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Cerebral hyperemia is not a sole modulator of postexercise executive function benefit: evidence from hypercapnia and passive exercise

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Abstract

A single bout of exercise improves executive function (EF); however, the physiological mechanism(s) contributing to this benefit are unclear. One candidate mechanism for the benefit is an exercised-mediated increase in cerebral blood flow (CBF) that improves neural efficiency. In my thesis, I conducted two experiments to assess the relationship between an increase in CBF and EF. In Experiment 1, I examined passive exercise, and in Experiment 2, I examined a 2.5% hypercapnic environment given that both interventions increase CBF independent of the metabolic demands of volitional muscle activity. Experiment 1 indicated that passive exercise increased CBF and was associated with a postexercise EF benefit. In Experiment 2, result showed that a hypercapnic environment increased CBF but did not lead to improved EF. As such, my thesis indicates that an increase in CBF does not impart a unitary EF benefit.

Keywords

Antisaccades

Passive Cycling

Carbon dioxide

Cerebral blood flow

Summary for Lay Audience

Executive function represents a set of mental processes that supports activities of daily living. Notably, a single bout of exercise improves executive function, and this benefit has been linked to an exercise-based increase in blood flow to the brain. To better evaluate the relationship between brain blood flow and executive function, my thesis examined whether an increase in cerebral blood flow independent of the metabolic demands of exercise improves executive function. In Experiment 1, I examined brain blood flow and executive function in a passive exercise condition; that is, exercise wherein participants'' limbs were moved via an external force (i.e., a mechanically driven stationary bike). In Experiment 2, participants inhaled a higher-than-atmospheric concentration of carbon dioxide given that it provides a well-defined increase in brain blood flow. Results from Experiment 1 indicated that passive exercise increased brain blood flow and provided a post-intervention executive function benefit, whereas results from Experiment 2 found that a higher-than-atmospheric concentration of carbon dioxide increased brain blood flow but did not benefit executive function. Accordingly, an increase in brain blood flow may only represent one of several mechanisms contributing to a postexercise executive function benefit.

Co-Authorship Statement

The work in this master's thesis was conducted by the author, under the supervision of Dr. Matthew Heath. With the counsel of Dr. Matthew Heath, I created and designed the experiments, recruited participants, collected, analyzed and interpreted data, and composed the final manuscripts, for which I serve as first author. For Chapter Two, I received assistance from fellow graduate students (James Van Riesen, Benjamin Tari and Connor Dalton) with participant recruitment, data collection and interpretation. For the manuscript, Benjamin Tari, Connor Dalton, James Van Riesen, Michael Marsala and Dr. Matthew Heath served as co-authors for the work which is published in the journal Psychophysiology (Shirzad et al., 2022). For Chapter Three, graduate students James Van Riesen and Nikan Behboodpour assisted with participant recruitment, data collection and interpretation. For the manuscript, James Van Riesen, Nikan Behboodpour and Dr. Matthew Heath served as co-authors (manuscript under review).

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Chapter 1

1 Literature Review

The goal of my thesis was to examine the relationship between an exercise-mediated increase in cerebral blood flow (CBF) and an executive function (EF) improvement. To accomplish this, I employed two separate manipulations in independent experiments. In Experiment 1, I employed a passive exercise intervention (i.e., limb movement independent of volitional muscle activation via a motorized cycle ergometer), whereas in Experiment 2, I employed a hypercapnic intervention (i.e., higher-than-atmospheric concentration of CO_2). Notably, both manipulations have been shown to increase CBF independent of the metabolic demands of "active" exercise; however, it is unknown as to whether each imparts an EF benefit. In developing my thesis, the below Literature Review outlines: (1) the components and neural correlates of EF, (2) the relationship between exercise and EF, 3) the physiological mechanism(s) theorized to contribute to a postexercise EF improvement, and (4) the physiological mechanism(s) and psychological adaptations to passive exercise and hypercapnia. Following the Literature Review, my thesis presents Experiment 1 and 2 in the form of separate manuscripts (e.g., Chapters 2 and 3).

1.1 Executive Function

Executive function (EF) refers to the top-down cognitive processes utilized to adapt and navigate a dynamic or unfamiliar environment. EF is composed of three core components: (1) inhibitory control (2) working memory, and (3) cognitive flexibility (Miyake et al., 2000; Diamond, 2013). An individual may rely on one or more components of EF to successfully complete tasks of daily living. An example of a common task requiring EF is navigating a motor vehicle through a four-way stop. Successful navigation requires appropriately yielding to pedestrians and motor vehicles (i.e., inhibitory control) and proceeding through the intersection in the appropriate order in which the vehicles arrived (i.e., working memory). As well, the multi-level decision making requires effective task-switching (i.e., cognitive flexibility). A combination of neuroimaging and lesion studies have demonstrated that the prefrontal cortex (PFC) is the

main cortical region supporting EF. In particular, the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) have been shown to play a primary role in EF (Royall et al., 2002).

The DLPFC facilitates advanced cognitive processes, such as planning, organizing, monitoring oneself, shifting between tasks, inhibitory control and working memory. Inhibitory control entails overriding an internal predisposition or external temptations to focus on more appropriate or necessary actions (Diamond, 2013). A common task used to assess this EF component is the Stroop Interference task. This task entails the presentation of a word in which the meaning of the word is congruent (e.g., "RED") or incongruent (e.g., "RED") with the color of the ink in which it is written. Notably, reaction times (RTs) are longer and response errors are greater in incongruent trials (Stroop, 1935) because of the top-down EF demands of inhibiting a standard word-naming response in favour of a non-standard color-naming response (i.e., Stoop Interference Effect; for meta-analysis, see MacLeod 1992). Extensive work involving neuroimaging and lesion studies have shown that the inhibitory control component of the Stroop task is associated with activity of the DLPFC. For example, Liu and colleagues (2008) employed functional magnetic resonance imaging (fMRI) and assessed Stroop performance in 10 healthy adults. They found that incongruent Stroop trials produced longer RTs and increased activation of the DLPC and ACC compared to their congruent trial counterparts. Moreover, work by Stuss et al. (2001) recruited 51 individuals with either frontal or non-frontal lesions, as well as 26 healthy controls and had them perform the Stroop task. Results showed that individuals with frontal lobe lesions exhibited longer RTs and more errors during the incongruent Stroop trials compared to individuals with non-frontal lesions and healthy controls. Accordingly, these studies demonstrate the importance of the DLPFC in supporting the inhibitory control component of EF.

Working memory is an EF component and is unlike short- and long-term memory given that it entails holding information in mind for dynamic manipulation (Diamond, 2013). An exemplar task to assess working memory is the n-back task. The task involves the presentation of a series of stimuli (e.g., letters, numbers, or shapes) and requires that an individual identify whether a current stimulus matches a target presented 'n' trials

earlier in the series. For example, in a 2-back task, the participant would indicate whether the current stimulus matches a target presented two items earlier in the sequence. The level of difficulty on the n-back task can be manipulated by increasing the value of 'n' and this increase in complexity is indexed by increased RT and decreased response accuracy (Jaeggi et al., 2010). Owen et al.'s (2005) meta-analysis reported increased DLPFC and ACC activation as a function of n- back task complexity (i.e., greater activation in the 3-back task relative to the 1-back task). Further, Tsuchida and Fellows (2009) assessed performance on the 2-back task between 27 patients with focal damage to their DLPFC, and 29 healthy controls. They found that the participants with DLPFC lesions exhibited longer RTs and more errors during the n-back task. Together, these studies demonstrate the role of prefrontal regions (i.e., DLPC, ACC) in supporting the working memory component of EF.

Cognitive flexibility is the ability to change one's perspective and alternate between different tasks (i.e., set-shifting) to support complex problem solving (Diamond, 2013). Cognitive flexibility is commonly assessed via the AABB task-switching paradigm, which consist of two types of trials: one where a task is followed by the same task (task-repetition) and the other wherein a task is followed by a different one (task-switch). Notably, task-switch trials have been shown to produce longer RTs and more errors and is a phenomenon referred to as a task-switch cost (for review, see Kiesel et al., 2010). The executive demands associated with task-switching are well outlined in neuroimaging and lesion studies. For example, Liston et al's (2006) fMRI work showed that the efficiency of task-switch trials was associated with increased activity within the DLPFC and ACC. In turn, Kopp and colleagues (2015) assessed cognitive flexibility via the Trail Making task (TMT) in individuals with frontal lobe lesions and observed that these individuals produced longer completion times and more errors than age-matched healthy controls. Moreover, Jiao et al's (2022) recent meta-analysis reported that the DLPFC plays a primary role in supporting task-switching efficiency.

1.2 Exercise and Executive Function

An extensive literature has reported that chronic exercise benefits EF (for review, see Allan et al., 2016; Etnier et al., 2020). For example, Padilla and colleagues (2013)

evaluated the effects of chronic exercise on inhibitory control via the Stop Signal Task (SST). In the SST participants are required to complete a preplanned response or inhibit the response at the time of response cuing (see Verbruggen & Logan, 2008). The authors found that regular exercisers (i.e., individuals exercising for a minimum of 3 days a week for at least 10 years) demonstrated reliably shorter SST RTs and fewer errors (i.e., failure to withhold response during Stop trials) than those who did not exercise at least 2 hours per week over the last 4 years.) Moreover, it has been well-documented that a single bout of exercise provides a "boost" to EF (for meta-analyses, see Ludyga et al., 2016). For example, Yanagisawa et al (2010) examined the acute effects of moderate-intensity aerobic exercise (70% of predicted maximum heart rate: HR_{max}) on Stroop performance and prefrontal cortex activation. Participants were randomly assigned to either an exercise group that completed 30-min of moderate intensity aerobic exercise or a non-exercise control group. Following the 30-min intervention, both groups completed the Stroop task and concurrent fMRI. Results showed that the exercise group produced shorter incongruent trial RTs and demonstrated increased activity in the DLPFC and ACC. Another study by Stute and colleagues (2020) employed the n-back task and assessed cerebral oxygenation via functional near-infrared spectroscopy (fNIRS) – a tool used to detect changes in oxygenated hemoglobin to provide an estimate of cortical activity – before and after 15 min bout of moderate intensity (50% VO_2peak) aerobic exercise. The authors found a postexercise improvement in n-back performance and this benefit was linked to increased cerebral deoxygenation of the PFC region. These results accord the conclusions from Chang and colleagues' (2012) influential meta-analysis asserting that a single bout of aerobic exercise benefits EF, and that such a benefit is linked to increased activity of PFC regions (i.e., DLPFC, ACC).

Recent work by Samani and Heath (2018) had participants exercise at a moderate-to-high intensity (i.e., 60–85% HR_{max}) for a duration of 10 min and assessed EF via antisaccades prior to an following the exercise intervention. The antisaccade task involves the inhibition of a standard prepotent prosaccade (i.e., saccade toward presented stimuli) and vector inversion to direct one's gaze mirror-symmetrical to the target. Antisaccades serve as an exemplary assessment of inhibitory control (Munoz and Everling, 2004) and are associated with longer RTs and less accurate and more variable

endpoints than their prosaccade counterparts (Hallett, 1978; Gillen and Heath, 2014). The authors found a decrease in antisaccade RTs following the exercise intervention and thus demonstrated that a single bout of exercise, for as little as 10 min, benefits EF. Further, Shukla and Heath (2022) assessed the persistence of an EF benefit following 20 min of heavy intensity aerobic exercise (80% HR_{max}) via an AABB pro- and antisaccade paradigm (i.e., measure of cognitive flexibility) and found improved task-switching performance for up to 47 min postexercise. In turn, Tari and colleagues (2020) examined EF following 20 min of light (25 W), moderate- (80% estimated LT), and heavy-intensity (15% of the difference between LT and $\dot{V}O_{2peak}$) exercise intensities and reported improved antisaccade RTs for each intervention; that is, the magnitude of the postexercise EF benefit did not vary as a function of exercise intensity. Accordingly, results evince that a postexercise EF benefit: (1) can be accrued in as little of 10-min of exercise, (2) persists for up to 47 min, and (3) is observed across a continuum of exercise intensities.

1.3 Candidate mechanisms for an exercise-induced improvement in executive function

Exercise engenders a number of neurophysiological changes that have been linked to a postexercise EF benefit and include increased biomolecule levels such as catecholamines (e.g., norepinephrine: NE, dopamine: DA) and brain derived neurotropic factor (BDNF), increased CBF, and enhanced resting state functional connectivity within EF networks (for review, see Barnes 2015; Budde & Wegner, 2018).

An exercise-mediated increase in catecholamine concentrations elevates physiological and psychological arousal and some work has shown this to be linked to improved EF (Hershey et al., 2004). More specifically, it is theorized that the release of neurotransmitters DA and NA work cohesively to increase the strength of neural signaling (Rammsayer, 1993) and improve signal to “noise” ratio allowing increased efficiency of the PFC (Arnsten, 1988). Indeed, Gibbs and D’Esposito (2006) found improvements in working memory and increased fMRI activation of PFC regions following the administration of a DA receptor agonist (i.e., a substance used to increase DA receptor activation). In the exercise literature, exercise intensity has been shown to

directly mediate the level of physiological and cognitive arousal. In particular, some work has shown that moderate intensity exercise optimally influences cognitive arousal (McMorris et al., 2011), whereas low and high intensities are considered insufficient or detrimental, respectively, to arousal-based changes (Cooper, 1973; for review, see McMorris 2021). However, this is inconsistent with recent literature reporting that light (e.g., 40-60% HRmax) and heavy (e.g., high intensity interval exercise: HIIE) intensity exercise improve EF (Hashimoto et al 2018; Morris et al., 2020; see also Tari et al. 2021). Moreover, Ando et al (2022) assessed pre- and postexercise inhibitory control and serum catecholamine levels following a 30 min bout of light intensity (~50%HRmax) aerobic and resistance training. The authors found expected improvements to inhibitory control; however, the improvement was not related to changes in catecholamine levels. Thus, evidence does not support the view that catecholamine concentration is a primary moderator for a postexercise EF benefit.

