, & Roemmich, 2019). Moreover, Toups *et al.* (2017) found that 12 weeks of aerobic exercise reduced self-reported anhedonia among depressed patients as a part of the Treatment with Exercise Augmentation for Depression trial. Other evidence supports the cognitive benefits of exercise (Alderman, Olson, & Brush, 2019; Stillman, Esteban-Cornejo, Brown, Bender, & Erickson, 2020). Greer *et al.* (2015) found that 12 weeks of aerobic exercise improved cognitive control performance among depressed patients with residual cognitive complaints following a round of SSRI treatment (Trivedi *et al.*, 2006). The present study aims to extend these findings by determining whether the RewP and ERN are associated with the antidepressant effects of exercise.

Exercise is not universally effective. Previous studies have shown variable response to exercise among patients with depression (Dimeo, Bauer, Varahram, Proest, & Halter, 2001; Dunn, Trivedi, Kampert, Clark, & Chambliss, 2005; Knubben *et al.*, 2007; Schuch *et al.*, 2015). Emerging research has aimed to identify subgroups of individuals who benefit most from exercise as a treatment for depression (Rethorst *et al.*, 2013; Rethorst, South, Rush, Greer, & Trivedi, 2017; Schuch, Dunn, Kanitz, Delevatti, & Fleck, 2016a; Suterwala *et al.*, 2016; Toups *et al.*, 2017; Trivedi *et al.*, 2016). This study is an important first step towards examining changes in reward processing and cognitive control as neural mechanisms of the antidepressant effects of exercise and identifying individuals most likely to benefit. Given promising evidence indicating that neural measures may be used as predictors of treatment response (Hajcak, Klawohn, & Meyer, 2019), the present study examined whether pre-treatment reward processing and cognitive control predicted successful treatment response, which may inform personalized treatment for depression.

The first aim was to replicate previous findings of the antidepressant effects of exercise (Schuch *et al.*, 2016b). We predicted a medium-to-large reduction in depressive symptoms following the exercise intervention (Olson, Brush, Ehmann, & Alderman, 2017). A secondary aim was to examine whether RewP or ERN changed from pre-to-post intervention. We hypothesized that the RewP and ERN would increase from pre-to-post intervention and that the magnitude of change would correlate with depressive symptom reduction. No research has explored whether pre-treatment RewP or ERN can be used to identify individuals most likely to benefit from an exercise intervention; therefore, we examined whether pre-treatment RewP or ERN moderated changes in depressive symptoms across time and whether RewP or ERN predicted treatment response (Hajcak *et al.*, 2019).

## Method

### Participants

Individuals ( $N=81$ ) were recruited from Rutgers University. Eligible participants were adults with a current depression diagnosis who reported no regular exercise (i.e. energy expenditure <35 kcal/kg/day or exercise performed <3 days/week for <20 min/session over the previous month), no contraindications to exercise, and no vision impairments. Individuals of all depressive symptom severity were included. Exclusion criteria consisted of current or history of psychotic, bipolar, or substance use disorders, suicidal ideation, any head injury resulting in a loss of consciousness, and any current treatment beyond stable ( $\geq 6$  weeks) SSRI treatment. Participants provided informed consent and the study protocol was in accordance with ethical guidelines of the Helsinki Declaration and approved by the university's Institutional Review Board. Study enrollment included 66 individuals who could earn up to \$80 (\$40 per assessment) plus \$25 for completion of pre- and post-assessments of the doors task (\$12.50 per assessment). Pre- and post-assessments were separated by 10.32 weeks [95% confidence interval (CI) 10.00–10.64]. Pre-assessments were completed 7.58 days (95% CI 6.25–8.90) before the first intervention session and post-assessments were completed 6.88 days (95% CI 5.89–7.88) after the last intervention session (see online Supplementary Figs. S1 and S2 for a study timeline and CONSORT diagram, respectively).

## Interventions

Participants completed three sessions of moderate-intensity aerobic exercise or light stretching per week across eight weeks.<sup>†</sup> Research staff supervised all sessions and monitored compliance of exercise intensity during each session at 10 min intervals. Heart rate (HR) and ratings of perceived exertion (RPE) using Borg's (1998) scale were recorded to measure compliance with the exercise prescription. Across the intervention, there was a higher HR and RPE for the exercise condition (HR = 147.24 bpm; RPE = 13.30) compared to the light stretching condition (HR = 88.19 bpm; RPE = 7.80).

