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**Increased Cerebral Blood Flow Supports a Single Bout Post-Exercise Benefit to Executive
Function: Evidence from Hypercapnia**

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Running Head: Exercise, executive function and cerebral blood flow

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Abstract

A single bout of aerobic exercise improves executive function; however, the mechanism for the improvement remains unclear. One proposal asserts that an exercise-based increase in cerebral blood flow (CBF) enhances the efficiency of executive-related cortical structures. To examine this, participants completed separate 10-min sessions of moderate aerobic exercise, a hypercapnic environment (i.e., 5% CO₂), and a non-exercise and non-hypercapnic control condition. The hypercapnic condition was included because it produces an increase in CBF independent of metabolic demands. An estimate of CBF was achieved via transcranial doppler ultrasound and near-infrared spectroscopy that provided measures of middle cerebral artery blood velocity (MCAfv) and deoxygenation (HHb), respectively. In the exercise condition, intensity was adjusted to match hypercapnic condition changes in MCAfv and HHb. Executive function was assessed prior to and after each session via antisaccades (i.e., saccade mirror-symmetrical to a target) as the task is mediated via the same executive networks that demonstrate task-dependent modulation following single- and chronic-bouts of aerobic exercise. Results showed that hypercapnic and exercise conditions were associated with comparable MCAfv and HHb changes, whereas the control condition did not produce a change in either metric. In terms of antisaccade performance, the exercise and hypercapnic – but not control – conditions demonstrated improved post-condition reaction times, and the magnitude of the hypercapnic- and exercise-based increase in estimated CBF was reliably related to the post-condition improvement in RT. Accordingly, an increase in CBF represents a reliable candidate mechanism for a post-exercise improvement in executive function.

Keywords: *antisaccade; near-infrared spectroscopy, oculomotor transcranial doppler ultrasound*

49 **New & Noteworthy**

50 Single bout aerobic exercise ‘boosts’ executive function and increased cerebral blood flow
51 (CBF) has been proposed as a mechanism for the benefit. Here, participants completed 10-min
52 of aerobic exercise and 10-min of inhaling a hypercapnic gas – a manipulation known to increase
53 CBF independent of metabolic demands. Both exercise and hypercapnic conditions improved
54 executive function for at least 20-min. Accordingly, an increase in CBF is a candidate
55 mechanism for the post-exercise improvement in executive function.

Introduction

Executive function is a cognitive construct including the core components of inhibitory control, working memory and cognitive flexibility – processes essential for successful activities of daily living (Diamond 2013). An accumulating literature demonstrates that a single bout of aerobic and/or resistance training provides a transient (i.e., <60 min) “boost” to executive function (for meta-analyses see Chang et al. 2012; Lambourne and Tomporoski 2010; Ludyga et al. 2016). One explanation for this benefit is an exercise-based increase in regional cerebral blood flow (CBF) leading to improved efficiency within the frontoparietal networks mediating executive function (Voss et al. 2010). This proposal is indirectly supported by animal and human research reporting that moderate intensity exercise provides a 20-50% steady-state increase in CBF (González-Alonso et al. 2004; Ogoh and Ainslie 2009; Seifert and Secher 2011) that persists for up to 5-min following exercise cessation (Ide et al. 1999) and is observed within frontoparietal structures (Colcombe et al. 2004; Byun et al. 2014; Moriarty et al. 2019). The exercise-based change in CBF may render mechanical- and temperature-based changes to the brain’s neural and glial networks that alters the gain of local cortical circuits to improve information processing (Moore and Cao 2008). Moreover, the link between CBF and executive function is supported by evidence that age- and disease-related disruption to CBF impairs executive function (Bertsch et al. 2009).

To our knowledge, no research has examined a benefit to executive function following a transient increase in CBF independent of an exercise manipulation. One method – independent of exercise – known to increase CBF is the inhalation of hypercapnic gas that leads to a rapid (i.e., <6 s) cerebrovascular vasodilation in response to elevated CO₂ and reduced pH (Ainslie and Duffin 2009; Hoiland et al. 2019). A hypercapnic environment increases CBF diffusely across

the cerebral cortex, and includes a specific increase in frontoparietal executive structures (Mehren et al. 2019). Accordingly, the present study examined executive function prior to and immediately after a 10-min hypercapnic interval. Estimates of CBF were determined via the combination of blood velocity through the middle cerebral artery (MCAfv) and deoxygenation (HHb) as measured by transcranial doppler ultrasound (TCD) and near-infrared spectroscopy (NIRS), respectively. TCD changes in MCAfv during a hypercapnic environment robustly correlate with direct measures of CBF (i.e., Xenon tracing of the MCA) and is considered a valid and non-invasive proxy for a direct measure of CBF (see Bishop et al. 1986). As well, changes in NIRS-derived HHb have been linked to changes in oxygen (O₂) delivery – assuming O₂ uptake is unchanged –and is indicative of a vascular response (see DeLorey et al. 2003). In addition to the hypercapnic manipulation, executive function was examined prior to and after separate sessions involving 10-min of moderate aerobic exercise (via cycle ergometer) and 10-min of a non-exercise and non-hypercapnic control (i.e., participants sat and rested on the cycle ergometer). In the aerobic exercise session, participant-specific exercise intensities were determined from the end-tidal carbon dioxide (P_{ET}CO₂) in the hypercapnic condition – a measure providing an indication of CBF responsiveness (Ainslie and Duffin 2009; McSwain et al. 2010; Regan et al. 2014). The control condition was used to determine whether a putative pre- to post-improvement in executive function reflects a change in CBF or relates to a practice-based performance benefit on the antisaccade task (see details below).

Pre- and post-condition executive function was examined via the antisaccade task. Antisaccades involve a goal-directed eye movement (i.e., saccade) mirror-symmetrical to the location of an exogenously presented target (i.e., 180° spatial transformation) and result in longer reaction times (RT) (Hallett 1978) and less accurate and more variable endpoints (Gillen and

Heath 2014a) than counterparts directed to a veridical target location (i.e., prosaccades). Extensive evidence has tied the antisaccade behavioural ‘costs’ to the two-component executive demands of inhibiting a prepotent prosaccade (i.e., response suppression) and inverting a target’s coordinates (i.e., vector inversion) (for review, see Munoz and Everling 2004). The task therefore engages each core component of executive function (i.e., inhibitory control, working memory and cognitive flexibility). Moreover, antisaccades are mediated via the same frontoparietal executive networks that show increased task-dependent activity following single- (Hiura et al. 2010; Seifert and Secher 2011; Verburgh et al. 2014) and chronic-bout exercise manipulations (Colcombe et al. 2004; Voss et al. 2010). In addition, recent work by our group has shown that 10-min of aerobic exercise completed across a continuum of metabolically sustainable intensities (i.e., 80% of lactate threshold to 50% of the difference between lactate threshold and VO_{2peak}) engenders a reliable decrease in antisaccade (but not prosaccade) RTs immediately and up to 60-min post-exercise (Dirk et al. 2020; Heath et al. 2016, 2017, 2018; Petrella et al. 2019; Samani and Heath 2018) – a result attributed to an exercise-based improvement in executive control. Accordingly, the hands- and language free nature of antisaccades coupled with the task’s known neuroanatomical substrates provides the requisite resolution to identify subtle changes to executive function (see Kaufmann et al. 2012; Peltsch et al. 2014).

