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Exercise modulates the interaction between cognition and anxiety in humans

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Abstract

Despite interest in exercise as a treatment for anxiety disorders the mechanism behind the anxiolytic effects of exercise is unclear. Two observations motivate the present work. First, engagement of attention control during increased working memory (WM) load can decrease anxiety. Second, exercise can improve attention control. Therefore, exercise could boost the anxiolytic effects of increased WM load via its strengthening of attention control. Anxiety was induced by threat of shock and was quantified with anxiety-potentiated startle (APS). Thirty-five healthy volunteers (19 male, age $M = 26.11$, $SD = 5.52$) participated in two types of activity, exercise (biking at 60–70% of heart rate reserve) and control-activity (biking at 10–20% of heart rate reserve). After each activity, participants completed a WM task (*n*-back) at low- and high-load during safe and threat. Results were not consistent with the hypothesis: exercise vs. control-activity increased APS in high-load ($p = .03$). However, this increased APS was not accompanied with threat-induced impairment in WM performance ($p = .37$). Facilitation of both task-relevant stimulus processing and task-irrelevant threat processing, concurrent with prevention of threat interference on cognition, suggests that exercise increases cognitive ability. Future studies should explore how exercise affects the interplay of cognition and anxiety in patients with anxiety disorders.

Keywords

Working memory; anxiety-potentiated startle; threat; attention control; limited resources theory

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Interest in exercise as a treatment for anxiety disorders is steadily growing after exercise studies have shown anxiolytic effects (Deboer, Powers, Utschig, Otto, & Smits, 2012; Trine & Morgan, 1997). However, the mechanism underlying the anxiolytic effects of exercise

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remains unclear (Stonerock, Hoffman, Smith, & Blumenthal, 2015). One possibility is that exercise increases attention control. We recently showed that engaging attention to task-relevant processing by loading working memory (WM) reduces anxiety induced experimentally (Balderston et al., 2016). The present study examines whether exercise can boost the anxiolytic effect of increased WM-load.

The rationale for this study is based on two observations. First, anxiety can be down-regulated by engaging attention away from threat processing. Second, exercise can improve attention control. Regarding the former, the relationship between cognition and anxiety has been studied extensively (Ernst, Lago, Davis, & Grillon, 2016; Shackman et al., 2006; Vytal, Cornwell, Arkin, & Grillon, 2012). Several studies show that increase in WM-load decreases anxiety (Clarke & Johnstone, 2013; Patel, Stoodley, Pine, Grillon, & Ernst, 2017; Vytal et al., 2012). This phenomenon may facilitate cognitive performance in stressful situations by shifting attention toward the task at hand and away from worrisome thoughts (Kiyonaga & Egner, 2013; McRae et al., 2010). One practical implication of these findings is that occupying mental space with tasks that engage cognitive control such as creative work (e.g. writing, painting) or mental games (e.g. sudoku, crossword puzzles) may be helpful in reducing anxiety.

Regarding the effects of exercise on cognition, the association of exercise with cognitive improvement is well established (Crush & Loprinzi, 2017; Hillman, Snook, & Jerome, 2003; Loprinzi & Kane, 2015), although the responsible mechanism is unclear (Chen et al., 2017). Specific to the current study, acute exercise has been shown to improve WM (Pontifex, Hillman, Fernhall, Thompson, & Valentini, 2009; Sibley & Beilock, 2007). Therefore, exercise may decrease anxiety by enhancing task-relevant processing. Consistent with this notion, a neuroimaging study by Li et al. (2014) revealed that exercise increased activation of a cortical region associated with WM, the middle prefrontal gyrus, and reduced activation of a cortical region associated with appraisal of emotional stimuli, the anterior cingulate cortex (Li et al., 2014). These data support that exercise may enhance the down-regulation of anxiety by improving attention control.

The present study addresses whether exercise boosts the anxiolytic effect of increased WM-load. This work circumvents the common limitation of empirical works that rely on self-reports by employing a physiological measure of anxiety, the startle reflex. Specifically, this study uses anxiety-potentiated startle (APS), a robust cross-species measure of anxiety (Grillon & Baas, 2003). Additionally, this experiment builds upon our previous studies, which have consistently revealed APS reduction with high WM-load (Patel et al., 2017; Vytal et al., 2012). The main hypothesis posits that exercise will enhance the reduction of APS by high-load WM performance.