BDNF is a protein important for neural growth and survival (Vaynman et al., 2004) and has been linked to improved EF. Exercise has been found to increase serum BDNF and it has been proposed that this increase contributes to a postexercise EF benefit (Gómez-Pinilla et al., 2002). For example, Hwang et al. (2016) assessed EF (via inhibitory control) and concentrations of serum BDNF following a 20 min bout of heavy intensity (85-90% $\dot{V}O_2$max) exercise. The authors found that improved inhibitory control was related to increased serum BDNF concentration. In contrast, Ferris and colleagues (2007) had participants complete 30 min of high (10% over ventilatory threshold) or low (20% below ventilatory threshold) intensity exercise. Results showed improved Stroop RTs following both exercise conditions; however, this benefit was unrelated to serum BDNF levels. What is more, Chang et al. (2017) reported the same null relationship between EF performance and serum-BDNF following a single bout of moderate-to-high intensity (60-70% of heart rate reserve: HRR) exercise. Thus, literature pertaining to BDNF and postexercise EF benefits remains equivocal.

Resting state functional connectivity is defined as information processing between structurally and functionally connected brain regions and some research has proposed that this process is improved following a single bout of exercise (for review, see Moore et

al., 2020). A common tool used to assess functional connectivity is fMRI; the blood oxygen level dependent (BOLD) signal utilized during fMRI depicts oxygen delivery and consumption of cortical regions (i.e., a measure of cortical activity; Ogawa et al., 1990). Schmitt and colleagues (2019) assessed functional connectivity via fMRI before and after 30 min of exercise at two different intensities (low: 35% below lactate threshold: high: 20% above lactate threshold). The authors found increased resting state connectivity over an extensive frontoparietal regions (including the ACC, DLPFC) following both exercise interventions and proposed that such a change reflects improved efficiency and effectiveness of neural networks. In contrast, Peven et al (2019), found no association between individual Stroop performance (i.e., RTs and error rates) and functional connectivity of the PFC region following maximal graded exercise. More recently, Voss et al. (2020) assessed functional connectivity and working memory (via n-back) following a 20 min bout of moderate (i.e., 65% of HRmax) intensity and passive exercise (i.e., cycling via mechanically driven stationary bike; see section 1.4). The authors reported improved n-back performance following exercise and demonstrated that this behavioural improvement was linked to increased activation of the DLPFC. Notably, however, the authors reported that the aforementioned changes were not linked to improved resting state functional connectivity. Therefore, the association between exercise-induced changes in functional connectivity and postexercise improvements to EF remains unclear.

Exercise increases CBF and this change has been proposed to contribute – in part – to a postexercise EF benefit. More specifically, exercise generates CO_2 as a by-product of cellular respiration that alters blood pH and triggers CO_2 sensitive chemoreceptors that induce systemic vasodilation resulting in an increase in CBF (for review, see Ainslie & Duffin, 2009; Hoiland et al., 2019; see also, section 1.4). In addition to the release of diffusible molecules (e.g., CO_2), mechanical stimulation (i.e., flexion and extension of muscles) during exercise triggers mechanosensitive Group III muscle afferents which have been shown to increase cardiac output and CBF (Nóbrega & Araujo, 1993; see section 1.4 for more detail). Indeed, elevated levels of CBF are thought to produce temperature-and mechanical-based changes to the brain's neural and glial pathways improving neural efficiency (i.e., the hemo-neural hypothesis; see Moore & Cao, 2008).

This relationship is exemplified in work by Tari and colleagues (2020) who assessed EF (via antisaccades) in a condition requiring a 10 min bout of moderate- to heavy-intensity (65 to 150 W) exercise, and a separate non-exercise condition wherein participants inhaled a high-than-atmospheric concentration of CO_2 for 10-min (i.e., a hypercapnic environment). The hypercapnic environment was used because it produces a rapid increase in CBF independent of the metabolic demands of exercise (Kety & Schmidt, 1948; Raper et al., 1971; Ito et al., 2000). Notably, Tari et al. had participants perform the hypercapnic condition first so that changes in CBF across conditions could be matched via real-time transcranial Doppler ultrasound (TCD) monitoring of blood flow velocity through the middle cerebral artery (MCAv). Tari et al. employed a pre- and post-condition assessment of EF via antisaccades and results showed that exercise and hypercapnia conditions produced reliable – and equivalent magnitude – improvements in EF. Based on these results, Tari et al. proposed that an increase in CBF supports a postexercise improvement in EF. Further, Byun et al. (2014) examined Stroop task performance and frontoparietal activity via fNIRS prior to an after a 10-min bout of light intensity exercise (30% $\dot{V}O_2$peak). Results showed the expected improvement in Stroop RTs and this benefit was linked to increased neurovascular coupling in the DLPFC. Accordingly, convergent evidence indicates that an increase in CBF represents a strong candidate mechanism for a postexercise EF benefit.

1.4 Passive exercise, hypercapnia, and their effects on cerebral blood flow and executive function

1.4.1 Passive Exercise

Passive exercise entails movement of limbs via an external force and is independent of volitional/active muscle recruitment. Previous work by Doering et al. (1998) found increases to CBF (via TCD) concurrent with 20 s sessions of passive flexion/extension of the upper- and lower- limbs. Further, Sato and colleagues (2009) reported increased CBF concurrent with 2 min of passive elbow flexion. Passive exercise has been theorized to contribute to an increase in CBF via two distinct mechanisms: (1) passive flexion and extension of large muscle groups (e.g., quadriceps) increases the discharge frequency of Group III mechanoreceptor (i.e., sensitive to muscle stretch) and activate neurons in the

brainstem and primary somatosensory cortex resulting in cerebral hyperemia (Nobrega,& Araujo, 1993; Nurhayati & Boutcher, 1998) and (2) increased central command drive, a feedforward mechanism that increases cardiac output in preparation of movement/exercise (Christensen et al., 2000; Matsukawa, 2012).

Passive exercise has also been shown to elicit structural changes and improve behavioral outcomes related to cognition. In rat models, chronic passive exercise interventions have been shown to increase hippocampal density, trigger the release of vascular endothelial growth factor (VEGF) and BDNF, and improve learning and memory (Uysal et al., 2015). In humans, Ridgel et al, (2013) found that a single 6-9 min bout of passive cycling, in participants with Parkinson's disease, improved task-switching performance. Notably, however, the authors did not concurrently assess CBF and it is thus not clear how passive exercise may benefit EF.

1.4.2 Hypercapnia

Hypercapnia is defined as an increase in the partial pressure of carbon dioxide ($PaCO_2$) above 45 mmHg (i.e., higher-than-atmospheric concentrations of CO_2) and is a stressor that can be generated externally (e.g., via inhalation of hypercapnic gas) or internally (i.e., as a by-product of cellular respiration) (for review, see Fabregas & Fernandez-Candill, 2016). Prolonged exposure to hypercapnia results in elevated blood acidity and risk of extracellular acidosis. Accordingly, excess levels of CO_2 are detected by aortic and carotid body chemoreceptors that trigger calcium (Ca_2^+) and K^+ channels to open, resulting in systemic vasodilation and an increase in CBF (for reviews see, Ainslie & Duffin, 2009). Indeed, Faraci and colleagues (1988) assessed the diameter of cerebral vasculature in rabbits when exposed to hypercapnic gas (5- 8% CO_2) and found that the diameter of the blood vessels increased relative to the CO_2 concentration (i.e., greater dilation at higher concentrations). In humans, an extensive literature has demonstrated a reliable increase in CBF concurrent with a hypercapnic environment (for review, see Ogoh 2019).

An interesting link between hypercapnia and EF can be found in the clinical literature wherein persons with chronic obstructive pulmonary disorder (COPD) and persons with

sleep apnea have been reported to have positive correlations between CO_2 concentrations and cognitive impairment (Beaudin et al., 2022; Dodd et al., 2010). Moreover, previous work examining the effects of acute hypercapnic exposure in healthy adults found detrimental effects on cognition concurrent with exposure to a hypercapnic environment (Satish et al. 2012). However, more recent work has reported no concurrent cognitive impairments (Rodeheffer et al., 2018; Scully et al., 2019). Further, and most recently, Tari et al (2020) found improvements to EF following a 10 min exposure to a 5% hypercapnic environment. Thus, there remains a high degree of heterogeneity in work regarding hypercapnia and cognitive function.

1.5 Research Predictions

Chapter 2 and 3 of my theses sought to address whether a 20 min single bout of passive cycle ergometry and a 10 min exposure to a 2.5% hypercapnic environment, respectively, increase CBF and provide a post-intervention EF benefit (assessed via antisaccades). In Chapter Two, EF was assessed prior to and immediately following the intervention, whereas in Chapter 3, EF was assessed prior to, concurrent with, and following hypercapnic exposure. In both Chapters 2 and 3, CBF was concurrently estimated via TCD measures of MCAv.

In terms of research predictions, if passive exercise and hypercapnia increases CBF then I predict that this physiological change will render a decrease in antisaccade RTs; that is, I predict that an increase in CBF will be linked to a postexercise EF benefit.

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Chapter 2

2 Introduction »

Executive function entails the high-level cognitive control components of inhibitory control, working memory, and cognitive flexibility – components essential to successful activities of daily living (Diamond, 2013; Miyake et al., 2000). Accumulating literature has demonstrated that a single bout of aerobic and/or resistance exercise across a continuum of intensities provides a transient improvement (i.e., <60-min) to executive function (Barella et al., 2010; Hung et al., 2013; Shukla & Heath, 2021; for meta-analyses see, Chang et al., 2012; Lambourne & Tomporowski, 2010; Ludyga et al., 2016). A candidate mechanism contributing to this improvement is an exercise-mediated increase in cerebral blood flow (CBF). Indeed, exercise initiates a rapid rise in CBF via CO_2 production from volitional muscle activation, increased diffusible molecules (e.g., nitric oxide: NO), heart rate, ventilation, and concomitant vascular deformation increasing systolic blood pressure (Smith & Ainslie, 2017). The increase in CBF has been linked to temperature- and mechanical-based changes to the brain's neural and glial networks that enhance the efficiency of local neural circuits involved in information processing (i.e., the hemo-neural hypothesis; see Moore & Cao, 2008). As well, chronic hypoperfusion linked to age- and disease-related states impairs executive function (Bertsch et al., 2009). Accordingly, the combined exercise and hypoperfusion literature evince a bi-directional relationship between CBF and executive function. In further support for the role of CBF in a postexercise executive function benefit, our group had participants complete a 10-min single bout of aerobic exercise via cycle ergometer, and a condition wherein participants inhaled a higher-than-atmospheric concentration of CO_2 for 10-min without exercising (i.e., hypercapnia) (Tari et al., 2020). The hypercapnic environment was used because it produces a rapid increase in CBF independent of the metabolic demands of exercise (Ito et al., 2003; Kety & Schmidt, 1948; Raper et al., 1971). Notably, Tari et al. had participants perform the hypercapnic condition first so that changes in CBF across conditions could be matched via real-time transcranial Doppler ultrasound (TCD) monitoring of blood flow velocity (BV) through the middle cerebral artery (MCA). Tari et al. employed a pre-and post-condition assessment of executive

function via an oculomotor task (see details below) and results showed that exercise and hypercapnia conditions produced reliable – and equivalent magnitude – improvements in the oculomotor-based index of executive function, whereas a non-exercise, non-hypercapnic control condition did not elicit a pre- to post-condition change in the same index of executive function. Based on these results, Tari et al. proposed that an increase in CBF supports a postexercise improvement in executive function. Although ample evidence indicates that aerobic and resistance exercise (so-called active exercise) increases CBF and leads to a postexercise improvement in executive function, to our knowledge no work has examined whether passive exercise similarly benefits executive function. Passive exercise occurs when a limb or joint is manipulated/moved without volitional control and is an established rehabilitation technique frequently used to improve local blood flow following an acute musculoskeletal injury, and to support long-term rehabilitation in populations with reduced (e.g., hemiparesis following stroke) or absent (e.g., spinal cord injury) mobility (for review see Trinity & Richardson, 2019). In spite of the fact that passive exercise does not generally entail any volitional muscle activation (cf. Bell & Duffin, 2003), it does induce hyperemia and increases CBF in healthy individuals (Doering et al., 1998; Matteis et al., 2003; Nagaya et al., 2015). For example, passive cycle ergometry of the lower limbs increases CBF from baseline in concert with increased cardiac output, stroke volume and systolic blood pressure (Doherty et al., 2018; Nobrega et al., 1994). Also, some work has shown that passive exercise does not alter heart rate or respiration and occurs independent of a change in diffusible CO_2 and NO (Asahara & Matsukawa, 2018). Thus, the mechanisms associated with a passive-exercise increase in CBF are different from those associated with active exercise. The passive exercise increase in CBF has been linked to the activation of (1) mechanosensitive Group III muscle afferents that stimulate the primary somatosensory cortex and increase cardiac output and stroke volume (Gladwell & Coote, 2002; Nobrega & Araujo, 1993; Nurhayati & Boutcher, 1998) and (2) feedforward command mechanisms that alter cardiovascular centers via descending central neural pathways involved in somato-motor activity (Eldridge et al., 1985; Goodwin et al., 1972; Krogh & Lindhard, 1913; Matsukawa, 2012; Victor et al., 1995). The goals of the current study were to examine whether a passive exercise-mediated increase in CBF is associated with

a postexercise improvement in an oculomotor-based index of executive function, and to contrast whether a putative improvement is equivalent to that observed following active exercise. To that end, separate passive exercise, active exercise and control conditions were included here. In the active exercise condition, participants pedaled a cycle ergometer for 20-min at a light-intensity, whereas in the passive exercise condition the same duration of exercise was implemented, and the cycle ergometer flywheel was mechanically driven with revolutions per minute (rpm) matched to the active exercise condition. In the control condition, participants sat on the cycle ergometer without passive or active exercise. In a pre-investigation procedural vali dation, electromyography (EMG), respiratory ($\dot{V}_E$ as well as heart rate and blood pressure) and gas exchange (i.e., $\dot{V}O_2$, $\dot{V}CO_2$) variables were measured across each condition to ensure that our passive exercise condition did not produce volitional activation of agonist muscles and/or a task-based increase in metabolic demands. This was deemed necessary given work by Duffin and colleagues (Bell et al., 2003; Bell & Duffin, 2003, 2004) reporting that passive cycle ergometry (via tandem bicycle) can increase ventilation and produce a steady-state hyperpnea with continued exercise – a response that would alter blood pH and decrease CBF without a concomitant change in blood pressure. That Duffin and colleagues observed an increase in respiration during passive exercise may relate to the mode of delivery (i.e., tandem ergometer vs. mechanically driven flywheel) and/or the pedal frequency used in their work. In particular, Duffin and colleagues had participants 'passively' cycle on a tandem ergometer (i.e., the experimenter pedaled) without a feedforward cue related to pedal frequency (i.e., metronome) – a passive exercise mode requiring activation of lower leg musculature that can increase respiration. In contrast, externally timed and mechanically driven passive leg extensions did not influence respiration (see Bell & Duffin, 2006). Accordingly, we sought to verify that the passive cycle ergometry (via mechanical flywheel and a metronome-paced frequency) used here did not alter respiratory, gas exchange or cardiorespiratory measures. Subsequently, in the main experiment, TCD was used to estimate BV through the MCA in each condition. As in previous work by our group (Dirk et al., 2020; Heath et al., 2016; Petrella et al., 2019; Samani & Heath, 2018; Shukla & Heath, 2021) an antisaccade task completed pre- and post-condition was used to provide an oculomotor-based index of executive function.

