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Exercise decreases defensive responses to unpredictable, but not predictable, threat

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Abstract

Background: Research supports the anxiolytic effect of exercise, but the mechanism underlying this effect is unclear. This study examines the influence of exercise in healthy controls on two distinct defensive states implicated in anxiety disorders: fear, a phasic response to a predictable threat, and anxiety, a sustained response to an unpredictable threat.

Methods: Thirty-four healthy volunteers (17 male, age $M = 26.18$, $SD = 5.6$) participated in sessions of exercise (biking at 60–70% of heart rate reserve) and control (biking at 10–20% of heart rate reserve) activity for 30 min, separated by 1 week. Threat responses were measured by eyeblink startle and assessed with the “Neutral-Predictable-Unpredictable threat test,” which includes a neutral (N) and two threat conditions, one with predictable (P) and one with unpredictable (U) shock.

Results: Results show that exercise versus control activity reduces startle potentiation during unpredictable threat ($P = .031$), but has no effect on startle potentiation during predictable threat ($P = .609$).

Conclusions: These results suggest that exercise reduces defensive response to unpredictable, but not predictable, threat, a dissociation that may help inform clinical indications for this behavioral intervention, as well as provide clues to its underlying neurobehavioral mechanisms.

Keywords

anxiety/anxiety disorders; electrophysiology; exercise; PTSD/posttraumatic stress disorder; startle; treatment

1 | INTRODUCTION

Health care providers have proposed exercise as a first-line treatment for anxiety disorders, largely due to its efficacy, accessibility, and adverse event profile (Stein & Craske, 2017). However, despite evidence supporting the anxiolytic effects of exercise (for meta-analyses: Ensari, Greenlee, Motl, & Petruzzello, 2015; Stonerock, Hoffman, Smith, & Blumenthal, 2015; Stubbs et al., 2017), its mechanism of action remains elusive. Past studies have primarily focused on the effect of exercise on baseline mood and anxiety subjective states without threat challenges (Arent, Alderman, Short, & Landers, 2007; Arent, Landers, Matt, & Etnier, 2005; Bartholomew, 1999; Cox, Thomas, Hinton, & Donahue, 2004; Focht, 2002; Hansen, Stevens, & Coast, 2001; Petruzzello, Landers, Hatfield, Kubitz, & Salazar, 1991). The present study goes beyond self-reported measures, and attempts to identify potential mechanisms underlying exercise's effect by examining distinct responses to threat, i.e., fear and anxiety, using an objective measure of defensive responses, the startle reflex.

A growing body of evidence indicates that fear and anxiety are different defensive responses mediated by partly distinct neural circuits (for review, see Davis, Walker, Miles, & Grillon, 2010; Shackman & Fox, 2016). Fear is a phasic response to a predictable threat, and anxiety is a sustained state of apprehension evoked by an unpredictable threat (Davis et al., 2010). Fear and anxiety have been distinguished at the neural level in both humans (Herrmann, Beier, et al., 2016; Herrmann, Boehme, et al., 2016; Klahn et al., 2016, 2017) and animals (for reviews: Davis et al., 2010; Walker, Toufexis, & Davis, 2003). Additionally, a plethora of psychopharmacological (Bradford, Shapiro, & Curtin, 2013; Grillon, Baas, Pine, et al., 2006; Grillon et al., 2015; Grillon, Chavis, Covington, & Pine, 2009; Hogle, Kaye, & Curtin, 2010; Moberg & Curtin, 2009) and clinical (Bradford, Curtin, & Piper, 2015; Chamberlain et al., 2013; Gorka et al., 2013; Gorka et al., 2016; Gorka, Lieberman, Shankman, & Phan, 2017; Gorka, Liu, Sarapas, & Shankman, 2015; Grillon et al., 2008; Grillon, Pine, Lissek, et al., 2009; Grillon, Morgan, Davis, & Southwick, 1998; Hogle et al., 2010; Klahn et al., 2016, 2017; Moberg & Curtin, 2009; Schroyen et al., 2016) studies have advanced knowledge of mental health and treatment by comparing these two states. Indeed, fear and anxiety distinctly characterize psychiatric disorders (American Psychiatric Association, 2013) and constitute separate negative valence system constructs in the National Institutes of Health Research Domain Criteria (NIH RDoC).

