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A Postexercise Executive Function Benefit From Passive and Active Exercise Does not Extend to Mental Fatigue Mitigation

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Abstract

A single bout of aerobic exercise improves executive function (EF) and is a benefit, in part, attributed to an increase in cerebral blood flow (CBF). It is, however, unknown whether a postexercise EF benefit mitigates mental fatigue (MF). My thesis assessed EF prior to and following separate 20-min conditions of active and passive cycle ergometry and a non-exercise control. Subsequently, a 20-min psychomotor vigilance task (PVT) was employed to determine whether the exercise intervention(s) decreased susceptibility to MF. Transcranial Doppler ultrasound was used throughout the protocol to estimate exercise- and PVT-based changes in CBF. Both exercise conditions increased CBF and produced a postexercise EF benefit. In turn, the PVT decreased CBF and increased subjective and objective measures of MF; however, frequentist and Bayesian statistics indicated the preceding exercise condition did not ameliorate these changes. Accordingly, exercise did not provide a neuroprotective mechanism mitigating MF in a sustained vigilance task.

Keywords

Executive function

Mental fatigue

Cerebral blood flow

Exercise

Passive cycling

Summary for Lay Audience

Executive function refers to cognitive processes that regulate activities of daily living. A single bout of volitional aerobic exercise (i.e., active exercise) provides a 'boost' to executive function and is a benefit that has been linked to an exercise-based increase in brain blood flow. Passive exercise, wherein movement is generated via an external force (e.g., mechanically driven stationary bike) provides a similar postexercise executive function benefit and associated increase in brain blood flow. In contrast, mental fatigue impairs executive function and is associated with a reduction in brain blood flow. It is, however, unknown whether passive and active exercise lessen the performance decline experienced during a mental fatigue inducing task and whether this is linked to the documented postexercise executive function benefit. Accordingly, I had participants complete an executive function task prior to and immediately following separate conditions involving 20 minutes of passive and active stationary bike riding as well as a non-exercise control condition. Subsequently, participants completed a 20-min psychomotor vigilance task (PVT) to determine whether a postexercise executive function benefit mitigates subjective and objective measures of mental fatigue. As well, transcranial Doppler ultrasound was used to measure middle cerebral artery velocity to determine potential links between brain blood flow with exercise, executive function and mental fatigue. As expected, both exercise conditions increased brain blood flow and improved executive function. Notably, completing an exercise condition in advance of the PVT did not mitigate subjective and objective measures of mental fatigue or an associated decrease in brain blood flow. Accordingly, my findings demonstrate that passive and active exercise provide a selective benefit to executive function that does not extend to reducing a mental fatigue-induced performance decline.

Co-Authorship Statement

Under the supervision of Drs. Matthew Heath and Lindsay Nagamatsu, I conducted the work in this master's thesis. With the counsel of Drs. Matthew Heath and Lindsay Nagamatsu, I created and designed the experiment, recruited participants, collected, analyzed, and interpreted data, and composed the final manuscripts, for which I serve as first author. For Chapter Two, I received support from graduate students (Lian Buwadi, Denait Haile, and Azar Ayaz) with participant recruitment and data collection.

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Chapter 1

1 Literature Review

The primary goal of my thesis was to examine whether the documented single bout of active and passive exercise postexercise executive function (EF) benefit mitigates objective and subjective measures of mental fatigue (MF) associated with a sustained attention/vigilance task (i.e., psychomotor vigilance task: PVT). The secondary goal of my thesis was to examine whether cerebral blood flow (CBF) as estimated via a transcranial Doppler ultrasound (TCD) measure of middle cerebral artery velocity (MCAv) is linked to postexercise EF benefits and putative performance changes associated with MF. To address these goals, I measured EF prior to and immediately following separate 20-min conditions of active and passive exercise cycle ergometry, and additionally included a non-exercise control condition. Following each condition, participants completed a 20-min PVT and objective measures of MF were assessed during the first and last five minutes of the protocol. Throughout the protocol MCAv was measured. In developing my thesis, the below Literature Review outlines: (1) the behavioural and neuroanatomical correlates of EF, (2) the impact of active exercise on postexercise EF, (3) the mechanisms supporting a postexercise EF benefit following a single bout of exercise, (4) the effects of a single bout of passive exercise on EF and CBF and (5) measures of MF, the neural correlates of MF and the relationship between MF and exercise.