Antisaccades require a goal-directed eye movement (i.e., a saccade) mirror-symmetrical to an exogenously presented target and produce longer reaction times (RT) (Fischer & Weber, 1992; Hallett, 1978) and less accurate and more variable endpoints than their prosaccade (i.e., saccade to veridical target) counterparts (Dafoe et al., 2007; Gillen & Heath, 2014). Extensive evidence has shown that the behavioral 'costs' of antisaccades are attributed to the two-component executive function demands of response inhibition and vector inversion (i.e., 180° spatial transformation of a target location and a feature of cognitive flexibility) (for review see, Munoz & Everling, 2004). Moreover, human functional neuroimaging and lesion studies, and non-human primate work involving cryogenic deactivation of the prefrontal cortex, has shown that a directionally correct antisaccade is supported by a task-set that flexibly maintains behavioral rules on a moment-to-moment basis (for review see Everling & Johnston, 2013). Hence, antisaccades require top-down control supported via each core component of executive function. What is more, the frontoparietal networks supporting antisaccades are the same as those showing task-based changes in activity following single and chronic bouts of exercise (Colcombe et al., 2004; Verburgh et al., 2014; Voss et al., 2010). As such, antisaccades provide a framework for examining subtle exercise-mediated changes in executive function. In terms of research predictions, if an increase in CBF is related to an improvement in an oculomotor-based index of executive function then antisaccade RTs should decrease from pre- to post-condition assessments in passive and active exercise conditions. In contrast, if an increase in CBF is an epiphenomenon associated with passive and active exercise then the postcondition improvement in antisaccade RTs should be selectively restricted to the active exercise condition.

2.1 Methods

2.1.1 Participants

In the pre-investigation procedural validation, two participants (one female and one male aged 22 and 21, respectively) were recruited. In the main experiment, 28 participants were recruited (11 female, age range: 19– 26 years) with sample size determined a priori via an effect size derived from previous work examining pre- to postexercise changes in antisaccade RTs ($\alpha = 0.05$, power = 0.99, $d_z = 1.30$) (Tari et al., 2020). All participants

were naïve to the purpose of this study and were recruited from the University of Western Ontario community. Participants were self-reported right-hand dominant (i.e., “what hand do you write with?”), with normal or corrected-to-normal vision, no history of smoking and/or cardiorespiratory, metabolic, musculoskeletal, neurologic (including concussion), or neuropsychiatric disorder. Participants reported that they did not take medication that may affect metabolic, cardiac, respiratory, or hemodynamic responses to exercise. It was requested that participants not consume alcohol or caffeine 12h prior to the study and that they get 8 h of sleep on the night prior to each data collection session. The order in which conditions were performed (in both the procedural validation and main experiment) were randomized with each completed on a different day separated by at least 24h. All data collection took place between 9:30 am and 12:00pm with participants in a hydrated state (i.e., 555ml consumed 1-h in advance of data collection). Prior to data collection, participants read a letter of information approved by the Health Sciences Research Ethics Board, University of Western Ontario and provided informed written consent. This study was conducted according to the most recent iteration of the Declaration of Helsinki with the exception that participants were not registered in a database. All participants obtained a full score on the 2020 Physical Activity Readiness Questionnaire (PARQ+) and completed the Godin Leisure-Time Exercise Questionnaire (GLTEQ). For the pre-investigation procedural validation, GLETQ scores for the female and male participant were 70 and 84, respectively. In the main experiment, the average GLETQ score was 62 (SD = 26; range: 36–96) – results indicating that all participants were active.

2.2 Apparatus and procedure

The pre-investigation validation procedure and main experiment involved three conditions: active exercise, passive exercise, and a control condition. For all conditions, participants sat upright on an active-passive cycle ergometer (E-PAT AP; Healthcare International, Langley, WA, USA) equipped with a mechanically driven flywheel and their feet secured to the ergometer pedals via Velcro straps. Participants were positioned such that their legs achieved approximately 85% of full extension at the end of an active pedal stroke. All conditions were preceded by a 2-min baselining in which participants remained stationary on the ergometer. In the active exercise condition, a 2-min warm-up

followed baselining and required active cycling against a resistance of 15W at a cadence of 40 rpm. Subsequently, a step-transition to active cycling against a resistance of 37W (cadence = 70 rpm) was completed for a 20-min interval, after which a 2-min cool-down was performed as per the warm-up. The active exercise condition corresponds to a “light” intensity in the exercise work-rate continuum (Shim et al., 2013; Takata et al., 1990; Tari, Shirzad, Behboodpour, et al., 2021). The passive exercise condition employed the same timeline as the active exercise condition (i.e., baseline, warm-up, intervention, cool-down); however, pedal cadence during warm-up, intervention and cool-down was mechanically driven and participants were instructed to not actively engage their leg muscles. During the warm-up/cool-down, cadence was set at 40 rpm and transitioned to 70 rpm during the 20-min intervention. For the control condition, participants sat on the cycle ergometer for the baseline procedure and an additional 24-min (i.e., 26-min total: a period equivalent to warm-up, intervention, and cool-down in the exercise conditions) and watched a television sitcom on a popular streaming application. For all conditions, a metronome (MA-2-BKRD; Korg, Tokyo, Japan) was played. The metronome was used to support equivalent pedal cadence in the active and passive conditions.

2.3 Pre-investigation procedural validation

For the procedural validation, EMG from primary agonists involved in cycling were collected (Hug & Dorel, 2009) as were ventilatory, gas exchange and cardiovascular (i.e., heart rate and blood pressure) variables. Given the objective of this validation, we did not include pre- and postcondition measures of executive function.

2.3.1 EMG data collection

Surface EMG were recorded from 10mm Ag/AgCL electrodes (Trigno Avanti Sensor; Delsys, Inc. Natick, MA, USA) placed on the right vastus lateralis (i.e., 2/3 distance between anterior iliac spine and the lateral side of the patella), right biceps femoris (i.e., 1/2 distance between participants' ischial tuberosity and lateral epicondyle of the tibia), and right lumbar erector spinae (i.e., ~2.5 cm laterally from the spine and in line with the iliac crest). A reference electrode was placed on the superior iliac crest. Electrode sites were cleaned with an alcohol swab, lightly abraded and coated with EMG gel (Nu-prep,

Weaver and Company, CO, USA). EMG signals were amplified, bandpass filtered (i.e., 20–450Hz) and collected (EMGworks; Delsys, Inc. Natick, MA, USA) at 1926Hz for the vastus lateralis and biceps femoris, and at 1260Hz for the lumbar erector spinae. MATLAB (2018b: Mathworks, Natick, Mass., USA) was used to identify windows for inspection and visually compare conditions.

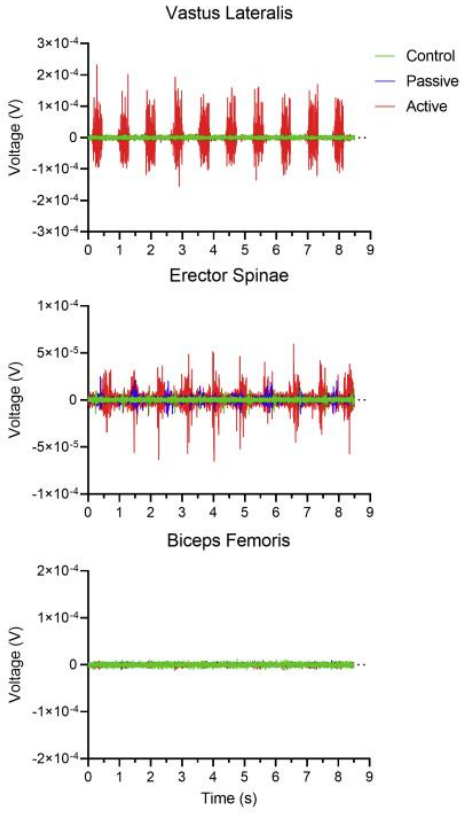

Figure 1. Vastus lateralis (a), erector spinae (b), and biceps femoris (c) electromyography (EMG) of the female participant in the active exercise (red), passive exercise (blue) and control (green) conditions of the procedural validation investigation. The figure demonstrates ten successive pedal strokes starting at the 10-min mark of the active and passive exercise conditions and shows an equivalent time frame for the control condition. The figure shows that the primary agonist (i.e., vastus lateralis) involved in leg extension elicited periodized activity during the active exercise condition, whereas periodized activity did not occur in the passive exercise or control conditions.

2.3.2 Ventilatory and gas exchange data collection

Participants were fitted with a face mask (7450 Series V2 Oro-Nasal Reusable Face Mask; Hans Rudolph, Shawnee, KS, USA) providing an airtight seal around the mouth and nose to assess breath-by-breath gas exchange of O_2 uptake ($\dot{V}O_2$) and CO_2 output ($\dot{V}CO_2$) via metabolic cart (CPET; Cosmed, Rome, Italy). Prior to data collection , the metabolic cart was calibrated according to the manufacturer's guidelines using room air and a precision -mixed cylinder of known concentrations, and turbine volume was calibrated with a syringe of known volume. The facemask was attached in series to a volume turbine and a non-rebreathing valve (Han s Rudolph) . A 2-ft hose connected the inspiratory end of the non-rebreathing valve to a 3-way valve that was interfaced with a Douglas bag. The 3 -way valve permitted the rapid switching from room air to the Douglas bag which contained either a hypercapnic or normocapnic (control) gas mixture. Heart rate was measured continuously by a heart rate monitor (Polar Electro T34, Kempele, Findland) using PowerLab (ML132/ML880, ADInstruments, Colorado Springs, CO, USA) and was calculated (using a 5 s rolling average) based on successive heart beats (i.e., RR interval), and blood pressure was taken at regular intervals (i.e., 3, 6, 9, 12, 15, 18, 21 and 24min) via a manual sphygmomanometer and stethoscope (Welch Allyn FlexiPort reusable blood pressure cuff; Welch Allyn Inc. Skaneateles Falls, NY, USA) secured to participants' left upper arm. All data post-processing matches that outlined in previous work by our group (Dirk et al., 2020; Heath et al., 2018; Petrella et al., 2019; Tari et al., 2020; Tari, Shirzad, Behboodpour, et al., 2021). EMG data for the female participant are presented in Figure 1 across ten successive pedal revolutions at the 10-min mark in the active and passive conditions and an equivalent time period in the control condition. The active exercise condition shows periodized activation of the vastus lateralis – a result consistent with a wealth of evidence demonstrating muscle activation patterns for active cycling (for extensive review, see Hug & Dorel, 2009). In contrast, the passive exercise condition shows no discernable change in muscle activation and mirrors that associated with the control condition. The ventilatory and gas exchange variables for the female participant are shown in Figure 2. The active condition showed increased $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ from baseline to warm-up and a further increase during the 20-min intervention. Moreover, the baseline-to-intervention increases in $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ are

directly in line with the “light-intensity” protocol employed by Tari, Shirzad, Behboodpour, et al. (2021) which required 10-min of cycling on an upright ergometer at 25W (75rpm). In contrast, the passive exercise condition did not show a substantial change in any variable across baseline, warm-up, and intervention and corresponded to the control condition. Table 1 shows that active condition heart rate and systolic blood pressure increased from baseline, warm-up, and intervention, whereas passive exercise and control condition values did not demonstrate an appreciable change across each assessment period. EMG, ventilatory and gas exchange data for the male participant were comparable to the female participant. Thus, the procedural validation demonstrates that the passive exercise condition did not lead to activation of agonist musculature and did not render increased task-based cardiovascular or ventilatory demands.

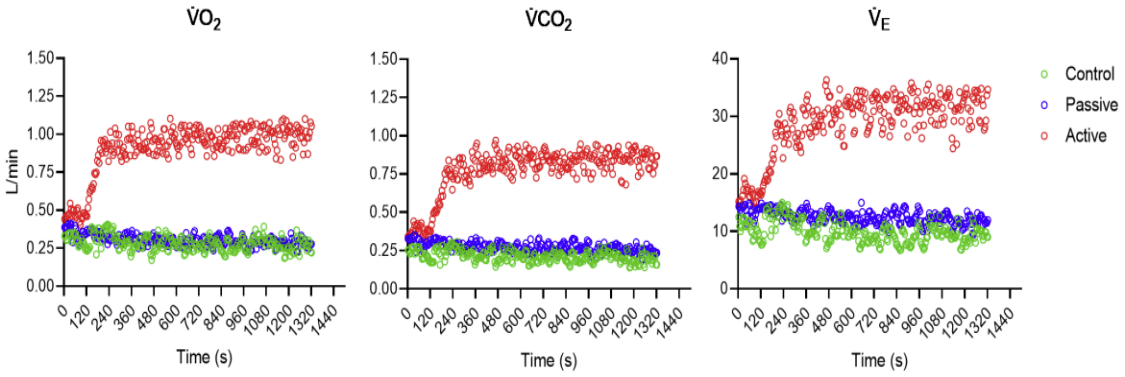

Figure 3. O_2 consumption (**$\dot{V}O_2$**), CO_2 output ($\dot{V}CO_2$) and ventilation (**$\dot{V}_E$**) data of the female participant in the active exercise (red), passive exercise (blue) and the control (green) conditions of the procedural validation pilot investigation. Data were sampled at 5 s intervals across a 24-min (i.e., 2-min baseline, 2-min warmup, and 20-min intervention period) and show that the active exercise condition produced a baseline to steady-state increase in **$\dot{V}O_2$**, $\dot{V}CO_2$ and **$\dot{V}_E$**, whereas no such change was observed for the passive exercise or control conditions.

