



Pupillometric indices of locus-coeruleus activation are not modulated following single bouts of exercise

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ABSTRACT

Single bouts of exercise have been observed to enhance numerous domains of cognition including inhibitory aspects of cognitive control and neuroelectric indices of attention. Given that the locus-coeruleus norepinephrine system regulates alertness and attention, this system may underlie these exercise-induced enhancements. The present study used pupillometry to examine the extent to which a single bout of exercise induces changes in aspects of locus-coeruleus activation, as well as the extent to which changes in locus-coeruleus activation were associated with changes in inhibition and neuroelectric indices of attention. Using a within-participants cross-over design, behavioral, neuroelectric, and pupillometric measures were assessed in response to an inhibitory control task before and after 20-min of either aerobic exercise or an active-control condition during two separate, counterbalanced sessions. The aerobic exercise condition consisted of walking/jogging on a motor driven treadmill at an intensity of approximately 70% of age-predicted maximum heart rate. The active control condition consisted of walking on the treadmill at 0.5 mph and 0% grade. Replicating prior findings, enhancements in both reaction time and neuroelectric indices of attention were observed in response to the exercise condition. However, neither the exercise nor the active control conditions were observed to induce changes in activation of the locus-coeruleus as indexed by pupil size, and changes in activation of the locus-coeruleus were not associated with exercise-induced changes in inhibition and neuroelectric indices of attention. Accordingly, these findings provide evidence to suggest that activation of the locus-coeruleus is not a mechanism underlying exercise-induced enhancements in cognition.

1. Introduction

Although compelling evidence exists to support the claim that inhibitory control and aspects of attention are enhanced following a single bout of exercise (Kamijo et al., 2009; Kao et al., 2017; Kao et al., 2017; Pontifex et al., 2015), the neurobiological mechanisms underlying these improvements remain to be elucidated. Given its pivotal role in regulating the brain's attentional state (Murphy et al., 2011; Nieuwenhuis, Aston-Jones and Cohen, 2005; Pontifex et al., 2015), one proposed mechanism is that exercise improves cognition as a result of modulations in activation of the locus-coeruleus norepinephrine system. However, no direct evidence exists to substantiate the supposition of exercise-induced changes in aspects of locus-coeruleus activation in humans. Accordingly, the aim of the present investigation was to examine the extent to which single bouts of exercise induce changes in aspects of activation within the locus-coeruleus and to assess the extent to which changes in locus-coeruleus activation are associated

with exercise-induced changes in cognition.

The facilitative effects of single bouts of aerobic exercise on cognition have been well documented, with improvements being observed across a wide range of cognitive processes including simple motor speed/learning (Audiffren et al., 2008; Kamijo et al., 2004a; Snow et al., 2016), information processing (Córdova et al., 2009; Hogervorst et al., 1996; Kashiara and Nakahara, 2005), scholastic achievement (Bass et al., 2013; Castelli et al., 2007; Chu et al., 2016; Hillman et al., 2009; Kamijo et al., 2012; Loprinzi and Kane, 2015; Nanda et al., 2013), and memory (Basso et al., 2015; Coles and Tomporowski, 2008; Etnier et al., 2014; Loprinzi and Kane, 2015). However, the vast majority of the extant literature has focused on inhibition (Ludya et al., 2016; Pontifex et al., 2019), an aspect of cognitive control related to overriding a dominant response in order to perform a less potent but correct response, suppressing task irrelevant information in the stimulus environment, or stopping an ongoing response (Davidson et al., 2006). This ability to inhibit attention to task irrelevant or distracting stimuli is

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central to the ability to sustain attention and to allow control over one's actions. Across pediatric, young adult, and geriatric populations, investigations assessing the effect of an acute bout of exercise on inhibition have generally observed exercise-induced enhancements in inhibition — with a greater ability to focus attention and to ignore distractions following the cessation of a moderate intensity bout of aerobic exercise (Hillman et al., 2009; Hillman et al., 2003; Hogervorst et al., 1996; Kamijo et al., 2009; Kamijo et al., 2007; Lichtman and Poser, 1983; Pontifex et al., 2013; Sibley et al., 2006; Tomporowski et al., 2005).

Beyond only relying upon overt behavioral outcomes to assess the effect of exercise on aspects of cognition, a growing body of literature has also used neuroelectric measures to gain insight into the effects of single bouts of exercise on attentional processes as indexed by the P3 event-related brain potential (ERP). The amplitude of this endogenous component is proportional to the attentional resources allocated towards the suppression of extraneous neuronal activity in order to facilitate attentional processing (Polich, 2007). Investigations assessing the influence of acute bouts of exercise on the P3 ERP component have generally observed larger P3 amplitude following the cessation of an aerobic exercise bout at moderate intensity, relative to following a control condition, suggesting that acute exercise serves to enhance attentional processing (Hillman et al., 2009, 2003; Kamijo et al., 2009, 2007; O'Leary et al., 2011; Pontifex et al., 2015, 2013). Given the concurrent findings across both behavioral and neuroelectric approaches indicating that acute bouts of exercise appear to induce changes in cognition related to attentional processes, it should follow that these acute-exercise effects may manifest as a result of exercise acting upon neural systems that regulate attention.

The locus-coeruleus is a collection of noradrenergic neurons located within the brainstem and is implicated in modulating the neural system's level of alertness (Kinomura et al., 1996). In particular, a growing body of concurrent evidence across both human and nonhuman animal models suggests that activation of the locus-coeruleus and the associated release of norepinephrine serve an important role in influencing the attentional state of the brain (Sara and Bouret, 2012). Modern perspectives of the locus-coeruleus suggest that this system has a dual pattern of activation. During tasks requiring focused attention, neurons in the locus-coeruleus exhibit a moderate level of activation that enables dynamic bursts of activity to occur coupled with the execution of a response to task-relevant stimuli (Aston-Jones and Cohen, 2005). Such moderate levels of tonic (baseline) activity in the locus-coeruleus may therefore entrain other neural systems to limit responsiveness to irrelevant stimuli, thereby preventing spurious distractions (Bouret and Sara, 2005)—with the task-related phasic bursting of activity and associated release of norepinephrine providing a brief attentional filter to selectively facilitate goal-directed behaviors (Aston-Jones and Cohen, 2005). This temporal attentional filter may therefore allow for more rapid on-line adjustments in behavioral responses and strategic approaches to maximize performance (Bouret and Sara, 2005). Conversely, the attentional system exhibits a greater level of distractibility when the locus-coeruleus has greater tonic (baseline) activation (Bouret and Sara, 2005). Importantly, the activation pattern of the locus-coeruleus exhibits a causal relationship with behavioral performance and attention, as microinjection experiments have demonstrated that increasing the tonic activation of this system increased distractibility and decreased performance, whereas suppressing tonic activation to moderate levels decreased distractibility and optimized performance in primate models (Aston-Jones and Cohen, 2005). Accordingly, activation of the locus-coeruleus and the associated release of norepinephrine appear to exhibit a dose-dependent relationship with cognitive control, as increasing levels of tonic activity appear to transition neural systems away from focusing on goal-directed behaviors, instead prioritizing the sensitivity of the neural system towards detecting potential threats within the external environment (Sara and Bouret, 2012). Stated more plainly, the ability to focus attention is diminished as tonic (baseline)

activity shifts outside of moderate levels of activation.