Fear and anxiety have been explored experimentally using the Neutral-Predictable-Unpredictable (NPU) threat test (Bradford et al., 2013; Chamberlain et al., 2013; Gorka, Nelson, Sarapas, et al., 2013; Gorka, Nelson & Shankman, 2013; Gorka et al., 2015; Gorka et al., 2017; Gorka, Lieberman, Phan, & Shankman, 2016; Grillon et al., 1998; Grillon, Baas, Pine, et al., 2006; Grillon, Pine, Baas, et al., 2006; Grillon, Chavis, Covington, et al., 2009; Grillon, Pine, Lissek, et al., 2009; Grillon et al., 2008, 2011, 2015; Grillon, Cordova, Morgan, Charney, & Davis, 2004; Herrmann, Beier, et al., 2016; Herrmann, Boehme, et al., 2016; Hogle et al., 2010; Kaye, Bradford, & Curtin, 2016; Klahn et al., 2016, 2017; Klinkenberg et al., 2016; Moberg & Curtin, 2009; Nelson, Hodges, Hajcak, & Shankman, 2015; Schroyen et al., 2016). The NPU threat test consists of a neutral condition (N), and two threat conditions that involve administration of predictable (P) and unpredictable (U) shocks (Schmitz & Grillon, 2012). As mentioned previously, past studies of exercise have

relied on subjective measures of anxiety (for reviews, Sciolino & Holmes, 2012; Stubbs et al., 2017). The NPU threat test provides an objective assessment of anxiety using a highly reliable cross-species measure of aversive state, the startle reflex (for review, Grillon & Baas, 2003). Additionally, the test concurrently manipulates fear and anxiety via threat predictability: increased startle reactivity to a predictable threat's cue operationally defines fear (i.e., fear-potentiated startle (FPS)), while increased startle reactivity to an unpredictable threat defines anxiety (i.e., anxiety-potentiated startle (APS)) (Schmitz & Grillon, 2012).

With regard to internalizing disorders, the NPU threat test offers a valuable means to explore clinically relevant mechanisms (Ballard et al., 2014; Gorka, Nelson & Shankman, 2013; Gorka et al., 2015, 2017; Grillon et al., 1998, 2008; Grillon, Pine, Lissek, et al., 2009; Klahn et al., 2016, 2017). For example, individuals with posttraumatic stress (Grillon, Pine, Lissek, et al., 2009) and panic disorders (Gorka et al., 2013; Grillon et al., 2008; Nelson et al., 2013) display elevated anxiety-potentiated, but not fear-potentiated, startle. Additionally, the anxiolytic medications alprazolam and citalopram reduce APS without affecting FPS (Grillon, Baas, Pine, et al., 2006; Grillon, Chavis, Covington, et al., 2009, Grillon et al., 2015). Therefore, the NPU threat test provides a reliable and valid tool to explore the defensive mechanisms that may underlie exercise's therapeutic effect.

Since enhanced APS is increased in trauma-related and anxiety disorders (Gorka et al., 2013, 2017; Grillon et al., 2008; Grillon, Pine, Lissek, et al., 2009; Nelson et al., 2013, 2015), and is decreased by anxiolytic drugs (Grillon, Baas, Pine, et al., 2006; Grillon, Chavis, Covington, et al., 2009; Grillon et al., 2015), the beneficial effect of treatment, such as drugs or exercise, may primarily affect response to unpredictable threat. Accordingly, we hypothesize that exercise will preferentially act on APS.