1.1 Executive function

Executive function (EF) consists of the top-down cognitive processes needed to navigate the complexities of daily living and includes the core components of: (1) inhibitory control, (2) working memory, and (3) cognitive flexibility (for reviews, see Diamond, 2013; Miyake et al., 2000). As examples, inhibitory control entails the ability to ignore/inhibit distracting information (e.g., a phone ringing) while performing an attention demanding task (e.g., studying for an exam). In turn, working memory supports the ability to perform mental math while grocery shopping, whereas cognitive flexibility

represents one's ability to alternate between the different tasks associated with operating a motor vehicle. An extensive lesion and neuroimaging literature has shown that prefrontal cortex (PFC) structures including the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and orbitofrontal cortex (OFC) play significant roles in supporting EF (Royall et al., 2002).

Inhibitory control refers to the ability to suppress a strong internal tendency to execute a response in favour of a volitional non-standard alternative (Diamond, 2013). Inhibitory control is frequently evaluated via the Ericksen flanker (Eriksen and Eriksen, 1974) and Stroop (Stroop, 1935) tasks. The Eriksen flanker task entails a central target (i.e., "<") with flankers (i.e., non-targets) that are directionally congruent (i.e., "<<<") or incongruent (i.e., "><>") to the target. The goal of the task is to respond according to the direction of the central target regardless of the flankers' directions. Eriksen and Eriksen's (1974) work revealed that incongruent stimuli produced longer reaction times (RT) and increased response errors compared to their directionally congruent counterparts and was a finding attributed to the "noise" (i.e., distracting information) present during incongruent trials that interferes with an individual's processing response to salient information and thus increases RT. Moreover, Blasi et al.'s (2006) functional magnetic resonance imaging (fMRI) study reported greater bilateral DLPFC activation during "correct" than "incorrect" incongruent trials. In turn, Luks et al. (2010) employed voxel-based morphometry (VBM) to examine the relationship between grey matter atrophy and Flanker task performance. The authors reported that individuals with left hemisphere DLPFC atrophy had more errors and longer RTs on incongruent trials when compared to the age-matched healthy controls. Accordingly, the aforementioned studies provide support for the role of the DLPFC in inhibitory control during the Flanker task.

The Stroop task presents participants with a word wherein the colour of the ink a word is written is congruent (i.e., "RED") or incongruent (i.e., "RED") to the word's meaning. For this task, participants are required to respond to the colour of the ink the word is written in (i.e., non-standard task) and this results in longer RTs and increased response errors compared to congruent trials (i.e., standard task) (Stroop, 1935). The poorer performance in incongruent trials is attributed to the EF demands of inhibiting the

standard response (i.e., the word-naming response) in favour of the non-standard response (i.e., the color-naming response) (for meta-analysis, see MacLeod, 1992). An extensive literature of neuroimaging and lesion studies have highlighted the association between DLPFC activity and incongruent Stroop performance. For example, Liu et al.'s (2008) fMRI study revealed that longer incongruent trial RTs were associated with increased DLPFC and ACC activation when compared to congruent trials. Furthermore, Stuss et al. (2001) reported that individuals with frontal lobe lesions exhibited poorer performance on incongruent trials (i.e., longer RTs and more errors) when compared to healthy controls. Moreover, Plenger et al.'s (2016) functional near-infrared spectroscopy (fNIRS) study compared neural activity and Stroop performance between individuals with traumatic brain injury (TBI) and healthy controls. The authors reported that individuals with TBI had longer RTs and more errors during incongruent trials when compared to the healthy control group and this deficit was linked to a bilateral decrease in oxygenated hemoglobin in the DLPFC. Thus, there is evidence demonstrating the role of the DLPFC in inhibitory control during the Stroop task.