In this context, acute-exercise-induced cognitive enhancements may therefore result from exercise regulating aspects of locus-coeruleus activation to maintain moderate levels of tonic (baseline) activation, thereby entraining other neural systems to focus attention and enabling task-related phasic bursts of locus-coeruleus activity and the associated release of norepinephrine to facilitate attentional control mechanisms. Although no direct evidence for such a relationship exists to date, treadmill-based aerobic exercise in nonhuman animal models has observed modulations in norepinephrine levels within the locus-coeruleus, amygdala, and hippocampus (Dishman et al., 2000). Further, hippocampal infusions of norepinephrine have been found to result in similar enhancements in object recognition learning as those observed following a single bout of treadmill running (da Silva de Vargas et al., 2017), whereas exercise-induced enhancements in object recognition learning were blocked in rodent models by pharmacologically inhibiting norepinephrine receptors (da Silva de Vargas et al., 2017). Conceptually, such a framework aligns with the popular assertion — built upon a variety of indirect evidence (Davey, 1973; Hogervorst et al., 1996; Ludyga et al., 2018; Murray and Russoniello, 2012; Weingarten and Alexander, 1970) — that cognitive enhancements following exercise occur as a result of changes in arousal. Indeed, the locus-coeruleus acts as a key component of the arousal system (Benarroch, 2009), thus exercise-induced changes in aspects of locus-coeruleus activation have been hypothesized to contribute to the enhancements in cognition observed following exercise (Pontifex et al., 2015). Despite findings from nonhuman animal models supporting the positive effects of aerobic exercise for aspects of cognition related to memory and learning (Voss et al., 2013), a majority of the evidence examining these same effects in humans has examined aspects of cognitive control (Chang et al., 2012; Ludyga et al., 2016; Pontifex et al., 2019). Therefore, to replicate well-established findings from the acute exercise-cognition literature, the present study investigated exercise-induced changes in inhibition and attention while testing the supposition that these enhancements are related to changes in aspects of locus-coeruleus activation.

Pupillometry has emerged as a reliable metric of this dual pattern of activation of the locus-coeruleus, with baseline pupil diameter corresponding to tonic activity in the locus-coeruleus while task-evoked pupillary reactivity corresponds to phasic activity (Gilzenrat et al., 2010; Murphy et al., 2014a). Although changes in luminance provide a potent extrinsic driver of pupil size—such as in the case of the light-evoked pupillary reflex—an extensive body of literature has demonstrated that task-evoked (phasic) pupillary reactivity is also reflective of the internal activity in the locus-coeruleus. Specifically, in vivo multi-unit recordings have observed a strong correlation between moment-to-moment fluctuations in pupil size and the firing rate of noradrenergic neurons in the locus-coeruleus, with changes in neuronal activity reliably preceding changes in pupil diameter (Costa and Rudebeck, 2016; Joshi et al., 2016). Moreover, a growing body of evidence measuring both brain activity and pupil diameter suggests that changes in pupil size provide insight into patterns of neuronal activity in the locus-coeruleus (Aston-Jones and Cohen, 2005; Gilzenrat et al., 2010; Murphy et al., 2014a; Murphy et al., 2011). Indeed, using task-related stimuli that are matched in novelty and luminance, an extensive body of literature in human models has demonstrated that task-evoked pupillary reactivity modulates in response to cognitive workload, with greater pupil dilation occurring in response to higher mental load/conflict (Causse et al., 2016; Geva et al., 2013; Heitz et al., 2008; Scharinger et al., 2015; van Steenbergen and Band, 2013). In contrast to task-evoked pupillary reactivity, tonic (baseline) pupil size is recorded during resting-state periods under stable luminance conditions that do not temporally overlap with stimulus-related activity. Collectively then, assessment of pupil size and task-related changes in pupillary metrics have been recognized as reliable non-invasive indices of tonic and phasic activity in the locus-coeruleus, both at rest and during decision-

making tasks (Costa and Rudebeck, 2016; Murphy et al., 2014a; Sara and Bouret, 2012; Varazzani et al., 2015).

Accordingly, behavioral, neuroelectric, and pupillometric measures were concurrently assessed in response to an inhibitory control task prior to and following 20-min of either aerobic exercise or an active-control condition during two separate, counterbalanced sessions to examine the extent to which this dual-pattern of activation of the locus-coeruleus as indexed by pupil size may underlie acute exercise-induced changes in inhibition and neuroelectric indices of attention. This randomized within-participants repeated-measures cross-over design enabled characterizing the extent to which baseline pupil size (as an index of tonic activation of the locus-coeruleus) and task-evoked pupillary reactivity (as an index of phasic activation of the locus-coeruleus) were influenced by an acute bout of exercise. Further, this approach allowed for determining the extent to which changes in pupil size and pupillary reactivity were associated with exercise-induced changes in inhibition and neuroelectric indices of attention. It was hypothesized that acute bouts of exercise would serve to maintain moderate levels of tonic activation of the locus-coeruleus and enhance task-evoked pupillary reactivity (i.e., larger phasic pupil size), and these changes would be associated with enhancements in inhibition (i.e., shorter reaction time) and neuroelectric indices of attention (i.e., larger P3 amplitude).

2. Method

2.1. Participants

A sample of 58 college-aged young adults ($M = 19.2 \pm 1.0$ years, 32 females; 16% nonwhite) participated in this investigation at Michigan State University. An initial sample of 59 participants were recruited, however one was excluded due to equipment failure. See Fig. 1 for a CONSORT flow diagram of enrollment. All participants reported being free of neurological disorders or physical disabilities, indicated normal or corrected-to-normal vision, and provided written informed consent. The present study was approved by the Institutional Review Board at Michigan State University. Demographic and fitness data for all participants are provided in Table 1.

2.2. Inhibitory control task

Inhibitory control was assessed using a letter version of the Eriksen flanker task (Eriksen and Eriksen, 1974; Moser et al., 2011). Participants were instructed to attend to and to respond as accurately as possible to a centrally presented letter nested among a lateral array of letters that were either congruent (e.g., “T T T T T” or “I I I I I”) or incongruent (e.g., “I I T I I” or “T T I T T”) with the centrally presented letter. Participants completed 80 practice trials followed by 160 trials grouped into two blocks of 80 trials, each consisting of equiprobable congruency. For each block of trials, participants were presented with perceptually similar letter pairs (e.g., pretest block 1: I – T, pretest block 2: U – V, posttest block 1: M – N, posttest block 2: E – F) and were instructed to respond by pressing the button assigned to the centrally presented target stimulus. To ensure a high degree of task difficulty, the button-letter assignments were reversed at the midpoint of each block (e.g., left button press for “T” through the first 40 trials of Block 1, then right button press for “T” through the last 40 trials of Block 1). Flanking letters were presented 55 ms prior to target letter onset, and all five letters remained on the screen for a subsequent 100 ms (for a total stimulus duration of 155 ms) with a response window of 1000 ms and a variable inter-trial interval of 2300, 2400, 2500, 2600, or 2700 ms. All stimuli were 1.5 cm tall white block letters with a mean luminance of 112.2 cd/m^2 . Stimuli were presented focally on a black background on an Asus VG248QE 144 Hz LCD monitor (24.6 cd/m^2) at a distance of approximately 50 cm using PsychoPy, 1.85.2 (Peirce, 2009). Throughout the task, a central fixation dot was presented and participants were instructed to minimize eye blinks. Reaction time was

quantified as the mean speed of responding following the onset of the stimulus only for correct trials while response accuracy was quantified as the proportion of correct responses relative to the number of trials administered. To ensure the integrity of the data, reaction times exceeding the upper bound and response accuracy below the lower bound of 3.5 times the interquartile range were identified as outliers and removed from analysis.