Materials and methods

Participants

Prior data from our lab (Ernst et al., 2016; Vytal et al., 2012) indicated an expected moderate effect size for startle potentiation (Cohen's $d = 0.45$). A priori calculations indicated that testing of 36 participants at an alpha of 0.05 would provide the power of 0.95 to detect a significant 2 (Activity) × 2 (Load) interaction on startle. Approximating a 20% attrition rate, we recruited 44 participants.

Healthy adults were recruited from the Washington, DC metropolitan area via advertisements and flyers. Of the 44 participants enrolled in the study, 9 were excluded: 1 for exercising immediately prior to the visit, 1 for knee injury preventing exercise, 1 because of equipment failure, and 6 because of inability to perform the task adequately (accuracy less than 3 SD from mean of entire sample in at least one condition). The final sample included 35 participants (19 male) with a mean age (SD) of 26.11 (5.52) (Table 1). Participants excluded due to task performance had a greater predominance of females compared to males than the final sample (83% vs 51%) but did not differ from the final sample on any other characteristics.

Individuals were screened for the following inclusion criteria: (1) no current diagnosis of Axis I psychiatric disorder as assessed by SCID-I/NP (First, 2002), (2) no contraindications to exercise (e.g. heart disease), (3) normal ECG, and (4) no use of illicit drugs or psychoactive medications. All participants gave written informed consent approved by the NIMH Combined Neuroscience Institutional Review Board and were compensated for their participation.

Study design

The study used a within-subject design. Participants completed three visits separated by 5–8 days, all starting at noon. During the first visit, participants performed a graded peak exercise test on a cycle ergometer (VO_2-peak test) (Bruce, Blackmon, Jones, & Strait, 2004) in order to obtain their peak oxygen consumption, a measure of cardiorespiratory fitness, as well as their peak heart rate (Table 1). At the second and third visits, participants completed a 30-minute activity at either 10–20% (“control-activity”) or 60–70% (“exercise”) of their individual heart rate reserve (HRR). Activity order was randomised and counter-balanced. Participants completed a WM task under conditions of safe and threat, approximately 30 minutes after activity.

VO_2-peak test

After verifying inclusion criteria and obtaining informed consent on the first visit, participants were given a standardised lunch. Ninety minutes later participants were prepared for the VO_2-peak test with the placement of a 12-lead ECG (Mortara Instruments), a face mask (Hans Randolph, Inc.), and a blood pressure cuff. Heart rate (HR) and indirect calorimetry (ParvoMedics, TrueOne 2400) were collected for 120 s. Then, participants pedalled on a stationary cycle ergometer (Corival, Lode) with increasing resistance until the peak rate of oxygen consumption was reached (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 and HR returned to near baseline.

Activity manipulation

Activity for each study visit was achieved by maintaining a goal HR that corresponded to 60–70% of HRR (exercise) or 10–20% of HRR (control-activity). HRR was calculated using the Karvonen Formula (Karvonen, Kentala, & Mustala, 1957) with the resting HR from the screening visit and the peak HR during the VO_2-peak test.

Subjects were given the same lunch as at the VO_2-peak visit. Ninety minutes later, participants were fitted with a Holter HR monitor (SpaceLabs Health-care). HR was displayed on the stationary bike handle (same as VO_2-peak test). Participants were instructed to bike for 30 min, including a 5-min warm-up, 22-min of HR within the specified range, and a 3-min cool-down. During warm-up, bike resistance was gradually increased, then continuously adjusted to maintain the HR goal. Resistance was removed during cool down.

Shock

Anxiety was evoked by threat of shock (Schmitz & Grillon, 2012). Shocks were delivered through electrodes (Biopac Systems) placed on the left forearm. During the shock work-up, shocks were administered at increasing intensities until a level that corresponded to subjective discomfort, but not pain, was reached. This intensity was used throughout the study visit.