The second core component of EF is working memory. It refers to the ability to retain information in mind during active manipulation (Diamond, 2013). The n-back task is often used to assess working memory (Kirchner, 1958; Yaple and Arsalidou, 2018). The task presents a sequence of stimuli and participants are instructed to determine whether a current stimulus matches an exemplar presented "n" steps earlier in the sequence. For example, the 3-back task requires that participants report whether a current stimulus matches an exemplar presented three steps earlier in the stimulus sequence. As the "n" value increases, participants exhibit increased RTs and response errors due to the increased processing demands, and hence provides a means to manipulate task complexity (Jaeggi et al., 2010). Neuroimaging and lesion studies have highlighted the link between the DLPFC and n-back performance. For example, Owen et al.'s (2005) meta-analysis of neuroimaging studies examining *n*-back task performance reported that increased task complexity was associated with heightened activation of the DLPFC. Further, Tsuchida and Fellows (2009) employed the 2-back task to evaluate performance differences in individuals with focal damage within the DLPFC and healthy controls. The authors reported individuals with DLPFC lesions demonstrated more errors and longer

RTs when compared to the healthy controls. In turn, Dores et al. (2017) contrasted 2-back performance between individuals with working memory impairments caused by an acquired brain injury and their healthy controls, and showed increased activation in the DLPFC in the latter group was associated with improved task performance (less errors and shorter RTs), whereas no such change was observed in individuals with a brain injury. Finally, Yaple et al.'s (2019) meta-analysis reported that the age-related decline in the efficiency of PFC engagement is associated with poorer working memory performance as measured via the n-back task and thus provides further evidence demonstrating the link between frontal cortical structures and EF.

The final component of EF is cognitive flexibility and is a component frequently assessed via a task-switching paradigm (Diamond, 2013; Miyake et al., 2000). Task-switching consists of two different trial-types: (1) a task-repeat trial wherein trial *n* is preceded by its same task-type (e.g., congruent Stroop trial preceded by a congruent Stroop trial), and (2) a task-switch trial wherein trial *n* is preceded by a different task-type (e.g., congruent Stroop trial preceded by an incongruent Stroop trial). Task-switch trials are associated with longer RTs and greater errors (i.e., a "switch-cost") (for review, see Kiesel et al., 2010). Allport et al. (1994) employed a task switching paradigm using the Stroop task and reported that the congruent Stroop trial exhibits longer RTs when preceded by an incongruent Stroop trial, whereas the converse switch (i.e., incongruent Stroop trial preceded by congruent Stroop trial) did not impact RT (i.e., the unidirectional switch-cost). Allport et al. (1994) proposed that the unidirectional switch-cost reflects the activation of a non-standard task-set (i.e., incongruent Stroop trial) that inertially persists and delays the planning of a subsequent standard task-set (i.e., congruent Stroop trial) (i.e., task-set inertia hypothesis). In support of the task-set inertia hypothesis, Weiler et al.'s (2015) electroencephalographic study demonstrated that the amplitude of the P300 event-related brain potential (ERP) (i.e., a component associated with EF) increased when a non-standard trial was followed by a standard-trial; however, no such change in amplitude occurred when a non-standard trial followed a standard-one. Further, Liston et al.'s (2006) fMRI study demonstrated that greater efficiency of task-switch trials was associated with heightened DLPFC and ACC activity. Moreover, Kopp et al. (2015) examined cognitive flexibility using the Trail Making task (i.e., participants alternate

between connecting randomly arranged encircled numbers and letters in ascending order) and reported that individuals with frontal lesions demonstrated longer RTs and greater errors when compared to healthy controls. Thus, the literature provides evidence to suggest that the PFC serves as a mediator supporting the core components of EF.