2.4 Main Experiment

The conditions used in the main experiment (i.e., active exercise, passive exercise and control) matched the procedural validation with the exception that neither EMG nor ventilatory data were captured. Instead, the main investigation provided an estimate of

CBF via TCD through the MCA and included a pre- and post-condition examination of executive function. In addition, for the main experiment heart rate and blood pressure were taken at regular intervals (i.e., heart rate: 2, 12, 22min; blood pressure: 12min).

2.4.1 TCD data collection

For each condition, a TCD probe (Neurovision 500M, Neurovision TOC2M; Multigon Industries, Elmsford, CA) was coated in an aqueous ultrasound gel (Aquasonic Clear, Parker Laboratories Inc., Fairfield, NJ) and secured via headband to participants' left anterior temporal window to measure blood flow velocity (BV) through the MCA. Importantly, TCD is a valid proxy for a direct measure of changes in CBF (Bishop et al., 1986).

2.4.2 Executive function assessment

To provide an index of executive function, an oculomotor task (with which participants were not familiarized) was completed prior to and immediately following each condition. For each assessment, participants sat on a height-adjustable chair in front of a table on which an LCD monitor (60Hz, 8-ms response rate, 1280×960 pixels; Dell 3007WFP, Round Rock, TX) was located 550mm 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, Canada) sampling at 1000Hz. Prior to data collection, a nine-point calibration and validation of the viewing space was completed (i.e., <1° of error). All experimental events were controlled via MATLAB (R2018a; The MathWorks, Natick, MA, USA) and the Psychophysics Toolbox extension (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/m2) and included a midline-located red fixation cross (1°: 50 cd/m2) presented at participants' eye level and targets (i.e., open white circle; 2.5° in diameter: 127 cd/ m2) 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 signaled participants to direct their gaze to its location. Once a stable gaze was achieved (i.e.,±1.5° for 450ms),

a uniformly distributed randomized foreperiod (1000–2000ms) was introduced after which the fixation disappeared and a target appeared 200ms 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).

2.4.3 Data reduction

TCD data corrupted by signal aliasing and/or signal loss (e.g., a sudden head shift) were omitted (Terslev et al., 2017) and systolic BVs were retained for analysis (Clyde et al., 1996). Systolic BVs were analyzed given Rosengarten and Kaps' (2002) demonstration that they provide a valid measure for TCD-based changes in BV through the MCA and provide a measure for increased task-based demands in oculomotor control (Duschek et al., 2018; Tari, Shirzad, Badcock, et al., 2021). Mean values were determined via the last minute of rest (i.e., baseline) and the last minute of each intervention (i.e., steady-state). Gaze position data were filtered offline using a dualpass Butterworth filter with a low-pass cut-off frequency of 15Hz. A five-point central-finite difference algorithm was used to compute instantaneous velocities and accelerations. Saccade onset was determined when velocity and acceleration exceeded 30°/s and 8000°/s2 , respectively. Saccade offset was determined when velocity fell below 30°/s for 40ms. Trials involving a signal loss (e.g., an eyeblink) were removed as were anticipatory responses (RTs 2.5 standard deviations from a participant- and task-specific mean (Gillen & Heath, 2014). Less than 4% of trials for any participant were omitted. Trials involving a directional error (i.e., a prosaccade instead of an instructed antisaccade) were excluded from subsequent analyses because they are associated with planning mechanisms distinct from their directionally correct counterparts (DeSimone et al., 2014) and accounted for less than 5% of trials. This low error rate is attributed to the fact that antisaccades were not interleaved with prosaccades.

2.4.4 Dependent variables and statistical analyses

BV data were analyzed via 3 (condition: active exercise, passive exercise, control) by 2 (time: baseline, steady-state) fully repeated measures ANOVA ($\alpha = 0.05$). Heart rate was analyzed via 3 (condition: active exercise, passive exercise, control) by 3 (time: 2-min, 12-min, 22-min) fully repeated measures ANOVA ($\alpha = 0.05$), and systolic, and diastolic blood pressure captured at the 12-min interval of each condition were assessed via separate one-way (condition: active exercise, passive exercise, control) ANOVA ($\alpha = 0.05$). Oculomotor dependent variables included RT (i.e., time from response cueing to saccade onset), interquartile range of RT (i.e., IQR of RT), saccade duration (i.e., time from saccade onset to saccade offset) and saccade gain (i.e., saccade amplitude/veridical target location). Oculomotor dependent variables were examined via 3 (condition: active exercise, passive exercise, control) by 2 (time: pre-, post-) fully repeated measures ANOVA ($\alpha = 0.05$). For the majority of our dependent variables, mean values were used in our ANOVA models given that data were not skewed (g11.00) and as a result medians were used. Where appropriate, Huynh-Feldt corrections for violations of sphericity are reported (i.e., degrees of freedom adjusted to one decimal place). All interactions and appropriate main effects were decomposed via simple-effects (i.e., reduced model ANOVA and/or paired-samples t-test).

2.5 Results

2.5.1 Heart rate and blood pressure

Heart rate produced main effects for condition, $F(1.7, 44.7) = 106.25$, $p < .001$, $\eta_p^2 = 0.80$, time, $F(1.7, 46.1) = 28.52$, $p < .001$, $\eta_p^2 = 0.51$, and a condition by time interaction, $F(2.2, 59.5) = 29.49$, $p < .001$, $\eta_p^2 = 0.52$. Passive exercise and control condition heart rates did not vary across the 2- (passive: 83, SD = 12, control: 75, SD = 8), 12- (passive: 82, SD = 12, control: 76, SD = 8) and 22- min (passive: 82, SD = 11, control: 76, SD = 8) intervals (all $t[27] < 1.16$ and < -0.98, ps = .26 and = .33, $d_z < 0.22$ and < -0.19), whereas active exercise condition heart rates increased from the 2- (98, SD = 18) to 12- min (113, SD = 20) interval ($t[27] = -5.73$, $p < .001$, $d_z = -1.08$) and the latter did not differ from the 22- min (115, SD = 17) interval ($t[27] = -0.88$, $p = .39$, $d_z = -0.17$).Systolic and

diastolic blood pressure yielded main ef-fects of condition, all F(2, 54) = 21.59 and 5.86, ps <.001 and .004, η_p^2 = 0.35 and 0.13. For systolic blood pressure, pas-sive (127 mmHg, SD = 15) and active (145 mmHg, SD = 18) exercise conditions produced larger values than the control condition (121 mmHg, SD = 8) (all t[27] > −2.42, ps <.02, all d_z > −0.46), with values in the active exercise condition being larger than the passive exercise condition (t[27] = −5.88, p < .001, d_z = −1.11). For diastolic blood pressure, active exercise condition values (88 mmHg, SD = 11) were larger than control (81 mmHg, SD = 8) and passive exercise (82 mmHg, SD = 8) conditions (all t[27] > −2.51, ps <.02, all d_z > −0.47) and the latter two conditions did not reliably differ (t[27] = −0.28, p = .78, d_z = −0.05).

Table 2. Heart rate (HR) and blood pressure (systolic pressure: SBP; diastolic pressure: DBP) for the female participant in the procedural validation investigation at discrete timepoints during the control, passive exercise and active exercise conditions

Time (min)	Control HR	Passive HR	Active HR	Control SBP	Passive SBP	Active SBP	Control DBP	Passive DBP	Active DBP
0	96	92	96	126	124	126	96	94	90
3	92	92	106	120	130	132	96	98	98
6	91	90	124	130	132	142	96	92	98
9	96	96	130	126	136	150	96	88	96
12	94	92	128	124	130	148	94	94	92
15	94	94	132	118	132	142	98	98	96
18	96	96	138	136	136	144	100	92	98
21	96	96	130	126	136	142	100	80	102
24	92	94	134	128	132	148	94	82	98
Average (SD)	94 (2)	93 (2)	124 (14)	126 (5)	132 (4)	141 (8)	96 (2)	90 (6)	96 (4)

2.5.2 TCD blood flow velocity through the MCA

Systolic BV produced main effects for condition, F(1.8, 49.3) = 5.17, p = .009, η_p^2 = 0.16, and time, F(1, 27) = 103.87, p < .001, η_p^2 = 0.79, and their interaction, F(1.7, 46.8) = 53.26, p < .001, η_p^2 = 0.66. Figure 3 demonstrates that passive and active exercise conditions in-creased BV from baseline to steady- state (all t[27] = −5.33 and − 9.98, ps <.001, d_z = −1.01 and − 1.89), whereas no reliable change from baseline was observed for the control con-dition (t[27] = 0.57, p = .57, d_z = 0.11). To

address whether the magnitude of the baseline to steady- state change in BV varied across active and passive exercise conditions we computed participant- specific BV difference scores (i.e., steady-state minus baseline) and observed that values were larger in the active (25 cm/s, SD = 13) than passive (7 cm/s, SD = 7) exercise condition ($t[27] = -6.81$, $p < .001$, $d_z = -1.29$).

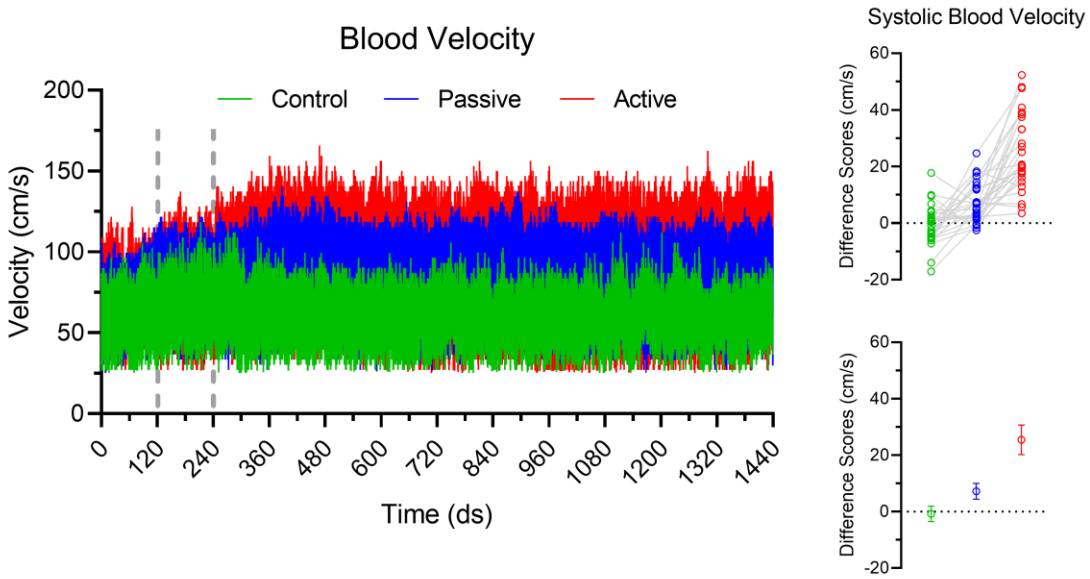

Figure 4. The central panel depicts an exemplar participant's systolic blood velocity (BV) from the middle cerebral artery sampled during the active exercise (red), passive exercise (blue) and the control (green) conditions of the main experiment. Data from each condition are overlayed and represent BV over a 24-min (i.e., 2-min baseline, 2-min warmup, and 20-min intervention) period. The vertical gray dotted lines represent the onset of warm-up (i.e., 120 s) and the intervention periods (i.e., 240 s), respectively. Offset panels indicate individual mean (top) and group (bottom) difference scores (i.e., steady-state minus baseline), respectively. The top offset panel includes gray connecting lines to denote participant-specific changes across conditions, and the bottom panel includes 95% between-participant confidence intervals for each condition. In the bottom panel the absence of overlap between the error bar and zero (i.e., horizonal gray line)

represents a reliable difference inclusive to a test of the null hypothesis (Cumming, 2014).

2.5.3 Oculomotor performance

RT produced a main effect for time, $F(1, 27) = 20.67$, $p < .001$, $\eta_p^2 = 0.43$, and a condition by time interaction, $F(2, 54) = 10.64$, $p < .001$, $\eta_p^2 = 0.28$. Figure 4a shows that control condition RTs did not reliably vary pre- to post- condition ($t[27] = -0.19$, $p = .85$, $d_z = -0.04$), whereas passive and active condition RTs decreased postexercise (all $t[27] = 2.23$ and 5.75, ps = .034 and <.001, $d_z = 0.42$ and 1.09). Given the nature of our research objective, we computed active and passive exercise condition RT difference scores (i.e., post- minus pre- condition) and Figure 4b shows a larger magnitude reduction in the former ($t[27] = 2.14$, $p = .042$, $d_z = 0.40$).RT IQR yielded a main effect of condition, $F(2, 54) = 3.80$, $p = .03$, $\eta_p^2 = 0.12$: passive exercise condition RTs (49 ms, SD = 18) were more variable than control (43 ms, SD = 14) or active exercise (44 ms, SD = 16) conditions (all $t[27] = -2.59$ and 2.11, ps = .02 and .044, $d_z = -0.48$ and 0.39), and the latter two conditions did not reliably differ ($t[27] = -0.58$, $p = .57$, $d_z = -0.11$).The grand means for saccade duration and saccade gain were 64 ms (SD = 19) and 0.74° (SD = 0.22), respectively, and neither variable elicited reliable main effects or interactions, all $F(1,27) < 3.85$, ps >.06, $\eta_p^2 < 0.13$.