Startle

Eye-blink startle magnitude (mV) was recorded with electromyographic (EMG) electrodes placed under the left eye, and was elicited by 40-ms duration 103-dB bursts of white noise (probes) delivered over headphones. EMG data were digitised (1000 Hz), filtered (30–500 Hz), rectified, and smoothed using a 20-ms sliding window. All stimuli and recordings were delivered via the commercial system (Presentation and Biopac, respectively). Immediately prior to the WM task, subjects were presented with four startle probes to reduce initial startle reactivity.

N-*back task*

Thirty minutes after activity, subjects were tested with the WM (*n*-back) task. Task latency was chosen to reduce the physiological effects of exercise, as heart rate on average returns to normal levels 15 min after exercise (Chang, Kim, Jung, & Kato, 2017). Participants were asked to remember a continuous series of letters presented sequentially on a computer screen (Figure 1). For each letter, participants pushed a key to indicate if the letter matched (i.e. “x”) or did not match (i.e. “y”) a previously presented letter. In low-load (“1-back”), the target letter was presented 1 letter before, and in high-load (“3-back”) the letter was presented 3 letters before, the current letter. Participants completed four runs of the task, each run consisting of 6 blocks. Each block began with an instruction screen (e.g. “1-back”). Then, 18 letters were presented in succession for 500 ms each, separated by 2-s intertrial intervals. Overall, the WM task consisted of 75% mismatched and 25% matched trials. Performance variables were reaction time (RT, ms) and accuracy (percent correct).

Participants were told they would perform *n*-back in two conditions, safe and threat, as indicated by the coloured circle surrounding each letter (blue for safe and orange for threat). Participants knew that during safe they would not receive a shock, and during threat, they could receive a shock at any time. Each run included 0–3 shocks and 9 startle probes, for a total of 12 shocks and 36 probes per visit. Shocks and startle probes were presented randomly and had no systematic relationship with letter presentation.

Retrospective ratings

After each run, participants rated their subjective anxiety for each load (1-back, 3-back) and each condition (safe, threat) on an analog scale ranging from 1 (not at all) to 10 (extremely). Participants also rated discomfort of the shock on a similar scale.

Data analysis

All analyses were conducted in In SPSS 21.

Anxiety-potentiated startle—Startle peak blink amplitude was determined in the 20–120 ms window following the probe relative to the 50 ms immediately prior to the probe. Peak amplitudes were averaged for each block type. To control for interindividual variability in startle reactivity, startle magnitudes were standardised using within-subject *t*-scores ([*z*-scores × 10] + 50). APS was calculated as the difference score of startle between the threat and safe conditions. APS was analysed using a repeated measure analysis of variance (rANOVA) with activity (control-activity, exercise) and load (1-back, 3-back) as within-subject factors. As a foremost test of the core assumption that high-load reduces APS, the effect of load on APS was examined in the control-activity.

Subjective reports and performance—Subjective reports, RT, and accuracy were averaged within each load and condition, after removing all trials contaminated by shocks and probes. These measures were analysed with a 3-way activity (control-activity, exercise) × Load (1-back, 3-back) × Condition (safe, threat) rANOVA.

Results

Manipulation checks

Threat-of-shock increased startle response ($F(1,34) = 40.08$, $p < .001$, $\eta^2 = .54$) and subjective anxiety ($F(1,34) = 99.79$, $p < .001$, $\eta^2 = .75$) compared to safe (Table 2). High-load reduced APS compared to low-load in the control-activity ($t(1,34) = 2.32$, $p = .03$; Figure 2). Order (counter-balance), sex, age, and fitness level (baseline HR, VO_2-peak) were tested in preliminary analyses and found to not affect results; as such, they were not included in the final analyses.

Anxiety

Anxiety-potentiated startle—The 2-way rANOVA revealed a significant interaction of Activity × Load on startle magnitude ($F(1,34) = 5.94$, $p = .02$, $\eta^2 = .15$; Table 2; Figure 2). Main effects of Load and Activity were not significant.