1.1.1 The antisaccade task

My thesis employed the pro- and antisaccade tasks to assess EF. Prosaccades require an individual to execute a goal-directed eye movement towards a target and are mediated largely independent to top-down EF via direct retinotopic projections to the superior colliculus (SC) (Wurtz and Albano, 1980). In turn, antisaccades require an individual to inhibit a standard prosaccade in favour of a response mirror-symmetrical to a target. Antisaccades have longer RTs (Hallett, 1978), more directional errors (Pierce and McDowell, 2016), and increased endpoint variability compared to prosaccades (Heath et al., 2010; Gillen and Heath, 2014). The 'costs' associated with antisaccades have been attributed to the EF demands of suppressing a pre-potent prosaccade (i.e., inhibitory control) and the 180° spatial transposition of a target's coordinates (i.e., vector inversion) (Munoz and Everling, 2004). Neuroimaging research in humans, and single-cell and transient cooling studies in non-human primates, have shown that the execution of a directionally correct antisaccade is associated with increased task-based activity in the PFC (DeSouza et al. 2004; for review see, Munoz and Everling, 2004). Further, human and non-human primate work has shown that decreased activation in the DLPFC impairs the ability to execute antisaccades, and results in increased directional errors (Johnston et al., 2014; see also Condy et al., 2004). What is more, antisaccades provide a hands- and language-free basis to examine EF and do not require the non-EF cognitive processes of language (i.e., Stroop task), colour (i.e., Stroop task), geometric figure identification (i.e., Ericksen flanker) and numerosity (i.e., n-back) included in other more traditional EF tasks (Kaufman et al., 2012). As well, antisaccades have been shown to provide the resolution to detect subtle and EF-specific changes to environmental stressors in healthy young and older adults (e.g., Heath et al., 2018; Kaufman et al., 2012; Petrella et al. 2019). Moreover, because prosaccades are primarily mediated via retinotopic projections from the SC (Wurtz and Albano, 1980), and operate independently of EF (Pierrot-

Deseilligny et al., 1995), they serve as an excellent control to evaluate EF-specific changes following manipulations such as an exercise intervention.

1.2 Aerobic exercise and executive function

Meta-analyses report that chronic (e.g., ≥ 3 months) exercise positively influences EF in children (Liu et al., 2020; Amatriain-Fernández et al., 2021) young adults (Verburgh et al., 2014), older adults (Chen et al., 2020) and individuals experiencing cognitive decline (Heath et al. 2016; 2017). For example, Colcombe et al. (2004) evaluated structural and EF changes in older adults who completed either an aerobic exercise or stretching and toning (control) class three times a week for six months. Results showed that individuals in the aerobic training group showed improved EF compared to the control group (via the Ericksen flanker task) and showed increased task-dependent activity in frontoparietal EF networks. The authors posited the EF benefits associated with the exercise intervention group reflected enhanced cardiovascular fitness and improved brain plasticity within EF networks. Moreover, Chen et al.'s (2020) systematic review and meta-analysis of randomized controlled trials examined how exercise training interventions influence EF in older adults. The authors' results demonstrated postexercise training benefits to EF.

In addition to chronic exercise, convergent literature has shown that a single bout of aerobic and/or resistance exercise provides an EF benefit (for meta-analysis, see Chang et al., 2012; Ludyga et al., 2016). For example, Yanagisawa et al. (2010) evaluated the effects of a single bout of moderate-intensity aerobic exercise (70% of predicted maximum heart rate: HRmax) on inhibitory control (via Stroop task). The authors implemented a between-subjects design where participants were assigned to either an exercise group or a non-exercise control group. Results showed that the postexercise performance of the exercise group was associated with shorter RTs and increased task-based activity in the DLPFC and ACC compared to the control group. Further, Alves et al. (2012) compared inhibitory control performance via the Stroop task in a between-subjects design. Stroop performance was evaluated following 30-min of walking (i.e., 50-60% heart rate reserve (HRR)) or a non-exercise control in postmenopausal women. The authors reported that incongruent Stroop RTs were shorter following the exercise condition when compared to the control condition.

In terms of working memory, Chen et al. (2016) examined the effects of acute moderate-intensity (60-69% HR_{max}) aerobic exercise on working memory performance via the 2-back task. The authors employed a within-subjects design where participants completed control (no exercise) and exercise conditions. Results demonstrate that the exercise condition produced shorter postexercise RTs compared to the control condition. Moreover, Stute et al. (2020) examined working memory via the n-back task prior to and post a 15-min session of moderate intensity aerobic exercise (i.e., 50% VO_{2peak}) and demonstrated that improved exercise-based performance was associated with increased PFC oxygenation as measured via fNIRS.

In terms of cognitive flexibility, Shi et al. (2022) employed a task switching paradigm prior to and post high-intensity interval training (alternating between 1 min bouts at 90% HRR and 50% HRR), moderate-intensity exercise (40-59% HRR), and a control (no exercise) condition. Results showed that task-switch trial RTs were shorter following the exercise conditions as compared to the control condition. Moreover, Bae and Masaki (2019) reported that following 30 min of treadmill exercise (i.e., 70% HR_{max}), participants had shorter task-switch RTs when compared to baseline values.