In terms of research predictions, if the post-exercise benefit to executive function is – in part – attributed to an increase in CBF, then the exercise *and* hypercapnic conditions should demonstrate a post-condition reduction in antisaccade RTs. In contrast, if increased CBF is an epiphenomenon associated with improved executive function then the exercise – but not

hypercapnia – condition should selectively demonstrate a post-condition decrease in antisaccade RT.

Methods

Participants

Prior to data collection participants read a letter of information and provided informed written consent via a protocol approved by the Health Sciences Research Ethics Board, University of Western Ontario (ID#: 113156). This study conformed to the ethical standards set by the most recent iteration of the Declaration of Helsinki with the exception that participants were not registered in a database.

Sixteen (seven female, aged 20 – 25 years) undergraduate and graduate students from the School of Kinesiology, University of Western Ontario, volunteered for this study and reported normal or corrected-to-normal vision, self-reported right-hand dominance, no history of smoking, and/or cardiorespiratory, metabolic, musculoskeletal or neurological (including concussion) or neuropsychiatric disorder. Participants reported that they did not take any medication that may affect metabolic, cardiac, respiratory or hemodynamic responses to exercise. Participants obtained a full score on the 2019 Physical Activity Readiness Questionnaire (PAR-Q+) and completed the Godin Leisure-Time Exercise Questionnaire (GLTEQ). The average GLETQ score was 65 (SD=25; range=28-104) and therefore indicated that all participants were recreationally active. Participants abstained from strenuous exercise, alcohol and caffeine consumption 12 hr prior to the protocol described below and were encouraged to get eight hours of sleep the night before data collection with all data collection occurring between 9 and 10:30 am.

Experimental overview

Four experimental conditions were used with each completed on a different day separated by at least 24 h. In one condition, an incremental ramp test to volitional exhaustion was used to determine peak oxygen consumption ($\dot{V}O_{2\text{peak}}$). A second condition (i.e., hypercapnic) entailed a 10-min exposure to a hypercapnic environment via the inhalation of a gas mixture containing a higher-than-atmospheric concentration of CO_2 (i.e., 5% CO_2 , 21% O_2 , 74% N_2). In a third condition (i.e., exercise), participants completed a 10-min bout of moderate aerobic exercise (via cycle ergometer) at an intensity producing an increase in CBF matched to the hypercapnic condition. In a fourth condition (i.e., control), participants sat on the cycle ergometer for 10-min without exercise or being exposed to a hypercapnic environment (i.e., the condition was isocapnic: 0.03% CO_2 , 21% O_2 , 78.97% N_2 was inhaled). The hypercapnic condition was always completed prior to the exercise condition so that exercise intensity in the latter could be matched to the increase in CBF associated with the hypercapnic state.

The duration of the hypercapnic and exercise conditions was based on work demonstrating that 10-min of aerobic exercise provides a reliable and large magnitude benefit to post-exercise executive function (Johnson et al. 2016; Samani and Heath 2018).

Apparatus and procedures

For the hypercapnic, exercise and control conditions transcranial doppler ultrasound (TCD) (Neurovision 500M, Neurovision TOC2M Multigon Industries, Elmsford, CA, USA) and near-infrared spectroscopy (NIRS) (Oxiplex TS, Model 92505, ISS, Champaign, IL, USA) probes were used to measure: (1) blood velocity through the middle cerebral artery (MCAfv) (2) absolute cerebral deoxygenation (HHb), and (3) total hemoglobin concentration (THC) – measures that provide a valid proxy for a direct measure of CBF (Bishop et al. 1986; DeLorey et al. 2003). NIRS and TCD probes were placed on the frons and the left anterior temporal

window, respectively, and secured via a headband. The TCD probe was coated in an aqueous ultrasound gel (Aquasonic Clear, Parker Laboratories Inc., Fairfield, NJ, USA). Heart rate (HR) was continuously measured via a heart-rate monitor (Garmin Premium Heart Rate Monitor, Garmin Ltd., Olathe, KS, USA) and watch (Garmin Vivoactive GPS Watch, Garmin Ltd., Olathe, KS, USA). Blood pressure (BP) was taken at regular intervals (i.e., 3-, 6-, 9-, 13-, 16- and 19-min) (see below for session-specific timelines) via a manual sphygmomanometer (Welch Allyn FlexiPort Reusable Blood Pressure Cuff, Welch Allyn Inc., Skaneateles Falls, NY, USA) secured to participants' left upper-arm.

$\dot{V}O_{2peak}$ condition

The $\dot{V}O_{2peak}$ condition was used to determine participants' maximal O_2 consumption. We did not include a confirmation ride (i.e., $\dot{V}O_{2max}$) given that participants were undergraduate or graduate students in kinesiology (see above) and were all familiar with volitional tests to exhaustion (Chidnok et al. 2013). This is important to note because $\dot{V}O_{2peak}$ is a reliable measure of maximal O_2 consumption for individuals familiar with maximal exercise testing (Poole and Jones 2017). For this test, participants exercised on a cycle ergometer (Velotron; RacerMate, Seattle, WA, USA) with power output independent of pedal cadence, and the cadence set at 70 rpm. This condition involved an incremental ramp test to volitional exhaustion with a work rate increment of 15 Watts (W) per minute (average time to exhaustion: 16 min, SD=4). Strong verbal encouragement was given to facilitate peak effort. Participants wore a nose-clip to prevent breathing from the nose and a rubber mouthpiece similar to breathing through a snorkel for breath-by-breath gas exchange analysis of O_2 uptake and CO_2 production. Air flow and volumes were measured via a bi-directional turbine of 100 mL deadspace (VMM 110; Alpha Technologies, Laguna Hills, CA, USA) and pneumotach (model 4813; Hans Rudolph, Shawnee,

KS, USA). Fractional concentrations of O₂, CO₂, and diatomic nitrogen (N₂) at the mouth were measured using mass spectrometry (AMIS 2000, Innovision ApS, Glamsbjerg, Denmark). To provide a profile of each breath, a peak-detection algorithm was used to determine end-tidal CO₂ (P_{ET}CO₂) and O₂ (P_{ET}O₂) pressures with inspired and expired gas volumes and durations were time aligned at a sampling rate of 100 Hz.

Hypercapnia condition

As per the $\dot{V}O_{2\text{peak}}$ condition, participants sat on a cycle ergometer and ventilated through a modified breathing apparatus that consisted of a mouthpiece attached to a Douglas bag containing hypercapnic gas. The Douglas bag was placed on its side to ensure a constant flow. A two-way valve controlled the nature of the gas concentration (i.e., isocapnic or hypercapnic). When participants were comfortably seated on the ergometer with the mouthpiece appropriately fitted, they were instructed to breathe normally and were provided isocapnic gas for a period of 10-min to establish a resting baseline. Following the 10-min baseline, the two-way valve was flipped and hypercapnic gas was introduced via the Douglas bag and was continued for the 10-min intervention after which the mouthpiece was removed.