For interpretation, the 2-way interaction was decomposed by Load. In 1-back, APS was not affected by Activity ($t(1,34) = .59$, $p = .56$). However, in 3-back, APS was higher in the exercise than the control-activity ($t(1,34) = 2.30$, $p = .03$).

Retrospective anxiety—Participants tended to report overall lower retrospective anxiety with exercise than with the control-activity (trend main effect of Activity: $F(1,34) = 3.05$, $p = .09$; $\eta^2 = .08$). Additionally, participants rated higher retrospective anxiety during 3-back compared to 1-back $F(1,34) = 61.44$, $p < .001$; $\eta^2 = .64$) (Table 2). None of the interactions were significant.

Working memory

Reaction time—There was a 3-way interaction of Activity × Condition × Load on RT ($F(1,34) =6.45$, $p = .02$, $\eta^2 = .16$, Table 2, Figure 3). For interpretation, the interaction was decomposed by Activity. After the control-activity, threat decreased RT during 3-back compared to safe ($F(1,34) = 5.55$, $p = .02$, $\eta^2 = .14$; $t(1,34) = 2.52$, $p = .02$). Condition did not affect RT during 1-back ($t(1,34) = .60$, $p = .56$). After exercise, Condition did not affect RT ($F(1,33) = .83$, $p = .37$, $\eta^2 = .02$) or the effect of Load ($F(1,33) = .24$, $p = .63$, $\eta^2 = .01$).

Overall, there was a main effect of Load, with shorter RT during 1-back than 3-back ($F(1,34) = 97.71$, $p < .001$, $\eta^2 = .74$). Neither Activity ($F(1,34) = .77$, $p = .39$, $\eta^2 = .02$) nor Condition ($F(1,34) = .00$, $p = .95$, $\eta^2 = .00$) had a main effect on RT.

Accuracy—Accuracy was lower in 3-back compared to 1-back ($t(1, 34) = 12.31$, $p < .001$; Table 2). Neither Activity ($F(1,34) = .29$, $p = .60$; $\eta^2 = .01$) nor Condition ($F(1,34) = 1.25$, $p = .27$; $\eta^2 = .04$) affected accuracy. There were no interactions.

Shock intensity and discomfort rating

Activity did not affect shock level across participants (shock mA (*SD*): control-activity 9.32 (6.26); exercise 8.84 (6.04); $t(34) = .92$, $p = .36$), or retrospective shock discomfort (shock discomfort (*SD*): control-activity 7.51 (1.91), exercise 7.38 (1.90), $t(33) = .39$, $p = .70$).

Discussion

The objective of this study was to examine whether exercise could strengthen the anxiolytic effect of high WM-load (Shackman et al., 2006; Vytal et al., 2012), based on the assumption that exercise facilitates attention to task-relevant stimuli and away from threat stimuli. Outcome measures included anxiety-poten-tiated startle (APS), subjective anxiety and WM (RT, accuracy). Activity was manipulated by maintaining HR at 10–20% (control-activity) or 60–70% (exercise) of HRR while biking on a stationary bicycle. Anxiety was induced by threat of shock. This threat manipulation was validated by both higher subjective ratings of anxiety and startle magnitude (APS). Most importantly, the basic tenet of high-load's anxiolytic effect was validated by decreased APS in 3-back compared to 1-back.

The main novel finding revealed that exercise, vs. control-activity, modulated APS only in high-load (3-back). The prediction that exercise would reduce APS was not supported. Exercise amplified APS in 3-back compared to control-activity. However, this effect was not accompanied by performance impairment, which would have been expected from increased anxiety. This finding stands in contrast to decreased APS in the control-activity during 3-back, which was accompanied by improved 3-back performance in threat vs. safe.

These findings may be interpreted in several ways. First, upon examination of Figure 3(b), it appears that although 3-back RT was highest in the safe condition of the control-activity, RT was at the same level in the other conditions (threat-control-activity, safe-exercise, threat-exercise). This pattern could indicate the presence of a floor effect, preventing exercise from further improving performance. However, previous studies using a similar task reported shorter RT-threat at similar accuracy levels (Patel et al., 2017; Vytal et al., 2012). Naturally, slight differences in task parameters may account for discrepancies in performance, which preclude us from formally ruling out the floor hypothesis.