The findings outlined above provide support for the conclusions from Chang and colleagues' (2012) meta-analysis asserting that a single bout of aerobic exercise is linked to improvements in each component of EF and is associated with greater activity in EF networks. Furthermore, work by my lab group has employed the antisaccade task to examine postexercise EF benefits following a single bout of exercise. For example, Shukla and Heath (2022) employed an AABB task-switching paradigm to assess cognitive flexibility following a 20-min bout of high-intensity (80% HRmax) aerobic exercise. Results demonstrated a task-switching benefit that persisted for up to 47 minutes following exercise cessation. Moreover, Tari et al. (2021) evaluated EF via the antisaccade task prior to and immediately following a 20-min bout of light- (25 W), moderate- (80% estimated lactate threshold [LT]), and heavy-intensity (15% difference between LT and VO_2peak) aerobic exercise. Results showed a postexercise EF benefit of equivalent magnitude across the continuum of metabolically sustainable work rates. In turn, Dalton et al. (2023) compared moderate-intensity exercise (60% HRR) to body

weight squat-stand exercise and evaluated pre- to postexercise EF changes via the antisaccade task. The authors reported that both conditions produced a comparable magnitude postexercise EF benefit as indicated via decreased antisaccade RTs. Thus, results indicate that the postexercise benefit persists for at least 47 min and is present across a range of intensities and modalities.

1.3 Candidate mechanisms responsible for an acute exercise-mediated executive function benefit

As detailed in the previous section, chronic and single bouts of exercise across various intensities and modalities elicit a postexercise EF benefit. However, the proposed mechanisms underlying chronic exercise EF benefits (i.e., neuroplasticity; Chirles et al., 2017) are posited to be distinct from those for a single bout of exercise. This section will detail the proposed mechanisms supporting a postexercise EF benefit following a single bout of exercise. The proposed mechanisms include: (1) an increase in biomolecules including catecholamines (i.e., brain-derived neurotrophic factor (BDNF), dopamine (DA), and norepinephrine (NE)) (Hershey et al., 2004; McMorris, 2021), (2) improved resting state functional connectivity within EF networks (Gómez-Pinilla et al., 2002), and (3) enhanced CBF (Guiney et al., 2015).

A single bout of exercise results in an increase in NE and DA and this change in biomolecule levels increases psychological and physiological arousal and is thought to benefit EF (Hershey et al., 2004; Ott and Nieder, 2019). More specifically, an increase in NE and DA is posited to improve EF by improving signaling efficiency within the PFC (Arnsten et al., 1988; Rammsayer, 1993). For example, Gibbs and D'Esposito's (2006) within-subjects fMRI study compared the effects of a dopamine receptor agonist (i.e., pergolide) and a lactose placebo on working memory. The authors reported that pergolide treatment was associated with enhanced PFC activity and improved working memory performance. In the exercise neuroscience literature, there is conflicting evidence regarding the relationship between catecholamine levels and postexercise EF improvements. For example, McMorris et al.'s (2011) meta-analysis reported that moderate-intensity exercise provides the optimal work rate for improving working memory and is linked to ideal catecholamine concentrations (Hyyppä et al., 1986; Koch

et al., 1980; Musso et al., 1990; see also McMorris, 2021). However, some studies have suggested that light- and heavy intensity exercise also elicit postexercise EF benefits (Hashimoto et al., 2018; Morris et al., 2020; Tari et al., 2021) and thus questions the role of catecholamines in eliciting a postexercise EF benefit. In turn, Ando et al. (2022) had participants complete an inhibitory control task prior to and post a single bout of aerobic exercise (40% peak oxygen uptake) and perceived-intensity matched resistance exercise. Results showed improved inhibitory control postexercise; however, this benefit was not associated with catecholamine concentrations. Thus, I cannot conclude that catecholamines serve as the primary mechanism for a postexercise EF benefit.