### Moderate-intensity aerobic exercise

Participants performed 45 min of steady-state exercise on a treadmill or cycle ergometer at an intensity corresponding to 40–65% to their HR reserve which was determined from the baseline cardiorespiratory fitness assessment.

### Light-intensity stretching

The comparator consisted of 30–45 min of stretching major muscle groups. These exercises were performed while sitting and standing. Each stretch was held for 20 s in sets of 3 with a 40 s rest period between each stretch. This comparator was used to minimize potential demand characteristics and has been implemented in a previous exercise trial for depression (Olson et al., 2017).

## Randomization and allocation

Eligible participants were randomized to treatment groups using 1:1 allocation following the baseline assessment. A computer-generated list of random assignments was used for stratified, block randomization. Stratification was based on baseline depressive symptom severity and block randomization used block sizes of 4 and 6 (see Olson et al., 2017 for the same approach).

## Sample size determination

An a priori power analysis was conducted to determine the sample size required to detect a significant Treatment Group  $\times$  Time interaction at 95% power with a two-tailed  $\alpha = 0.05$  and  $r = 0.50$  for repeated measures. In total, 26 participants were required to detect differences exceeding  $f = 0.38$ , which was based on an effect size of  $\eta_p^2 = 0.13$  from Olson et al. (2017). No previous studies have examined the effects of exercise on RewP and ERN; thus, we assumed the same sample size calculation for detecting significant Treatment Group  $\times$  Time interactions for RewP and ERN.

## Measures

### General health history

A general health history questionnaire was used to assess family medical history, cardiovascular health and risk factors, current and past medical diagnoses, past surgeries, tobacco/alcohol use, and prior and current medication use, including psychotropics and beta-blockers. The Physical Activity Readiness Questionnaire (Thomas, Reading, & Shephard, 1992) was administered to ensure safe exercise participation and physical activity behavior was

measured using the International Physical Activity Questionnaire (IPAQ; Craig et al., 2003).

### Mini-International neuropsychiatric interview (MINI)

The MINI (Sheehan et al., 1998) is a short, structured diagnostic interview designed to make diagnoses of psychiatric disorders according to criteria consistent with the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5; American Psychiatric Association, 2013) and International Classification of Diseases-10 (ICD-10; World Health Organization, 2004). All modules were administered at baseline by interviewers who were trained under the supervision of experienced clinical staff and had previous experience in conducting structured clinical interviews with psychiatric patients (see Alderman et al., 2015; Brush et al., 2019; Olson et al., 2017).

### Clinical symptoms

Twenty-one item versions of the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) and Beck Anxiety Inventory (BAI; Steer & Beck, 1997) were used to assess the presence of depressive and anxiety symptoms over the past 2 weeks, respectively. The BDI-II was administered at five assessment points (pre-intervention; weeks 2, 4, and 6 of the intervention; and post-intervention) using an online survey platform (Qualtrics, Provo, UT, USA). The BAI was assessed pre- and post-intervention.

### Cardiorespiratory fitness ( $VO_2$ peak)

A modified Bruce protocol, which involved increasing the speed and grade of the treadmill every 2 min, was used to determine  $VO_2$  peak (ml/kg/min) before and after the intervention.  $VO_2$  peak was determined from direct expired gas exchange data from a computerized metabolic system (ParvoMedics, Inc., Sandy, UT, USA) and averaged across 15 s intervals. Testing procedures and criteria to establish  $VO_2$  peak were based on established exercise testing guidelines (American College of Sports Medicine, 2018).

### EEG tasks

Participants were given 10 practice trials on both tasks and were required to achieve 80% accuracy on the flankers task before commencing the experiment. Tasks were presented using E-Prime Professional version 2.0 (Psychology Software Tools, Inc. Pittsburgh, PA, USA) and a Logitech® F310 gamepad (Logitech G, Newark, CA, USA) was used for responses. The 17 in. computer monitor was positioned 71 cm from participants centered to the nasion. Tasks were administered at pre- and post-intervention assessments.

### Doors task

There were five blocks of 20 trials. First, a fixation cross was presented at the center of the screen for 1000 ms followed by the presentation of two side-by-side doors which remained on the screen until the participant executed a left or right button press. Following door presentation, another fixation cross was presented at the center of the screen for 2000 ms before the feedback stimulus was presented at the center of the screen for 2000 ms. Feedback indicated whether the participant won (green up arrow) or lost (red down arrow). After feedback presentation, a fixation cross was displayed for 1500 ms, which was followed by a short break prior to the next trial. Participants were told they

<sup>†</sup>The notes appear after the main text.

could either win \$0.50 or lose \$0.25 on each trial. Fifty gain and 50 loss trials were presented pseudo-randomly throughout the task.