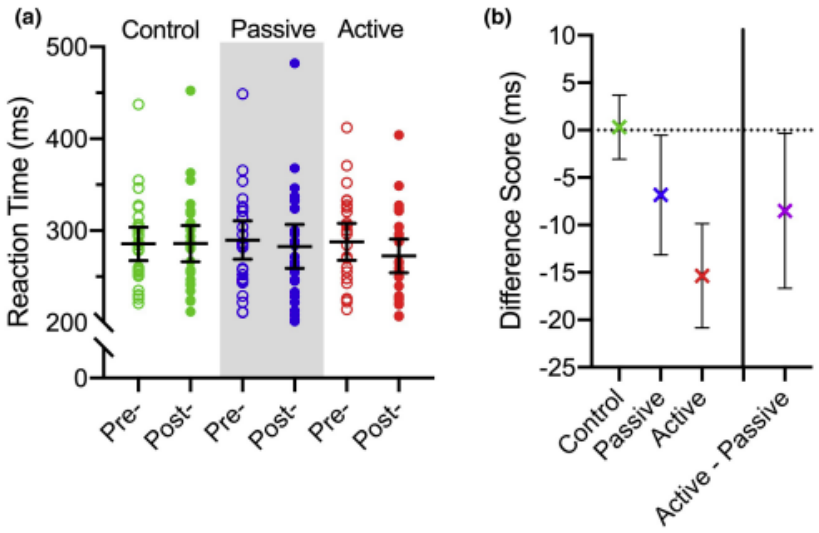

Figure 5. Panel a depicts participant-specific median pre- and post-condition antisaccade reaction times (RT) for the active exercise (red), passive exercise (blue) and control (green) conditions (Pre- and post-conditions values are denoted via open and closed circle symbols, respectively). The solid black lines represent the group mean and associated 95% within-participant confidence intervals. Panel B shows RT difference scores (i.e., post-intervention minus pre-intervention) with error bars representing 95% between-participant confidence intervals, as well as the mean RT difference score (i.e., passive minus active) between passive and active exercise conditions.

2.5.4 Correlation of steady-state BV and antisaccade RT in active and passive exercise conditions

A Pearson r correlation for the active exercise condition indicated that steady- state BVs increased with decreasing post- exercise antisaccade RTs (p = .049), whereas for the passive condition the relationship approached – but did not attain – a conventional level of significance (p = .081).

2.6 Discussion

We sought to determine if passive exercise increases CBF and relates to a postexercise benefit to executive function, and we examined whether the magnitude of a putative ex-executive function benefit for passive exercise is comparable to active exercise. In outlining our findings, we first de-scribe results for the active exercise condition before

turning to the hemodynamic and executive function findings in the passive exercise condition.

2.6.1 The metabolic demands of active exercise increase CBF and decrease antisaccade RTs

The active exercise condition entailed 20- min of volitional cycling and produced a baseline to steady- state increase in HR, blood pressure (systolic and diastolic) and BV. These findings correspond to the well- documented cardio- and neurovascular changes mediating the increased metabolic demands of active exercise (for re-views see Lavie et al., 2015; Smith & Ainslie, 2017). In line with these changes, the oculomotor assessment showed a postexercise reduction in antisaccade RTs. The decrease in antisaccade RTs cannot be attributed to a practice- related effect given that values in the non-exercise control condition did not vary from pre- to post-assessment. Moreover, that saccade duration and gain did not vary pre- to postexercise indicates that the RT reduction was unrelated to an explicit or implicit strategy designed to reduce planning times to enhance response accuracy (i.e., so- called speed- accuracy trade- off) (Fitts, 1954). Instead, the RT findings support a myriad of studies reporting that a single bout of active exercise elicits a short- term “boost” to executive function (for meta- analyses see Chang et al., 2012; Lambourne & Tomporowski, 2010; Ludyga et al., 2016; see also Renke et al., 2022). As well, the increase in BV during the active exercise condition – and not the non-exercise control condition – suggests that an exercise- mediated increase in CBF may support improved executive function (Kleinloog et al., 2019; Tari et al., 2020; for review of cerebral hypoperfusion and executive function see Poels et al., 2008). One issue to address in the active exercise condition is that the work- rate was set at a light intensity (i.e., 37 W). This is a notable because the inverted- U theory asserts that moderate-intensity exercise benefits executive function, whereas light- and heavy- intensities elicit a smaller, null, or negative effect (see Chang et al., 2012; Chang & Etnier, 2009; Tsukamoto et al., 2017). In reconciling this issue, studies have typically used a percentage of participants' $\dot{V}O_2$peak/max in determining intensity – a potential limitation given that $\dot{V}O_2$ and power output are not linearly related (for review Keir et al., 2018). As such, exercise intensity determined via a percentage of $\dot{V}O_2$peak/max does not provide

participant-specific equivalence in determining a dose– response relationship across the continuum of metabolically sustainable work rates. More recent work by our group employed lactate thresh-old (LT) in determining participant-specific work rates across light- (i.e., 25 W), moderate- (80% of participant-specific LT), heavy- (15% of the difference between participants' estimated LT and $\dot{V}O_2$peak) and very- heavy-(50% of the difference between participants' estimated LT and $\dot{V}O_2$peak) intensity exercise. As expected, ventilatory ($\dot{V}_E$) and gas exchange ($\dot{V}O_2$, $\dot{V}CO_2$, $PETCO_2$) variables increased across the light- to very- heavy intensities, as did cortical hemodynamics measured via TCD and near- infrared spectroscopy (Heath et al., 2018; Petrella et al., 2019; Tari, Shirzad, Behboodpour, et al., 2021). Tari et al. reported that light- , moderate- and heavy-intensity work rates produced an average baseline to steady-state increase in BV of 22 cm/s, 32 cm/s, and 46 cm/s, respectively. In spite of the scaling of BV to exercise intensity, null hypothesis, equivalence testing and Bayesian evaluation of the null hypothesis indicated that the magnitude of a postexercise benefit to antisaccade RTs did not vary with exercise intensity (see also Dirk et al., 2020; Heath et al., 2018; Petrella et al., 2019). Additionally, in the present work we used independent samples t- tests to contrast active exercise condition baseline to steady-state changes in BV and postexercise antisaccade RT difference scores to those reported in Tari, Shirzad, Behboodpour, et al.'s (2021) light- intensity condition. Results showed that between-experiment BV and RT values did not reliably differ ($ts[42] = 0.94$ and 1.45, $ps = .37$ and .14, $d_z = 0.28$ and 0.46). In other words, findings evince that active light intensity exercise provides sufficient reactivity to elicit a consistent magnitude postexercise benefit to an oculomotor- based index of executive function.

2.6.2 Passive exercise increases CBF and decreases antisaccade RTs independent of task- based ventilatory and metabolic demands

The present work included a procedural validation to determine if the passive cycle ergometry used here resulted in volitional activation of agonist musculature and increased ventilatory and metabolic demands. As mentioned previously, we deemed the procedural validation as necessary given that some work has shown that passive exercise produces an early increase in ventilation and steady- state hyperpnea (e.g., Bell & Duffin, 2004). In

our passive exercise condition, EMG of the vastus lateralis (i.e., primary agonist in leg extension) did not show periodized activation during the extension phase of each pedal stroke and produced an activation pattern on par to the non- exercise control condition. As well, the passive exercise and control conditions did not elicit baseline to steady- state changes in $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$ or heart rate. In contrast, the active exercise condition showed periodized activation of the vastus lateralis and this activation was associated with a robust increase in $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, blood pressure and heart rate. The procedural validation therefore demonstrated that the passive exercise protocol (i.e., cycle ergometer with mechanical flywheel and metronome- specified cadence) provided a basis to evaluate whether a change in BV in-dependent of the metabolic demands of active exercise support a postexercise improvement in antisaccade RTs. In our main experiment, passive exercise and control condition interventions did not produce a change in heart rate or diastolic blood pressure, whereas in the active exercise condition the aforementioned values reliably increased from baseline to steady-state. It is, however, important to recognize that both active and passive exercise conditions – but not the control condition – produced a baseline to steady-state increase in BV; albeit the magnitude of the increase was larger in the active (25 cm/s) than passive (7 cm/s) exercise condition. The increased BV in the active exercise condition reflects increased volumetric CBF arising from increased O_2 delivery (Hoiland et al., 2019) and is a well-defined consequence of the metabolic demands of volitional muscle activation in continuous aerobic exercise (Smith & Ainslie, 2017). In turn, results for the passive exercise condition are in line with work showing that involuntary movement of the limbs results in an increase in CBF. For example, Nagaya et al. (2015) had participants complete 1- min sessions of active and passive (via clinician manipulation) ankle plantar- and dorsiflexion and found that both conditions produced a baseline to steady-state increase in CBF with the magnitude of the increase being larger in the active condition. As well, Doering et al. (1998) showed that 20 s sessions of passive and active flexion/extension of the upper- and lower- limbs increased CBF (but see Sato et al., 2009). The basis for the increased CBF during passive exercise is thought to reflect: (1) increased discharge frequency of mechanosensitive Group III muscle afferents (so-called ergo receptors) that stimulate brain stem (Amann, 2012) and primary somatosensory

cortex (Gladwell & Coote, 2002) neurons supporting cerebral autoregulation, and (2) feedforward signals from primary and supplementary motor areas to the auto-nomic nervous system (Eldridge et al., 1985; Goodwin et al., 1972; Krogh & Lindhard, 1913; Matsukawa, 2012; Victor et al., 1995). In spite of the different mechanisms associated with the increase in CBF, both active and passive exercise conditions produced a pre- to postexercise decrease in antisaccade RTs with a larger magnitude re-duction in the former condition. As well, correlations indicated that steady-state BV related to the magnitude of active and passive condition post-exercise antisaccade RTs. As such, our results provide a first demonstration that passive exercise benefits an oculomotor- based index of executive function and evince that an increase in CBF independent of the metabolic costs of active exercise re-lates – and possibly contributes – to this improvement (i.e., the hemo- neural hypothesis: Moore & Cao, 2008).At least two issues require addressing. The first relates to the fact that passive exercise increased systolic blood pressure without concomitant changes in diastolic blood pressure, heart rate, gas exchange, and ventilatory measures. The basis for these results can be drawn from the so-called “muscle pump” effect wherein passive exercise increases venous return and increases stroke volume and cardiac output without influencing heart rate (Lujan & DiCarlo, 2014). The second issue relates to the larger postexercise reduction in antisaccade RTs in the active than passive exercise condition. This represents an unexpected finding given previous work by our group showing that intensity-specific modulations in an active exercise intervention do not impart additive CBF-executive function benefits (Tari, Shirzad, Behboodpour, et al., 2021). In considering this issue, we note that the change in BV for the passive exercise condition (7 cm/s) was smaller than that associated with the active exercise condition (25 cm/s), and the light- intensity condition (22 cm/s) used by Tari, Shirzad, Behboodpour, et al. (2021). Given these findings there may be a minimum threshold by which an increase in CBF imparts a non-additive benefit to the oculomotor- based measure of executive function used here.

2.7 Study limitations

We recognize the present work is limited by a number of methodological constraints. First, we used a single active and passive exercise duration (i.e., 20- min) and evaluated

postexercise executive function at one time point (i.e., immediately postexercise). As a result, it is unclear whether shorter or longer passive exercise durations similarly benefit antisaccade RTs, and it is entirely unclear for how long a passive exercise executive function benefit persists. Indeed, in active exercise, an executive function benefit can persist up to 60- min postexercise (Joyce et al., 2009; Hung et al., 2013; Shukla & Heath, 2021; but see Chang et al., 2012). Hence, it would be informative to examine whether a passive exercise benefit exhibits the same temporal persistence as its active exercise counterpart. Second, our results are specific to healthy young adults and cannot be directly extended to older populations or those with compromised CBF given that such groups exhibit distinct reactivity to active and passive exercise (McLeod & Stromhaug, 2017; see also, Ludyga et al., 2016). Third, a change in BV measured via TCD does not take into consideration vessel diameter. This represents a possible limitation because under specific physiological conditions the MCA is capable of dilation and constriction (Coverdale et al., 2015); however, to our knowledge such changes have not been shown to influence the validity of TCD in evaluating exercise- mediated MCA changes in BV. Fourth, a single bout postexercise benefit to executive function has not only been linked to increased CBF but also an increase in biomolecule concentrations (i.e., brain- derived neurotrophic fac-tor, catecholamines, serotonin) (Knaepen et al., 2010; Zouhal et al., 2008) and enhanced resting state functional connectivity within frontoparietal networks (e.g., Voss et al., 2010). Accordingly, we are unable to conclude directly that an increase in CBF selectively elicited the observed benefit to executive function following passive and active exercise. Regardless of the aforementioned limitations, we believe the present findings add importantly to the literature insomuch as they provide a first demonstration that a 20- min single bout of passive exercise increases CBF and improves an oculomotor- based measure of executive function in healthy young adults. Such results provide not only an improved direction for understanding the mechanism by which exercise benefit’s executive function, but also supports a potential clinical understanding that individuals with reduced mobility (e.g., spinal cord injury) may accrue transient and additive benefits to brain health via passive exercise.

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Chapter 3

3 Introduction

The earth's atmosphere contains a trace amount (0.03%) of carbon dioxide (CO_2), whereas space flight and space exploration are associated with increased levels due to weight and physical space limitations related to buffering excess environmental CO_2 (National Research Council, 2008). CO_2 concentrations aboard spacecraft and exploration vehicles are typically 0.5% with intermittent fluctuations of 0.2% occurring throughout the day (James, 2008), and a 2.0% concentration represents the Spacecraft Maximum Allow Concentration (SMAC) for acute (<1 h) exposure) (Law et al., 2010; Demontis et al., 2017). Notably, the regulation of a constant – and low-level – of CO_2 is important because changes in this compound are rapidly detected by aortic and carotid body chemoreceptors that elicit a cascade of physiological adaptations (e.g., increased ventilation) to increase the body's elimination of CO_2 (Marshall, 1994). Further, an increase in CO_2 is associated with systemic vasodilation and increased cerebral blood flow (CBF) (Raichle et al., 1970). As such, exposure to a higher-than-atmospheric concentration of CO_2 (i.e., hypercapnic environment) alters physiological homeostasis and some work has reported that it contributes to psychophysiological "space fog" adversely impacting cognition and psychomotor performance (Clément et al., 2020).

A limited number of terrestrial studies examined cognitive and psychomotor performance during and/or after participants' exposure to a hypercapnic environment. Satish et al. (2012) used the strategic management simulations (SMS) task to assess cognition prior to and concurrent (i.e., during the hypercapnic exposure) with a 2.5 h graded hypercapnic exposure (0.06, 0.10 and 0.25% CO_2). The SMS entails a number of simulation tasks (e.g., stepwise procedures required to deal with an emergency or management decision) and has been used to measure complex decision making and cognitive dysfunction following traumatic brain injury (e.g., Streufert et al., 1988). Satish et al. reported that increasing CO_2 levels were associated with diminished SMS task performance. As well, Allen et al. (2016) reported that in comparison to a baseline condition, chronic exposure (i.e., 6 days at 6-8 h/day) to 0.09% and 0.14% hypercapnic environments resulted in 15%

and 50% reductions, respectively, in concurrent SMS task performance. Accordingly, these studies demonstrate a dose-response relationship between CO_2 and concurrent cognitive impairment.

