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SCIENTIFIC REPORTS



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Fatigue-related impairments in oculomotor control are prevented by norepinephrine-dopamine reuptake inhibition

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Fatigue-induced reductions in saccade velocity have been reported following acute, prolonged exercise. Interestingly, the detrimental impact of fatigue on oculomotor control can be prevented by a moderate dose of caffeine. This effect may be related to central catecholamine upregulation via caffeine's action as an adenosine antagonist. To test this hypothesis, we compared the protective effect of caffeine on oculomotor control post-exercise to that of a norepinephrine-dopamine reuptake inhibitor. Within a placebo-controlled crossover design, 12 cyclists consumed placebo, caffeine or a norepinephrine-dopamine reuptake inhibitor (bupropion) during 180 minutes of stationary cycling. Saccades, smooth pursuit and optokinetic nystagmus were measured using infrared oculography. Exercise fatigue was associated with an $8 \pm 11\%$ reduction in the peak velocity of prosaccades, and a $10 \pm 11\%$ decrement in antisaccade peak velocity. Optokinetic nystagmus quick phases decreased in velocity by $15 \pm 17\%$. These differences were statistically significant ($p < 0.05$). Norepinephrine-dopamine reuptake inhibition and caffeine prevented fatigue-related decrements in eye movement velocity. Pursuit eye movements and visual attention were unaffected. These findings show that norepinephrine-dopamine reuptake inhibition protects oculomotor function during exercise fatigue. Caffeine's fatigue-reversing effects on eye movements appear to be mediated, at least in part, via modulation of central catecholamines.

Saccades are rapid changes in fixation that align the foveae with salient targets in the visual field¹. In a recent study, we reported that saccade velocity is reduced following prolonged exercise and that this effect can be prevented by the administration of caffeine². This suggests that caffeine exerts a protective effect on oculomotor control during exercise-induced fatigue². Furthermore, the detrimental effect of a corticospinal motor system fatigue on the oculomotor system suggests that aspects of exercise-induced central fatigue are ubiquitous within the brain.

The mechanisms responsible for central fatigue are not well understood; though research involving exercising rodents suggests that prolonged physical activity is associated with widespread alterations in the activity of neurotransmitters such as serotonin, dopamine and noradrenaline^{3–5}. As such, it has been proposed that these monoamines are involved in the development of fatigue during exercise⁶. Contrary to early hypotheses regarding the involvement of serotonin in the development of central fatigue⁷, it appears that serotonin does not act as a key factor⁸. Instead, the central catecholamines dopamine and norepinephrine are thought to play a principal role in central fatigue.

Studies exploring the influence of central catecholamines on human performance report positive effects on exercise capacity (time to exhaustion), time trial performance and subjective effort sense following the enhancement of central catecholaminergic neurotransmission via targeted pharmacological treatments^{9–13}. Additionally, caffeine, which indirectly upregulates dopamine and accelerates the synthesis and turnover of norepinephrine via adenosine antagonism¹⁴, is a common ergogenic aid in prolonged exercise^{15–18}. Overall, these findings provide indirect evidence for an involvement of central catecholamines in the development of central fatigue during whole-body, prolonged exercise. However, measures of exercise performance may be susceptible to confounds

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from peripheral factors, subject motivation and learning effects. Furthermore, while the benefits of caffeine on exercise performance are largely attributed to its effects on the central nervous system, caffeine also has several actions in the periphery that influence the contractile properties of skeletal muscle, such as increased mobilization of intracellular calcium, and inhibition of phosphodiesterases¹⁹, that may contribute to certain performance enhancements.

Our previous findings in the oculomotor system demonstrated direct, fatigue-related impairments on motor control and showed that these impairments can be prevented by a moderate dose of caffeine². We propose that the protective effects of caffeine on oculomotor control during fatiguing exercise are the result of indirect upregulation of central catecholaminergic neurotransmission. In this study the effects of caffeine were compared to bupropion, a drug that modulates noradrenergic and dopaminergic reuptake inhibition, increasing the concentration of dopamine and norepinephrine in several brain regions^{20–23}. Acute therapeutic doses of bupropion have previously been reported to confer an ergogenic effect during exercise^{9,10}.

Oculomotor control was investigated by assessing saccades, smooth pursuit eye movements and optokinetic nystagmus (OKN). Like saccades, smooth pursuit eye movements are constantly utilised during normal visual activity, stabilising visual images on the retina as objects of interest move through the visual field^{24,25}. OKN is an involuntary oculomotor response elicited by large-scale movement of the visual field, resulting in alternating slow tracking movements (slow phase) followed by rapid, resetting eye movements (quick phase), similar to smooth pursuit and saccades, respectively^{26,27}. The oculomotor control of eye movements is related to the spatial orienting of attention²⁸. To quantify any effects of fatigue on attention, covert spatial attention, or the orienting of attention that occurs without an eye movement toward the attended location, was measured using a cueing paradigm²⁹.

In this study a three-hour cycling exercise protocol was used to provide a physiological challenge capable of inducing central fatigue. Prolonged cycling has long-lasting effects on the central nervous system, reducing voluntary activation of the knee extensors for up to 45 minutes following exercise cessation³⁰ and causing significant perturbations to cerebral energetics^{31,32}. Saccades, smooth pursuit, optokinetic nystagmus and covert spatial attention were assessed to investigate the influence of caffeine and norepinephrine-dopamine reuptake inhibition (NDRI) on oculomotor control in the context of prolonged, fatiguing exercise. We predicted that caffeine's ability to preserve oculomotor control following fatiguing exercise is related to its actions on central catecholamines, therefore a similar influence will be exerted by NDRI.

Experimental Procedures

Participants. Twelve healthy volunteers (7 females, maximal aerobic capacity $56 \pm 6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) with a mean age of 25 (20–48) years and body mass of $74 \pm 16 \text{ kg}$, participated in the study. Participants provided written informed consent and visited the laboratory on four occasions to take part in a protocol conducted in accordance with the Declaration of Helsinki and approved by the University of Auckland Human Ethics Committee. Based on responses to a health screening questionnaire, participants were free of medical contraindications to exercise, medication influencing central nervous system function, and had normal or corrected to normal vision.

Experimental design. Caffeine ($7.5 \text{ mg} \cdot \text{kg}^{-1}$ body mass), bupropion (Zyban, GlaxoSmithKline, Auckland, NZ; maximum therapeutic dose: 300 mg/day) or placebo (maltodextrin) treatments were administered by capsule within a double-blind, placebo-controlled, repeated measures, randomised cross-over design. Participants completed three experimental trials involving 180 minutes of continuous cycling with a self-selected cadence at a work rate equivalent to 60% of maximal aerobic capacity. A minimum of 5 days separated cross-over phases. Caffeine was administered in two doses – a $2.5 \text{ mg} \cdot \text{kg}^{-1}$ body mass dose 1 hour before the exercise protocol, and a $5 \text{ mg} \cdot \text{kg}^{-1}$ body mass at 90 minutes into exercise. A 300 mg dose of a NDRI (bupropion) was administered before the exercise protocol, and a placebo pill was given 90 minutes into exercise. In the placebo treatment, a capsule filled with maltodextrin was administered before the exercise protocol and at the 90 minute time point. During exercise, participants were given a carbohydrate solution to maintain hydration and euglycaemia (see *Experimental protocol* below). In all experimental trials, participants completed a battery of visual tasks (see below, *visual performance measures*) before exercise (pre-exercise), and immediately after the exercise protocol (post-exercise). A schematic of the experiment workflow and design is depicted in Fig. 1.