### Flankers task

Participants were presented with five arrows aligned horizontally on the center of the screen and were instructed to execute a left or right button press corresponding to the direction of the central arrow. There were congruent and incongruent trials, with the central target arrow pointing in the same direction as the flanking arrows for congruent trials, and pointing in the opposite direction of flanking arrows for incongruent trials. Each trial began with a white fixation cross presented for 500 ms on a black computer screen and was followed by white arrows centered focally for 100 ms. After stimulus offset, participants were given a 1500 ms response window, which was followed by an intertrial interval of 900–1300 ms. There were two blocks of 120 equiprobable congruent and incongruent trials with a 2 min rest between blocks. Participants were instructed to respond as quickly and as accurately as possible.

### EEG data acquisition and reduction

These procedures are described in the Supplementary materials and were conducted by a blinded assessor.

### ERP measurement

Using a collapsed localizers approach (Luck & Gaspelin, 2017), mean electrical activity was averaged across a frontocentral region-of-interest including Fz, FC1, FCz, FC2, and Cz electrode sites for the ERP analyses. At both pre- and post-intervention assessments, the mean RewP peak latency occurred at 240 ms, which was first identified within an a priori time window of 200–300 ms (Brush et al., 2018). The RewP was scored as the average activity in the 50 ms window surrounding the peak during a 215–265 ms time window following feedback presentation. The ERN was scored as the average activity in a time window of 0–100 ms locked to responses (Klawohn et al., 2020b). Due to the commission of less than six errors at baseline (Meyer et al., 2013), 11 participants ( $n=4$  exercise;  $n=7$  stretching) were excluded from the ERN analyses. RewP was computed as the ERP to gains minus ERP to losses. ERN was computed as the ERP to errors minus ERP to correct trials. RewP and ERN difference scores were used for all ERP analyses.

### Data analyses

Analyses were performed by a blinded assessor using SPSS version 26 (IBM Corp., Armonk, NY, USA) and R version 3.6.3 (R Core Team, 2020) with a two-tailed  $\alpha=0.05$ . Baseline analyses were conducted using chi-square tests, correlations, and independent-samples  $t$  tests. Intervention effects were analyzed using Treatment Group  $\times$  Time mixed analyses of variance (ANOVAs).

A Treatment Group  $\times$  Time multilevel model (MLM) was used to track within-subject change in depressive symptom severity. MLMs included a random intercept for each participant, fixed effects of treatment group (0 = stretching, 1 = exercise; level 2) and time (centered; level 1), and an unstructured covariance matrix. Follow-up simple slopes and effects analyses were conducted. RewP and ERN were entered as level 2 predictors in

separate MLMs to determine if they moderated within-subject change in depressive symptom severity.

Treatment response was a dichotomous outcome using the same criteria as previous treatment-related research (see Burkhouse et al., 2016; McClintock et al., 2011). A logistic regression analysis was used to predict responder status (0 = non-responder, 1 = responder;  $\geq 50\%$  reduction in depressive symptoms) with baseline depressive symptoms, baseline ERP measures, treatment group (0 = stretching, 1 = exercise), and VO<sub>2</sub> peak as independent variables. Separate logistic regressions were conducted among exercise and stretching groups only.

Intention-to-treat analyses were conducted for all outcomes. To handle missing data due to non-compliance, the last observation carried forward method was used to derive post-intervention measures; restricted maximum likelihood estimation was used for MLMs.

## Results

There were no significant baseline differences by treatment group in any measure (Table 1). There were no significant gender differences among baseline measures, except for VO<sub>2</sub> peak,  $t(22.44) = 3.89$ ,  $p = 0.001$ , with higher cardiorespiratory fitness among males ( $M = 46.42$  ml/kg/min,  $s.d. = 10.46$ ) *v.* females ( $M = 35.65$  ml/kg/min,  $s.d. = 7.77$ ). Depressive symptom severity was related to increased anxiety symptoms,  $r(61) = 0.313$ ,  $p = 0.012$ ; and smaller ERN,  $r(53) = 0.336$ ,  $p = 0.012$ . All other relationships were non-significant,  $ps > 0.063$ . Current comorbidities (~27% of the sample) and psychotropic medication use (~15% of the sample) are reported in Table 1. After accounting for current comorbidity and psychotropic medication use, the outcomes did not change; therefore, analyses are reported excluding these variables.