2.3. ERP recording

During completion of the flanker task, EEG activity was recorded from 64 electrode sites (Fpz, Fz, FCz, Cz, CPz, Pz, POz, Oz, Fp1/2, F7/5/3/1/2/4/6/8, FT7/8, FC3/1/2/4, T7/8, C5/3/1/2/4/6, M1/2, TP7/8, CB1/2, P7/5/3/1/2/4/6/8, PO7/5/3/4/6/8, O1/2) arranged in an extended montage based on the International 10-10 system (Chatrian et al., 1985) using a Neuroscan Quik-Cap (Compumedics, Inc., Charlotte, NC). Recordings were referenced to averaged mastoids (M1, M2), with AFz serving as the ground electrode. Additional electrodes were placed above and below the left orbit and on the outer canthus of both eyes to monitor electrooculographic (EOG) activity with a bipolar recording. Continuous data were digitized at a sampling rate of 500 Hz and amplified 500 times with a DC to 70 Hz filter using a Neuroscan SynAmps RT amplifier. The EEG data were then imported into EEGLAB (Delorme and Makeig, 2004) and prepared for temporal ICA decomposition. Data > 2 s prior to the first event marker and 2 s after the final event marker were removed to restrict computation of ICA components to task-related activity. The continuous data were filtered using a 0.05 Hz high-pass Butterworth IIR filter to remove slow drifts (Pontifex et al., 2017a), and the mastoid electrodes were removed prior to ICA decomposition. ICA decomposition was performed using the extended infomax algorithm to extract sub-Gaussian components using the default settings called in the MATLAB implementation of this function in EEGLAB with the block size heuristic ($\text{floor}[\sqrt{\text{EEG.pnts}/3}]$) drawn from MNE-Python (Gramfort et al., 2013). Following ICA decomposition, the eyeblink artifact components were identified using the ica-blinkmetrics function (Pontifex et al., 2017b) and the EEG data were reconstructed without the eyeblink artifact. Following removal of the eye blink components, stimulus-locked epochs were created for correct trials from –100 to 1000 ms around the stimulus, baseline corrected using the –100 to 0 ms pre-stimulus period, and filtered using a zero phase shift low-pass filter at 30 Hz. Trials with artifact exceeding $\pm 100 \mu\text{V}$ were rejected. To ensure the integrity of the signal, stimulus-locked epochs were visually inspected blind to the experimental condition, time point, and congruency prior to computing mean waveforms (mean number of included trials: exercise pretest = 57.7 ± 12.1 , exercise posttest = 55.2 ± 11.8 , active control pretest = 55.7 ± 12.0 , active control posttest = 55.9 ± 11.1). Based on the topographic maxima of the P3 ERP component, the P3 (as an index of attention) was evaluated as the mean across a 9-electrode site region of interest over the central-parietal and parietal regions (C1/Z/2, CP1/Z/2, P1/Z/2; Parks et al., 2015). Amplitude was quantified as the mean amplitude within a 50 ms interval surrounding the largest positive going peak within a 250 to 700 ms latency window following onset of the target stimulus (Pontifex et al., 2015). Peak latency was identified as the time point at which the maximum peak amplitude occurred.

2.4. Pupillometry

During completion of the flanker task, pupillometric activity was recorded at a sampling rate of 60 Hz using a table-mounted infrared eye tracker (The Eye Tribe, Copenhagen, Denmark). Gaze position was calibrated prior to task initiation using a 9-point calibration procedure to ensure quality of the recorded signal. Pupil diameter was recorded in arbitrary units and then imported into EEGLAB (Delorme and Makeig, 2004) where it was scaled to millimeters using the formula $Y = (0.089 \times \text{arbitrary unit}) + (0.005 \times \text{distance from monitor})$ to

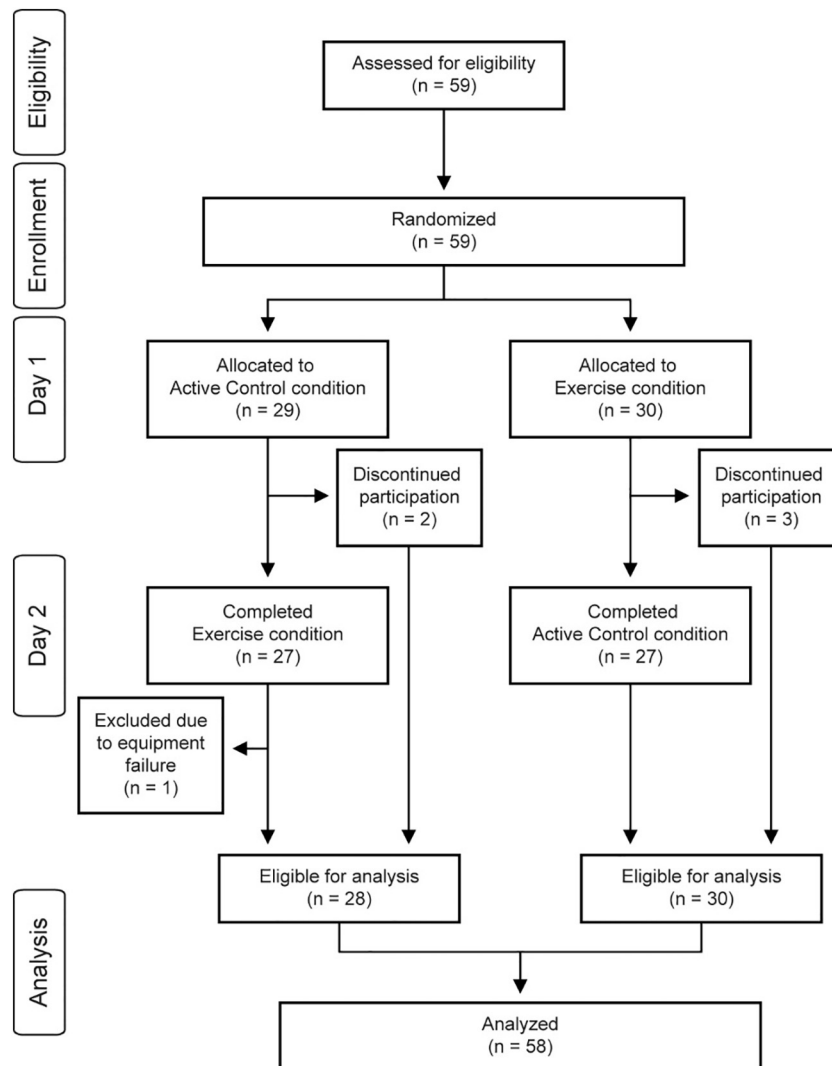


Fig. 1. CONSORT flow chart showing retention of participants through each testing period.

Table 1

Participant demographic and fitness characteristics (mean $\pm$ SD).