Preliminary tests. A minimum of one week before the first experimental trial, participants visited the lab for familiarisation with study protocols and the visual test battery tasks (see below, *Visual test battery*). A maximal cardiopulmonary exercise test on an electromagnetically braked cycle ergometer (Velotron Dynafit Pro, Seattle, WA, USA) with respiratory gas analysis equipment (pneumotachometer, MLT1000L, ADInstruments; paramagnetic oxygen analyser, S-3A/I, AEI Technologies; infrared carbon dioxide analyser, CD-3A, AEI Technologies) was performed to measure peak oxygen uptake. Maximal aerobic capacity ($\text{VO}_2 \text{ max}$) was estimated and used to prescribe a power output requiring 60% $\text{VO}_2 \text{ max}$ for the experimental trials.

Experimental protocol. Participants arrived at the laboratory following a 12 hour overnight fast. Participants were instructed to abstain from caffeine-containing items for 24 hours before each experimental session. Body mass was measured following voiding of the bladder. After this, the first treatment dose was consumed with a breakfast cereal. The quantity of breakfast was self-selected on the first visit and repeated for the remaining trials. Immediately following breakfast, participants completed the visual test battery (~50 minutes). Participants then began 180 minutes of continuous cycling performed in a temperature-controlled exercise chamber maintained at 18° Celsius. At 90 minutes into exercise, participants received a second treatment dose. A carbohydrate solution ($0.7 \text{ g carbohydrate} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) was ingested every 15-minutes throughout exercise. Mean rates of fluid and carbohydrate ingestion were $645 \pm 141 \text{ ml} \cdot \text{h}^{-1}$ and $52 \pm 11 \text{ g} \cdot \text{h}^{-1}$, respectively. Heart rate was recorded at 15 minute intervals using a heart rate monitor (FS1, Polar Electro, Kempele, Finland). Coincident with heart rate

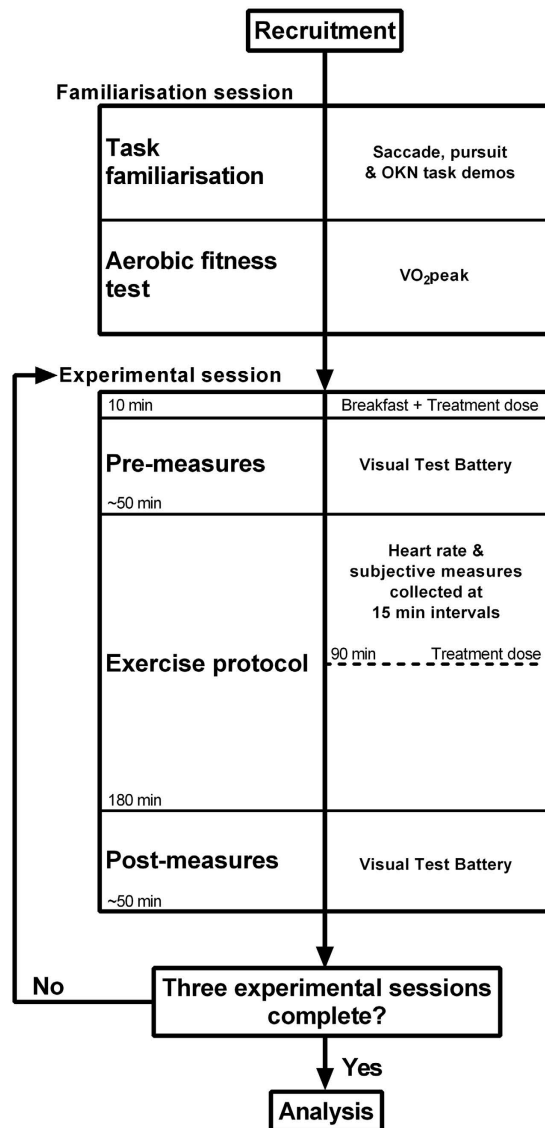


Figure 1. Experimental workflow. Twelve participants were recruited. A familiarisation session accustomed participants with the visual test battery. The three experimental sessions involved completion of the visual test battery at two time points, separated by prolonged cycling exercise lasting 180 minutes. Treatment doses were administered with breakfast, immediately before initial performance of the visual test battery (pre measures), and at 90 minutes through exercise.

recording, participants' perceived exertion and felt arousal was self-rated on visual analogue scales. After the exercise protocol, participants completed the visual task battery. A post-exercise measurement of body mass was obtained to assess fluid loss or gain as a result of exercise.

Visual test battery. The visual test battery consisted of five discrete tasks. Participants were comfortably seated in a quiet, darkened room for the duration of the visual test battery. Stimuli were presented on a cathode ray tube monitor (Philips 109S2; 1280 × 1024 pixel resolution; 85 Hz refresh rate) at a viewing distance of 66 cm. Head movements were minimized using a chin and forehead rest. In four of the tasks, eye movements were tracked with infrared cameras sampling at a rate of 400 Hz (ViewPoint Eye Tracker, Arrington Research Systems, Scottsdale, USA). A 16-point calibration procedure was carried out before the beginning of each task. All participants completed visual tasks in the same order for all experimental sessions. This reduced variance caused by task sequencing effects at the expense of causing the time from exercise cessation to vary across the different tasks.

Antisaccade. Each trial began with the presentation of a black, centrally-located circular fixation point subtending a visual angle of 0.5°. A black, circular peripheral target stimulus (0.5° diameter) appeared ± 10° to the left or right of the central fixation point and was visible for a duration of 1000 ms. The peripheral target was presented in *gap* or *overlap* conditions³³. In the *gap* condition, the central fixation point was presented for 800 ms and extinguished 200 ms before peripheral target presentation. In the *overlap* condition, the central fixation point

remained visible throughout the trial. Participants were instructed to “look away from the peripheral target stimulus to a mirror opposite position on the screen, and to move your eyes to that position as quickly and accurately as possible”. A total of 100 trials, 50 trials per condition, were presented. The sequence of gap, overlap, right target location and left target location was randomised.

Prosaccade. Prosaccade and antisaccade tasks had identical stimulus presentation. However, in the prosaccade task, participants were instead instructed to move their eyes to look at the target stimulus as quickly and accurately as possible.