### Intervention effects

Online Supplementary Table S1 displays means, 95% CIs, and effect size estimates of pre-to-post intervention effects.

### Reward processing and cognitive control

All main effects and Treatment Group  $\times$  Time interactions were non-significant,  $ps > 0.051$  (see Fig. 1 for the ERP difference waveforms by treatment group, online Supplementary Figs. S3 and S4 for ERP parent waveforms; and online Supplementary Tables S2 and S3 for number of trials contributing to each ERP and internal consistency measures of self-reports and ERPs).

### Cardiorespiratory fitness and physical activity

For cardiorespiratory fitness, there was a significant time main effect,  $F_{1,64} = 7.23$ ,  $p = 0.009$ ,  $\eta_p^2 = 0.10$ , with a pre-to-post increase in VO<sub>2</sub> peak. Other main effects and interactions were non-significant,  $ps > 0.170$ .

### Depressive symptoms

There was a significant time main effect for depressive symptoms, which was superseded by a significant Treatment Group  $\times$  Time interaction (online Supplementary Table S4). There was a larger symptom reduction for exercise ( $b = -2.89$ ,  $p < 0.001$ , 95% CI  $-3.49$  to  $-2.28$ ) compared to stretching ( $b = -1.65$ ,  $p < 0.001$ , 95% CI  $-2.29$  to  $-1.02$ ; Fig. 2). Treatment group differences were only significant at the post-intervention assessment,  $p = .021$ ,  $g_s = 0.56$ ; all other  $ps > .080$ .

**Table 1.** Baseline sample characteristics by treatment group for reward positivity (RewP) and error-related negativity (ERN) analyses

	RewP analyses ( <i>n</i> = 66)							ERN analyses <sup>a</sup> ( <i>n</i> = 55)							
	Exercise ( <i>n</i> = 35)			Stretching ( <i>n</i> = 31)				<i>p</i>	Exercise ( <i>n</i> = 31)			Stretching ( <i>n</i> = 24)			
	<i>N</i>	<i>M</i>	s.d.	<i>N</i>	<i>M</i>	s.d.	<i>N</i>		<i>M</i>	s.d.	<i>N</i>	<i>M</i>	s.d.	<i>p</i>	
Sex							0.263							0.188	
Male	11			6				10			4				
Female	24			25				21			20				
Racial group							0.461							0.357	
White	10			8				9			8				
Asian	10			15				8			11				
Black/African American	3			1				3			1				
Other	12			7				11			4				
Age (years)		20.26	2.84		20.19	1.78	0.915		19.74	1.26		20.17	1.81	0.310	
BMI (kg/m <sup>2</sup> )		23.87	4.23		23.64	4.58	0.838		23.70	4.16		23.88	5.13	0.892	
VO <sub>2</sub> peak (ml/kg/min)		38.06	9.90		38.84	9.61	0.749		38.80	10.27		38.52	9.82	0.918	
IPAQ (MET*min/wk)		508.71	490.77		472.07	407.27	0.746		543.50	503.89		453.02	417.69	0.483	
BDI-II Score		22.06	8.03		20.35	7.04	0.366		21.81	7.93		20.83	7.59	0.647	
BAI Score <sup>b</sup>		13.73	9.90		12.47	8.08	0.584		13.66	9.69		12.70	8.85	0.714	
Current Comorbidity <sup>c</sup>	12			6			0.174	11			4			0.120	
Currently Medicated <sup>d</sup>	4			6			0.370	4			6			0.249	