Exercise condition

Participants sat on the cycle ergometer for 4-min to achieve a resting baseline and then pedalled for 6-min at 25 W (i.e., light intensity) to achieve a physiological “steady-state” baseline. Following the steady-state, a step transition was introduced to an intensity corresponding to participants’ elevated steady-state P_{ET}CO₂ during the hypercapnic condition. Specifically, participants’ P_{ET}CO₂ during the hypercapnic condition were compared to time-point specific P_{ET}CO₂ during the $\dot{V}O_{2\text{peak}}$ task. The delay of the metabolic response (i.e., the time between ramp increment onset and VO₂ response) and the time spent at baseline during the $\dot{V}O_{2\text{peak}}$

condition (i.e., 6-min) were subtracted from the total participant-specific ramp time (i.e., 16 min, SD=4). This time was then used to obtain participant-specific work-rates (see Keir et al. 2016, 2018). In particular, the programming for the cycle ergometer was altered to transition in a step-wise fashion from 25 W to a participant-specific wattage that ranged between 65 and 150 W. As per the $\dot{V}O_{2peak}$ condition, power output was independent of pedal cadence, and cadence was set at 70 rpm.

Control condition

Participants sat on the cycle ergometer for a time period equivalent to the hypercapnic and exercise conditions (i.e., 20-min) without being exposed to a hypercapnic or exercise intervention. During this time participants were able to watch a movie of their choice or browse their mobile device. As in the above three conditions, participants wore a nose-clip and breathed through a rubber mouthpiece.

Oculomotor assessment

Participants completed an oculomotor assessment prior to and after the hypercapnic, exercise and control conditions. For each assessment, participants sat on a height adjustable chair in front of a table on which an LCD monitor (60 Hz, 8 ms response rate, 1280 x 960 pixels; Dell 3007WFP, Round Rock, TX) was located 550 mm from the table's front edge. Participants placed their head in a head-chin rest and the gaze location of their left eye was tracked via a video-based eye tracking system (EyeLink 1000 Plus, SR Research, Ottawa, ON) sampling at 1000 Hz. Prior to data collection, a nine-point calibration and validation of the viewing space was completed (i.e., $<1^\circ$ of error). All experimental events were controlled via MATLAB (R2018a; The Math Works, Natick, MA) and the Psychophysics Toolbox extensions (v. 3.0) (Brainard 1997; Kleiner

et al. 2007) including the Eyelink Toolbox (Cornelissen et al. 2002). The lights in the experimental suite were extinguished during data collection.

Visual stimuli were presented on a black screen (0.1 cd/cm^2) and included a midline located red fixation cross (1° : 50 cd/m^2) presented at participants' eye-level and targets (i.e., open white circle: 2.5° in diameter: 127 cd/cm^2) presented 15° (i.e., proximal target) and 20° (i.e., distal target) to the left and right of fixation and in the same horizontal plane. Fixation onset signalled participants to direct their gaze to its location. Once a stable gaze was achieved (i.e., $\pm 1.5^\circ$ for 450 ms) a uniformly distributed randomized foreperiod (1,000-2,000 ms) was introduced after which the fixation disappeared and a target appeared 200 ms thereafter (i.e., gap paradigm). Target onset cued participants to saccade mirror-symmetrical to the target location (i.e., antisaccade) as "quickly and accurately as possible". For each oculomotor assessment, 20 trials to each target location (i.e., left and right visual field) and eccentricity (i.e., proximal and distal) were randomly presented (i.e., 80 total trials).

Data reduction, dependent variables and statistical analyses

In terms of ventilatory and NIRS variables, data points three standard deviations from a participant-specific mean were removed (Lamarra et al. 1987). Further, data were linearly interpolated on a second-by-second basis, time-aligned to the onset of an experimental session and averaged into 5 s time bins (Keir et al. 2015). For TCD, data corrupted by signal aliasing and/or signal loss (e.g., a sudden head shift) were omitted (see Terslev et al. 2017).

For the oculomotor task, trials involving a signal loss (e.g., an eye blink) were omitted. Trials involving anticipatory responses (i.e., $RTs < 50 \text{ ms}$; see Wenban-Smith and Findlay 1991) or RTs greater than 2.5 standard deviations of a participant- and task-specific mean were excluded, as were trials with amplitudes less than 2° or greater than 2.5 standard deviations of a

participant- and task-specific mean (Gillen and Heath 2014b). Less than 10% of trials for any participant were omitted. Trials involving a direction error (i.e., a prosaccade instead of an instructed antisaccade) were not included in the analysis of RT or amplitude because they are associated with planning mechanisms distinct from their directionally correct counterparts (DeSimone et al. 2014).

Dependent variables for physiological measures included: O_2 consumption (VO_2), CO_2 production (VCO_2), ventilation (V_E), $P_{ET}CO_2$, THC, HHb and mean blood velocity (BV_m). Mean values were determined via the last minute of baseline for hypercapnic and exercise conditions and for the last minute of each intervention (i.e., steady-state). For the control condition, physiological measures were computed along a timeline that matched the hypercapnic and exercise conditions. Physiological dependent variables were analyzed via 3 (condition: hypercapnia, exercise, control) by 2 (time: baseline, steady-state) fully repeated measures ANOVA ($\alpha=.05$).

Oculomotor dependent variables included RT (i.e., time from response cueing to saccade onset), interquartile range of RT (IQR of RT), the percentage of directional errors (i.e., the completion of a prosaccade instead of an instructed antisaccade), saccade gain (i.e., saccade amplitude/veridical target location) and gain variability (i.e., within-participant variability of saccade gain). For RT we computed median values given the skewness of their distribution ($.94 < g_1 < 1.4$; mean=1.11), whereas mean values were used for saccade gain ($.48 < g_1 < .69$; mean=.56). Oculomotor dependent variables were examined via 3 (condition: hypercapnia, exercise, control) by 2 (time: pre-, post-) fully repeated measures ANOVA ($\alpha=0.05$).

Results

Ventilatory and hemodynamic measures

Ventilatory Variables. VO_2 , VCO_2 , V_E and P_{ETCO_2} produced main effects for condition, all $F(1,15) > 15.68$, $p < 0.001$, all $\eta^2 > 0.51$, time, all $F(1,15) > 31.97$, $p < 0.001$, all $\eta^2 > 0.68$, and their interactions, all $F(1,15) > 34.63$, $p < 0.001$, all $\eta^2 > 0.70$. **Figure 1** shows that for the exercise condition, ventilatory variables increased from baseline to steady-state (all $t(15) > -2.40$, $p < 0.03$, all $d_z > -0.60$). For the hypercapnic condition, P_{ETCO_2} and V_E increased from baseline to steady-state (all $t(15) > -6.87$, $p < 0.001$, all $d_z > -1.72$), whereas VO_2 baseline and steady-state values did not reliably differ ($t(15) = -0.25$, $p = 0.80$, $d_z = -0.06$), and VCO_2 decreased from baseline to steady-state ($t(15) = 3.07$, $p = 0.01$, $d_z = 0.77$). For the control condition, ventilatory measures did not reliably vary from baseline to steady-state (all $t(15) < 0.39$, $p > 0.15$, all $d_z < 0.10$).