Smooth pursuit. A triangular target waveform was presented at three velocities ($5^\circ \cdot s^{-1}$, $10^\circ \cdot s^{-1}$ and $30^\circ \cdot s^{-1}$). The target, a circular black dot (0.8° diameter), was presented in the centre of the screen (0°) for 1000 ms at the start of each trial. Following fixation, the target moved horizontally until it reached $\pm 15^\circ$, where it reversed direction abruptly and moved to the opposite side. The direction of the initial ramp was randomised. One trial consisted of 5.5 passes of the target across the display screen. 21 total trials were performed, with each target velocity presented 7 times. The sequence of target velocity and initial ramp direction were randomised. Participants were instructed to follow the target with their eyes as accurately as possible.

Optokinetic nystagmus (OKN). To evoke an OKN response, participants were presented with a stimulus screen consisting of 100% contrast square wave gratings with a fundamental spatial frequency of 0.833 cycles per degree. Gratings were shown for a duration of 20 seconds per trial at two velocities ($5^\circ \cdot s^{-1}$ and $10^\circ \cdot s^{-1}$) and two stimulus directions (right to left, or left to right) for two trials each, resulting in 8 total trials. A blank, black screen was presented between trials for 4 seconds. Participants were instructed to watch the screen, keeping the stimulus in focus. The objective of these instructions was to encourage a “stare” OKN.

Covert spatial attention. A Posner cueing task²⁹ with endogenous and exogenous cueing conditions assessed covert attentional orienting. This task has been employed previously to assess the influence of caffeine on covert spatial attention³⁴. The start of each trial was marked with a display (1000 ms duration) consisting of a central fixation cross and two peripheral boxes located 10° laterally to the fixation cross. A visual cue was then presented for 200 ms and extinguished. After a further 200 ms, a peripheral target (black circle, radius of 0.5°) appeared in the right or left peripheral box for 150 ms. Participants were instructed to maintain fixation on the central cross and respond as quickly as possible with a key press (left arrow key or right arrow key) when they detected a peripheral target. Two types of cues were presented. *Endogenous cues* consisted of a centrally presented arrow pointing to the left or right peripheral box. Arrows were centred 0.2° above the visual fixation cross and subtended 0.5° . *Exogenous cues* consisted of an increase in the line width of the peripheral box from 0.15° to 0.20° . Cues were presented in valid, invalid or neutral trials. In valid trials the target appeared in the cued location, whilst on invalid trials the peripheral target appeared opposite to the cued location. Neutral trials provided no information regarding the target location. Neutral cues were a doubled-headed arrow, or a change in line width of both peripheral boxes, for endogenous and exogenous conditions, respectively. 90 trials for each condition were presented. In the exogenous condition, valid, invalid and neutral trials occurred with equal probability (30 trials per cue), while for the endogenous condition, the valid cues correctly predicted target location 80 percent of the time. Thus, neutral cues were presented in 30 trials, valid cues in 48 trials and invalid cues in 12 trials. The cue-target contingency for exogenous and endogenous conditions was based on previous literature^{29,35,36}. In both conditions, targets appeared in the right or left peripheral box with equal probability. Cue type was randomised within endogenous and exogenous blocks.

In the preliminary testing session, participants completed abbreviated versions of all visual tasks to ensure they were familiar with stimulus presentation, experimental setup and task requirements.

Data treatment and analysis. Stimulus presentation, data collection and data analysis were performed using custom software written in Matlab (MathWorks R2010b, Massachusetts, USA). The experimenter visually inspected all eye movement traces. Final sample size satisfied *a priori* power analyses. Sample size was estimated using an expected effect size of 0.4. This effect size was derived from a previous study investigating eye movement kinematics within a similar experimental design². Previous research suggests a high correlation (0.62–0.97) across repeated measures for saccades and smooth pursuit³⁷. Thus, with power set to 0.95, $p < 0.05$, and correlation among repeated measures of 0.62, a sample size of 12 participants was estimated to provide appropriate statistical power for eye movement kinematic measures.

Prosaccade and antisaccades. Initiation of a saccade was identified using an amplitude deviation (deviation of $> 1^\circ$ from fixation) and a velocity criterion ($\geq 30^\circ \cdot s^{-1}$). The end of the saccade was detected by a drop in the saccade velocity below $30^\circ \cdot s^{-1}$ ^{38,39}. Anticipatory saccades (latency < 70 ms) were excluded from analysis⁴⁰. Latency (ms), amplitude ($^\circ$), peak velocity ($^\circ \cdot s^{-1}$) and task performance (percentage of saccades in the correct direction) were the dependent variables derived from the saccade tasks. For kinematic measures, only saccades performed in the correct direction were included in statistical analysis.

Smooth pursuits. Saccades and blinks during pursuit were identified by computing a velocity signal from the horizontal eye position during each trial and applying a velocity criterion ($\geq 64^\circ \cdot s^{-1}$). Sections of pursuit containing saccades and blinks were removed before applying a linear interpolation to the remaining data to calculate eye velocity. Eye velocity was used to derive pursuit gain (eye velocity/target velocity), the dependent measure of the smooth pursuit task. The initial ramp in which the target only completed a pass across half of the screen was not included in analysis.

Optokinetic nystagmus. Quick phases were also identified with a velocity criterion ($\geq 64^\circ \cdot s^{-1}$). Amplitude ($^\circ$) and peak velocity ($^\circ \cdot s^{-1}$) were derived from the quick phases. Quick phase identification permitted slow phase determination, as slow phases were assumed to occur between quick phases. Slow phase eye velocity was calculated by applying a linear interpolation to the slow phase, thereby allowing the calculation of slow phase gain.

Covert spatial attention. Keyboard responses (response time and left/right key) were collected using custom software written in Matlab (Mathworks, R2010b, Massachusetts, USA). A “validity effect” in endogenous and exogenous task conditions for each participant was derived from response times to valid and invalid cues. This measure, which was calculated by subtracting valid response time from invalid response time, reflects the time required to disengage covert attention from an invalidly cued location, and shift attention to the target location. Eye movements were monitored throughout the task. Trials in which the eyes deviated $>1^\circ$ from fixation, or if response time was >1000 ms were rejected from analysis.

Statistical analyses. Repeated measures analyses of variance (ANOVA) with the factor TREATMENT (Caffeine/NDRI/Placebo) was used to explore the effect of exercise on fluid loss. The validity effect in endogenous and exogenous conditions within the covert spatial attention task was explored by adding the factor TIMEPOINT (pre-exercise/post-exercise) to the repeated measures ANOVA. TIMEPOINT (pre-exercise/post-exercise) and CONDITION (gap/overlap) were added as factors to statistical analyses for measures from the prosaccade and antisaccade tasks. Similarly, STIMULUS SPEED was added as a factor to statistical analyses for smooth pursuit gain ($5^\circ \cdot s^{-1}$, $10^\circ \cdot s^{-1}$ and $30^\circ \cdot s^{-1}$) and OKN slow and quick phases ($5^\circ \cdot s^{-1}$, and $10^\circ \cdot s^{-1}$). There was no influence of stimulus direction, so this was not included as a factor in the statistical analysis. To explore the influence of treatment on subjective experiences and heart rate, the number of levels within TIMEPOINT was extended to eleven.

The repeated measures design of the experiment increases possibility of task learning influencing our dependent variables. To identify possible learning effects repeated measures ANOVAs with the factor TRIAL (first vs. second) used in place of TREATMENT. The presence of a task learning effect is commented on where relevant.