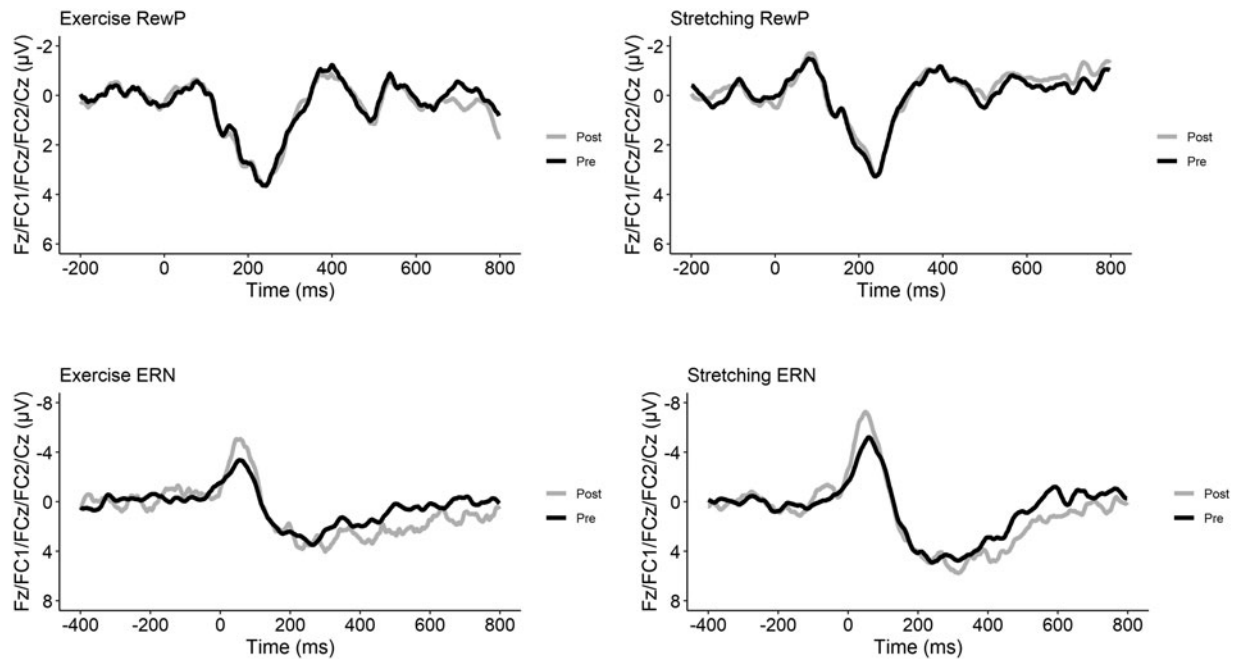
BMI, body mass index; kg, kilogram; m, meter; VO<sub>2</sub> peak, peak oxygen consumption; IPAQ, International Physical Activity Questionnaire; BDI-II, Beck Depression Inventory, Second Edition; BAI, Beck Anxiety Inventory; ml, milliliter; min, minute; MET, metabolic equivalents; wk, week; GAD, generalized anxiety disorder; SAD, social anxiety disorder; PTSD, post-traumatic stress disorder; OCD, obsessive-compulsive disorder.

<sup>a</sup>ERN analyses excluded 11 individuals due to the commission of less than six errors and noisy data.

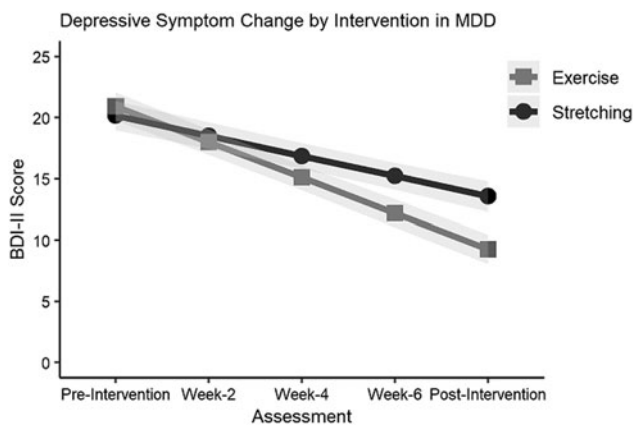
<sup>b</sup>BAI data were missing from three individuals for the RewP and ERN analyses (exercise: *n* = 2; stretching: *n* = 1).

<sup>c</sup>RewP analyses: [exercise: GAD (*n* = 8), panic disorder (*n* = 4), SAD (*n* = 2), PTSD (*n* = 2); stretching: GAD (*n* = 5), panic disorder (*n* = 2), OCD (*n* = 1), PTSD (*n* = 1)]; ERN analyses: [exercise: GAD (*n* = 7), panic disorder (*n* = 4), SAD (*n* = 2), PTSD (*n* = 1); stretching: GAD (*n* = 2), panic disorder (*n* = 2), OCD (*n* = 1), PTSD (*n* = 1)].

<sup>d</sup>Exercise: escitalopram (*n* = 3), sertraline (*n* = 1); stretching: escitalopram (*n* = 3), sertraline (*n* = 2), fluoxetine (*n* = 1).