2 | MATERIALS & METHODS

2.1 | Participants

Thirty-seven healthy adults were recruited from the Washington, DC metropolitan area via flyers and ads. Prior data from our lab (Grillon, Levenson, & Pine, 2007; Grillon et al., 2013, 2015) indicated an expected moderate effect size for startle potentiation (Cohen's $d = 0.5$). A priori calculations indicate that the testing of 30 participants at an alpha of 0.05 would provide power of 0.96 to detect a significant 2 (Activity) $\times$ 2 (Condition) interaction on startle response. Assuming a 20% attrition rate, we collected 36 participants, excluding one participant who failed to complete the protocol due to violation of eligibility criteria ($n = 1$). Of those 36 participants, two were excluded from all analyses due to technical problems preventing the recording of startle data ($n = 2$). The final sample included 34 subjects (17 male) with a mean age (SD) of 26.18 ($SD = 5.6$; Table 1).

All participants gave written informed consent approved by the National Institute of Mental Health (NIMH) Combined Neuroscience Institutional Review Board and were compensated for their participation. Inclusion criteria included: (1) no current diagnosis of any Axis I psychiatric disorder as assessed by SCID-I/NP (First, 2002), (2) no contraindications to exercise (e.g., heart disease, high blood pressure), (3) normal ECG as determined by a

cardiologist, and (4) no use of illicit drugs or psychoactive medications confirmed by negative toxicology screen.

2.2 | Study design

The study used a counter-balanced, within-subject design. Each participant completed three visits to the National Institutes of Health separated by 5–8 days. In the first visit, participants performed a graded peak exercise test on a cycle ergometer (VO₂-peak test) (Bruce, Blackmon, Jones, & Strait, 2004; Myers et al., 1991) to obtain their peak oxygen consumption, a measure of cardiorespiratory fitness, and peak heart rate (HR). In the second visit, participants completed a 30-min activity session at either exercise (60–70% of their individually determined heart rate reserve (HRR)) or control (10–20% of HRR) activity. Thirty minutes after activity, a shock workup procedure was conducted, during which shock was administered via electrodes on participants' left forearms at increasing intensities until a level was reached that was rated as uncomfortable but not painful. They then completed two tasks under threat of shock. The first task was a working memory task, results of which will be reported in another publication. The second task was the NPU threat test, for which we report all data collected. Participants rated their subjective state anxiety before and after both the activity manipulation and the NPU threat test using the 20-Item State-Trait Anxiety Inventory (STAI, Spielberger, 1983). The third visit was identical to the second visit, except for the type of activity (exercise vs. control). Activity order, as well as threat condition of the NPU threat test (see below), were randomized across participants.

2.3 | VO₂-peak test

After verifying inclusion criteria and obtaining informed consent on the first day, participants were given a standardized lunch (450 calories, 22.5% of daily requirement) to eat 90 min prior to the VO₂-peak test. At the end of 90 min, participants were escorted to the testing lab. Preparation for the VO₂-peak test included attachment of a 12-lead ECG (Mortara Instruments), a face mask (Hans Randolph, Inc.), and a blood pressure cuff to participants. HR and indirect calorimetry (ParvoMedics, TrueOne 2400) were collected for 120 s while the participants sat on a stationary cycle ergometer (Corival, Lode) without pedaling. Then participants pedaled with increasing resistance until: (1) ending the test voluntarily, (2) obtaining a 60-s plateau of HR or oxygen consumption near the end of the test, or (3) reaching a respiratory exchange ratio (RER) of greater than or equal to 1.1 (Fletcher et al., 2013). Throughout the test, a clinician monitored blood pressure, HR, and ECG for safety. After completion of the test, participants were monitored until their blood pressure returned to baseline and their HR decreased to near resting value.