BDNF is a protein upregulated by exercise and is responsible for synaptic growth and neuronal survival (Vaynman et al., 2004). Knaepen et al.'s (2010) extensive review concluded that in healthy participants, and those with chronic disease, there is a transient increase in plasma or serum BDNF concentration following a single bout of aerobic exercise. However, the literature regarding the relationship between BDNF and postexercise EF benefits is equivocal. For example, Hwang et al. (2016a) randomized participants into a high-intensity (85-90% VO_2max) exercise group and a non-exercise control and examined EF and BDNF levels pre- and postexercise. The authors reported that postexercise serum BDNF was related to the magnitude of an exercise-related EF benefit. In contrast, Ferris et al. (2007) employed a within-subjects design and had participants complete two 30-min cycle ergometer sessions at 20% below and 10% above participant-specific ventilatory thresholds. Results showed that a postexercise EF benefit (via Stroop task) was not related to exercise-based changes in serum BDNF. Further, it is important to recognize that serum BDNF may not reflect cerebral BDNF concentration because it remains uncertain as to whether the molecule crosses the blood-brain barrier (Trajkovska et al., 2007). Thus, the direct or indirect role of BDNF in expressing a postexercise EF benefit remains unclear.

Resting state functional connectivity is another proposed mechanism for modulating single bout postexercise EF benefits. This technique refers to the transfer of information between brain regions that are structurally and functionally connected (for review, see Moore et al., 2022). Resting state functional connectivity is measured via fMRI-based

blood oxygen level dependent (BOLD) signal quantification of specific cortical regions (Ogawa et al., 1990). Schmitt et al. (2019) examined resting state functional connectivity prior to and following 30 min bouts of light- (35% below lactate threshold) and high-intensity (20% above lactate threshold) exercise. The authors' results demonstrated resting state functional connectivity in the frontoparietal regions (including the DLPFC and the ACC) was increased following the exercise interventions. In contrast, Rajab et al. (2014) randomized participants into groups that completed either a single bout of moderate-intensity aerobic exercise or a time-matched non-exercise control and evaluated resting state functional connectivity prior to and post-intervention. The authors reported no change in resting state functional connectivity after both the exercise and control conditions. Moreover, Voss et al. (2020) evaluated the effects of light- (<57% HR_{max}) and moderate-intensity (64-76% HR_{max}) exercise on resting state functional connectivity and *n*-back performance. The results demonstrate that improvements to working memory following exercise were not associated with changes in resting state functional connectivity. Thus, improved resting state functional connectivity may not serve as a primary candidate mechanism for postexercise EF benefits following a single bout of exercise.

The final candidate mechanism for eliciting a postexercise EF benefit is an exercise-based increase in CBF. The energy demands of aerobic exercise results in increased cellular respiration that increases carbon dioxide (CO_2) and results in the activation of CO_2 sensitive chemoreceptors that facilitate systemic vasodilation and an increase in CBF (for review, see Ainslie and Duffin, 2009; Hoiland et al., 2019). Notably, the exercise-based increase in CBF is thought to elicit temperature- and mechanical-based changes to the brain's neural and glial networks that increase neural efficiency (i.e., the hemo-neural hypothesis; Moore and Cao, 2008). In demonstrating the role of CBF and EF, Tari et al. (2020) used transcranial Doppler ultrasound (TCD) to measure middle cerebral artery velocity (MCAv) as an estimate of CBF during 10-min time-matched conditions consisting of: (1) a hypercapnic environment (5% CO_2), (2) moderate-to-heavy intensity exercise, and (3) a non-exercise control. The hypercapnic condition was included because it results in a CBF increase independent of the metabolic demands of exercise (Ogoh and Ainsle, 2009). More specifically, inhalation of hypercapnic gas

rapidly leads to cerebrovascular vasodilation due to increased levels of CO_2 and lower pH levels (Ainslie and Duffin, 2009; Hoiland et al., 2019). Tari et al. (2020) employed the antisaccade task to assess pre- to post-condition changes in EF and reported that exercise and hypercapnia conditions increased CBF and this was accompanied by a post-intervention reduction in antisaccade RTs. Additionally, Byun et al. (2014) examined pre- to post-exercise changes in Stroop performance prior to and post 10-min of light intensity (30% VO_2 peak) exercise and used fNIRS to examine frontoparietal activation. Results demonstrated that Stroop RTs decreased after exercise, and this was associated with greater neurovascular coupling in the DLPFC. Finally, Zhao et al.'s (2013) work comparing CBF, inhibitory control and cognitive flexibility in individuals with cerebral angiostenosis/occlusion and healthy controls reported increased errors and RTs on the Stroop test were correlated with decreased CBF. Thus, an exercise-based CBF increase may serve as a candidate mechanism for eliciting postexercise EF improvements.