**Fig. 1.** Grand-averaged RewP (top) and ERN (bottom) difference waveforms averaged across a frontocentral region-of-interest (Fz, FC1, FCz, FC2, Cz) by treatment (exercise, left; stretching, right) before and after the intervention. *Note:* RewP is scored as the ERP to gains minus ERP to losses; ERN is scored as the ERP to errors minus ERP to correct trials.



**Fig. 2.** Change in depressive symptoms in young adults with major depression across the intervention for the exercise (gray) and stretching (black) conditions. *Note:* simple slopes and intercepts are obtained from the Treatment Group  $\times$  Time multilevel model. Shaded areas reflect one standard error from the model predictions.

### Correlates and moderators of depressive symptom reduction

Relationships between change in RewP and change in ERN with change in depressive symptoms were non-significant,  $p_s > 0.360$ . RewP and ERN failed to moderate within-subject depressive symptom reduction in separate MLMs,  $p_s > 0.199$ .

### Predictors of treatment response

Treatment group, baseline RewP, and baseline depressive symptoms were significant predictors of treatment response; baseline ERN and  $VO_2$  peak measures failed to predict treatment response. Notably, individuals with an increased RewP at baseline were more likely to respond to treatment (Table 2; Fig. 3).

Sub-group analyses were conducted by treatment group. For exercise, baseline depressive symptoms and baseline RewP were both significant predictors of treatment response; all predictors were non-significant for stretching (Table 2). Online Supplementary Tables S5 and S6 display sensitivity, specificity, positive and negative predictive values, and classification accuracies of baseline RewP predicting treatment response.

There were 41 non-responders ( $n = 25$  stretching;  $n = 16$  exercise) and 25 responders ( $n = 6$  stretching;  $n = 19$  exercise). Within the exercise group, the highest classification accuracy achieved for baseline RewP predicting treatment response was 69% at the +0.5 s.d. threshold, when RewP =  $5.06 \mu V$  (online Supplementary Table S6).

### Attrition rate and drop-out analyses

The attrition rate was 22.73%, with 15 individuals ( $n = 9$  exercise;  $n = 6$  stretching) dropping out of the intervention following allocation. There were no significant differences between drop-outs and those who completed the intervention for any of the outcomes,  $p_s > 0.179$ . Relationships between number of sessions attended and all outcome variables were non-significant,  $p_s > 0.150$ .

### Discussion

The present study examined the effects of an 8-week aerobic exercise intervention on reward processing, cognitive control, and depressive symptoms in individuals with major depression. RewP and ERN were examined as potential biomarkers of exercise-related treatment response in depression. Depressive symptom reductions were observed following both exercise and stretching, with greater symptom reduction following 8 weeks of aerobic exercise. Neither exercise nor stretching impacted the

**Table 2.** Logistic regression analyses predicting treatment responder status (responder, non-responder) from baseline measures

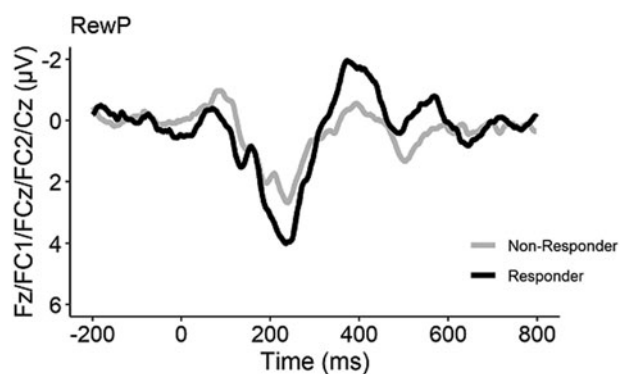
Parameter	Prediction of treatment responder status (responder, non-responder)						
	Model fit indices			Model estimates			
	$R^2$	$X^2$	$p$	Coeff	$p$	OR	95% CI
Model 1: whole sample <sup>a</sup>	0.42	20.70	0.001				
(Intercept)				-2.74	0.184	0.07	
BDI-II score				0.11	0.028	1.12	(1.01-1.24)
Treatment group				1.87	0.014	6.47	(1.47-28.60)
VO <sub>2</sub> peak				-0.06	0.108	0.94	(0.87-1.01)
RewP				0.23	0.028	1.26	(1.03-1.55)
ERN				-0.09	0.399	0.92	(0.75-1.12)
Model 2: exercise <sup>b</sup>	0.44	12.31	0.015				
(Intercept)				-3.21	0.220	0.04	
BDI-II score				0.17	0.024	1.18	(1.02-1.36)
VO <sub>2</sub> peak				-0.06	0.220	0.95	(0.87-1.03)
RewP				0.37	0.037	1.45	(1.02-2.05)
ERN				-0.30	0.092	0.74	(0.52-1.05)
Model 3: stretching <sup>c</sup>	0.33	5.69	0.223				
(Intercept)				1.01	0.782	2.75	
BDI-II score				0.08	0.400	1.08	(0.90-1.30)
VO <sub>2</sub> peak				-0.14	0.181	0.87	(0.72-1.07)
RewP				0.29	0.145	1.34	(0.90-1.98)
ERN				0.06	0.677	1.07	(0.79-1.44)