2.4 | Exercise manipulation

Activity for each study visit was achieved by maintaining a goal HR corresponding to 60–70% of HRR (exercise) or 10–20% of HRR (control). HRR was calculated using the Karvonen formula (Karvonen, Kentala, & Mustala, 1957) with the resting HR from the screening visit and the peak HR reached during the the VO₂-peak test. Subjects were given the same standardized lunch as during the VO₂-peak visit. After 90 min, participants completed a pre-activity STAI and were fitted with a Holter HR monitor (SpaceLabs Healthcare) around their chest. HR from the chest monitor was displayed on the stationary

bike handle (same as VO₂-peak test). Participants biked for 30 min, including a 5-min warm-up, 22 min within the specified HR range, and a 3-min cooldown. During warm-up, bike resistance was continuously adjusted to achieve the goal HR within 5 min. During exercise and control activity, the bike resistance was adjusted as needed to maintain the HR goal. Bike resistance was removed during cooldown, then participants completed the post-activity STAI.

2.5 | NPU threat test

Subjects began the NPU threat test 1 h after activity. One hour was expected to be a large enough delay to avoid confounding effects of activity-induced physiological arousal. As described above, the NPU threat test provides distinct measures of physiological (EMG startle blink reflex) and subjective fear and anxiety (Schmitz & Grillon, 2012). In each N, P, and U condition, three 8-s duration geometric cues were presented on a computer screen. These cues were separated by intertrial intervals (ITI) (Figure 1). Each condition lasted 120 s. No shock was administered in the N condition. The cue indicated the possibility of a shock in the P condition. Shocks were administered at any time in the U condition. Hence, while the cues signaled shocks in the P condition, they had no informative value in the N or U conditions. Each participant received one of the two following orders: P N U N U N P or U N P N P N U. The condition order was the same for both visits within participants, but was counterbalanced across participants. The duration of the NPU threat test was 14 min (120 s × 7). A total of eight shocks were delivered (two per P and U conditions). There were six startle probes (three during cue, three during ITI) for each condition. Startle probes were separated by at least 20 s, and occurred at least 8 s after a shock stimulus. Immediately prior to the NPU threat test, subjects were presented with four habituation startle stimuli to reduce initial startle reactivity.

Participants were informed of each condition's threat predictability prior to beginning the test. Conditions were signaled by words on top of the computer screen, i.e., "No Shock," "Shock during cue," or "Shock at any time." Participants were asked to continuously (online) rate their subjective anxiety on a scale of 0–10 throughout the task by pressing the left and right arrow keys on the keyboard.

Participants completed a STAI before (pre-NPU) and immediately after (post-NPU) the NPU threat test. After the test, they also rated shock discomfort on an analog scale ranging from 0 (not at all uncomfortable) to 10 (extremely uncomfortable).

Eye-blink startle was recorded with EMG electrodes under the left eye, and was elicited by 40-ms bursts of 103-dB white noise delivered over headphones. EMG data were digitized (1,000 Hz) and filtered (30–500 Hz). All stimuli and recordings were delivered via commercial system (Presentation and Biopac, respectively).

2.6 | Data analysis

Peak blink amplitude was determined in the 20–120-ms window following probe onset relative to a 50-ms baseline EMG. Raw startle data were averaged across habituation probes for each visit. Results during the NPU threat test were analyzed with raw scores and with standardized within-subject *t*-scores ($[z\text{-scores} \times 10] + 50$) due to individual differences in

startle reactivity. Both the startle raw and t -scores were averaged within each condition (N, P, U) and stimulus type (cue, ITI) for each subject and session. An omnibus repeated measures analysis of variance (rANOVA) Activity (exercise, control) $\times$ Condition (N, P, U) $\times$ Stimulus Type (cue, ITI) was initially conducted on the raw scores.

In addition, as the study focused specifically on fear and anxiety, we operationally defined anxiety as the increase in ITI startle reactivity from the N to the U condition (APS), and fear as the increased startle reactivity from ITI to cue in the P condition (FPS) using t -scores as we have done in the past (e.g., Ballard et al., 2014; Grillon, Chavis, Covington, et al., 2009; Grillon et al., 2011, 2015, 2017). These data were then entered into an Activity (exercise, control) $\times$ Condition (APS, FPS) rANOVA.