1.4 Passive exercise, cerebral blood flow, and executive function

Passive exercise refers to movement of a limb, or limbs, via an external force that does not rely on volitional muscle activation/recruitment. Passive flexion/extension studies involving the lower- and upper-limbs have been found to elicit increased CBF (Doering et al., 1998; Sato et al., 2009). The mechanisms posited to produce a passive exercise increase in CBF are distinct from traditional "active" exercise (i.e., exercise described above and requiring volitional muscle activation) and reflect the activation of type *III* mechanosensitive muscle afferents and feedforward signals related to passive limb movement that stimulate the primary somatosensory and motor cortices leading to increases in cardiac output and stroke volume (Eldridge et al., 1985; Gladwell and Coote, 2002; Goodwin et al., 1972; Krogh and Lindhard, 1913; Matsukawa, 2012; Nobrega and Araujo, 1993; Nurhayati and Boutcher, 1998; Victor et al., 1995)

Work has shown that a passive exercise increase in CBF is linked to a postexercise EF benefit. For example, Shirzad et al. (2022) had participants complete three conditions: (1) 20-min of active exercise, (2) 20-min of passive exercise (i.e., mechanically driven flywheel passively pedaled participants' lower limbs) and (3) a non-exercise control.

Results showed that Shirzad et al.'s (2022) passive exercise condition did not result in volitional muscle activation (as assessed via electromyograph) or render an increase in cardiorespiratory measures (i.e., ventilation (V_E), oxygen consumption ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$), end-tidal CO_2 ($P_{ET}CO_2$)); however, the protocol did result in an increase in CBF – albeit with a magnitude less than the active exercise condition – and provided a postexercise EF benefit equivalent to active exercise. Hence, results show that an increase in CBF independent of the metabolic and intensity demands of active exercise provides an EF benefit (see also Tari et al. 2023).

1.5 Mental fatigue

Fatigue is generally characterized by feelings of tiredness at rest, reduced energy, decreased endurance, a lack of vigor, and exhaustion (Davis and Walsh, 2010). Fatigue is divided into two components: physical and mental. Physical fatigue occurs after prolonged physical exertion and is characterized by reduced exercise capacity, force production, power (i.e., slower muscle contraction velocity), and an impaired perception of force (Davis and Walsh, 2010). In contrast, mental fatigue (MF) refers to a reluctance in exerting effort, feelings of weariness, and decreased alertness (Borghini et al., 2014; Grandjean, 1979; Grandjean, 1988). MF is often induced after extended periods of mental exertion and leads to impairments in cognition and specific declines in EF (Holtzer et al., 2010; Kato et al., 2009; van der Linden et al., 2003) and attention (Dorrian et al., 2007; Langner et al., 2010; Lim et al., 2010). Regarding the impact of MF on EF, Kato et al. (2009) had participants complete a 60-min inhibitory control task (i.e., go/no-go) and reported longer RTs, more errors and higher ratings of subjective MF as a function of time spent on task. Further, Kato et al. reported that P300 and error-related negativity (ERN) ERP amplitudes during no-go (i.e., non-standard) trials decreased as a function of time. The authors reported that such results indicate that MF impairs EF and depletes the cognitive resources needed for task execution. Further, van der Linden et al. (2003) evaluated the effects of MF on exploration in an intricate computer task. Participants' exploration performance was assessed in terms of task completion and the number of decisions they made with negative consequences. The authors employed a between-subjects design and compared the exploration behaviour of participants who underwent a

complex scheduling task to induce MF, and a control group that was not exposed to a MF protocol. For the scheduling task participants were required to assign work to employees, which required task engagement and EF. Results revealed that participants in the fatigue group made more errors and completed less exploration compared to the control group. In terms of the effects of MF on sustained attention, Lim et al. (2012) had participants complete the 20-min psychomotor vigilance test (PVT: see details below) and measured subjective ratings of MF pre- and post-PVT. Participants demonstrated an increase in RTs as a function of the length of the PVT protocol. As well, participants reported increased subjective MF from pre- to post-PVT assessment.