Hemodynamic Variables. HHb produced a main effect of time, $F(1,15) = 42.71$, $p < 0.001$, $\eta^2 = 0.74$, and a condition by time interaction, $F(1,15) = 8.96$, $p = 0.001$, $\eta^2 = 0.37$. **Figure 2A** demonstrates that hypercapnia and exercise conditions produced a significant decrease in HHb from baseline to steady-state (all $t(15) > 4.02$, $p < 0.001$, all $d_z > 1.01$), whereas control condition baseline and steady-state values did not reliably vary ($t(15) = 0.87$, $p = 0.40$, $d_z = 0.22$). In terms of THC, a condition by time interaction, $F(1,15) = 3.55$, $p = 0.04$, $\eta^2 = 0.19$, indicated that THC for exercise and control conditions did not reliably vary from baseline to steady-state (all $t(15) < 0.82$, $p > 0.42$, all $d_z < 0.21$), whereas for the hypercapnia conditions values increased from baseline to steady-state ($t(15) = -3.70$, $p = 0.002$, $d_z = -0.93$) (**Figure 2B**).

BV_m produced main effects for condition, $F(1,15) = 16.87$, $p < 0.001$, $\eta^2 = 0.53$, time, $F(1,15) = 28.49$, $p < 0.001$, $\eta^2 = 0.66$, and their interaction, $F(1,15) = 25.93$, $p < 0.001$, $\eta^2 = 0.63$. **Figure 2C** shows that hypercapnic and exercise conditions produced an increase in BV_m from baseline to steady-state (all $t(15) > -3.83$, $p < 0.002$, all $d_z > -0.95$), whereas values for the control condition did not reliably differ ($t(15) = 1.04$, $p = 0.31$, $d_z = 0.26$).

Oculomotor performance measures

Reaction time. Main effects were observed for condition, $F(1,15)=4.06$, $p=0.03$, $\eta^2=0.21$, time, $F(1,15)=9.38$, $p=0.01$, $\eta^2=0.39$, and their interaction, $F(1,15)=3.39$, $p=0.047$, $\eta^2=0.18$. The left inset panel of **Figure 3** shows that RTs in the hypercapnic ($t(15)=2.46$, $p=0.03$, $d_z=0.61$) and exercise ($t(15)=5.20$, $p<0.001$, $d_z=1.3$) conditions decreased from pre- to post- assessments, and the magnitude of this difference did not reliably vary between conditions ($t(15)=-0.63$, $p=0.54$, $d_z=-0.16$). In turn, RTs for the control condition did not reliably vary from the pre- to post- assessments ($t(15)=0.69$, $p=0.50$, $d_z=0.17$). IQRs for RT demonstrated a main effect for time, $F(1,16)=10.86$, $p=0.005$, $\eta^2=0.42$: pre-assessments values (52, SD=25) were larger than their post-assessment (46, SD=21) counterparts..

Directional errors. Directional errors accounted for 4% of trials and did not elicit significant main effects or interactions, all $F(1,15)<2.10$, $ps>0.14$, all $\eta^2<0.13$.

Saccade gain and saccade gain variability. Results for saccade gain and gain variability did not produce significant main effects or interactions, all $F(1,15)<3.10$, $ps>0.06$, all $\eta^2<0.17$ (**Figure 3**).

Antisaccade difference scores in exercise and hypercapnia conditions correlate with hemodynamic changes

We sought to determine whether the magnitude of a post-exercise improvement in antisaccade RT was related to the magnitude of the baseline to steady-state change in hemodynamic responses in the hypercapnic and exercise conditions. Accordingly, we computed participant-specific antisaccade difference scores (i.e., pre- minus post-oculomotor assessment) and correlated those values to BV_m and HHb difference scores (i.e., baseline minus steady-state). **Figure 4** demonstrates that for the hypercapnic condition, RT and HHb difference scores were

related ($r(15)=-0.63$, $p=0.01$), whereas BV_m difference scores did not relate to RT difference scores ($r(15)=-0.10$, $p=0.75$). For the exercise condition, RT and BV_m difference scores were related ($r(15)=-0.53$, $p=0.04$), whereas RT and HHb difference scores were not reliably related ($r(15)=0.43$, $p=0.10$). For the control condition, RT difference scores were not related to HHb ($r(15)=-0.11$, $p=0.69$) or BV_m ($r(15)=0.17$, $p=0.53$) difference scores.

Discussion

This study examined the effect of aerobic exercise and hypercapnia on post-condition executive function. In outlining our findings, we first discuss the physiological changes associated with our interventions, and then address whether our exercise and hypercapnia conditions differentially influenced a post-manipulation benefit to executive function.

Ventilatory and hemodynamic data: increased CBF during exercise and hypercapnia

As expected, the control condition did not show a change in ventilatory variables. Furthermore, the exercise condition produced an increase in baseline to steady-state VO_2 , VCO_2 , $P_{ET}CO_2$ and V_E , whereas the hypercapnic condition VCO_2 decreased and $P_{ET}CO_2$ and V_E increased from baseline to steady-state. The findings for the exercise condition are well-documented and reflect a change in venous and muscular CO_2 concentrations and oxidative phosphorylation (Coggan et al. 1993; Thompson 2010; Smith and Ainslie 2017; see also Stowe et al. 1975); that is, the change in ventilation variables underscore an adaptive response to the increased metabolic demands of exercise. In turn, findings for the hypercapnia condition indicate an increase in vascular CO_2 concentration (Coggan et al. 1993; Ainslie and Duffin 2009). These findings accord a wealth of evidence that a hypercapnic increase in $P_{ET}CO_2$ and V_E represent a chemoreceptor-induced change in ventilation (Duffin, 2005). Importantly, the increases in $P_{ET}CO_2$ during exercise and hypercapnia are the result of distinct CO_2 sources that similarly

stimulate central and peripheral chemoreceptors to increase V_E (Ainslie and Duffin 2009; McBryde et al. 2017; Smith and Ainslie 2017).

As hypothesized, the control condition did not alter BV_m , HHb or THC. For the exercise and hypercapnia conditions, BV_m increased and HHb decreased from baseline to steady-state, whereas only the latter condition showed a baseline to steady-state increase in THC. For the exercise and hypercapnia conditions, the respective changes in the above hemodynamic measures reflect an increase in volumetric flow due to CO_2 (for review see Hoiland et al. 2019). The increase in THC, in combination with a decrease in HHb during hypercapnia, reflects an increase in O_2 delivery and is a vascular response that may be associated with increased plasma CO_2 (Robbins et al. 1990; Ainslie and Duffin 2009; Hoiland et al. 2019; see also Kety and Schmidt 1948; Wasserman and Patterson 1961). Thus, results indicate that exercise and hypercapnic conditions increased CBF due to ventilation induced changes resulting from increased muscle and venous CO_2 concentrations.