Where necessary, interaction effects were explored using within-subject paired comparisons. The multiple comparison type I error rate was controlled using a false discovery rate criterion procedure⁴¹. Violations of sphericity were controlled with the Greenhouse–Geisser correction. Statistical significance was set at $\alpha = 0.05$. Results are reported as mean \pm standard deviation (SD) unless otherwise stated.

Results

Visual performance measures. Prosaccades. There was an effect of exercise on peak prosaccade velocity that was modulated by treatment (interaction TREATMENT \times TIMEPOINT, $F_{2,22} = 7.67$, $p < 0.01$). Changes in prosaccade velocity after exercise were similar in magnitude for gap and overlap conditions (Fig. 2, panel a). Post-hoc analysis of peak velocity, collapsed across gap and overlap conditions, revealed that with placebo, exercise-induced fatigue significantly reduced peak velocity compared to pre-exercise by $8 \pm 11\%$ ($t_{23} = 3.51$, $p < 0.05$). In the majority of participants, prosaccade peak velocity was influenced by exercise-induced fatigue in the placebo trial, with eight of twelve participants exhibiting a lower post-exercise peak prosaccade velocity compared to pre-exercise. To explore the magnitude of this change while accounting for within-subject variability, an effect size comparing pre-exercise prosaccade velocity to post exercise was calculated for each participant. The average effect size of the eight participants that displayed a drop in peak prosaccade velocity with placebo was 0.77 ± 0.41 . The remaining participants displayed an increase in peak velocity post-exercise with an average effect size of 0.19 ± 0.13 . Conversely, caffeine prevented this exercise-induced decrement in prosaccade velocity and increased velocity significantly above pre-exercise levels ($6 \pm 9\%$, $t_{23} = -2.96$, $p < 0.05$) (see Fig. 2, panel a). Ten of twelve participants exhibited an increase in prosaccade velocity above pre-exercise levels. However, a large increase was evident in one participant (effect size >1.0), while the remaining nine participants exhibited only a small to moderate increase in velocity post exercise (average effect size, 0.24 ± 0.17). Two participants displayed a drop in prosaccade peak velocity following exercise, however, this was only of a small magnitude (average effect size, 0.09 ± 0.06). NDRI also prevented post exercise decrements in peak prosaccade velocity, maintaining velocity at pre-exercise levels ($-1 \pm 12\%$, $t_{23} = 0.33$, $p = 0.74$). Seven participants displayed a slight increase in prosaccade velocity post-exercise, with an average effect size of 0.40 ± 0.32 , while five participants exhibited a moderate decrease post-exercise (average effect size, 0.66 ± 0.24). Figure 3 depicts average peak prosaccade velocity (collapsed across gap and overlap conditions) pre and post-exercise for placebo, caffeine and NDRI treatments for each participant.

A robust main effect of condition was observed for prosaccade latency ($F_{1,11} = 45.27$, $p < 0.01$) whereby prosaccades in the overlap condition were performed with slower latencies compared to the gap condition. The influence of condition on prosaccade latency pre and post exercise for each treatment is illustrated in panel b of Fig. 2. No significant changes were observed across time point or between treatments for prosaccade latency. Similarly, condition also influenced task performance, with higher performance in the overlap condition ($F_{1,11} = 14.12$, $p < 0.05$). However, task performance in both conditions was modulated by an interaction between treatment and time point ($F_{2,22} = 4.11$, $p < 0.05$). Post-hoc analyses revealed a significant drop in task performance post exercise with NDRI ($t_{23} = 2.93$, $p < 0.05$), while there was no change in task performance following exercise with caffeine or placebo treatments. There were no alterations in prosaccade amplitude as a result of condition, time point or treatment. These data are reported in Table 1.

Antisaccades. There was an effect of exercise-induced fatigue on antisaccade peak velocity that was modulated by treatment and condition (3-way interaction TREATMENT \times TIMEPOINT \times CONDITION, $F_{2,22} = 7.98$, $p < 0.01$). Post-hoc analysis revealed that exercise-induced fatigue significantly reduced the peak velocity of antisaccades in the gap condition compared to pre-exercise by $10 \pm 11\%$. Nine participants displayed a moderate