Measure	All participants	Males	Females
N	58	26	32
Age (years)	19.2 $\pm$ 1.0	19.3 $\pm$ 1.2	19.2 $\pm$ 0.9
Nonwhite	16%	27%	6%
Body Mass Index (kg/m ²)	24.6 $\pm$ 7.7	24.9 $\pm$ 4.0	24.4 $\pm$ 10.2
VO ₂ max (ml/kg/min)	46.5 $\pm$ 8.7	52.5 $\pm$ 7.7	40.7 $\pm$ 4.8
VO ₂ max Percentile	58.3 $\pm$ 32.5	64.8 $\pm$ 33.3	52.0 $\pm$ 31.0
Lowest Observed Heart Rate (bpm)	72.6 $\pm$ 10.9	70.7 $\pm$ 11.0	74.2 $\pm$ 10.8
Maximum Heart Rate (bpm)	192.7 $\pm$ 10.6	195.8 $\pm$ 9.6	190.1 $\pm$ 10.9
Age Predicted Maximum Heart Rate (bpm)	192.6 $\pm$ 0.7	192.6 $\pm$ 0.8	192.7 $\pm$ 0.6

Note: VO₂max percentile based on normative values for VO₂max (Shvartz and Reibold, 1990).

ensure that any modulations in pupil diameter were not the result of differences in the distance between the pupil and eye tracker across testing sessions (Murphy et al., 2014b). Dilation speed outliers and eyeblinks were removed including a 150 ms window prior to and following each artifact. After linear interpolation of discontinuities in the data, the continuous tonic pupil data were filtered using a 4 Hz low-pass Butterworth IIR filter (Knapen et al., 2016). Response-locked epochs for task-evoked pupillary reactivity were filtered using a 0.02 to 4 Hz

bandpass Butterworth IIR filter (Knapen et al., 2016). Low-pass filtering decreases measurement noise not originating from physiological sources since the pupil functions as a low-pass filter on fast inputs (Hoeks and Levelt, 1993), and high-pass filtering removes slow drift from the signal unaccounted for in the subsequent deconvolution analysis (Knapen et al., 2016). The pupillary response following the eye-blink was then corrected using Finite Impulse Response deconvolution (Knapen et al., 2016).

Tonic pupil size (as an index of tonic activity of the locus-coeruleus) was assessed as the mean pupil diameter within both left and right pupils across 43 epochs of 8000 ms during non-task related fixation periods (a blank black screen presented prior to each block of trials in the flanker task, during the midpoint period when the button-letter assignments were reversed, and at the end of the flanker task). This approach ensured that tonic pupil size was not confounded by phasic changes in pupil size associated with performing the inhibition task (Gilzenrat et al., 2010). As phasic locus-coeruleus activation has been observed to be more strongly related to responses than the target stimulus presentation itself (Rajkowski et al., 2004), task-evoked epochs were created for correct trials from −1500 to 2000 ms around the response and baseline corrected using the −1500 to −1000 ms pre-response period. Trials were automatically rejected if > 60% of the raw data were missing. To ensure the integrity of the signal, all epochs (both tonic and task-evoked) were visually inspected blind to the experimental condition, time point, and congruency prior to computing mean

waveforms across both left and right pupils (mean number of included trials: exercise pretest = 58.0 ± 14.7 , exercise posttest = 57.6 ± 16.4 , active control pretest = 57.1 ± 15.4 , active control posttest = 58.2 ± 14.1). Phasic pupillary reactivity (as an index of phasic activity of the locus-coeruleus) was quantified as the mean pupil size within -1000 to 1500 ms surrounding the response (Laeng et al., 2011; Murphy et al., 2014a; Murphy et al., 2011).

2.5. Cardiorespiratory fitness assessment

In order to quantify participants' level of aerobic fitness and relative exercise intensity, relative peak oxygen consumption (ml/kg/min) was measured using a computerized indirect calorimetry system (ParvoMedics True Max 2400). While participants ran or walked on a motor-driven treadmill (Trackmaster TMX425C) at a constant speed, grade was increased in increments of 2.5% every 2 min until the participant was no longer able to maintain the exercise intensity (American College of Sports Medicine, 2018) alongside recordings of heart rate (Model: H7; Polar Electro, Kempele, Finland) and OMNI rating of perceived exertion (RPE). Consistent with previous investigations, attainment of maximal effort was evidenced by attainment of two of four criteria for reaching $VO_{2\max}$ (Pontifex et al., 2009).

2.6. Procedure

Using a within-participants design, participants visited the laboratory on two separate days (mean days apart 7.9 ± 5.8 days; mean time of day difference, 2.3 ± 2.2 h) in which they had not previously participated in exercise. During the first visit, participants completed informed consent and the Physical Activity Readiness Questionnaire (Thomas et al., 1992) and were counterbalanced into two different session orders (Day 1: exercise, Day 2: active control or Day 1: active control, Day 2: exercise; see Fig. 2) to ensure that any observed effects were unrelated to the specific order in which participants received the experimental conditions (Pontifex et al., 2019). During each session, heart rate was measured at two-minute intervals throughout the experimental condition using a Polar HR monitor (Model H7, Polar Electro, Finland) alongside OMNI ratings of perceived exertion (Robertson et al., 2000). The exercise experimental condition consisted of 20 min of exercise on a motor-driven treadmill at an intensity between 65 and 75% of age predicted maximum ($205.8 - (0.685 * \text{Age})$) (Robergs and Landwehr, 2002) heart rate (HR = 137.0 bpm [95% CI: 135.5 to 138.4]; Heart Rate Reserve = 54.0% [95% CI: 51.4 to 56.5]). To maximize internal validity, an active-control experimental condition was used to reduce confounds related to body position, demand

characteristics/expectancy, and locomotion patterns. This active-control condition consisted of 20 min of walking on a motor-driven treadmill at the lowest possible speed and grade (0.5 mph and 0% grade; HR = 88.9 bpm [95% CI: 84.1 to 93.8]; Heart Rate Reserve = 13.8% [95% CI: 10.2 to 17.4]; see Table 2). To reduce experimenter interaction and non-exercise related stimuli, participants watched an emotionally-neutral video (minutes 65–85 and 85–105; *Wonders of the Universe*, 2011) during the entire period of both experimental conditions. Assessment of behavioral, neuroelectric, and pupillometric indices of cognition were performed in a sound-attenuated testing chamber with standardized luminance using a chair equipped with a chin rest (Earthlite Avila II, Earthlite, LLC, Vista, CA) to minimize head movements. Testing was conducted approximately 30 min prior to and 10 min following each experimental condition (see Table 2). At the end of the second experimental session, participants completed the cardiorespiratory fitness assessment to ensure that the maximal exercise test did not induce potential changes in cognition.

2.7. Statistical analysis

Data was analyzed using multi-level modeling as this approach is robust to unbalanced data (i.e., missing observations) and accounts for a number of sources of variability (Goldstein, 2011; Volpert-Esmond et al., 2018). This approach maximized experimental power by allowing participants with incomplete data due to discontinued participation or outlier removal to be retained within analysis (see Table 3). Dependent variables were mean reaction time, response accuracy (% correct), P3 amplitude, P3 latency, tonic pupil size, and task-evoked pupillary reactivity. Analyses were conducted with $\alpha = 0.05$ and Benjamini-Hochberg false discovery rate control = 0.05 for post-hoc decompositions. All analyses were conducted separately using a 2 (Mode: exercise, active control) $\times$ 2 (Time: pre-test, post-test) $\times$ 2 (Congruency: congruent, incongruent) univariate multi-level model including the random intercept for Participant and Participant by factor interactions. All analyses were performed using the lme4 (Bates et al., 2015), lmerTest (Kuznetsova et al., 2017), and emmeans (Lenth et al., 2017) packages in R version 3.4.0 (R Core Team, 2013) with Kenward-Roger degrees of freedom approximations. For each inferential finding, Cohen's d with 95% confidence intervals were computed as standardized measures of effect size, using appropriate variance corrections for repeated-measures comparisons (d_{rm} ; Lakens, 2013). Given a sample size of 58 participants and beta of 0.20 (i.e., 80% power), the present research design theoretically had sufficient sensitivity to detect t -test differences exceeding $d = 0.37$ (with a two-sided alpha) as computed using G*Power 3.1.2 (Faul et al., 2007). Finally, exploratory Pearson