Online ratings were recorded continuously. To match the startle measures, only ratings recorded just prior to the startle probe (within approximately 2 ms) were analyzed. Scores were standardized using within-subject t -scores, then averaged within each condition and stimulus type for each subject. Online anxiety was operationally defined as the change in score during ITI from the N to U condition, and online fear was the change in score from ITI to cue in the P condition. Online ratings were analyzed with an Activity (exercise, control) $\times$ Condition (online fear, online anxiety) rANOVA. STAI measures were analyzed with an Activity (exercise, control) $\times$ Time (pre-activity, post-activity, pre-NPU, post-NPU) rANOVA. Statistics were conducted in SPSS 21.

3 | RESULTS

3.1 | Startle

Activity did not affect raw startle reactivity during habituation (control: $M = .12$, $SD = .13$ mV; exercise: $M = .09$, $SD = .09$ mV; $t(33) = 1.34$, $P = .189$).

Startle raw scores are presented in Table 2. The rANOVA showed a significant main effect of Activity ($F(1,33) = 4.17$, $P = .049$, $\eta_p^2 = .112$), due to overall smaller startle reactivity after exercise compared to control activity. As expected, there was a significant Condition $\times$ Stimulus type interaction ($F(2,66) = 20.36$, $P < .001$, $\eta_p^2 = .382$). The interaction of Activity $\times$ Condition (trend: $F(2,66) = 3.01$, $P = .056$, $\eta_p^2 = .084$) was accompanied by a significant linear trend of Activity $\times$ Condition ($F(1,33) = 8.68$, $P = .006$, $\eta_p^2 = .208$). This strong linear trend indicated that the increase in raw startle magnitude from the N to U conditions was significantly reduced after exercise compared to the control activity.

The startle t -scores are presented in Table 2 and the FPS and APS data are presented in Figure 2. The rANOVA revealed an Activity (exercise, control) $\times$ Condition (APS, FPS) interaction ($F(1,33) = 4.66$, $P = .038$, $\eta_p^2 = .124$). This interaction reflected lower APS after exercise compared to control ($t(33) = 2.25$, $P = .031$), but no effect of exercise on FPS ($t(33) = .52$, $P = .609$). This interaction was not affected by order of activity visit ($F(3,30) = .56$, $P = .646$, $\eta_p^2 = .053$). There was a main effect of Condition, with overall larger FPS than APS ($F(1,33) = 7.92$, $P = .008$, $\eta_p^2 = .194$), and no main effect of Activity ($F(1,33) = .86$, $P = .362$, $\eta_p^2 = .025$).

3.2 | Subjective anxiety

The rANOVA for online ratings (Table 2) revealed a Condition main effect, with higher scores for online anxiety than online fear ($F[1,31] = 202.80, P < .001, \eta_p^2 = .867$). The Activity main effect ($F(1,31) = .43, P = .519, \eta_p^2 = .014$) and the Activity $\times$ Condition interaction ($F[1,31] = 2.33, P = .137, \eta_p^2 = .070$) were not significant.

Results for state anxiety (STAI) scores showed a main effect of Time ($F[3,90] = 22.09, P < .001, \eta_p^2 = .424$), with no change in STAI from pre- to post-activity ($t[30] = 1.32, P = .196$), an increase in STAI prior to NPU threat test ($t[30] = 5.00, P < .001$), and a decrease in STAI after NPU threat test ($t[30] = 2.70, P = .011$). STAI was higher at the end compared to the beginning of the study visits ($t[30] = 4.80, P < .001$) (Figure 3). The main effect of Activity was not significant ($F[1,30] = 2.56, P = .120, \eta_p^2 = .079$), but there was a significant Activity $\times$ Time interaction ($F[3,90] = 5.45, P = .002, \eta_p^2 = .154$). The interaction was due to the fact that STAI increased from post-activity to pre-NPU ($t[30] = 5.00, P < .001$), but this increase was less pronounced after exercise compared to control activity ($t(1,30) = 3.20, P = .003$). Activity did not affect STAI pre- to post-activity ($t(1,30) = 1.62, P = .117$), nor pre- to post-NPU ($t(1,30) = 1.53, P = .136$).