Increased CBF improves executive function

The exercise and hypercapnic conditions produced a post-condition reduction in antisaccade RTs. These results cannot be attributed to a practice-related performance benefit given that control condition RTs did not change from pre- to post-condition assessments. Moreover, directional errors, gains and gain variability in exercise and hypercapnic conditions did not vary from pre- to post-condition assessments. This demonstrates that RT changes are independent of a speed-accuracy trade-off (Fitts 1954). In other words, participants did not decrease planning times at the cost of decreased endpoint accuracy. Results for the exercise condition directly support previous work by our group involving a spectrum of exercise durations and intensities (e.g., Heath et al. 2018; Samani and Heath 2018; Petrella et al. 2019), and is a result attributed to

a post-exercise improvement in executive function. Further, our exercise findings correspond to work reporting that a single bout of exercise elicits an improvement across a number of executive function tasks (e.g., Stroop task, Tower of London, Ericksen flanker) (for review see Chang et al. 2014). For the hypercapnic condition, the post-condition decrease in RT demonstrates that executive function is improved independent of an exercise-based increase in metabolic demands. In particular, the combined ventilatory, hemodynamic and behavioural findings suggest that the improved executive function associated with the hypercapnic condition is related to enhanced CBF.

The exercise and hypercapnia RT difference scores (i.e., pre-condition minus post-condition) correlated with baseline to steady-state changes in BV_m and HHb, respectively. The RT- BV_m correlation during exercise indicates that the exercise-specific vascular response relates to the magnitude of a post-exercise improvement in executive function. This result is in line with literature demonstrating a link between BV_m and improved executive function during exercise. Specifically, Lucas et al. (2012) found that MCAfv was strongly correlated with executive function, whereas the link with oxygenation was not as robust (see also Fox and Raichle 1986; Stevens et al. 2018). In turn, the RT-HHb correlation in the hypercapnia condition suggests that improved executive function relates to an CBF-mediated increase in O_2 delivery. This finding is similar to Ji et al.'s (2019) report that a fNIRS measure of increased oxygenation during exercise was correlated with improved performance on the executive-mediated Stroop Interference task.

As stated by the hemo-neural hypothesis, an increase in CBF induces mechanical and temperature-based changes to the brain's neural and glial networks that improve the efficiency of local neural circuits (Moore and Cao, 2008) and may serve to enhance resting state functional

connectivity within frontopareital executive networks (Kelly et al. 2017; Schmitt et al. 2019).

Accordingly, we propose that an increase in CBF reflects the post-exercise and post-hypercapnia improvement in executive function observed here.

Limitations and future directions

We recognize that our study is limited by several methodological traits. First, we examined executive function within the first 20 minutes following the completion of exercise and hypercapnic conditions. As a result, it is unclear whether a hypercapnia-induced increase in CBF and associated improvement in executive function persists along the same timeline as that associated with an exercise intervention (i.e., <60 min) (see Johnson et al. 2016). Second, the change in MCAfv reported here via TCD does not quantify changes in vessel diameter and therefore does not provide a direct measure of CBF. As previously mentioned however, Bishop et al. (1986) stated that changes in MCAfv provide a valid and non-invasive proxy for a direct measure of CBF (Bishop et al. 1986). Third, the current work did not assess menstrual cycle phase for female participants. This may represent a limitation given the oft-reported view that hormonal variations associated with the menstrual cycle are associated with increased variability in cognitive and physiological variables. In accounting for this potential limitation, a purpose-designed study by our group found that the post-exercise benefit to executive function does not vary in magnitude across the different stages of the menstrual cycle (Dirk et al. 2020). Moreover, physiological (i.e., O₂ uptake, muscle deoxygenation, blood lactate) and performance (i.e., time to fatigue) variables do not reliably vary across the different phases of the menstrual cycle (Lebrun et al. 1995; Redman et al. 2003; McCracken et al. 1994). Thus, evidence suggest that the phase of a female participants' menstrual cycle should not determine their inclusion – or exclusion – in exercise neuroscience research. Last, our work involved healthy young adults

422 completing a 10-min exercise/hypercapnic manipulation. It is therefore unclear whether our
423 results would extend to older and less physically active individuals and whether our findings
424 would be differentially influenced by a longer exercise/hypercapnic bout (i.e., >10-min).

425 ***Conclusion***

426 The present findings demonstrate that a 10-min single bout of moderate aerobic exercise or
427 exposure to a hypercapnic environment increase CBF and improves executive function. We
428 therefore propose that an increase in CBF is a likely candidate mechanism for the well-
429 documented single bout post-exercise benefit to executive function.

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434 **Disclosures**

435 The authors declare no conflict of interest.

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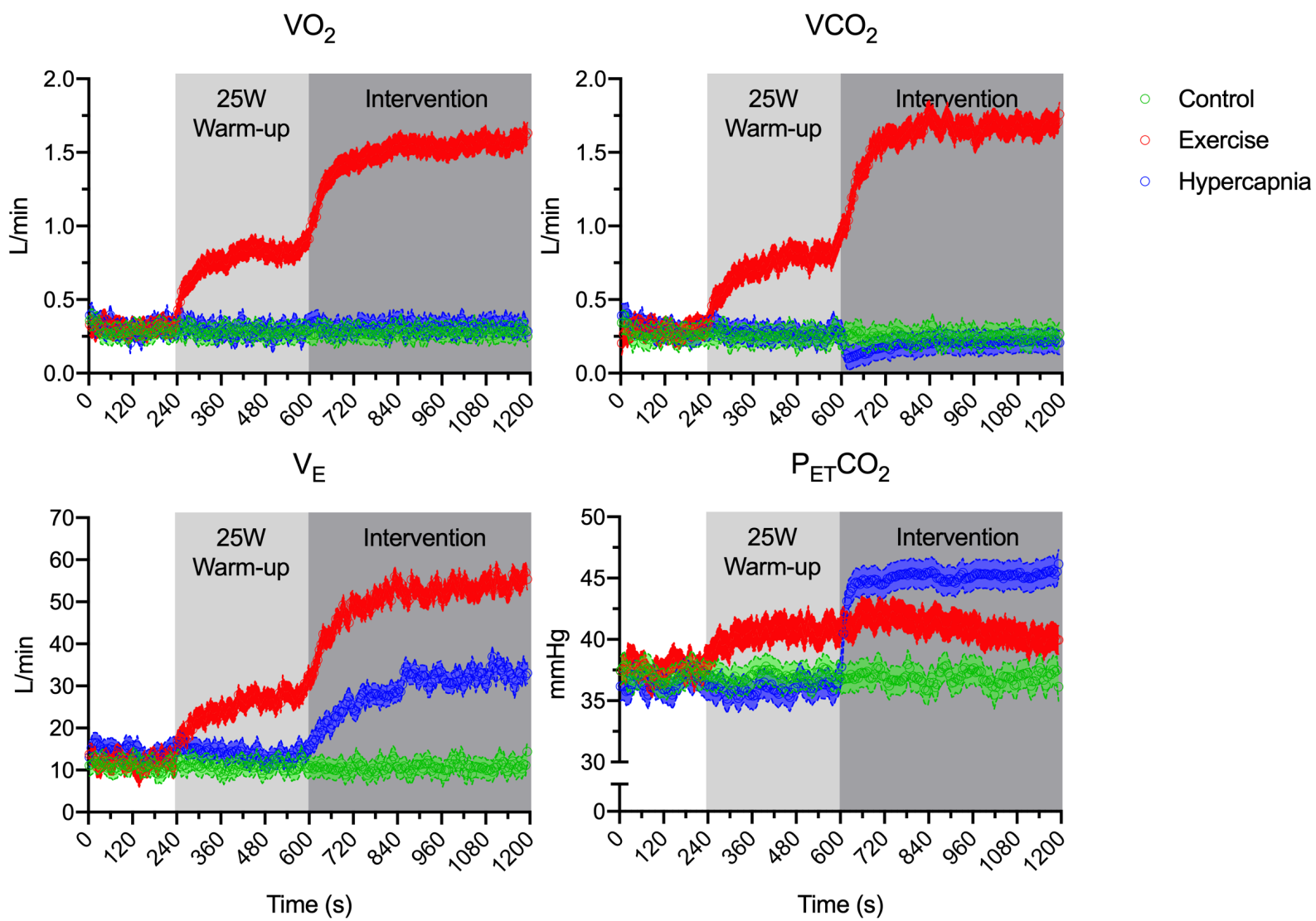
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Figure Captions