The second interpretation addresses the possibility that exercise enables the concurrent processing of WM and threat, potentially by increasing cognitive efficiency or capacity. This latter possibility stands against the limited resources theory, which posits that cognitive resources are finite (Eysenck & Calvo, 1992). This limitation in resources would lead to competition of various processes that, together, exceed the finite capacity. This theory has been used to support the finding of reduced APS during high-load (Vytal et al., 2012). However, studies report findings that are inconsistent with immutable capacity, for example, evidence for improved WM-capacity after cognitive training (Holmes, Gathercole, & Dunning, 2009; Klingberg, Forssberg, & Westerberg, 2002). Exercise may increase processing efficiency or capacity, thereby (1) facilitating the processing of both WM and threat, and (2) decreasing the cognitive load of 3-back. Therefore, exercise vs. control-activity may require a higher load (ex. 4-back) to effectively decrease APS.

This interpretation is reminiscent of the effects of methylphenidate on the same experimental design (Ernst et al., 2016). In this study, researchers used methylphenidate, a cognitive enhancer (Husain & Mehta, 2011), to probe the relationship between cognition and anxiety. Similar to exercise, methylphenidate influenced only 3-back results. Specifically, methylphenidate increased APS while preventing threat-induced impairment of cognitive performance. These results suggest that methylphenidate increased cognitive-capacity, permitting both cognitive and threat processing. Although not measured in the present experiment, studies show that, akin to methylphenidate, exercise increases dopamine (Meeusen, Piacentini, & De Meirleir, 2001) and norepinephrine (Dishman et al., 1997). Modulation of these neuro-transmitters may underlie the observed increase in WM-capacity (Unsworth & Robison, 2017) and APS (Fendt, Koch, & Schnitzler, 1994).

In summary, exercise vs. control-activity allows both high WM-load and threat to be fully processed, as evidenced by enhanced APS with no threat-related performance impairment. The most parsimonious interpretation, to be tested in the future, is that exercise enhances cognitive abilities, thus facilitating the processing of both cognitive and threat demands, while preventing threat interference on performance.

This study has several strengths and limitations. A significant strength is the use of a physiological measure of anxiety and a well-established method of evoking anxiety. Relative to self-report, objective measures are less likely to be influenced by subjective bias and demand characteristics (Levenson, 2007; Ome, 1962), especially when experimental manipulations (i.e. exercise) cannot be blinded. Indeed, a limitation for this study is the absence of blindness to the activity manipulation, which may have contributed to investigator and participant bias. Additional strengths include mitigation of potential confounds, such as individual fitness level, with within-subject study design and by tailoring exercise intensity to individual fitness (HRR). A study limitation was the fact that the subjective reports did not match the startle data. Such dissociation between objective and subjective measures are frequently observed (Grillon et al., 2015; Harmer, Rogers, Tunbridge, Cowen, & Goodwin, 2003). Startle is an online probe of affective reactivity, whereas the subjective reports are retrospective and are subject to interference from recollection. In addition, subjects may have rated their anxiety level not only about the shock but also about performing the task. This is suggested by the fact that both the main effect of Condition (threat) and Load were significant, the latter probably reflecting the difficulty to perform well in 3-back.

Finally, this study design did not include a noactivity control. For example, contrary to expectations (Ernst et al., 2016; Shackman et al., 2006; Vytal et al., 2012), the threat did not impair WM (accuracy or RT) in the control-activity. This result may be due to effects of light intensity activity, but without a no-activity control, this hypothesis cannot be tested.

In conclusion, the results suggest that exercise allows the simultaneous processing of both high WM-load and threat. Future studies should determine if these results are replicable and explore how exercise affects the interplay of cognition and anxiety in patients with anxiety disorders.

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Raw data were generated at the National Institutes of Health. Derived data supporting the findings of this study are available from the corresponding author (T.L.) on request.