3.3 | Shock intensity and pain rating

Activity did not affect shock intensity (control: $M = 9.9, SD = 6.5$ mA; exercise: $M = 9.6, SD = 6.1$ mA; $t[33] = .49, P = .625$), nor retrospective shock discomfort (control: $M = 7.3, SD = 2.0$; exercise: $M = 7.5, SD = 1.8$; $t[32] = .48, P = .638$) across participants.

4 | DISCUSSION

The objective of this study was to determine whether exercise modulates experimentally induced fear and/or anxiety. To this aim, eyeblink startle was used to quantify defensive responses, with predictability of threat distinguishing between fear and anxiety. The main finding was in line with expectations: exercise compared to control activity attenuated APS (during unpredictable threat) without affecting FPS (during predictable threat).

Findings of a decrease in APS during unpredictable threat with exercise could be explained by potential differences in shock between visits, i.e., exercise may have reduced shock intensity during the shock work-up procedure or decreased the subjective adversiveness of the shock. However, both variables did not differ between visits. Therefore, the difference in APS between visits more likely reflects an effect of Activity on response to unpredictable threat, rather than on shock sensitivity.

Investigators have proposed several potential mechanisms underlying the anxiolytic effects of exercise, including, but not limited to, serotonin (Fox, Hammack, & Falls, 2008; Greenwood, Foley, Burhans, Maier, & Fleshner, 2005), cortisol (Zschucke, Renneberg, Dimeo, Wüstenberg, & Ströhle, 2015), brain-derived neurotrophic factor (BDNF) (Ströhle et al., 2010), dopamine (Byun et al., 2014; Chen et al., 2017), acetylcholine (Byun et al., 2014), beta-endorphins (Stubbs et al., 2017), self-esteem (Zschucke et al., 2015), and self-efficacy (Petruzzello et al., 1991). As indicated in the introduction, fear and anxiety are considered separable processes, the former being mediated by the central nucleus of the

amygdala (CeA), and the latter by the bed nucleus of the stria terminalis (BNST) (reviewed in Davis et al., 2010; but see Shackman & Fox, 2016). Since our findings indicate that exercise decreases APS, and not FPS, we will discuss mechanisms that may impact the BNST, including modulation of cortisol and serotonin.

First, exercise may attenuate anxiety by reducing cortisol released during threat. Acute exercise reduces cortisol response to a stressful test, the Montreal Imaging Stress Task (Zschucke et al., 2015). A reduction of cortisol release would preferentially affect anxiety as opposed to fear. According to Davis and colleagues, anxiety to unpredictable threat is maintained via the sustained activation of corticotropin-releasing factor (CRF) receptors in the BNST (review Davis et al., 2010). This effect is potentiated by corticosterone in rodents, because corticosterone increases the effect of CRH in the BNST (Makino, Gold, & Schulkin, 1994). Similarly, acute hydrocortisone increases anxiety, but not fear, in humans (Grillon et al., 2011). Taken together, these results are consistent with the hypothesis that acute exercise decreases APS by downregulating the release of extra-hypothalamic cortisol. However, given that we did not assay cortisol in the present experiment, this interpretation should be taken with caution.