It is, however, important to recognize that not all work has reported a concurrent hypercapnic-based cognitive and/or psychomotor impairment. Rodeheffer et al.'s (2018) work involving submariners found that 80-min exposure to hypercapnic environments of 0.06%, 0.25% and 1.5% CO_2 did not impact SMS performance compared to baseline. The authors proposed that the null findings reflect a psychophysiological adaptation owing to submariners prolonged occupational exposure to a hypercapnic environment (i.e. submariners are typically deployed for a period of three months with CO_2 concentrations up to 0.5%). As well, Scully et al. (2019) recruited astronaut-like participants (i.e., individuals holding an advanced degree with > 1,000 hours of jet aircraft pilot-in-command time) and employed a 175-min exposure to 0.06%, 0.12%, 0.25%, and 0.50% hypercapnic environments. Cognitive and psychomotor skills were assessed via the SMS and a neurocognitive battery purpose-designed to evaluate cognitive skills in trained spaceflight crews (i.e., Cognition). Results indicated a null change between baseline and concurrent cognitive and psychomotor performance as assessed by both measures. Scully et al. proposed that the discrepancy in the hypercapnic literature may reflect test resolution in detecting subtle changes in cognitive and psychomotor performance. Accordingly, it was recommended that future work employ tasks providing a directed evaluation of cognition in a hypercapnic environment.

Executive function (EF) represents a high-level cognitive construct that includes the core components of inhibitory control, working memory and cognitive flexibility. EF tasks provide the resolution to identify subtle changes in brain-behaviour relations not available in neuropsychological batteries (Miyake et al., 2000; Diamond, 2013). For example, antisaccades represent an exemplar EF task requiring that an individual "look" (i.e., saccade) in a direction opposite an exogenously presented target. Antisaccades result in longer reaction times (RTs) (Hallett, 1978), increased directional errors (Fischer et al., 1997) and less accurate and more variable endpoints (Dafoe et al., 2007; Gillen & Heath, 2014) than their prosaccade (i.e., saccade to veridical target location) counterparts.

Extensive human neuroimaging and lesion studies, as well as and single-cell recording and transient cooling research in non-human primates, has reported that antisaccade behavioural 'costs' reflects the high-level operation of each core component of EF (for reviews see Munoz & Everling, 2004; Everling & Johnston, 2013). Work by our group employed the antisaccade task prior to (i.e., pre-) and immediately after (i.e., post-) healthy young adults were exposed to a 5% hypercapnic environment for 10-min and this performance was contrasted to pre- and post- measures of EF in a condition with an atmospheric concentration of CO_2 (i.e., normocapnic) (Tari et al., 2020). The basis for our group's manipulation was that: (1) a hypercapnic environment leads to a well-defined increase in CBF due to cerebrovascular dilation (for review, see Ogoh & Ainslie, 2009), and (2) a transient increase in CBF has been linked to a post-intervention improvement in the efficiency and effectiveness of EF networks (i.e., the hemo-neural hypothesis) (Moore & Cao, 2008). Our group used transcranial Doppler ultrasound (TCD) to measure middle cerebral artery velocity (i.e., MCAv) – a protocol Bishop et al. (1986) showed to provide a valid proxy for a direct measure of CBF. The hypercapnic environment produced an expected baseline to steady-state increase in MCAv (i.e., 21 cm/s) and produced a reliable pre- to post-intervention reduction in antisaccade RTs, whereas no such changes were associated with the normocapnic condition. In other words, a 5% hypercapnic environment resulted in a post-intervention improvement in an oculomotor index of EF and was a resulted interpreted to reflect that a short-term hypercapnic-based increase in CBF supports improved EF network efficiency and effectiveness.

Two notable limitations with generalizing our group's previous hypercapnic results (Ogoh & Ainslie, 2009) to extraterrestrial travel is that the protocol: (1) examined EF only after – and not concurrent – with the hypercapnic intervention, and (2) examined a CO_2 concentration (i.e., 5%) outside of the SMAC threshold (National Research Council, 2008). Accordingly, the present work employed a 10-min exposure to a 2.5% hypercapnic environment to provide a relative proxy to the SMAC threshold and evaluated EF – via the antisaccade task – pre-, concurrent, and post-intervention. In addition, EF was assessed at the same time points during a normocapnic (i.e., control) condition. For hypercapnic and control conditions, baseline and steady-state measures of CBF were estimated via TCD monitoring of MCAv. In terms of research predictions, if a

2.5% hypercapnic environment increases CBF, then a reduction in antisaccade RTs should be observed during concurrent and post-intervention assessments – a pattern of results in line with the hemo-neural hypothesis' assertion of a CBF-based improvement in EF network efficiency. In contrast, if the hypercapnic environment does not elicit a reliable increase in CBF – or does not elicit a CBF change of sufficient magnitude – then concurrent and post-intervention antisaccade RTs should be equivalent to their pre-intervention counterparts.

3.1 Methods

3.1.1 Participants

Fourteen (6 female, aged 19–25 years, average=23, SD=2) undergraduate and graduate students from the University of Western Ontario, volunteered for this study. Sample size was determined a priori based on an effect size (d_z=0.65) associated with previous work reporting hypercapnic-based post-intervention reductions in antisaccade RTs ($\alpha = 0.05$, power = 0.90) (Tari et al., 2020). Participants reported normal or corrected-to-normal vision, self-reported being right-hand dominant, with no history of smoking and/or cardiorespiratory, metabolic, musculoskeletal, neurological, or neuropsychiatric disorder. Participants declared that they did not take medication impacting metabolic, cardiac, respiratory, or hemodynamic responses. Further, because fitness level influences cerebrovascular reactivity to CO_2 changes (Miyamura et al., 1990; Zhu et al., 2013), participants completed the Goldin Leisure Time Exercise Questionnaire (GLTEQ). The average score on the GLETQ was 85 (SD = 11; range = 69-102) and thus indicated that all participants were recreationally active. Participants refrained from alcohol and caffeine 12 h prior to any study intervention and reported 8 h of sleep on the night prior to each study intervention. Data collection took place between 9:30 am and 12:00 pm with participants in a hydrated state (i.e., 555 ml consumed 1-h in advance of data collection).

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 (#119678). This study conformed to the ethical standards

of the most recent iteration of the Declaration of Helsinki with the exception that participants were not registered in a database.

3.1.2 Procedure and Apparatus

This study consisted of separate 10-min sessions involving hypercapnic (i.e., 2.5% CO_2, 21% O_2, 76.5% N_2) and normocapnic/control (i.e., 0.03% CO_2, 21% O_2, 78.97% N_2) conditions. The order of conditions was counterbalanced with each completed on a different day separated by at least 24 h. For each condition, participants were fitted with a face mask (7450 Series V2 Oro-Nasal Reusable Face Mask; Hans Rudolph, Shawnee, KS, USA) providing an airtight seal around the mouth and nose, VO_2, CO_2 excretion VCO_2, ventilatory V_E and end-tidal pressure end-tidal CO2: $PETCO_2$ were assessed via metabolic cart (CPET; Cosmed, Rome, Italy). Prior to data collection, the metabolic cart was calibrated according to the manufacturer's guidelines using room air and a precision-mixed cylinder of known concentrations, and turbine volume was calibrated with a syringe of known volume. The facemask was attached in series to a volume turbine and a non-rebreathing valve (Hans Rudolph). A 2-ft hose connected the inspiratory end of the non-rebreathing valve to a 3-way valve that was interfaced with a Douglas bag. The 3-way valve permitted the rapid switching from room air to the Douglas bag which contained either a hypercapnic or normocapnic (control) gas mixture. When participants were comfortably seated and with the face mask fitted, they were instructed to breathe normally and were provided normocapnic gas for 10 min to establish a baseline. Following the 10-min baseline in the normocapnic condition, participants continued to inhale the normocapnic gas for an additional 10-min, whereas in the hypercapnic condition following baseline a two-way valve on the Douglas bag was adjusted to provide a 10-min hypercapnic environment. Following the intervention in both hypercapnic and control conditions, a further 10-min period involved breathing normocapnic gas (see Figure 1 for timeline of events).

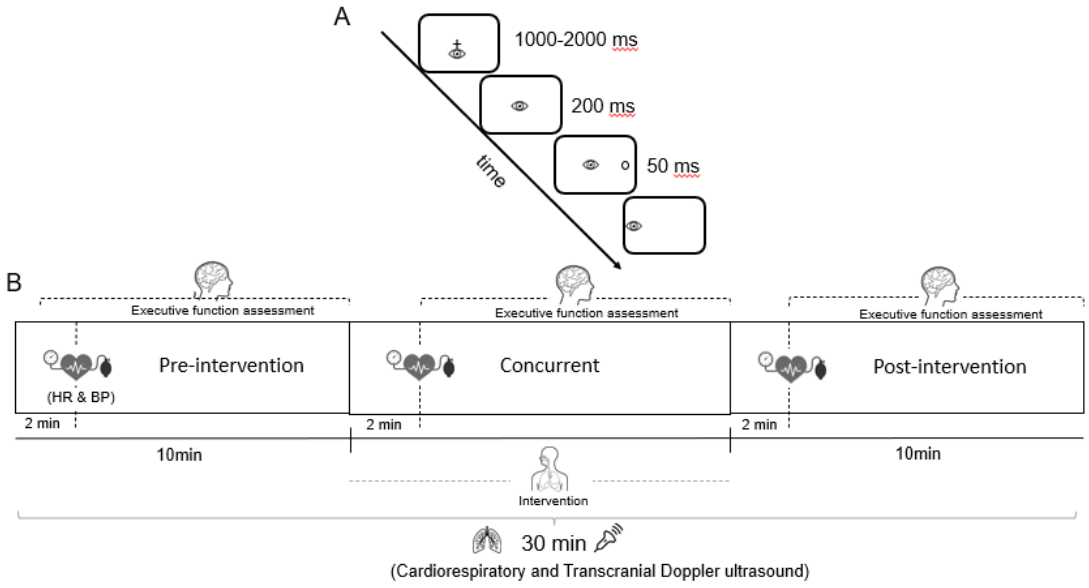

Figure 6. The top panel (A) shows a timeline of the visual- and movement-related events for the antisaccade task. The bottom panel (B) shows the timing of the pre-, concurrent- and post-intervention assessments in the hypercapnia condition. The control condition followed the same timing with the exception that participants were continuously exposed to a normocapnic environment. The panel shows that heart rate (HR) and blood pressure (BP) were measured at the start of each assessment window and that the antisaccade task was administered ~2 min following the onset of each assessment window. Transcranial Doppler ultrasound and the assessment of cardiorespiratory variables occurred continuously during each assessment window.

3.1.3 Cerebral hemodynamics

Prior to each condition, a TCD probe (Neurovision 500 M, Neurovision TOC2M; Multigon Industries, Elmsford, CA) coated in an aqueous ultrasound gel (Aquasonic Clear, Parker Laboratories Inc., Fairfield, NJ) was secured to participants' left anterior temporal window via an adjustable headband. The TCD probe was used to continuously measure MCAv during each of the pre-intervention, concurrent, and post-intervention assessments.

3.1.4 Cardiovascular variables

Figure 1 shows that heart rate was taken at pre-intervention, concurrent, and post-intervention time points (i.e., 2, 12, and 22 min) via a heart rate monitor (Polar Electro T34, Kempele, Finland). Blood pressure was taken at the same time points via manual sphygmomanometer and stethoscope (Welch Allyn FlexiPort reusable blood pressure cuff; Welch Allyn Inc. Skaneateles Falls, NY, USA) secured to participants' left upper arm.

3.1.5 Oculomotor executive function

Participants sat on and adjustable chair in front of a table on which an LCD monitor (60 Hz, 8-ms response rate, 1280 × 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, Canada) sampling at 1000 Hz. Prior to data collection, a nine-point calibration and validation were completed (i.e., <1° of error). All experimental events were controlled via MATLAB (R2018a; The MathWorks, Natick, MA, USA) and the Psychophysics Toolbox extensions (v. 3.0) (Brainard, 1997; Kleiner, 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/m2) and included a midline-located fixation cross (1°: 50 cd/m2) presented at participants' eye level and targets (i.e., open circle; 2.5° in diameter: 127 cd/m2) located 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 signaled participants to direct their gaze to its location. Once a stable gaze was achieved (i.e., ± 1.5° for 450 ms), a uniformly distributed randomized foreperiod (1000–2000 ms) was introduced after which the fixation disappeared and a target appeared 200 ms thereafter (i.e., gap paradigm) (Figure 1). Target onset cued participants to saccade mirror-symmetrical to the target location (i.e., antisaccade) as "quickly and accurately as possible". The oculomotor assessment was completed prior to (i.e., pre-

intervention), during (i.e., concurrent) and immediately following (i.e., post-intervention) each of the hypercapnic and control conditions. For each oculomotor assessment, 30 trials to each target location (i.e., left, and right visual field) and eccentricity (i.e., proximal, and distal) were randomly presented (i.e., 120 total trials). Each oculomotor assessment required approximately seven minutes to complete.

3.1.6 Data reduction and dependent variables

For ventilatory measures, data points +3 standard deviations from a participant-specific mean were removed (Lamarra et al., 1987) and data were linearly interpolated on a second-by-second basis, time-aligned to the onset of an experimental session and averaged into 5 s bins (Keir et al., 2015). For TCD, data corrupted by signal aliasing and/or signal loss (e.g., a sudden head shift) were omitted (Terslev et al., 2017).

For the oculomotor task, gaze position data were filtered offline using a dual-pass Butterworth filter with a low-pass cutoff frequency of 15 Hz and instantaneous velocities were computed via a five-point central finite difference algorithm. Acceleration data were similarly obtained from the velocity. Saccade onset was marked when velocity and acceleration exceeded 30°/s and 8,000°/s2, respectively. Saccade offset was marked when saccade velocity was below 30°/s for 40 ms. Trials involving signal loss (e.g., eye blink) were excluded as were trials with an amplitude less than 2° (Weiler & Heath, 2014) and or a RT less than 50 ms or +3 standard deviations from a participant-specific mean (Wenban-Smith, 1991). Less than 5% of trials were removed for any participant.