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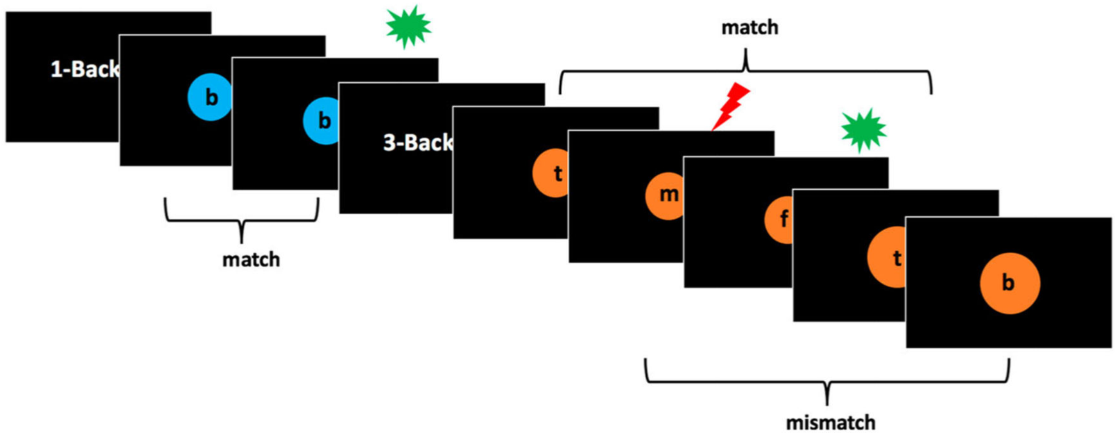

Figure 1.

N-back. Simplified schematic diagram of a sample run with alternating safe (blue) and threat (orange) blocks. During each block, three acoustic probes (green bursts) were delivered. Shocks (red bolts) were delivered three times during each run (0–4 shocks per threat block). Each block began with an instruction screen (“1-back” or “3-back”), followed by a fixation cross. Eighteen letters were presented in succession during each block, separated by 2-s intertrial intervals.

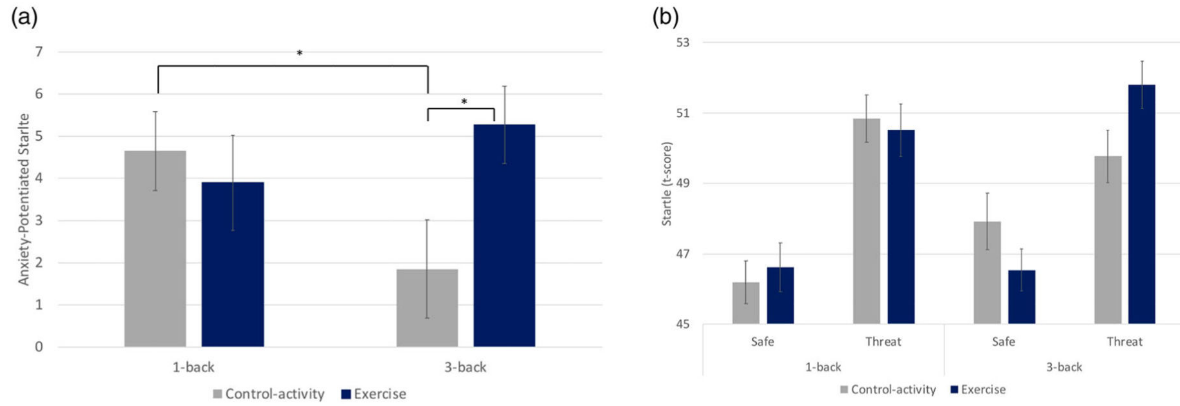

Figure 2.

Startle response (*t*-score). Error bars SEM. (a) Anxiety-potentiated startle (APS) was calculated as the difference score of startle between the threat and safe condition. (b) Startle response for each activity type, condition and load.