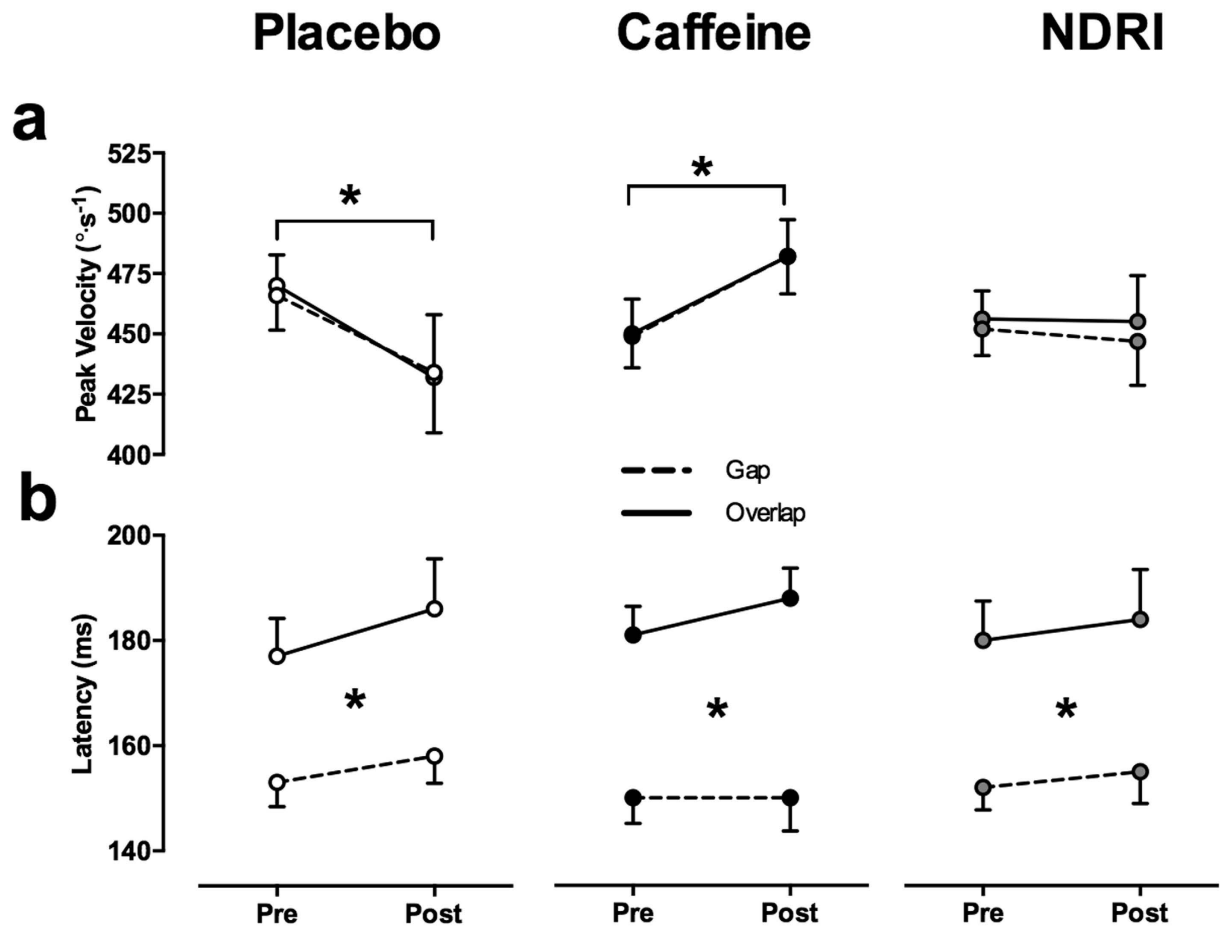


Figure 2. Prosaccade peak velocity and latency for placebo, caffeine and bupropion (NDRI) treatments. (Panel a) – Prosaccade velocity in gap (dashed line) and overlap (solid line) task conditions pre and post exercise. (Panel b) – Prosaccade latency for gap (dashed line) and overlap (solid line) conditions for pre and post exercise categories in placebo, caffeine and NDRI. Here and in Fig. 3, the connecting lines are shown for illustrative purposes only and do not infer the assumption of a linear change from pre to post exercise. Significance labelling between gap and overlap conditions indicates a main effect of condition. Data represent mean \pm SE. * <0.05 .

decrease in antisaccade peak velocity (average effect size, 0.58 ± 0.58) with the placebo. The remaining three participants exhibited a small to moderate increase in peak velocity following exercise after placebo (average effect size, 0.29 ± 0.10). Conversely, peak antisaccade velocity did not differ across time point in the placebo treatment for the overlap condition, nor were any significant alterations in antisaccade peak velocity detected across time and condition for caffeine and NDRI treatments.

A main effect of condition was observed for antisaccade latency ($F_{1,11} = 8.39$, $p < 0.05$) whereby antisaccades in the gap condition had faster latencies than the overlap condition. An interaction effect between condition and time point also modulated antisaccade latency ($F_{1,11} = 6.11$, $p < 0.05$). This appeared to stem from longer latencies post exercise in the overlap condition, whereas gap latencies remain stable across time. However, the increase in overlap latencies post exercise did not reach statistical significance after correcting for multiple comparisons ($t_{35} = 1.71$, $p = 0.05$, critical $p < 0.025$). A robust effect of condition was detected for task performance, with a higher percentage of antisaccades performed in the correct direction in the overlap condition ($91 \pm 9\%$) compared to the gap condition ($80 \pm 14\%$) ($F_{1,11} = 26.09$, $p < 0.01$). There were no alterations in antisaccade amplitude as a result of condition, time point or treatment.

Smooth pursuit. Pursuit gain differed depending on the stimulus speed presented ($F_{2,18} = 95.40$, $p < 0.01$). For the slowest stimulus speed ($5^\circ \cdot s^{-1}$), pursuit gain was closest to unity and progressively declined for faster stimulus speeds ($10^\circ \cdot s^{-1}$ and $30^\circ \cdot s^{-1}$). An interaction between stimulus speed and time point was detected for pursuit gain ($F_{2,18} = 7.78$, $p < 0.01$). Post-hoc tests revealed that this effect stems from a decrease in smooth pursuit gain post-exercise, irrespective of treatment, for the $30^\circ \cdot s^{-1}$ stimulus speed ($t_{29} = 4.69$, $p < 0.01$). These data are reported in Table 1.

Optokinetic nystagmus. Slow phase gain of OKN was modulated by an interaction between stimulus speed and treatment ($F_{2,20} = 4.53$, $p < 0.05$). Post-hoc tests revealed significantly reduced slow phase gain

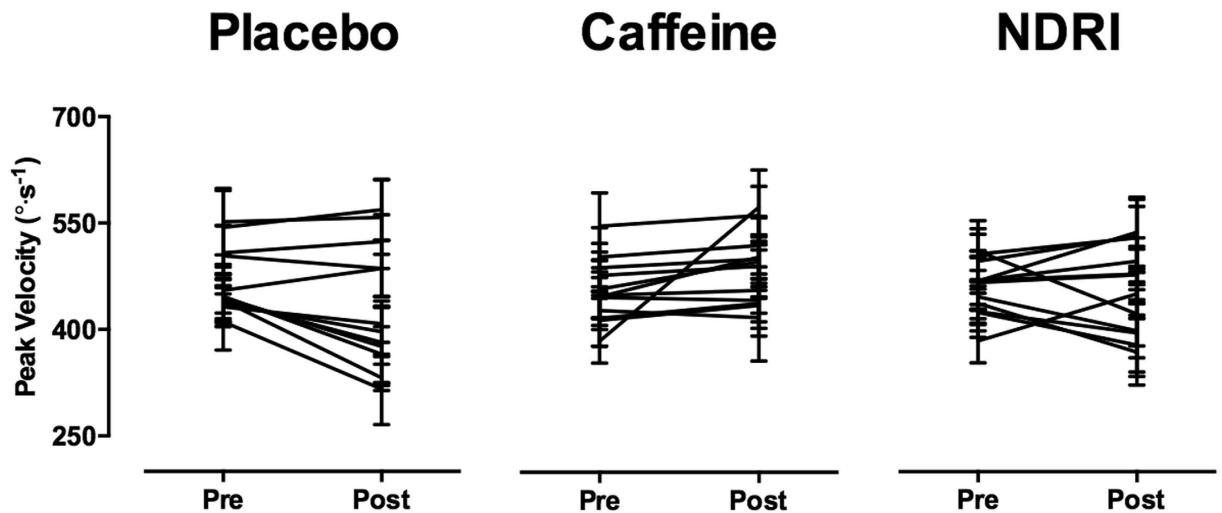


Figure 3. Prosaccade velocity in placebo, caffeine and bupropion (NDRI) treatments for each participant. Peak prosaccade velocity collapsed across task condition for pre and post exercise categories in placebo, caffeine and NDRI treatments. Each point represents mean peak prosaccade velocity \pm 95% confidence interval for each participant.

in response to the $10^\circ \cdot s^{-1}$ stimulus speeds with placebo compared to caffeine ($t_{21} = 2.79$, $p < 0.01$) and NDRI ($t_{21} = 2.87$, $p < 0.01$) respectively.

Alterations in amplitude and peak velocity of OKN quick phases were detected. Amplitude differed depending on stimulus speed presented ($F_{1,10} = 28.93$, $p < 0.01$), with slightly higher quick phase amplitudes in response to the $10^\circ \cdot s^{-1}$ speed ($5.3 \pm 1.6^\circ$) compared to the $5^\circ \cdot s^{-1}$ speed (4.3 ± 1.68). Amplitude was also modulated by an interaction between treatment and time point ($F_{2,20} = 3.88$, $p < 0.05$). This stemmed from a slight increase in amplitude post-exercise with caffeine (pre-exercise, $4.7 \pm 1.4^\circ$; post-exercise, $5.3 \pm 2.0^\circ$). However, this difference was not statistically significant after correcting for multiple comparisons.