Dependent variables for physiological measures included O_2 consumption ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$), ventilation ($\dot{V}_E$), end-tidal CO_2 ($PETCO_2$), heart rate, blood pressure and MCAv. MCAv was determined by averaging peak systolic MCAv for the final minute of each assessment window (i.e., pre-intervention, concurrent, and post-intervention), whereas $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, $PETCO_2$ were evaluated across the last five minutes of each assessment window (Figure 1). Oculomotor dependent variables included RT (i.e., time from response cueing to saccade onset), saccade duration (i.e., time from saccade onset to offset) and saccade gain (i.e., saccade amplitude/veridical target location)

Each dependent variable was analyzed via 2 (condition: hypercapnic, control) by 3 (time: pre-intervention, concurrent, post-intervention) fully repeated measures ANOVA (α = 0.05). Appropriate main effects and interactions were decomposed via simple effects. Where appropriate, the two one-sided test (TOST) statistic (d_z =0.61) was used to determine if results were within an equivalence boundary (Lakens et al., 2018).

3.2 Results

3.2.1 Ventilatory variables

Figure 7 presents an exemplar participant's $\dot{V}_E$ and $PETCO_2$ as a function of time across each assessment interval. The figure demonstrates that onset of the hypercapnic condition produced an immediate increase in both measures. Quantitative analyses indicated that $\dot{V}_E$ and $PETCO_2$ produced main effects for condition, $Fs_{(1,13)}$=21.40 and 139.63 for $\dot{V}_E$ and $PETCO_2$, respectively, ps<.001, η_p^2=0.64 and 0.92, time, $Fs_{(2,26)}$=52.83 and 6.41, ps<.001 and .006, η_p^2=0.81 and 0.34, and condition by time interactions, $Fs_{(2,26)}$=13.44 and 8.60, ps<.001 and .002, η_p^2=0.52 and 0.41. To decompose the interactions, we computed $\dot{V}_E$ and $PETCO_2$ difference scores separately for hypercapnic and control conditions by contrasting: (1) concurrent minus pre-intervention, and (2) post-intervention minus pre-intervention. Difference scores were subsequently contrasted to a value of zero via single-sample t-statistics. For the control condition, $\dot{V}_E$ and $PETCO_2$ difference scores did not differ from zero (ts(13)<1.77, ps>.10, all d_z<0.47). For the hypercapnic condition, **Figure 7** shows that $\dot{V}_E$ and $PETCO_2$ difference scores contrasting the concurrent and pre-intervention time points differed from zero (t(13)>9.60, ps<.001, all d_z>2.48), whereas difference scores contrasting post- and pre-intervention values did not (ts(13)<0.57, ps>.58, all d_z<0.16). In other words, onset of the hypercapnic condition increased $\dot{V}_E$ and $PETCO_2$ with values returning to baseline upon condition cessation.

$\dot{V}CO_2$ and $\dot{V}O_2$ did not produce reliable main effects for **condition**, $Fs_{(1,13)}$<3.25, ps>.097, η_p^2<0.21, **time**, $Fs_{(2,26)}$<2.69, ps>.088, η_p^2<0.184 nor their interactions, $Fs_{(2,26)}$<2.86, ps>.077,

η_p^2<0.19

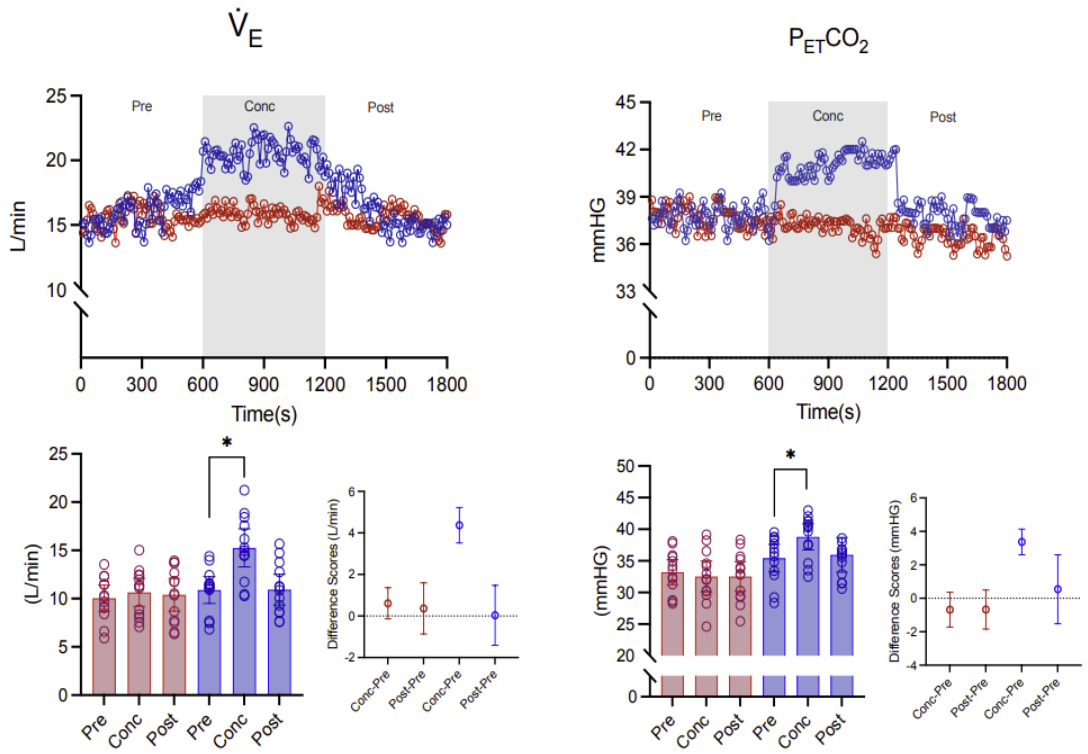

Figure 7. The top left and right panels present an exemplar participant's $\dot{V}_E$ and $PETCO_2$, respectively, throughout the pre-intervention (Pre), concurrent (Conc) and post-intervention (Post) assessment windows for the control (red line and symbols) and hypercapnic (blue line and symbols) conditions. The panels show that values for both variables rapidly increased with onset of the hypercapnic condition and rapidly returned to baseline with cessation of the hypercapnic environment. The bottom left and right panels show participant-specific and group mean $\dot{V}_E$ and $PETCO_2$, respectively, for control (blue bars and symbols) and hypercapnic (red bars and symbols) conditions at each assessment window with the smaller offset panel showing group mean $\dot{V}_E$ and $PETCO_2$ difference scores (concurrent minus pre-intervention, post-intervention minus pre-intervention) – and associated 95% between-participant confidence intervals – for control and hypercapnic conditions. For the smaller offset panels, the absence of overlap between the error bar and zero (i.e., horizontal dashed line) represents a reliable difference inclusive to a test of the null hypothesis.

3.2.2 Hemodynamic variables

Heart rate, systolic and diastolic blood pressure did not produce main effects for condition, $Fs_{(1,13)}<1.63$, $ps>.224$, $\eta_p^2<0.11$, time, $Fs_{(2,26)}<2.59$, $ps>.094$, $\eta_p^2<0.17$ nor their interactions, $Fs_{(2,26)}<2.07$, $ps>.146$, $\eta_p^2<0.14$. In contrast, MCAv produced a main effect of time, $F_{(2,26)}=6.12$, $p = .007$, $\eta_p^2 = 0.32$, and a condition by time interaction, $F_{(2,26)}=5.17$, $p=.013$, $\eta_p^2=0.29$. **Figure 8** shows and exemplar participant's MCAv in control and hypercapnic conditions as a function of assessment window. The figure shows that MCAv in the hypercapnic – but not control – condition increased rapidly to the onset of the hypercapnic environment and then decreased to pre-intervention levels following condition cessation (i.e., post-intervention). In line with $\dot{V}_E$ and $PETCO_2$, the MCAv interaction was decomposed via difference scores and indicated that control condition values did not reliably differ from zero ($ts(13< 0.62$, $ps>.54$, $d_z< 0.17$). For the hypercapnic condition, difference scores contrasting concurrent and pre-intervention time points differed from zero ($t(13)=3.19$, $p=.007$, $d_z=0.85$), whereas pre- and post-intervention values did not ($t(13)=0.27$, $p=.78$, $d_z=0.07$).

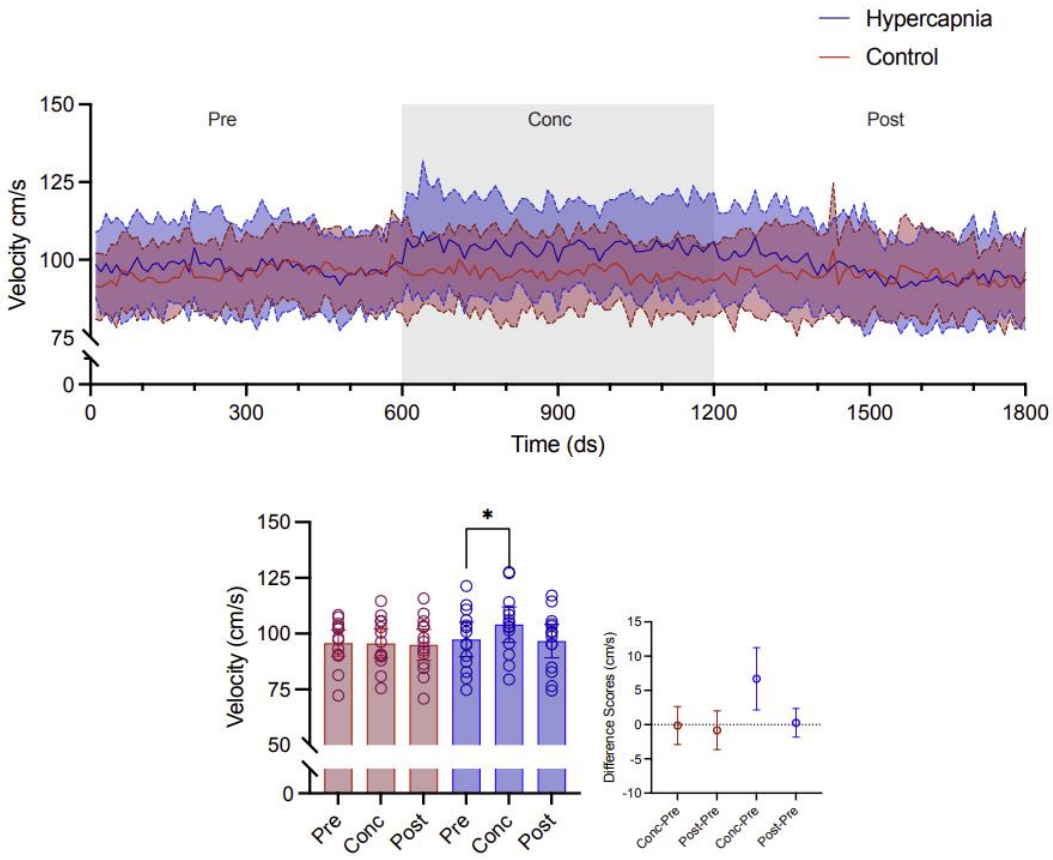

Figure 8. The top panel represents participant's mean middle cerebral artery velocity throughout the pre-intervention (Pre), concurrent (Conc) and post-intervention (Post) assessment windows for the control (red line and symbols) and hypercapnic (blue line and symbols) conditions. The bottom left panel shows participant-specific and group mean MCAv for control (red line and symbols) and hypercapnic (blue line and symbols) conditions as a function of each assessment interval with the bottom right panel showing group mean MCAv difference scores (concurrent minus pre-intervention, post-intervention minus pre-intervention) – and associated 95% between-participant confidence intervals.

3.2.3 Executive Function

Figure 9 presents antisaccade RT frequency histograms for hypercapnic and control conditions across each assessment interval and Kolmogorov-Smirnov tests indicated that pre- and concurrent ($Ds<.041$, $p>.36$) and pre- and post-intervention ($Ds<.036$, $p>.28$) distributions did not reliably differ. The evaluation of RT means did not yield main

effects for condition, $F_{(1,13)}$=0.01, p=.90, η_p^2<0.01, time, $F_{(2,26)}$=0.34, p=.71, η_p^2=0.02, nor their interaction, $F_{(2,26)}$=0.39, p=.67, η_p^2=0.03). Moreover, TOST statistics indicated that hypercapnic condition RTs for concurrent and pre-intervention (t(13)=2.22, p=.023) and post-intervention and pre-intervention (t(13)=2.24, p=.022, d_z=0.01) were within an equivalence boundary. In other words, results provide no evidence that the hypercapnic environment produced a concurrent or post-intervention change in EF.

The grand means for saccade duration and gain variability were 70 ms (SD=25) and 0.78 (SD=0.29), respectively, and neither variable produced significant main effects for condition, $Fs_{(1,13)}$<1.19, ps>.24, η_p^2< 0.04, time, $Fs_{(2,26)}$<0.68, ps>.50, η_p^2<.18) nor their interactions, $Fs_{(2,26)}$<0.60, ps>.055, η_p^2<.13.

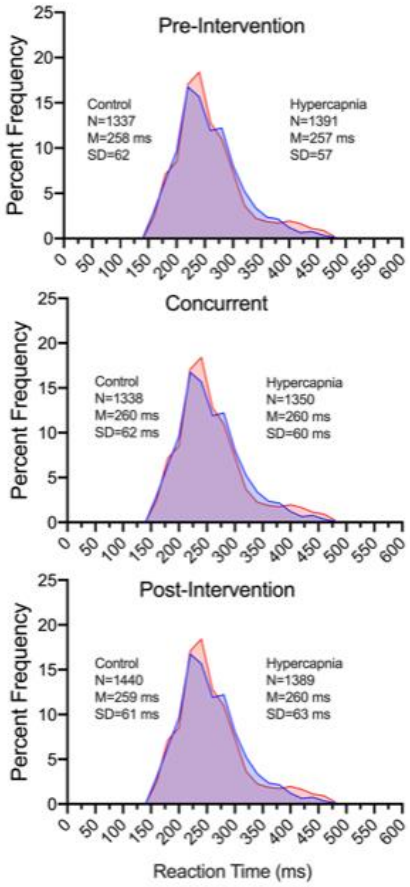

Figure 9. Antisaccade reaction time (ms) percent frequency histograms for control (blue) and hypercapnic (red) conditions as a function of each assessment window. Distribution summary statistics are presented in a textbox within each histogram.