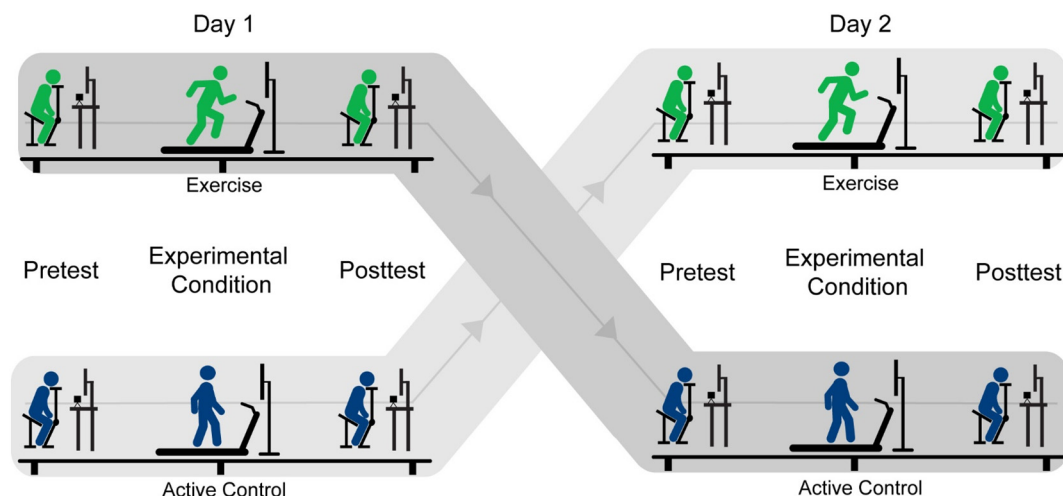


Fig. 2. Schematic diagram depicting within-participants counterbalanced study design.

Table 2
Mean ($\pm$ SD) values for characteristics of the experimental sessions.

Measure	Exercise	Active control	<i>t</i>	<i>p</i>	<i>d_s</i> [95% CI]
Pretest assessment					
Heart rate (bpm)	82.7 $\pm$ 14.8	82.9 $\pm$ 16.1	0.1	0.95	0.01 [−0.4 to 0.4]
Time preceding experimental condition (min)	33.0 $\pm$ 2.8	32.6 $\pm$ 3.5	0.6	0.55	0.1 [−0.3 to 0.5]
Experimental condition					
Heart rate (bpm)	137.0 $\pm$ 5.5	88.9 $\pm$ 17.8	19.1	< 0.001*	3.7 [3.0 to 4.2]
Heart rate reserve (%)	54.0 $\pm$ 9.4	13.8 $\pm$ 13.5	18.2	< 0.001*	3.5 [2.9 to 4.0]
Percent of heart rate max	71.3 $\pm$ 5.5	46.3 $\pm$ 9.9	16.4	< 0.001*	3.1 [2.6 to 3.7]
OMNI RPE	3.4 $\pm$ 1.4	0.4 $\pm$ 0.6	14.7	< 0.001*	2.8 [2.3 to 3.3]
Speed (mph)	3.6 $\pm$ 0.6	0.5	42.5	< 0.001*	5.7 [4.6 to 6.7]
Grade (%)	6.3 $\pm$ 3.1	0	15.3	< 0.001*	2.0 [1.6 to 2.5]
Post-test assessment					
Heart rate (bpm)	89.4 $\pm$ 12.7	81.4 $\pm$ 18.7	2.6	0.009*	0.5 [0.1 to 0.9]
Time following experimental condition (min)	10.4 $\pm$ 3.1	10.3 $\pm$ 2.7	0.2	0.83	0.04 [−0.3 to 0.4]

Note. The *t*-tests reflect the differences between exercise and active control at each time point for each measure of interest. *denotes the *t*-test was significant at *p* < 0.05.

product-moment correlations were computed to examine exercise-induced changes in tonic pupil size and task-evoked pupillary reactivity as they relate to modulations in behavioral and neuroelectric indices of cognition.

3. Results

3.1. Behavioral performance

3.1.1. Reaction time

Analysis of reaction time revealed a Mode $\times$ Time interaction, $F(1, 222) = 4.5$, $p = 0.035$, $f^2 < 0.001$ [95% CI: 0.00 to 0.03]. Post-hoc decomposition of the Mode $\times$ Time interaction was conducted by examining the effect of Time within each Mode. In response to the exercise experimental condition, reaction time was shorter at posttest

(378.5 $\pm$ 55.3 ms) relative to pretest (388.2 $\pm$ 59.2 ms), $t(101) = 3.4$, $p = 0.001$, $d_{rm} = 0.25$ [95% CI: 0.10 to 0.39], see Fig. 3. However, no significant differences in reaction time were observed in response to the active-control condition, $t(100) = 1.2$, $p = 0.2$, $d_{rm} = 0.09$ [95% CI: −0.06 to 0.23]. Analysis of reaction time also revealed a main effect of Congruency, such that congruent trials (358.0 $\pm$ 49.3 ms) were shorter than incongruent trials (409.3 $\pm$ 50.2 ms), $t(56) = 35.0$, $p < 0.001$, $d_{rm} = 1.08$ [95% CI: 0.87 to 1.28].

Response Accuracy: Analysis of response accuracy revealed a main effect of Congruency, $F(1, 56) = 80.5$, $p < 0.001$, $d_{rm} = 0.84$ [95% CI: 0.60 to 1.08], with greater accuracy for congruent (94.6 $\pm$ 5.7%) relative to incongruent (89.4 $\pm$ 8.6%) trials.

Table 3
Statistical summary of post-hoc comparisons at pre-test relative to post-test for each mode.

	Pre-test	Post-test	<i>t</i>	<i>p</i>	<i>d_{rm}</i> [95% CI]
Reaction time (ms)					
Exercise	388.2 $\pm$ 59.2	378.5 $\pm$ 55.3	3.4	0.001*	0.3 [0.1 to 0.4]
Missing cases (#)	2	3			
Active control	385.7 $\pm$ 54.4	382.3 $\pm$ 55.4	1.2	0.2	0.1 [−0.1 to 0.2]
Missing cases (#)	3	3			
Response accuracy (% correct)					
Exercise	91.6 $\pm$ 8.79	92.3 $\pm$ 7.9	1.3	0.2	0.2 [−0.1 to 0.4]
Missing cases (#)	2	3			
Active control	92.3 $\pm$ 6.9	91.7 $\pm$ 7.7	1.0	0.3	0.1 [−0.1 to 0.3]
Missing cases (#)	3	3			
P3 amplitude (μ V)					
Exercise	7.9 $\pm$ 2.9	8.2 $\pm$ 3.4	2.7	0.009*	0.2 [0.04 to 0.3]
Missing cases (#)	2	2			
Active control	7.9 $\pm$ 2.9	7.7 $\pm$ 3.0	1.7	0.09	0.1 [−0.01 to 0.2]
Missing cases (#)	4	3			
P3 latency (ms)					
Exercise	372.6 $\pm$ 53.3	371.2 $\pm$ 51.1	0.3	0.8	0.03 [−0.2 to 0.2]
Missing cases (#)	2	2			
Active control	384.8 $\pm$ 51.1	380.3 $\pm$ 60.0	0.9	0.4	0.1 [−0.1 to 0.3]
Missing cases (#)	4	3			
Tonic pupil diameter (mm)					
Exercise	3.7 $\pm$ 1.2	3.8 $\pm$ 1.0	0.3	0.8	0.04 [−0.2 to 0.3]
Missing cases (#)	2	2			
Active control	3.6 $\pm$ 1.2	3.7 $\pm$ 1.3	0.2	0.9	0.03 [−0.3 to 0.3]
Missing cases (#)	4	3			
Response-locked task-evoked pupillary reactivity (mm)					
Exercise	−0.003 $\pm$ 0.020	−0.001 $\pm$ 0.020	1.1	0.3	0.12 [−0.09 to 0.33]
Missing cases (#)	2	2			
Active control	−0.005 $\pm$ 0.026	0.000 $\pm$ 0.025	2.7	0.007*	0.26 [0.07 to 0.44]
Missing cases (#)	8	5			

Note. The *t*-tests reflect the differences between pre-test and post-test for each experimental condition for each dependent variable. *denotes the *t*-test was significant at *p* < 0.05.