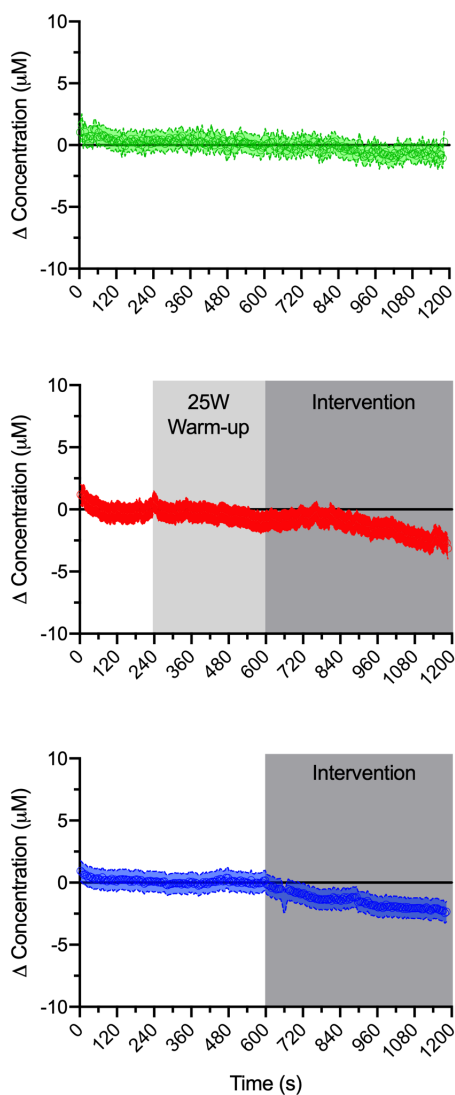
1. Group ventilatory data for control (green lines and shading), exercise (red lines and shading) and hypercapnia (blue lines and shading) conditions presented as 5 s intervals with associated 95% between-participant confidence interval bands. The light and dark grey panels serve to depict the durations of an exercise warm-up and intervention (i.e., exercise and hypercapnia), respectively.
2. Panels A and B depict normalized (i.e., zeroed to baseline) group average data for deoxygenated hemoglobin (HHb) and total hemoglobin (THC), respectively, presented as 5 s intervals with associated 95% between-participant confidence interval bands. Panel C depicts an exemplar participant's blood velocity through the middle cerebral artery (MCAfv: cm/s) via TCD. The light and dark grey panels serve to depict the durations of an exercise warm-up and intervention (i.e., exercise and hypercapnia), respectively.
3. The left and right main panels depict reaction time and saccade gain frequency distribution histograms, respectively, for control (green lines and symbols), exercise (red lines and symbols) and hypercapnia (blue lines and symbols) conditions. The light and dark grey rectangles in each panel represent anticipatory (i.e., <100ms) and short-latency (100<200ms) saccades, respectively. The inset panels depict group mean difference scores (i.e., pre- minus post-condition) and associated 95% confidence intervals for reaction time (left) and saccade gain (right).
4. Participants-specific blood velocity (BV_m) and deoxygenated hemoglobin (HHb) difference scores (i.e., baseline minus steady-state) correlated with their respective reaction time difference scores (i.e., pre- minus post-condition oculomotor assessment) as a function of control (top panels), exercise (middle panels) and hypercapnia (bottom

631 panels) conditions. Linear regression lines and associated regression equations (and
632 proportion of explained variance) are presented in each panel. Significant correlations
633 are denoted by (*).