3.2.4 Relationship between MCAv and antisaccade RT difference scores

We correlated MCAv difference scores (concurrent minus pre-intervention) and associated antisaccade RT difference scores at concurrent (i.e., concurrent minus pre-intervention) and post-intervention (i.e., post-intervention minus pre-intervention). Results showed that the variables were not reliably related at either assessment window ($rs < .261$, $ps > .70$).

3.3 Discussion

We examined whether a 10 min exposure to a 2.5% hypercapnic environment increases CBF and produces a concurrent and/or post-intervention EF benefit. In outlining our findings, we first discuss the physiological (i.e., ventilatory, cardiorespiratory and cerebral hemodynamic) changes associated with the hypercapnic condition before outlining our EF findings.

3.3.1 Ventilation and cerebral hemodynamic changes in response to a 2.5% hypercapnic environment

As expected, the control condition did not alter ventilatory variables; however, the hypercapnic condition produced a pre-intervention to concurrent increase in $\dot{V}_E$ and $PETCO_2$. This well-documented finding reflects chemoreceptor-induced changes in minute ventilation (Duffin, 2005) initiated by central and peripheral chemoreceptors to express excess CO_2 and prevent a further decrease in blood pH (Ainslie & Duffin, 2009; McBryde, et al., 2017; Smith et al., 2017).

Control and hypercapnic conditions did not alter heart rate, systolic or diastolic blood pressure and is a finding in keeping with reports that $PETCO_2$ concentrations less than 40 mmHg – as was observed here (see **Figure 7**) – do not alter these physiological variables. In addition, that $\dot{V}O_2$ or $\dot{V}CO_2$ were not influenced by the hypercapnic environment was expected given that we did not manipulate O_2 concentrations or provoke metabolic CO_2 production (Edelman et al., 1973). In terms of MCAv, results showed that control condition values did not vary across any assessment interval; however, in the hypercapnic condition a 7 cm/s increase was noted from the pre-intervention to concurrent intervention assessment window. At the hypercapnic

condition post-intervention assessment, MCAv values returned to pre-intervention levels. The hypercapnic-based increase in MCAv has been linked to a CO_2-based decrease in pH and an associated increase in cerebral vasodilation and volumetric flow (Brian, 1988; Kaufman et al., 2012). Accordingly, the combined $PETCO_2$ and MCAv findings reported here evince a well-defined physiological response to a hypercapnic environment and provide a platform to evaluate whether increased CBF influences concurrent and post-intervention EF.

3.3.2 Concurrent and post-intervention EF in a 2.5% hypercapnic environment

The antisaccade paradigm has been shown to provide the requisite resolution to detect subtle EF deficits not quantified by neuropsychological tests batteries (Kaufman et al., 2012; Peltsch et al., 2014; Webb et al., 2018). Moreover, the antisaccade paradigm provides a reliable framework to identify EF improvements following single bouts of aerobic exercise for as brief as 10-min and involving a continuum (i.e., very light to very heavy) of exercise intensities (Samani & Heath, 2018; Tari et al., 2021). This benefit has been linked – in part – to an exercise-based increase in CBF that improves the efficiency of EF networks (Shirzad et al., 2022; Tari et al., 2023). In the present study, hypercapnic and control conditions did not yield a pre-intervention to concurrent, or baseline to post-intervention, change in antisaccade RTs or their distributions and is a result supported by null hypothesis and equivalence tests. Thus, the combined null hypothesis and equivalence tests indicates that the absence of an RT difference cannot be attributed to an inadequate replication sample size (Lakens et al., 2018). Further, saccade duration and gain variability did not vary across hypercapnic and control conditions and indicates that participants did not engage in distinct planning strategies (i.e., speed-accuracy trade-off) (Fitts, 1954) across the different experimental conditions used here. Instead, results evince that a hypercapnic environment (i.e., concurrent and post-intervention) did not alter and oculomotor index of EF.

The null concurrent and post-intervention EF change in the hypercapnic condition counters our predictions derived from previous exercise (e.g., Heath et al., 2018; Petrella et al., 2019; Dirk et al., 2020) and hypercapnia (Tari et al., 2020) work. Indeed, Tari et al. (2020) reported that a 10-min exposure to a 5% hypercapnic environment increased

MCAv and produced a post-intervention decrease in antisaccade RTs commensurate to an exercise intervention involving a comparable MCAv increase. It is, however, important to recognize that the increase in MCAv reported by Tari and colleagues was larger (21cm/s, $CI_{95\%}$=7) than that observed here (7cm/s, $CI_{95\%}$=4). As a result, the absence of concurrent and post-intervention changes in antisaccade RTs may reflect an inadequate increase in CBF due to the use of a lower (i.e., 2.5%) CO_2 concentration. Moreover, that our hypercapnic environment did not impact concurrent EF is comparable to some work assessing a broader spectrum of cognition (i.e., SMS, *Cognition*) (Rodeheffer et al., 2018; Scully et al., 2019). Importantly, we believe the present results add importantly to the literature insomuch as they demonstrate that EF is not adversely impacted – or improved – *during* and *following* transient (10-min) exposure to a 2.5% hypercapnic environment.

3.3.3 Limitations and Future directions

We recognize that our study is limited by several methodological traits. First, we employed a 10 min hypercapnic exposure at a fixed CO_2 concentration of 2.5%. Hence, it is unclear whether longer and/or increased CO_2 concentrations may differentially impact concurrent and post-intervention EF. That said, the present results provide a direct demonstration that exposure to a 2.5% CO_2 concentration does not impact EF. Second, TCD was used to measure MCAv and estimate a hypercapnic-based increase in CBF. This is a salient consideration because TCD does not quantify changes in arterial diameter and has been shown to underestimate CBF during hypercapnia (Coverdale et al., 2015). Regardless of this limitation, the combined MCAv, $\dot{V}_E$ and $PETCO_2$ findings reported here evince a well-documented cerebrovascular response to a hypercapnic stressor. Third, all participants were young healthy adults, and it is therefore not possible to generalize our findings to older adults given age-related reductions in cerebrovascular compliance and CO_2 reactivity (Maeda et al., 1993; Riecker et al., 2003; Glodzik et al., 2013). Last, we did not provide a direct measure of cardiovascular fitness (i.e., VO_{2peak}) – a measure known to influence CO_2 cerebrovascular reactivity and CBF-based changes to EF. Future work by our group seeks to evaluate this issue via examining EF responses to a hypercapnic environment among low- and high-fit individuals.

3.4 Conclusion

The present research demonstrated that exposure to a 2.5% hypercapnic environment produced a rapid increase in CBF that returned to baseline following cessation of the stressor. Notably, however, concurrent and post-intervention antisaccade performance was refractory of the hypercapnic environment. These results indicate that transient exposure to a 2.5% CO_2 environment during space and other exploration challenges, does not impact EF efficiency or effectiveness.

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Chapter 4

4 General Conclusion

In Chapter 2, I evaluated whether a 20 min bout of passive exercise (via motorized cycle ergometer) differentially influenced pre- and post-exercise antisaccade performance and CBF. Results showed that passive exercise increased CBF and produced a post-intervention reduction in antisaccade RTs – findings that are in line with the hemo-neural hypothesis (Moore & Cao, 2008). Accordingly, results from Chapter 2 demonstrate that postexercise improvements to EF can be obtained independent of active muscle recruitment.

In Chapter 3, I evaluated CBF and antisaccade performance concurrent with, and following, exposure to a 10 min 2.5% hypercapnic environment. Results demonstrated an increase in CBF concurrent with hypercapnic exposure; however, no reliable change in antisaccade performance was observed during, or immediately following the intervention. The absence of a behavioral effect during 2.5% hypercapnia is consistent with some literature reporting no reliable change in cognition during mild hypercapnia (Rodeheffer et al., 2018; Scully et al., 2019). However, the absence of a post-intervention EF improvement contrasts the findings reported in Chapter 2.

The inconsistencies between experiments may be credited to the distinct pathways in which the interventions (i.e., passive exercise, hypercapnia) modulate CBF (i.e., mechanically vs. chemically). As stated previously, hypercapnia influences CBF via the chemoreceptor reflex: a defence mechanism against cellular acidosis. Indeed, a hypercapnic environment induces a state of physiological distress, and is commonly accompanied by adverse symptoms (e.g., headaches, dyspnea, discomfort; see Totaro et al., 1997). This is a salient issue as experiment two did not include a measure of participant symptomology, which could have interfered with post-intervention EF results. In contrast, the mechanisms modulating CBF during passive exercise are in not in response to an acute physiological stressor, but rather locomotion, and therefore do not produce the adverse symptoms associated with hypercapnia. Moreover, the feedforward

central command mechanism contributing to CBF modulation during passive exercise has been shown to increase physiological and cognitive arousal (Matsukawa et al., 2012), which may have positively influenced the post-passive exercise EF results. Taken together, results from my thesis suggest that an increase in CBF is not the sole-mediating factor to a postexercise EF benefit.

4.1 Future Directions

There are several considerations that should be given to future research examining the interventions and outcomes outlined in this thesis.

A simple, but important one should be to match the duration of the intervention between studies. Indeed, a rationale as to why only the passive exercise intervention produced an EF benefit, despite comparable increase is CBF (i.e., 7cm/s), is that the duration of passive exercise intervention was twice that of the hypercapnia (i.e., 20 min compared to 10 min, respectively). Thus, the temporal persistence of an increase in CBF may have contributed to the differences in outcome between the two interventions. Another concern, discussed in the previous section, is the interference of hypercapnia induced symptoms. Indeed, previous research has demonstrated that hypercapnia induced symptoms (e.g., headaches, dyspnea) can occur with mild (i.e., > 2% CO_2) hypercapnia (Satish et al., 2012). Thus, due to potential confoundment of EF results, it would be important to have participants report their symptoms on a Likert scale concurrent with hypercapnic exposure. Lastly, future researcher should consider including a measure of cognitive arousal, as both passive exercise and hypercapnia have been shown to stimulate the parasympathetic nervous system (Morita et al., 1994; Gladewell & Coote, 2002), which has been shown to mediate cognitive arousal (Barber, et al., 2020).

Appendices

Appendix A: Health Science Research Board Approvals

Western Research

Date: 23 February 2022

To: Dr. Matthew Heath

Project ID: 119678

Study Title: Cerebral hemodynamics and executive function changes in response to 2.5% CO2

Application Type: HSREB Initial Application

Review Type: Delegated

Meeting Date / Full Board Reporting Date: 15/Mar/2022

Date Approval Issued: 23/Feb/2022

REB Approval Expiry Date: 23/Feb/2023

Dear Dr. Matthew Heath

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. **All other required institutional approvals and mandated training must also be obtained prior to the conduct of the study**.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
Recruitment Advertisement	Recruitment Materials	25/Jan/2022	1
Email Script	Email Script	25/Jan/2022	1
LOI	Written Consent/Assent	25/Jan/2022	1
Research Protocol	Protocol	17/Feb/2022	2
Flow Diagram	Flow Diagram	17/Feb/2022	2
ParQPlus2022	Online Survey	01/Nov/2021	1
GLTEQ	Online Survey	01/Jan/2022	1

Documents Acknowledged:

Document Name	Document Type	Document Date	Document Version
Citations	References	21/Aug/2021	1
2022_01_03Itemized Study Budget	Study budget	03/Jan/2022	1
O2_CO2 Analyzer Tool	Other Data Collection Instruments	17/Feb/2022	2
Executive Function Assessment Tool	Other Data Collection Instruments	17/Feb/2021	1
Blood Pressure Tool	Other Data Collection Instruments	17/Feb/2022	2
Heart Rate Tool	Other Data Collection Instruments	17/Feb/2022	2
NIRS Tool	Other Data Collection Instruments	17/Feb/2022	2
TCD Tool	Other Data Collection Instruments	17/Feb/2022	2

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical

Western Research

Date: 8 October 2021

To: Dr. Matthew Heath

Project ID: 118422

Study Title: The hemodynamic and executive function responses to active and passive exercise

Application Type: HSREB Initial Application

Review Type: Full Board

Meeting Date: 10/Aug/2021

Date Approval Issued: 08/Oct/2021

REB Approval Expiry Date: 08/Oct/2022

Dear Dr. Matthew Heath

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. **All other required institutional approvals and mandated training must also be obtained prior to the conduct of the study**.

Documents Approved:

Document Name	Document Type	Document Date
GLTEQ (1)	Paper Survey	Received October 5, 2021
PARQPlus 2020 (1)	Paper Survey	Received October 5, 2021
NeuroBehavioural Lab COVID-19	Paper Survey	Received October 5, 2021
TCD Tool	Other Data Collection Instruments	Received October 5, 2021
NIRS Tool	Other Data Collection Instruments	Received October 5, 2021
Heart Rate Tool	Other Data Collection Instruments	Received October 5, 2021
O2_CO2 Analyzer Tool	Other Data Collection Instruments	Received October 5, 2021
Eye Tracking Tool (1)	Other Data Collection Instruments	Received October 5, 2021
Blood Pressure Tools	Other Data Collection Instruments	Received October 5, 2021
Recruitment Advertisement	Recruitment Materials	09/Jun/2021
Research Protocol	Protocol	09/Jun/2021
Email Script	Email Script	20/Aug/2021
LOI	Written Consent/Assent	07/Sep/2021

Documents Acknowledged:

Document Name	Document Type	Document Date
Itemized Study Budget	Study budget	03/Mar/2021

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C,

Curriculum Vitae

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Publications:

Shirzad, M., Van Riesen, J., Behboodpour, N., & Heath, M. (2023). 10-min Exposure to a 2.5% Hypercapnic Environment Increases Cerebral Blood Blow but does not Impact Executive Function. Life Sciences in Space Research. https://doi.org/10.1016/j.lssr.2023.07.003

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Tari, B., **Shirzad, M**., Badcock, N. A., Belfry, G. R., & Heath, M. (2021). 'Delaying' a saccade: Preparatory phase cortical hemodynamics evince the neural cost of response inhibition. Brain and Cognition, 154, 105808. https://doi.org/10.1016/j.bandc.2021.105808

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