Peak velocity of quick phases also differed between stimulus speeds ($F_{1,10} = 23.74$, $p < 0.01$), with higher velocities to the $10^\circ \cdot s^{-1}$ ($249 \pm 57^\circ \cdot s^{-1}$) compared to the $5^\circ \cdot s^{-1}$ per second stimulus speed ($134 \pm 28^\circ \cdot s^{-1}$). An interaction between treatment and time point was also evident ($F_{2,20} = 7.51$, $p < 0.01$). Post-hoc tests revealed a significant decrease in peak velocity post-exercise with placebo ($t_{21} = 3.80$, $p < 0.01$), while there were no differences pre to post-exercise in peak velocity with caffeine and NDRI treatments. These data, along with example OKN traces pre and post-exercise with placebo are illustrated in Fig. 4.

Covert spatial attention. The number of trials rejected due to deviations from fixation did not differ as a consequence of treatment or time point. The validity effect in endogenous and exogenous cueing conditions was equivalent between treatments and across time points. Table 2 reports the validity effect for both task conditions across time for each treatment.

Heart rate, fluid balance and subjective measures. Heart rate and fluid loss were equivalent between treatments. For placebo, caffeine and NDRI treatments average heart rate (beats per minute) was 147 ± 19 , 150 ± 18 , and 153 ± 20 respectively. Figure 5 (panel a) illustrates heart rate over time for each treatment. Mean change in body mass was $-0.2 \pm 0.7\%$, $-0.1 \pm 0.8\%$ and $-0.3 \pm 0.9\%$ of pre-exercise body mass, for placebo, caffeine and NDRI treatments respectively. There was no influence of treatment on change in body mass ($F_{2,22} = 1.00$, $p = 0.40$).

Figure 5 (panels b and c) shows average ratings of perceived exertion and felt arousal for placebo, caffeine and NDRI treatments. A main effect of time ($F_{10,110} = 20.01$, $p < 0.05$) was detected for ratings of perceived exertion. Perceived exertion steadily increased over the duration of the exercise protocol, to a similar extent for all treatments.

An interaction between treatment and time ($F_{20,220} = 2.50$, $p < 0.05$) was found for felt arousal. Felt arousal with NDRI appears relatively stable across the duration of the exercise protocol, and was higher than caffeine and placebo for the first 90 minutes of exercise. After 90 minutes, felt arousal with caffeine started to increase, reaching a maximum by 165 minutes into exercise. Conversely, after 90 minutes, felt arousal in placebo steadily declined. Post-hoc comparisons revealed a significant difference in felt arousal at the 165 minutes between caffeine and placebo ($t_{11} = 3.60$, $p < 0.05$), and NDRI and placebo ($t_{11} = 2.20$, $p < 0.05$), while there was no difference between caffeine and NDRI ($t_{11} = 1.01$, $p = 0.33$).

Discussion

This study provides evidence for a role of noradrenergic and dopaminergic neurotransmission in fatigue-related impairments in the oculomotor control of high-velocity eye movements. The findings suggest that caffeine exerts at least part of its protective effects through these neurochemicals. Furthermore, the detrimental effects of fatigue on eye movement kinematics were restricted to velocity, while eye movement amplitude, tracking performance of pursuit eye movements and visual attention were robust to fatigue and psychotropic drugs.

	Placebo				Caffeine				Bupropion			
	Pre exercise		Post exercise		Pre exercise		Post exercise		Pre exercise		Post exercise	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Prosaccade												
Peak velocity ($^{\circ} \cdot s^{-1}$)	468	47	433	88	454	44	485	50	458	37	455	62
Gap condition	466	50	434	87	453	44	485	52	456	37	451	61
Overlap condition	470	44	432	90	454	48	485	51	460	39	459	64
Latency (ms)	167	18	174	26	166	17	171	16	167	18	170	26
Gap condition	155	14	160	18	151	16	153	18	154	14	155	20
Overlap condition	179	26	187	34	182	20	189	19	181	25	185	33
Amplitude ($^{\circ}$)	9	0.5	9	0.9	9	0.4	9	0.6	9	0.6	9	0.9
Gap condition	9	0.6	9	0.5	9	0.6	9	0.7	9	0.6	9	0.9
Overlap condition	9	0.4	9	1.5	9	0.4	9	0.6	9	0.7	9	0.9
Task performance (% correct)	97	4	96	2	96	5	97	5	98	3	95	5
Gap condition	95	6	96	4	92	9	95	8	95	5	92	8
Overlap condition	99	3	100	1	99	1	99	2	100	1	98	3
Antisaccade												
Peak velocity ($^{\circ} \cdot s^{-1}$)	444	62	413	63	441	73	462	82	432	40	413	62
Gap condition	457	61	411	70	443	76	465	84	433	41	421	66
Overlap condition	432	66	416	58	439	70	458	81	431	43	404	61
Latency (ms)	231	61	247	43	238	38	233	37	242	45	242	52
Gap condition	228	63	239	47	232	41	225	43	240	49	236	56
Overlap condition	233	60	254	40	243	35	241	32	244	42	248	50
Amplitude ($^{\circ}$)	9	2.1	9	1	9	1.8	9	1.6	9	1.8	9	1.5
Gap condition	9	2.1	9	1	9	1.8	9	1.6	9	1.7	9	1.4
Overlap condition	9	2.1	9	1	9	1.9	9	1.6	9	2	9	1.7
Task performance (% correct)	82	17	87	8	87	7	87	8	88	10	85	11
Gap condition	76	18	82	12	83	11	80	13	82	15	78	14
Overlap condition	87	18	91	5	92	4	94	4	93	7	92	8
Smooth pursuit												
Gain	0.91	0.26	0.87	0.29	0.89	0.26	0.87	0.3	0.87	0.23	0.9	0.31
$5^{\circ} \cdot s^{-1}$ stimulus	0.97	0.27	0.96	0.26	0.96	0.25	0.94	0.33	0.93	0.23	0.96	0.29
$10^{\circ} \cdot s^{-1}$ stimulus	0.91	0.23	0.91	0.27	0.9	0.25	0.86	0.26	0.89	0.23	0.94	0.32
$30^{\circ} \cdot s^{-1}$ stimulus	0.75	0.19	0.66	0.25	0.73	0.22	0.7	0.22	0.74	0.17	0.67	0.23
Optokinetic Nystagmus												
Slow phase gain	0.67	0.11	0.64	0.11	0.74	0.08	0.72	0.07	0.7	0.1	0.73	0.1
$5^{\circ} \cdot s^{-1}$ stimulus	0.72	0.1	0.65	0.06	0.71	0.06	0.7	0.07	0.67	0.07	0.7	0.09
$10^{\circ} \cdot s^{-1}$ stimulus	0.64	0.21	0.65	0.16	0.76	0.14	0.74	0.1	0.72	0.16	0.75	0.14
Quick phase amplitude ($^{\circ}$)	5	1.4	4	1.5	5	1.2	5	1.9	5	1.5	5	1.8
$5^{\circ} \cdot s^{-1}$ stimulus	4	1.7	4	1.2	4	1.3	5	2.2	4	1.8	4	1.6
$10^{\circ} \cdot s^{-1}$ stimulus	5	1.4	5	1.8	5	1.3	6	1.9	6	1.4	6	2
Quick phase peak velocity ($^{\circ} \cdot s^{-1}$)	245	54	203	54	235	52	245	58	250	47	237	62
$5^{\circ} \cdot s^{-1}$ stimulus	223	59	182	51	213	52	232	71	218	23	208	57
$10^{\circ} \cdot s^{-1}$ stimulus	258	59	216	63	248	53	254	54	266	44	254	66