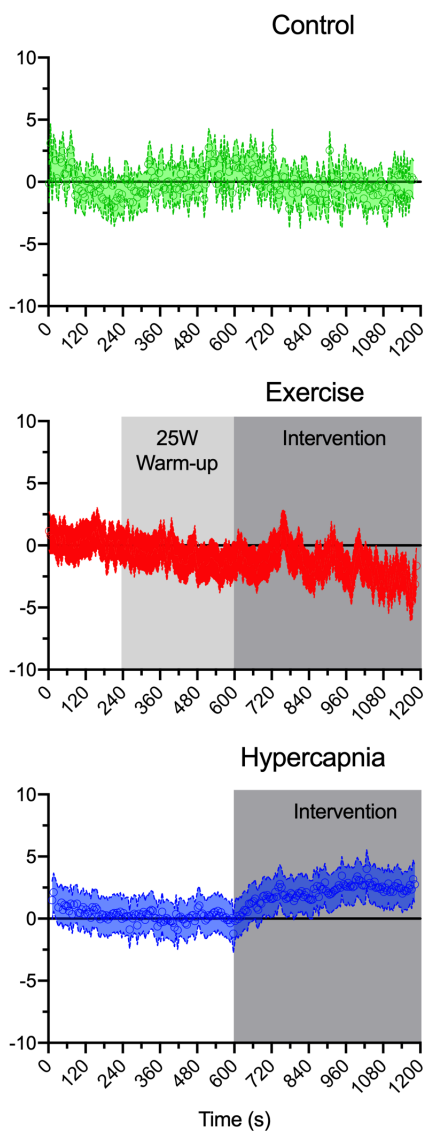
Ventilatory Measures



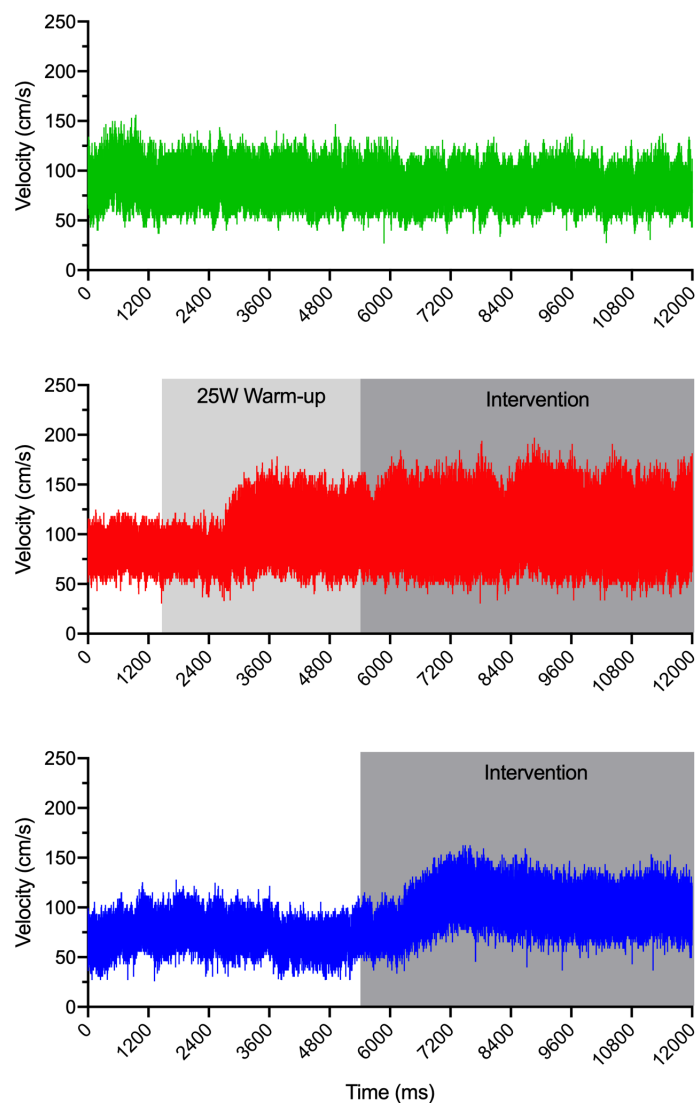
A Deoxygenated Hemoglobin



B Total Hemoglobin

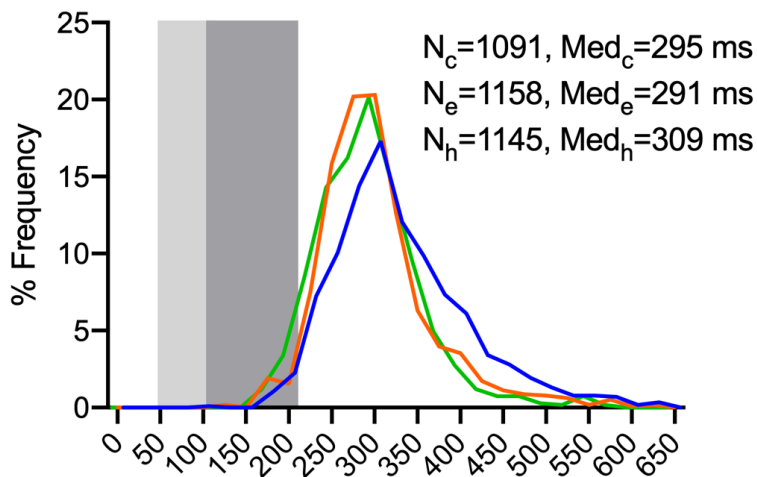


C Blood Velocity

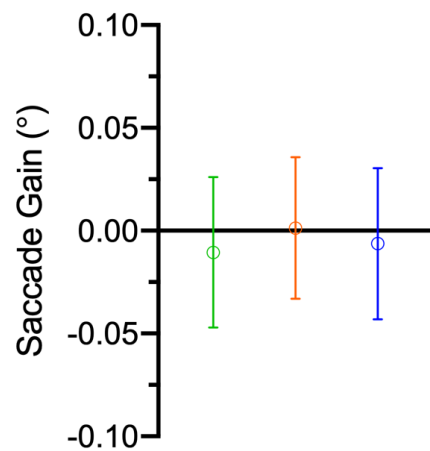
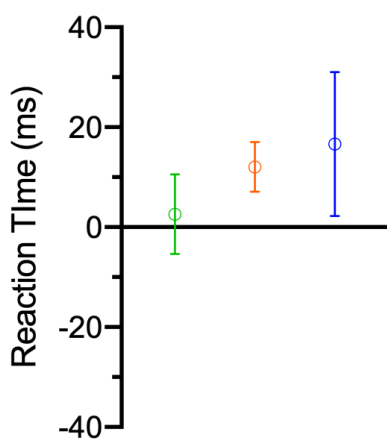
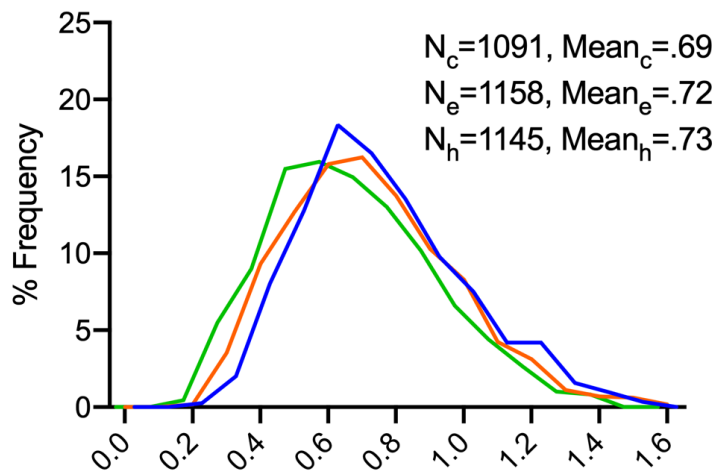


Reaction Time

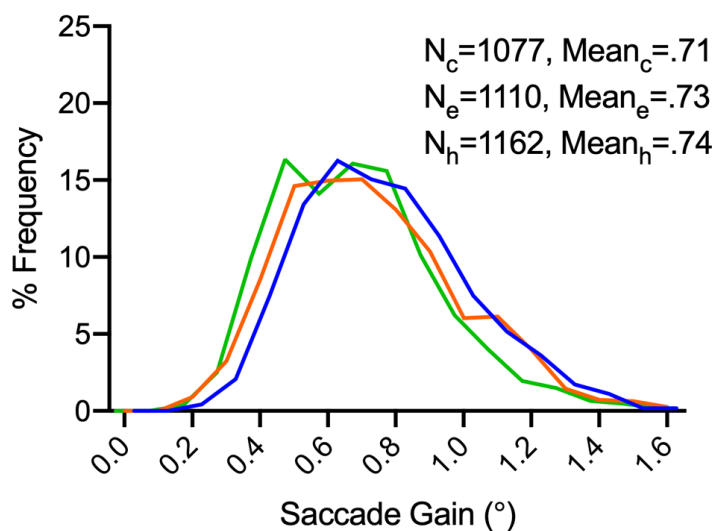
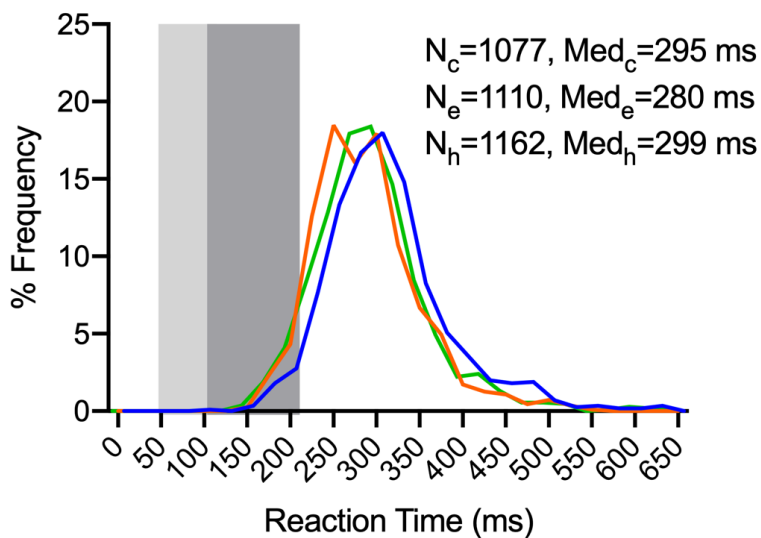
Pre-Intervention Antisaccades