Second, exercise may modulate the BNST via the dorsal raphe nucleus (DRN). The DRN is activated by uncontrollable stress (Grahn et al., 1999; Takase et al., 2004) and directly projects to the BNST (Singewald, Salchner, & Sharp, 2003). Previous research indicate DRN inhibition associated with the anxiolytic effects of exercise (Broocks et al., 2001; Fox et al., 2008; Greenwood et al., 2005). Exercise attenuates threat-induced hypersensitivity of the DRN (Greenwood et al., 2005) and protects against 5HT-2B agonist startle propagation in rodents (Fox et al., 2008). In humans, exercise prevented 5HT-2B agonist induction of cortisol release (Broocks et al., 2001). In sum, studies suggest an impact of exercise on serotonergic activity within the DRN, leading to BNST modulation and decreased anxiety. Ultra-high field fMRI may provide the means to examine this circuitry (Torrisi et al., 2015).

Interestingly, exercise reduced overall raw startle reactivity during the NPU threat test. This reduction may reflect two processes: central muscle fatigue or reduced contextual anxiety, i.e., anxiety associated with participation in an experiment where shocks are being administered. Physiological effects of exercise, for example, changes in muscle receptor properties, may have affected startle (Gandevia, 2008). Indeed, numerous physiology studies have shown reflex inhibition of motor neurons by fatigue and should not notably affect the muscles that did not exercise (Duchateau & Hainaut, 1993; Garland, 1991; Garland & McComas, 1990). However, this explanation does not appear to be supported by our data. Raw startle assessed during habituation after exercise, but before the threat experiment, was not modulated by activity.

The alternative possibility is that raw startle was increased by the overall threatening experimental context of the NPU threat test, an effect that is well documented (Grillon & Ameli, 1998; Grillon et al., 1998). The fact that the difference in raw startle reactivity between control activity and exercise emerges only during the NPU threat test supports the contextual anxiety hypothesis.

Regarding online ratings, during the NPU threat test, findings do not show a main effect nor an interaction of activity. This supports the commonly observed dissociation between physiological and subjective measures of fear and anxiety (Kozak & Miller, 1982; Lang, 1968; Rachman & Hodgson, 1974). Recently, LeDoux and Pine attributed this dichotomy to partly independent neural circuits. That is, sub-cortical circuits may contribute to subjective mood evaluation, while association cortex may regulate physiological correlates of aversive states (LeDoux & Pine, 2016).

There was an increase in state anxiety (STAI) prior to the NPU threat test, probably reflecting anticipatory anxiety associated with participation in an experiment where shocks are administered. Interestingly, exercise attenuated this increase in anticipatory anxiety.

This study presents several strengths and limitations. A significant strength is the use of an objective measure of defensive responses. Relative to self-report, objective measures are less likely to be influenced by subjective biases and demand characteristics (Levenson, 2007; Ome, 1962), especially when experimental conditions (i.e., exercise) cannot be blinded. In addition, the threat manipulation depended on a well-validated experimental model, which allowed the distinction between response to unpredictable and predictable threat (see references in Introduction). Potential confounds, such as fitness level, were addressed by the within-subject design, as well as by the quantification of exercise intensity based on individual fitness capacity, e.g., exercise defined as 60–70% of HRR. As an additional control, VO₂-peak, a measure of aerobic fitness (Table 1), did not affect results.

A notable limitation is the absence of blindness to the exercise manipulation, which may have contributed to investigator and participant bias. However, as discussed above, compared to subjective reports, startle is a reflex that is relatively free from demand characteristics and bias (Levenson, 2007; Ome, 1962). Additionally, it is unclear how biases would affect FPS and APS differently. Study design also prevents causal inferences of exercise itself on startle, compared to other aspects of the exercise visit, as the NPU-threat test was performed only after activity session to minimize habituation and discomfort to participants.

5 | CONCLUSION

Taken together, results support that exercise impacts defensive responses associated with anxiety (APS) but not fear (FPS). APS, but not FPS, is elevated in anxiety and trauma disorders (Grillon et al., 2008; Grillon, Pine, Lissek, et al., 2009), and is reduced by conventional anxiolytics such as citalopram and alprazolam (Grillon, Baas, Pine, et al., 2006; Grillon, Chavis, Covington, et al., 2009; Grillon et al., 2015). Findings now show that exercise preferentially affects response to unpredictable threat, supporting the hypothesis that the therapeutic effects of exercise may involve specific modulation of the anxiety and not the fear system.