Table 1. Measures of oculomotor control. Kinematic and task performance measures derived from prosaccade, antisaccade, smooth pursuit and OKN visual tasks, pre and post exercise for placebo, caffeine and NDRI treatments.

In a previous study², we reported a significant decrease in average prosaccade velocity following prolonged exercise that could not be accounted for by changes in saccade amplitude. This effect was proposed to result from central fatigue. In the present study, using measures of peak eye movement velocity, we extended these findings by observing that prolonged exercise exerts a similar effect on the velocities of pro- and antisaccades as well as the quick phase of OKN. This suggests that the detrimental influence of fatigue on saccade velocity is stable across differing task conditions and even extends to reflexive eye movements. Whether the velocity reductions we measured (8–10% reduction in peak velocity) have a discernible influence on visual function is yet to be determined. However, it is plausible that fatigue-related reductions in saccade velocity lengthen the time required to gather information from the visual field.

The detrimental effect of exercise-induced fatigue did not extend to smooth pursuit or the slow phase of OKN, as gain was not modulated as a result of exercise or treatment. The slow phase gain of OKN for the $10^{\circ} \cdot s^{-1}$

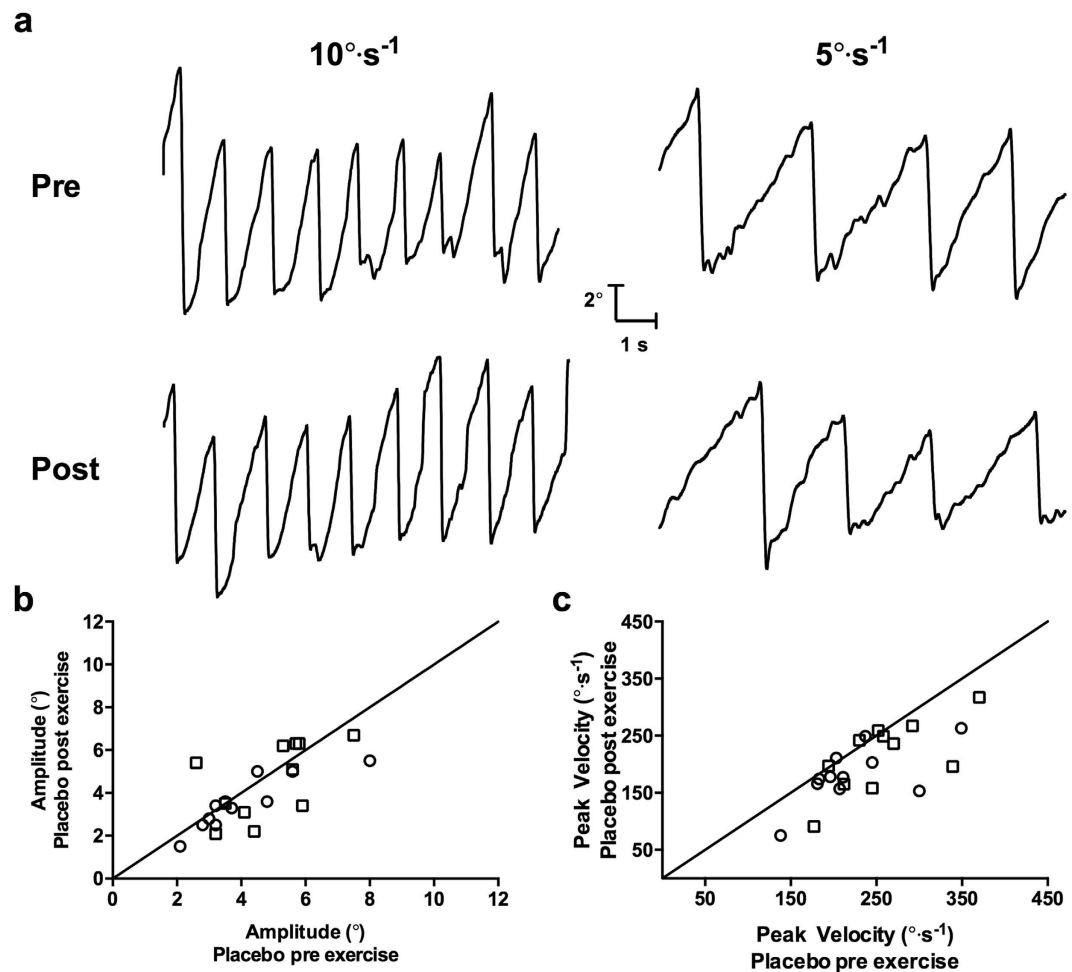


Figure 4. Kinematic characteristics of OKN quick phases in placebo treatment. (Panel a) – Sample eye movement traces of optokinetic nystagmus pre exercise (top traces) and post exercise (bottom traces) in response to $10^{\circ}\cdot\text{s}^{-1}$ (left traces) and $5^{\circ}\cdot\text{s}^{-1}$ (right traces) stimulus speeds. (Panel b) – Mean amplitude of OKN quick phases pre and post exercise categories with placebo. Each symbol represents one participant, while the shape of the symbol corresponds to one stimulus velocity: $5^{\circ}\cdot\text{s}^{-1}$ (circle) and $10^{\circ}\cdot\text{s}^{-1}$ (square). The diagonal unity line represents no difference between pre exercise and post exercise. (Panel c) – Mean peak velocity of OKN quick phases in placebo and caffeine.

	Placebo				Caffeine				NDRI				
	Pre exercise		Post exercise		Pre exercise		Post exercise		Pre exercise		Post exercise		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Validity effect													
Endogenous (ms)	48	33	58	46	42	36	58	45	42	35	61	51	
Exogenous (ms)	25	29	28	37	18	25	37	30	18	27	13	22	

Table 2. Measures of covert spatial attention. Validity effect for endogenous and exogenous conditions of the covert spatial attention task across placebo, caffeine and NDRI treatments.

stimulus was significantly lower in the placebo condition than the treatment conditions. This may reflect a pre-exercise influence of caffeine and norepinephrine-dopamine reuptake inhibition as participants received treatment doses before starting the pre-exercise visual test battery.