Saccade Gain

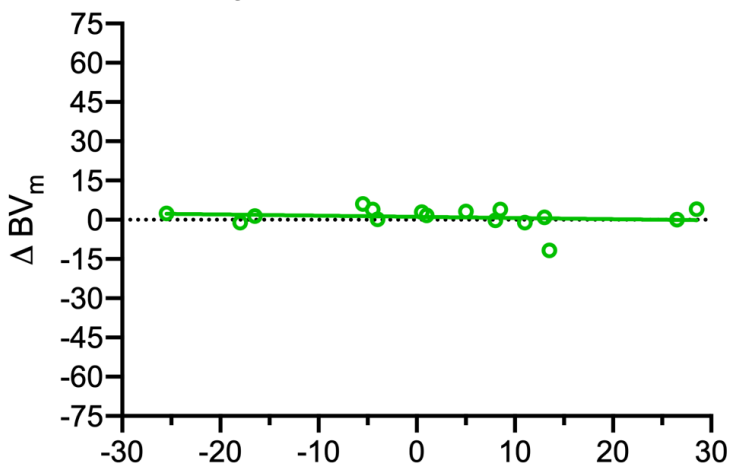


Post-Intervention Antisaccades



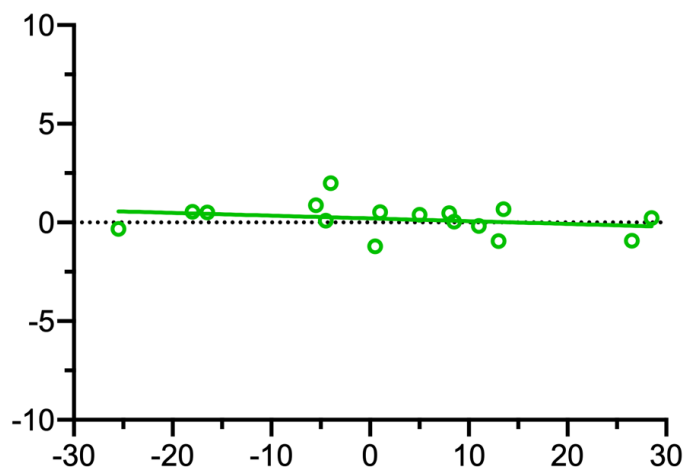
Blood Velocity

$$y=1.15+0.04x: R=0.03$$

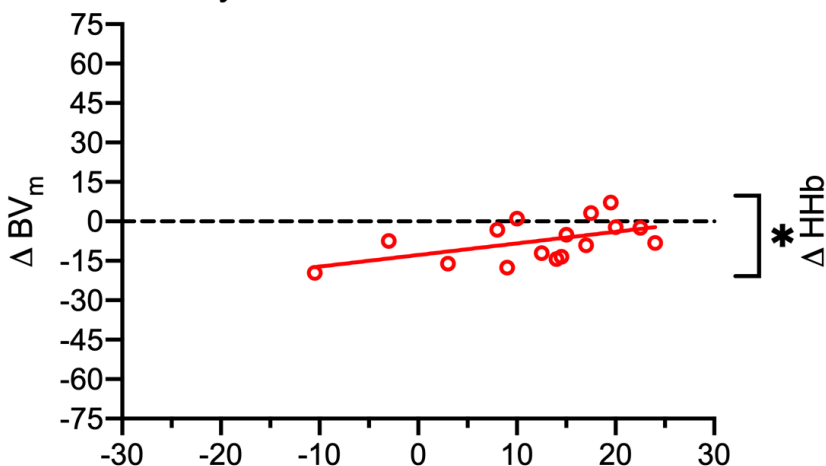


Deoxygenated Hemoglobin

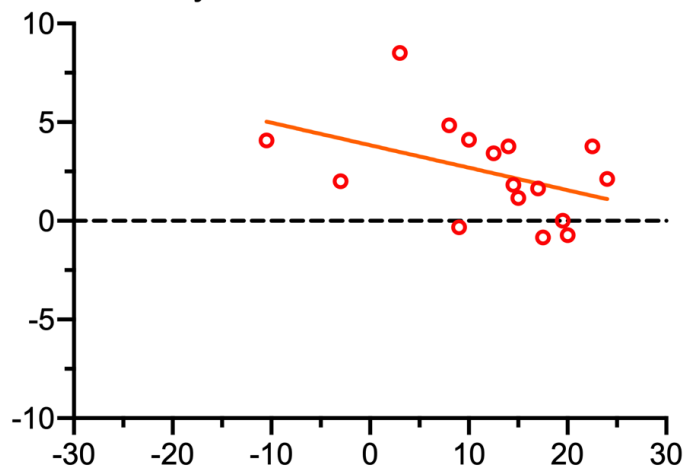
$$y=0.21-0.01x: R=0.07$$



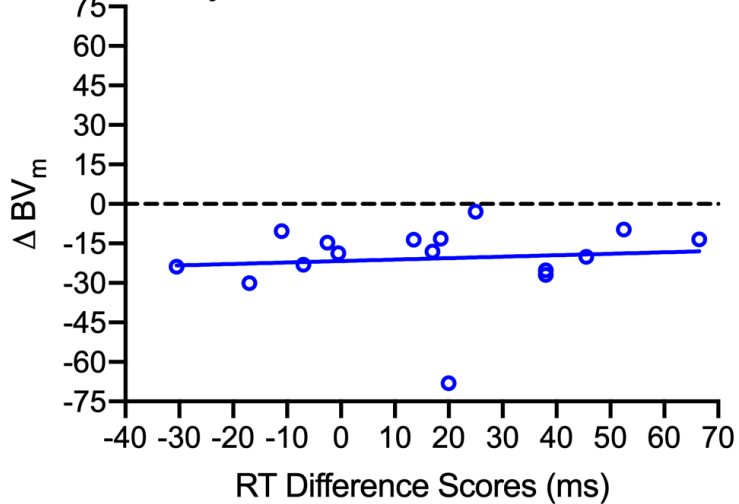
$$y=-12.77+0.44x: R=0.28$$



$$y=3.84-0.11x: R=0.19$$



$$y=-21.66+0.06x: R=0.01$$



$$y=1.70+0.03x: R=0.39$$