Treatment responder status was coded as a dichotomous variable (0 = non-responder; 1 = responder). The  $R^2$  value reported is the Nagelkerke  $R^2$  statistic. Coeff = regression coefficient; BDI-II = Beck Depression Inventory, second edition; treatment group is coded as 0 = stretching and 1 = exercise; VO<sub>2</sub> peak = peak oxygen consumption; RewP = reward positivity; ERN = error-related negativity.

<sup>a</sup> $N$  = 55. The sample size for Model 1 is reduced to 55 to account for the 11 individuals without usable ERN data.

<sup>b</sup> $N$  = 31. The sample size for Model 2 is reduced to 31 to account for the four individuals without usable ERN data in the exercise group.

<sup>c</sup> $N$  = 24. The sample size for Model 3 is reduced to 24 to account for the seven individuals without usable ERN data in the exercise group.



**Fig. 3.** Grand-averaged RewP difference waveform at baseline averaged across a frontocentral region-of-interest (Fz, FC1, FCz, FC2, Cz) in treatment responders and non-responders. Note: RewP is scored as the ERP to gains minus ERP to losses.

RewP or ERN. Increased baseline depressive symptom severity and a larger baseline RewP predicted successful treatment response to exercise. These findings suggest that 8 weeks of aerobic exercise reduces depressive symptoms in adults with

depression, particularly among those with increased depressive symptoms and a larger RewP at baseline. These findings are important for identifying those most likely to benefit from exercise-related interventions.

Notably, the exercise group experienced a ~55% depressive symptom reduction *v.* a ~31% reduction for the stretching group. Although the antidepressant effects of exercise became larger over time, differences in symptom reduction between groups were significant only at post-intervention, suggesting that 8 weeks of aerobic exercise may be the minimal dose required to elicit clinical antidepressant effects that exceed an active comparator. These findings are consistent with systematic reviews indicating that aerobic exercise has comparable antidepressant effects as traditional, first-line treatments for depression (Cooney et al., 2013). Reduced depressive symptoms following stretching echo early findings by Martinsen, Hoffart, and Solberg (1989) who observed similar symptom reduction among 99 patients with major depression following 8 weeks of aerobic exercise or a comparator consisting of muscular strength, flexibility, and relaxation exercises. Future research should incorporate multiple assessments of depressive symptoms to document individual-level change in response to exercise treatments.

Research shows that aerobic exercise interventions can increase cardiorespiratory fitness ( $g = 0.41$ ) among individuals with major depression (Stubbs, Rosenbaum, Vancampfort, Ward, & Schuch, 2016). Martinsen et al. (1989) found that the antidepressant effects of exercise were associated with increased cardiorespiratory fitness, suggesting that changes in cardiorespiratory fitness are required to derive an antidepressant response to exercise. In this study, there were small increases in cardiorespiratory fitness for the exercise ( $g = 0.17$ ) and stretching ( $g = 0.05$ ) groups across the intervention. These effects were not associated with symptom improvement, indicating that the antidepressant effects of exercise may be independent of changes in cardiorespiratory fitness. Future work should examine whether larger increases in cardiorespiratory fitness can be achieved with a longer, more vigorous exercise program and consider other mechanisms whereby exercise elicits antidepressant effects.

Numerous studies have shown a blunted RewP in depression (Brush et al., 2018; Foti et al., 2014; Klawohn et al., 2020a). There was no impact of exercise on the RewP, which is consistent with previous research examining other treatments for depression (cognitive behavioral therapy [CBT] or SSRIs); however, Barch et al. (2019) examined the effects of an 18-week parent-child interaction therapy program focusing on developing emotion strategies (PCIT-ED) among young children with depression and found that PCIT-ED increased the RewP, which suggests a treatment-induced malleability of the RewP. It is possible that the RewP may be modified in early childhood when reward-related networks are developing (Burani et al., 2019) but not during later developmental stages or in adulthood. Longer-term interventions may also be required for functional changes in reward-related neural activity. An 8-week aerobic exercise program may be too short in duration to modify the RewP. An understanding of treatment dosing and duration remains elusive and should be investigated further.