Caffeine and norepinephrine-dopamine reuptake inhibition exerted a similar effect on oculomotor control, protecting the peak velocity of saccades and the quick phases of OKN following exercise. Both treatments increase levels of norepinephrine and dopamine release^{20,42}. Therefore, we propose that prolonged exercise impaired the synthesis and metabolism of central catecholamines resulting in inhibitory tone that disrupted oculomotor function. This effect appeared to influence both subcortical and cortical components of the oculomotor control system. In particular, exercise fatigue affected reflexive eye movements (prosaccades, OKN quick-phase) that involve the paramedian pontine formation (PPRF), superior colliculus and basal ganglia^{43–45} as well as antisaccades that

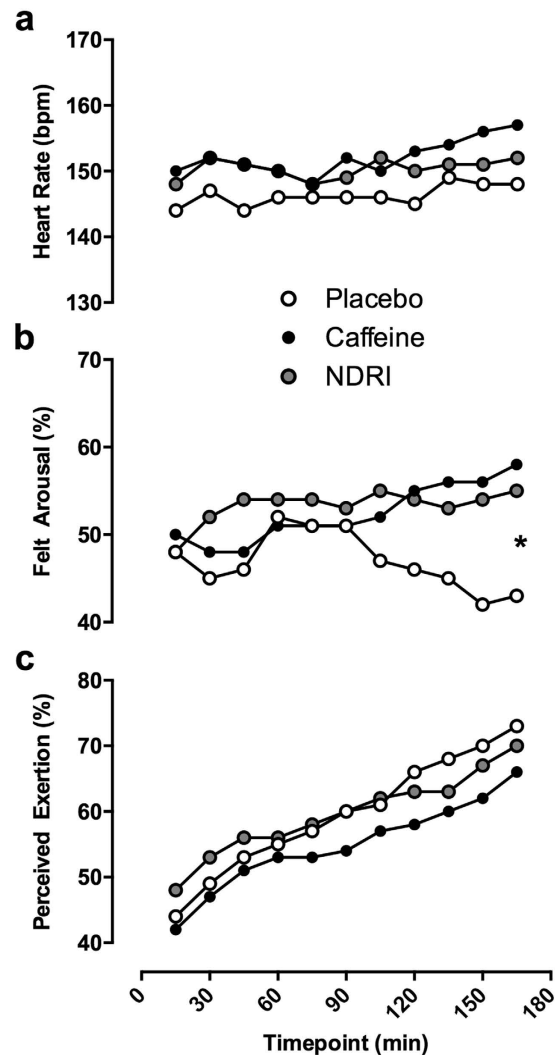


Figure 5. Heart rate, felt arousal and perceived exertion during exercise for placebo (white fill) caffeine (black fill) and NDRI (gray fill). (Panel a) – Heart rate across the 180 minute exercise protocol in experimental treatments. (Panel b) – Felt arousal across the 180 minute exercise protocol. Significance labelling represents a significant posthoc comparison between placebo versus caffeine and NDRI at the 165 minute time point through exercise. (Panel c) – Perceived exertion across the 180 minute exercise protocol. Standard error for each point is not depicted here to improve the clarity of the figure. * <0.05 .

also involve frontal cortical oculomotor regions such as the frontal eye fields, supplementary eye fields and dorsolateral prefrontal cortex⁴⁵. The effects may have been most pronounced for regions within the oculomotor network, such as the PPRF burst neurons, that generate the neural drive for high-velocity eye movements and that utilize dopamine and norepinephrine^{46–48}.

The measures of visual attention derived from the gap-overlap paradigm within the saccade tasks and the covert spatial attention task assessed the influence of exercise-induced fatigue on attentional factors involved in oculomotor control. A clear effect of gap and overlap conditions, similar in magnitude, was observed for saccade latency and task performance across all experimental treatments. In prosaccades and antisaccades, latencies in the gap condition were significantly shorter than those in the overlap condition (Fig. 2 and Table 1, respectively). Primate research has shown that gap trials are associated with higher preparatory neural activity in the frontal eye fields, the superior colliculus and the paramedian pontine reticular formation^{49–51}, and inhibition of fixation-related activity in the superior colliculus⁵⁰. This pattern of neural activity is thought to promote a reduction in saccadic latency and lower task performance rates in gap trials^{52,53}. Conversely, in the overlap trials, persistence of the fixation point during onset of the peripheral target promotes fixation-related neural activity after target appearance, causing slower saccade latencies⁵⁴. Thus, it appears that exercise-induced fatigue does not selectively influence the release or maintenance of visual fixation, nor does it exert a general effect on the mechanisms underlying the disengagement and re-engagement of visual attention. Further, the orienting of covert spatial attention was unaffected by exercise-fatigue. Overall, these findings suggest that components of visual attention relevant to oculomotor control are not vulnerable to the central effects of fatigue, and are unlikely to have contributed to the alterations in eye movement kinematics that were observed following exercise.

To our knowledge, this is the first study to compare the actions of caffeine and norepinephrine-dopamine reuptake inhibition during fatigue. Both treatments prevented fatigue-related alterations in oculomotor control with caffeine exerting a slightly larger effect. It is likely that the more pronounced effect of caffeine was a consequence of a dose discrepancy between the two treatments as it was not possible to titrate caffeine and bupropion doses to equivalent influence on catecholaminergic neurotransmission.

Because we imposed equivalent physiological stress between trials, within a protocol that elicits perturbations in cerebral energetics⁵⁵ we are able to contrast the influence of treatments on arousal during exercise, which has not been reported previously with these drugs. Caffeine and NDRI exerted a similar effect on subjective ratings of arousal, promoting significantly higher levels of arousal for 165 minutes of exercise compared to placebo. The observed effects on arousal confirm adequate dosing as this response is consistent with previous reports of the influence of caffeine during exercise⁵⁶.

One of the strengths of this study is that it averted some of the difficulties of investigating alterations in central nervous system function following whole-body exercise by measuring motor output from the relatively well understood neural circuitry of the human oculomotor system^{25,45,57,58}. However, the interpretation of our findings is somewhat limited to prolonged steady-state exercise. Further evaluation is required to establish the manner in which whole-body exercise of differing modes, intensities and durations influences the development of central fatigue detectable by changes in oculomotor control.

Overall, our findings suggest that caffeine's protective effect on oculomotor control following exercise-induced fatigue is mediated by its action on central catecholaminergic neurotransmission, as targeted manipulation of these neurotransmitter systems via norepinephrine-dopamine reuptake inhibition also prevented fatigue-related impairments to the peak velocity of quick phases and saccades. These observations cannot be explained by direct stress to the brain circuitry controlling the extra-ocular muscles as the oculomotor system is functionally independent of the locomotion, and was not challenged during cycling exercise.

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Author Contributions

Conceptualization, C.J.W.C., B.T. and N.G.; Methodology, C.J.W.C., B.T. and N.G.; Software, C.J.W.C. and J.T.; Formal Analysis, C.J.W.C.; Investigation, C.J.W.C.; Resources, N.G.; Writing, C.J.W.C., B.T. and N.G.; Medical Supervision, A.S.; Supervision, N.G.

Additional Information

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