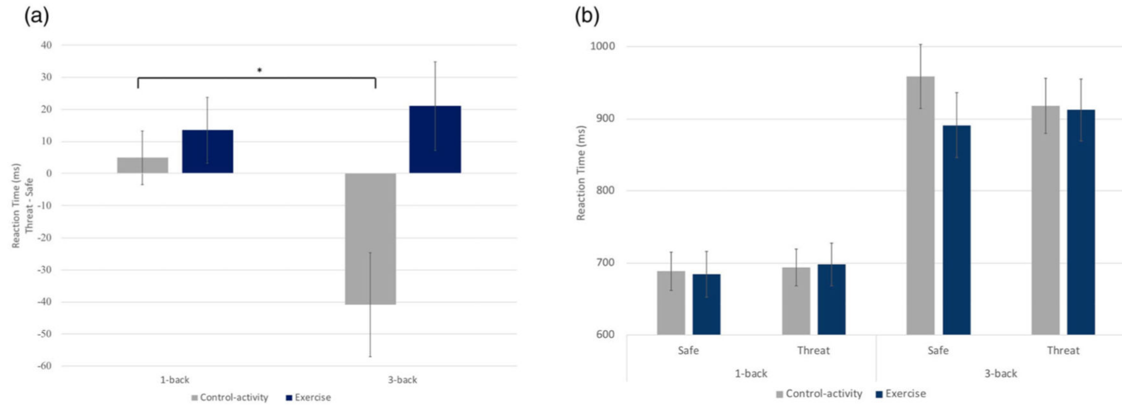

Figure 3.

Reaction Time (ms). Error bars SEM. (a) Difference score of reaction time between the threat and safe condition. (b) Reaction time for each activity type, condition and load.

Table 1.

Total sample.

Total Sample	
Sex	**19M, 16F Mean (SD)**
Age (years)	26.1 (5.5)
Heart rate peak (beats per minute)	186.4 (16.7)
Resting Heart Rate (beats per minute)	61.1 (9.4)
VO2-peak (mL/kg/min)	35.7 (9.4)

Table 2.

Results during the *n*-back task. Mean (*CI*). Retrospective anxiety (an analog scale: 1 = not at all anxious, 10 = extremely anxious), startle *t*-scores, accuracy and reaction time for each activity type (Control-activity, Exercise), Load (1-back, 3-back), and Condition (safe, threat).

	Control-activity				Exercise			
	1-back		3-back		1-back		3-back	
	Safe	Threat	Safe	Threat	Safe	Threat	Safe	Threat
Retrospective Anxiety [&]	2.57 (−.8–5.9)	4.97 (.4–9.6)	3.44 (.1–6.8)	6.14 (1.4–10.9)	2.33 (−.7–5.4)	4.47 (−.2–9.1)	3.27 (−.4–7.0)	5.46 (.4–10.6)
Startle [@] **(t-score)**	46.20 (39.2–53.2)	50.85 (43.6–58.1)	47.92 (38.7–57.2)	49.77 (41.1–58.4)	46.62 (38.5–54.7)	50.52 (41.9–59.2)	46.54 (39.6–53.5)	51.81 (44.0–59.6)
Accuracy [*] **(%)**	94.26 (82.1–106.5)	95.96 (88.3–103.6)	81.48 (64.7–98.3)	81.85 (65.3–98.4)	94.44 (83.5–105.3)	95.14 (83.5–106.8)	46.54 (39.6–53.5)	82.43 (63.4–101.4)
Reaction Time [#] **(ms)**	688.93 (377.9–1000.0)	693.92 (400.6–987.3)	959.36 (442.8–1475.9)	918.48 (418.1–1418.9	684.39 (315.4–1053.3)	697.89 (354.2–1041.6)	891.39 (365.8–1417.0)	912.43 (415.1–1409.8)

[&] higher during threat compared to safe ($p < .001$, $\eta^2 = .75$); trend lower during exercise compared to control-activity ($p = .09$; $\eta^2 = .08$); higher during 3-back compared to 1-back ($p < .001$; $\eta^2 = .64$).

[@] higher during threat compared to safe ($p < .001$, $\eta^2 = .54$); lower during high-load compared to low-load in the control-activity ($p = .03$)

[*] lower in 3-back compared to 1-back ($p < .001$).

[#] lower during threat compared to safe in control-activity-3-back ($p = .02$, $\eta^2 = .14$).