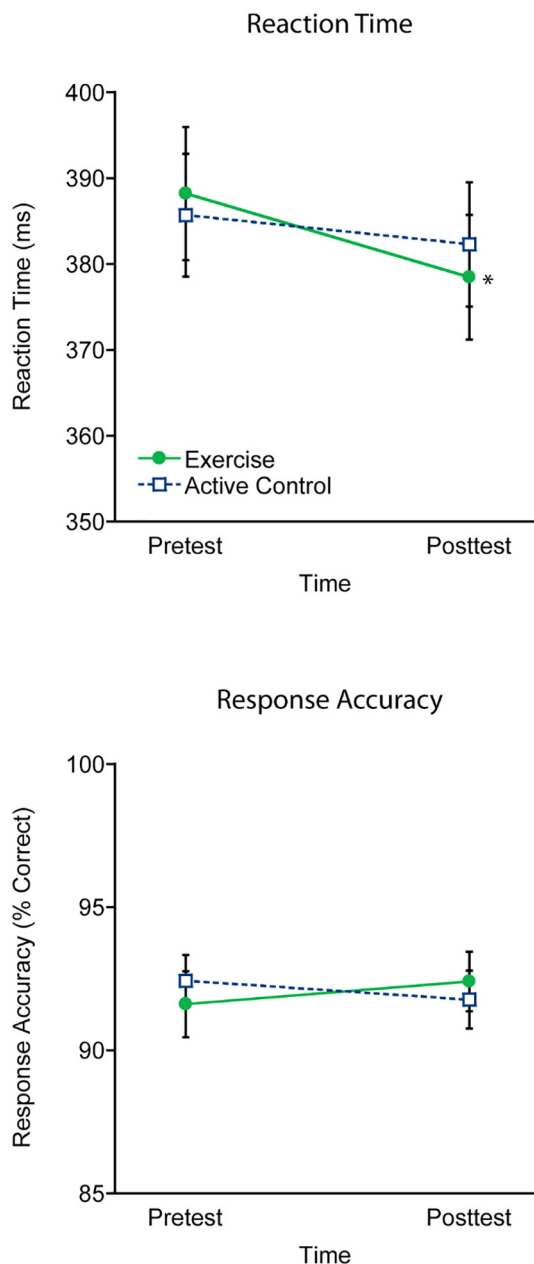


Fig. 3. Mean ($\pm$ SE) reaction time (top) and response accuracy (bottom) collapsed across congruency for each mode and time point. * $p < 0.05$.

3.2. Neuroelectric activity

3.2.1. P3 ERP amplitude

Analysis of P3 amplitude revealed a Mode $\times$ Time interaction, $F(1, 223) = 15.2$, $p < 0.001$, $f^2 = 0.55$ [95% CI: 0.22 to 1.11]. Post-hoc breakdown of the Mode $\times$ Time interaction was conducted by examining the effect of Time within each Mode. In response to the exercise condition, P3 amplitude was increased at posttest ($8.2 \pm 3.4 \mu\text{V}$) relative to pretest ($7.9 \pm 2.9 \mu\text{V}$); $t(109) = 2.7$, $p = 0.009$, $d_{rm} = 0.15$ [95% CI: 0.04 to 0.26], whereas no such difference manifested in response to the active-control condition, $t(113) = 1.7$, $p = 0.09$, $d_{rm} = 0.08$ [95% CI: -0.01 to 0.17]; see Figs. 4 and 5.

For comparison with prior investigations assessing changes in P3 amplitude only following exercise and control periods, the Mode $\times$ Time interaction was also broken down by examining the effect of Mode within each Time. At pretest, no differences were observed in P3 amplitude between the exercise and active-control conditions, t

(72) = 0.3, $p = 0.8$, $d_{rm} = 0.02$ [95% CI: -0.11 to 0.15]. Whereas at post-test, analysis revealed larger P3 amplitude for the exercise ($8.2 \pm 3.4 \mu\text{V}$) relative to the active-control ($7.7 \pm 3.0 \mu\text{V}$) condition, $t(71) = 2.7$, $p = 0.009$, $d_{rm} = 0.20$ [95% CI: 0.05 to 0.34], see Fig. 4. The overall analysis of P3 amplitude also revealed a main effect of Congruency, $F(1, 56) = 9.5$, $p = 0.003$, $f^2 = 0.34$ [95% CI: 0.09 to 0.74], with smaller amplitude for congruent ($7.8 \pm 3.0 \mu\text{V}$) relative to incongruent ($8.1 \pm 3.1 \mu\text{V}$) trials.

3.2.2. P3 ERP latency

Analysis of P3 latency revealed main effects of Mode and Congruency, $F_s(1, 56) \geq 4.0$, $p_s \leq 0.05$, $f^2_s \geq 0.04$ [95% CI: 0.00 to 1.79]. In response to the exercise condition, P3 latency was shorter (371.9 ± 52.1 ms) relative to the active-control condition (382.5 ± 55.7 ms), $t(54) = 2.0$, $p = 0.05$, $d_{rm} = 0.23$ [95% CI: 0.00 to 0.46]; however, this effect was not observed to interact with Time ($F(1, 222) = 0.4$, $p = 0.5$, $f^2 = 0.00$ [95% CI: 0.00 to 0.03]). Shorter P3 latency was also observed for congruent trials (361.8 ± 53.7 ms) relative to incongruent trials (392.6 ± 50.0 ms), $t(56) = 10.0$, $p < 0.001$, $d_{rm} = 0.73$ [95% CI: 0.53 to 0.92].

3.3. Pupillometric activity

3.3.1. Tonic pupil size

Analysis of tonic pupil size revealed no main effects or interactions, $F_s(1, 54) \leq 0.5$, $p_s \geq 0.5$, $f^2_s \leq 0.36$ [95% CI: 0.00 to 0.78]; see Fig. 4.

3.3.2. Task-evoked pupillary reactivity

Analysis of task-evoked pupillary reactivity revealed a main effect of Time such that pupillary reactivity was smaller at pretest (-0.004 ± 0.023 mm) than at posttest (0.0 ± 0.023 mm), $t(57) = 2.6$, $p = 0.011$, $d_{rm} = 0.21$ [95% CI: 0.05 to 0.37]. Analysis of task-evoked pupillary reactivity also revealed a main effect of Congruency, with diminished task-evoked reactivity for congruent (-0.005 ± 0.022 mm) relative to incongruent (0.0 ± 0.023 mm) trials, $t(58) = 3.1$, $p = 0.003$, $d_{rm} = 0.26$ [95% CI: 0.09 to 0.43].