We found that a reduced ERN at baseline was associated with greater depression symptom severity, which contributes to the extant literature on the ERN in depression. Exercise did not impact the ERN nor did the ERN predict treatment response, which is consistent with findings from Hajcak, Franklin, Foa, and Simons (2008) and Kujawa et al. (2016) who observed no treatment-related changes in ERN among patients with other psychopathology (i.e. obsessive-compulsive disorder and social anxiety disorder). Despite previously-reported cognitive benefits of aerobic exercise (Greer et al., 2015), it is possible that the ERN does not track changes observed in the stimulus-locked ERP (N2; Olson et al., 2017) or neuropsychological (Greer et al., 2015) outcomes following exercise. Future work should continue to identify neural mechanisms related to exercise and determine whether specific features of depression are modifiable by exercise interventions.

A larger baseline RewP emerged as a relatively specific predictor of successful treatment response to exercise, rather than stretching. This finding suggests that intact reward processing may identify individuals most likely to benefit from treatment with aerobic exercise. In previous work, a blunted RewP predicted greater potential for improvement following SSRI (Burkhouse et al., 2018) and CBT (Burkhouse et al., 2016; Kujawa et al., 2019). Therefore, individual differences in reward processing are clinically useful insofar as treatment selection can be informed by pre-treatment RewP. CBT and/or SSRI treatment might be best for patients with reduced reward processing whereas those

with intact reward processing might benefit from exercise or other alternative treatments.

### Limitations

There are several limitations worth noting. The active comparator was light-intensity stretching which may not be the most appropriate comparison. There has been a longstanding debate in the field of exercise and mental health about what is the most appropriate comparator because the psychobiological mechanisms activated by exercise may also be influenced by light activities such as stretching. The light-intensity stretching condition was chosen to control for potential demand characteristics (e.g. attention and expectancy effects) and has been successfully used in previous exercise trials (Knubben et al., 2007; Olson et al., 2017). Future research should compare the effects of exercise to traditional treatments (e.g. SSRI and/or CBT; Blumenthal et al., 1999). The duration of the present intervention was relatively short. The intervention and/or exercise dose may not have been sufficient to modify reward and cognitive control processes. Although 8 weeks of exercise has previously modified cognitive control processes in depression (Alderman, Olson, Brush, & Shors, 2016; Olson et al., 2017), other programs have utilized 18 weeks of treatment (i.e. PCIT-ED; Barch et al., 2019) to elicit changes in reward processing. Optimal intervention length and dosing should be investigated in future research. There were no follow-up assessments; thus, the extent to which reductions in depressive symptoms are maintained remains unknown. Future work should incorporate follow-up assessments to understand the lasting effects of exercise on depressive symptoms and whether individuals achieve or maintain remission following an exercise intervention. It may also be of interest to examine whether self-report measures related to specific features of depression (e.g. anhedonia, cognitive impairment) change in response to exercise and whether there is correspondence between changes in neural and self-report measures in response to exercise.

### Conclusions

The current findings indicate that a larger RewP predicts response to aerobic exercise in adults with major depression. To be clinically useful, neural measures must demonstrate *incremental predictive validity* beyond much more inexpensive and easy-to-administer clinical and demographic measures previously found to predict treatment response. In the present study, a larger baseline RewP independently predicted treatment response along with increased baseline depressive symptom severity. Although the investigation of clinical and biological predictors of treatment response to exercise in depression is nascent (e.g. Rethorst et al., 2017; Suterwala et al., 2016), the RewP may be a clinically useful tool to predict whether a patient will benefit from exercise treatment. Future treatment research should incorporate ERPs as neural predictors of response and mechanistically-based targets to inform treatment selection approaches for depression.

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## Notes

I Given the sample (i.e. university students) and time constraints of an academic semester, the intervention was restricted to 8 weeks, allowing for recruitment and completion of study procedures. Eight weeks of aerobic exercise as a stand-alone treatment (Olson et al., 2017) or combined with meditation (Alderman et al., 2016) has previously reduced depressive symptoms and modified the N2 component in individuals with and without major depression. Other studies (e.g. Martinsen et al., 1989) have also established the efficacy of an 8-week aerobic exercise program for alleviating depression.

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