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FIGURE 1.

NPU threat test. Schematic representation of stimulus presentation and shock delivery during each condition in the NPU threat test. The upper line represents one of two potential orders of P (predictable), N (no shock), U (unpredictable) threat conditions. The lower lines are examples of each threat condition, including startle probes, visual threat cues, and shock delivery. Each condition had three visual threat cues (8 s) separated by intertrial intervals. No shock was delivered in the N condition. In the P condition, shock was delivered only if a cue was on the computer screen. In the U condition, shock was delivered independently of cue. There were two shocks per P and U condition (total of eight), and six startle probes per N, P, and U condition. Adapted from Schmitz & Grillon, 2012

FIGURE 2. Anxiety-potentiated startle (APS) and fear-potentiated startle (FPS). Error bars are SEM

FIGURE 3.

State anxiety throughout study visit. State anxiety (20-item STAI) was assessed pre-activity, post-activity, pre-NPU threat test, and post-NPU threat test. STAI increased from post-activity to pre-NPU across visits, but this increase was less after exercise compared to control activity (Activity $\times$ Time: $F[3,90] = 5.45$, $P = .002$; $t[30] = 5.00$, $P < .001$). Activity did not affect STAI pre- to post-activity ($t(1,30) = 1.62$, $P = .12$), nor pre- to post-NPU ($t(1,30) = 1.53$, $P = .14$). Error bars are SEM

TABLE 1

Sample characteristics. Sex, age, heart rate, and fitness level (VO2-peak) of participants (means and SDs)

Total Sample	
Sex	17 Males, 17 Females
	Mean (SD)
Age (years)	26.2 (5.6)
Heart rate resting (bpm)	61.1 (8.9)
Heart rate peak (bpm)	188.4 (15.0)
VO2-peak(mL/kg/min)	35.4 (7.3)

TABLE 2
Mean (SD) of raw startle (mV), *t*-scores of startle, and *t*-scores of online ratings of anxiety during the NPU threat test

Variable	Activity	Neutral			Predictable			Unpredictable		
		ITI	Cue	ITI	ITI	Cue	ITI	ITI	Cue	ITI
Startle (raw)	Control	0.08 (0.1)	0.09 (0.1)	0.11 (0.1)	0.11 (0.1)	0.16 (0.1)	0.14 (0.1)	0.15 (0.1)	0.10 (0.1)	0.10 (0.1)
	Exercise	0.07 (0.1)	0.07 (0.1)	0.08 (0.1)	0.08 (0.1)	0.13 (0.1)	0.10 (0.1)	0.10 (0.1)	0.10 (0.1)	0.10 (0.1)
Startle (<i>t</i> -score)	Control	47.4 (4.0)	48.1 (4.9)	50.1 (5.0)	57.4 (6.9)	54.1 (5.9)	57.1 (6.5)	54.1 (5.9)	57.1 (6.5)	57.1 (6.5)
	Exercise	45.6 (3.7)	44.9 (3.3)	46.8 (4.6)	54.8 (8.1)	49.6 (4.6)	51.6 (6.1)	49.6 (4.6)	51.6 (6.1)	51.6 (6.1)
Online ratings	Control	43.9 (2.9)	42.5 (2.5)	56.1 (4.1)	48.3 (4.2)	57.5 (5.2)	57.9 (4.6)	56.6 (3.6)	57.1 (4.1)	57.1 (4.1)
	Exercise	43.9 (3.2)	42.6 (3.4)	54.3 (4.5)	48.2 (4.9)	56.6 (3.6)	57.1 (4.1)	56.6 (3.6)	57.1 (4.1)	57.1 (4.1)