3.4. Correlations between outcome variables

For both tonic pupil size and task-evoked pupillary reactivity, no associations were observed between the exercise-induced changes in pupil size and exercise-induced changes in either reaction time, response accuracy, P3 amplitude, or P3 latency ($p_s \geq 0.07$; see Table 4).

4. Discussion

The aim of the present investigation was to provide new insight into the extent to which aspects of locus-coeruleus activation are associated with improvements in inhibition and neuroelectric indices of attention following a single bout of aerobic exercise. Findings revealed that following a single bout of aerobic exercise at moderate intensity, participants exhibited shorter reaction time and enlarged P3 amplitude relative to the active-control condition. Contrary to our a priori hypothesis, however, no exercise-related effects were observed for either tonic baseline pupil size (as an index of tonic activation of the locus-coeruleus) or task-evoked pupillary reactivity (as an index of phasic activation of the locus-coeruleus), nor were pupillometric changes associated with exercise-induced changes in inhibition or neuroelectric indices of attention. These negative findings were obtained, in spite of the fact that task-evoked pupillary reactivity did differ as expected between congruent and incongruent trials, underscoring the validity of our pupillometric approach.

Collectively, findings from the present investigation replicate the extant acute-exercise literature, observing enhancements in inhibition and neuroelectric indices of attention following the cessation of a single 20-minute bout of moderate intensity aerobic exercise. Specifically,

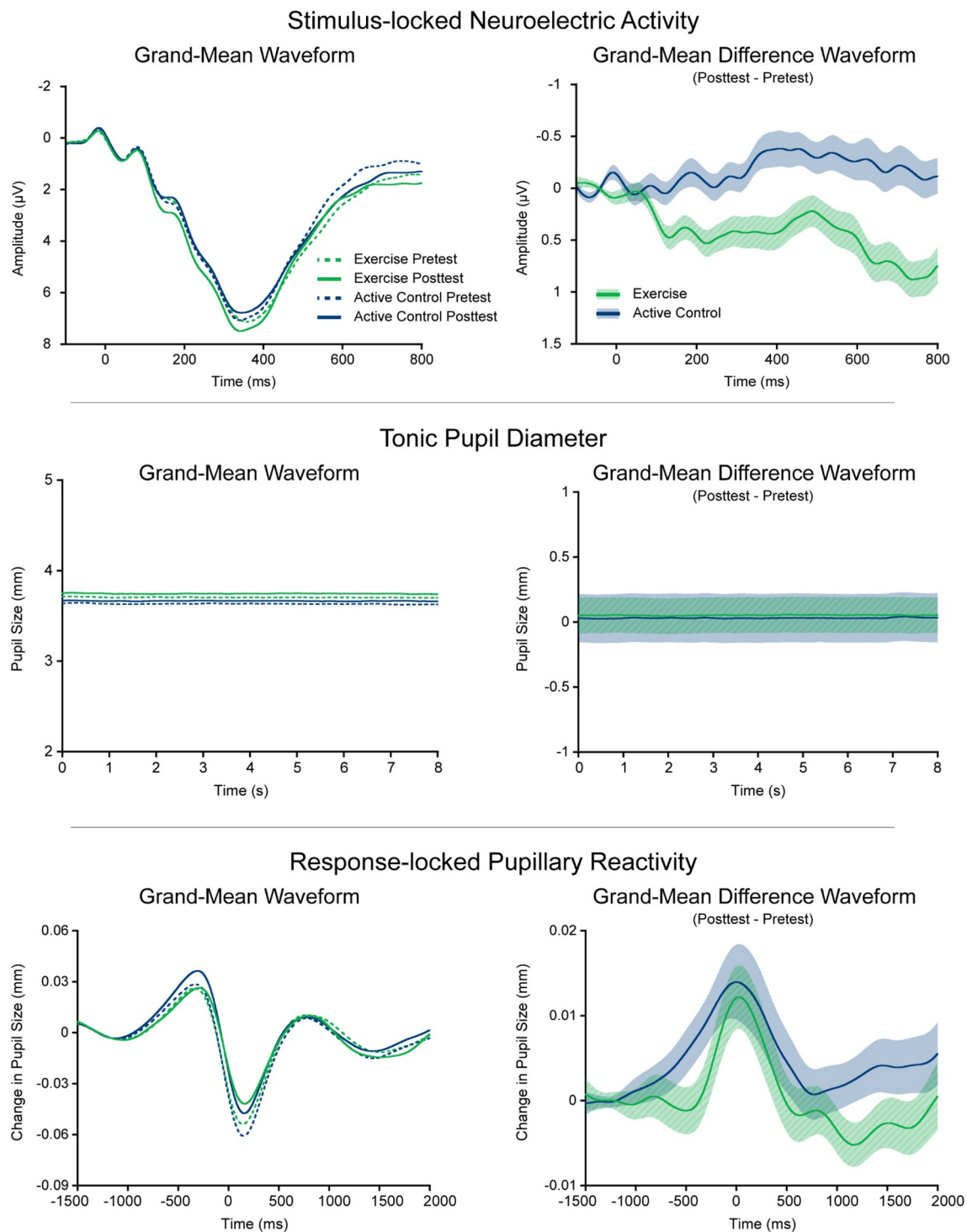


Fig. 4. Illustration of the effects of mode and time for stimulus-locked neuroelectric potentials and pupillometric activity. Figures on the left show the grand mean waveform for each mode and time point whereas figures on the right show the difference wave ($\pm$ SE) of the change from pre- to posttest for each mode. Top: Stimulus-locked ERP waveforms collapsed across congruency and the 9-electrode site region of interest over the central-parietal and parietal regions (C1/Z/2, CP1/Z/2, P1/Z/2). Middle: Tonic pupil size as assessed prior to, in the middle of, and following the cognitive assessment during a blank screen period. Bottom: Response-locked phasic pupillary reactivity collapsed across congruency.

consistent with [Kamijo et al. \(2007\)](#), in response to a letter flanker task, shorter reaction time was observed following exercise, relative to the active-control condition, thereby suggesting an enhanced ability to manage perceptually-induced response interference. Further, although the vast majority of the present literature investigating the effects of acute exercise on neuroelectric indices of attention has utilized either a within-participants post-experimental condition comparison ([Hillman](#)

[et al., 2009, 2003](#); [Kamijo et al., 2009, 2007](#); [Kamijo et al., 2004b](#); [Kao et al., 2017](#); [Pontifex et al., 2013](#); [Scudder et al., 2012](#)) or a between-participants pre-post exercise comparison ([Kumar et al., 2012](#); [Magnié et al., 2000](#); [Nakamura et al., 1999](#); [Yagi et al., 1999](#)), findings from the present investigation using a randomized, within-participants crossover pre/post experimental design observed similar exercise-induced enhancements in P3 amplitude. Specifically, greater P3 amplitude was

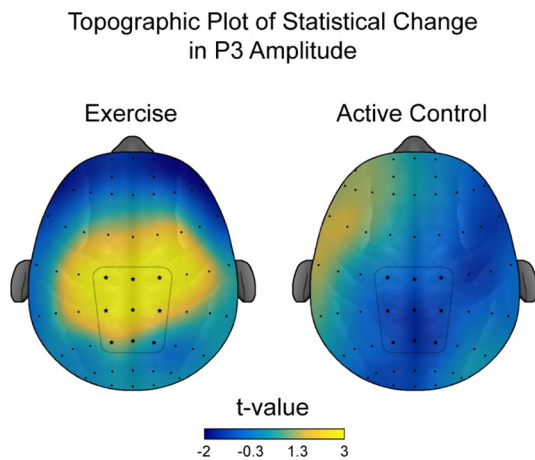


Fig. 5. Topographic maps of the statistical change (*t*-value statistic) from pre- to posttest for each mode for P3 amplitude collapsed across congruency. The 9-electrode site region of interest aligned with the topographic maxima of P3 amplitude (Polich, 2007) that was utilized for analysis is indicated by the bounding box.

observed following exercise relative to following the active-control condition, with an increase in P3 amplitude from pre- to post-exercise. Thus, the present investigation contributes to a growing body of evidence demonstrating the positive effects of acute bouts of exercise for inhibition and neuroelectric indices of attention, despite methodological differences in the research design and the use of an active-control rather than passive-control condition (Pontifex et al., 2019). In spite of using an active control condition, these findings replicate acute exercise-induced enhancements in cognition that have been obtained with other passive control conditions (Pontifex et al., 2019)—advancing our understanding of appropriate control conditions for these types of investigations.

Novel to the extant literature was the assessment of the influence of exercise on pupillometric measures as an index of the dual patterns of activation of the locus-coeruleus. In contrast to our a priori hypothesis, neither tonic baseline pupil size (as an index of tonic activity in the locus-coeruleus) nor task-evoked pupillary reactivity (as an index of phasic activity in the locus-coeruleus) were observed to modulate in response to either the exercise or active control conditions, despite

replication of behavioral and neuroelectric findings. Consequently, the present findings would appear to suggest that neither the exercise nor the active-control conditions serve to influence the level of activation of the locus-coeruleus. Given that neither baseline pupil size nor task-evoked pupillary reactivity were observed to change in response to acute exercise — as well as the lack of an association between changes in pupil size and exercise-induced enhancements in inhibition and neuroelectric indices of attention—the present findings provide compelling preliminary evidence to suggest that activation of aspects of the locus-coeruleus may not be a mechanism underlying such exercise-induced enhancements in college-aged adults.

However, the present findings do not necessarily rule out the potential influence of norepinephrine in this relationship. That is, although typically discussed as a neuromodulatory system, given that the locus-coeruleus serves as the primary cortical source of norepinephrine (Asan, 1998; Berridge and Waterhouse, 2003; Jones and Moore, 1977; Moore and Bloom, 1978; Nieuwenhuys, 2012; Samuels and Szabadi, 2008), the vast majority of the evidence demonstrating that the locus-coeruleus norepinephrine system is a potent modulator of the P3 ERP component — and attentional states more generally — has focused upon the influence of norepinephrine (Nieuwenhuis et al., 2005). In this context, increases in cortical norepinephrine concentrations have been found to enhance the synaptic responsivity of neurons such as pyramidal neurons that contribute to the generation of the P3 ERP (Nieuwenhuis et al., 2005). Thus, if acute exercise served to increase the production, availability, absorption, binding, or regulation of norepinephrine, then enhancements in cognition should manifest. Interestingly, psychopharmacological evidence has demonstrated that inhibiting the binding of norepinephrine to beta-adrenergic receptors in rodent models served to attenuate physical activity-induced object recognition learning (da Silva de Vargas et al., 2017). Conversely, in a separate group of rodents, hippocampal infusions of norepinephrine resulted in enhancements in object recognition learning at a level similar to those observed 21 days following a single 30 min bout of treadmill running (da Silva de Vargas et al., 2017). Accordingly, further research is necessary to examine the extent to which exercise influences norepinephrine in human models and the extent to which these changes relate to exercise-induced enhancements in cognition.

Despite the methodological strengths of the present investigation, there are a number of limitations that warrant further discussion. First, although the population assessed within the present investigation is

Table 4

Pearson correlations between exercise-induced changes in pupil size and exercise-induced changes in reaction time, response accuracy, P3 amplitude, and P3 latency.

Variable	Reaction time change	Response accuracy change	P3 amplitude change	P3 latency change	Tonic pupil size change	Task-evoked pupillary reactivity change
Reaction time change						
Correlation	–					
Sig.	–					
Response accuracy change						
Correlation	–0.107	–				
Sig.	0.456	–				
P3 amplitude change						
Correlation	–0.145	0.075	–			
Sig.	0.311	0.600	–			
P3 latency change						
Correlation	0.334	0.016	–0.015	–		
Sig.	0.017*	0.910	0.917	–		
Tonic pupil size change						
Correlation	–0.056	0.244	0.213	–0.024	–	
Sig.	0.698	0.085	0.133	0.866	–	
Task-evoked pupillary reactivity change						
Correlation	–0.256	–0.044	0.132	–0.060	0.058	–
Sig.	0.069	0.761	0.356	0.677	0.686	–

Note. Reaction time and response accuracy are collapsed across congruency. P3 amplitude and P3 latency are averaged across the 9-electrode site region of interest over the central-parietal and parietal regions (C1/Z/2, CP1/Z/2, P1/Z/2). *denotes correlation was significant at $p < 0.05$.

consistent with the vast majority of the extant acute exercise and cognition literature (Pontifex et al., 2019), the college-aged adult participants exhibited fairly consistent tonic pupil diameters suggestive of being in a moderate tonic state. Thus, there was likely little capacity for the locus-coeruleus to respond to exercise and active-control conditions. Changes in activity in the locus-coeruleus may therefore be more readily apparent in populations exhibiting a greater tendency to fall outside this optimal level of tonic engagement or in studies using passive-control conditions. Given that the pupil reacts slowly, the relatively rapid stimulus presentation rate may also have attenuated the task-evoked pupillary response. However, promisingly, the present investigation did replicate the robust finding of greater pupillary reactivity for incongruent relative to congruent trials (Laeng et al., 2011; Scharinger et al., 2015), demonstrating that phasic activity in the locus-coeruleus (as indexed by task-related pupillary reactivity) varies according to task demands (Critchley et al., 2005) and with cognitive control adjustments (Ebitz and Platt, 2015). Similarly, though luminance changes associated with the onset of the visual stimuli may have attenuated the task-evoked pupillary response, it is important to highlight that such a confound is similarly prevalent across both pre- and posttest for both the exercise and active-control conditions—reducing the extent to which luminance factors may have impacted the observed findings. Finally, additional research is necessary to understand the extent to which individual differences may moderate the effects of exercise on locus-coeruleus activation. Given that age and aerobic capacity have been associated with alterations to expression of neuromodulators in the locus-coeruleus (P. S. Murray et al., 2010) and these individual differences have been shown to modulate exercise-induced effects on cognitive function (Chang et al., 2012; Ludyga et al., 2016), further research is warranted to determine the degree to which these differences moderate exercise-induced changes in locus-coeruleus activation.

Collectively, findings from the present investigation indicate that enhancements in inhibition and neuroelectric indices of attention resulting from a single bout of moderately-intense aerobic exercise are not influenced by changes in aspects of locus-coeruleus activation as indexed by tonic baseline pupil size and task-evoked pupillary reactivity. Thus, these findings provide preliminary evidence to suggest that activation of the locus-coeruleus is not a mechanism underlying exercise-induced enhancements in cognition. Accordingly, future research should examine the potential contributions of norepinephrine, alongside other potential mechanisms, to determine how such alterations in cognition following single bouts of exercise manifest. Such knowledge might contribute towards a greater understanding of how best to optimize the dose of exercise to incur the greatest cognitive enhancements, the minimum dose necessary to induce such changes, and the persistence of enhancements in cognition following the cessation of exercise bouts.

CRedit author statement

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