1.5.1 Mental fatigue measures

A number of measures provide an objective assessment of MF (Díaz-García et al., 2021; Kunasegaran et al., 2023). For my thesis, I will outline heart rate variability (HRV) and EEG and will describe the PVT as a tool to both induce and measure MF.

HRV refers to the beat-to-beat variability in a heart rate cycle (van Ravenswaaij-Arts, 1993). It has frequently been used as an indicator of the balance between sympathetic (i.e., responsible for “fight or flight response”) and parasympathetic (responsible for “rest and digest response”) nervous systems (Csathó et al., 2024). Sympathetic nervous system activity causes an increase in overall HRV, whereas parasympathetic nervous system activity causes a decrease in overall HRV (Mohanavelu et al., 2017). HRV variability has been used as an index of MF given that it reflects the state of the autonomic nervous system which plays a key role in the execution of cognitively demanding tasks (Laborde et al., 2017; Matuz et al., 2021; Sassi et al., 2015). More specifically, vagal tone is a HRV index of particular interest due to its positive association with parasympathetic nervous system activity (Csathó et al., 2024; Matuz et al., 2021). Increased parasympathetic activity is associated with task disengagement and is a manifestation of MF (Matuz et al., 2021; Pattyn et al., 2008). Matuz et al. (2021) examined the association between vagal-mediated HRV and time-on-task during a modified version of the n-back task and randomized participants into groups that completed the task for a two-hour period and a group that watched a documentary for the same time duration. When compared to the documentary-viewing group, those in the cognitively demanding n-back group had higher

levels of subjective MF, increased vagal-mediated HRV, and poorer performance (i.e., more errors) as a function of time (Matuz et al., 2021). Thus, HRV may serve as a reliable metric for a physiological assessment of MF.

EEG is a functional neuroimaging tool that measures the brain's electrical activity through recording of cerebral electrical potentials from electrodes placed on the scalp (Binnie and Prior, 1994). EEG signals can be classified into frequency bands with different spectral ranges: delta (<4 Hz), theta (4-7 Hz), alpha (8-12 Hz), and beta (13-30 Hz) (Clark, 2009). Delta waves are associated with sleep, theta is indicative of deep relaxation and a meditative state, alpha represents the resting relaxed state, whereas beta dominates when one is alert and engaging cognitive resources (Kumar & Bhuvaneswari, 2012; Kirschfeld, 2005). The evaluation of the dominance of specific EEG band waves can therefore be used as an objective instrument for assessing MF (Díaz-García et al., 2022). Tran et al.'s (2020) systematic review with meta-analyses sought to establish how MF influences EEG activity. The authors reported large increases in theta and alpha bands, with small changes in delta and beta bands being associated with MF. Furthermore, Gharagozlou et al. (2015) measured brain activity using EEG while individuals operated a motor vehicle in a virtual reality simulator. The authors reported an increase in subjective ratings of MF and absolute alpha power during the final section of driving, suggesting that an increase in alpha is indicative of a decrease in alertness. Thus, EEG metrics may also serve as an index of MF.

The PVT is a RT task wherein participants are presented with target stimuli over random and varying intervals, and are required to respond to target onset "as quickly as possible." (i.e., via a keyboard response or computer mouse "click") (Rupp, 2013), The task is termed the 'gold standard' measure of sustained attention and vigilance (Rupp, 2013). The PVT is sensitive to changes in the circadian system and is thought to reflect arousal levels and attention (Drummond et al., 2005; Wright et al., 2002; Wyatt et al., 1999). The typical length of the PVT is 10-min; however, shorter (e.g., 3 min) and longer (e.g., 20-min) durations are frequently implemented (Ahn et al., 2023; Benderoth et al., 2021; Lim et al., 2010; Matsangas et al., 2017; Rupp, 2013). The PVT measures used to objectively evaluate levels of attention are mean and median RT, fastest 10% RTs, and response

lapses (i.e., RTs > 500 ms) (Rupp, 2013). The PVT has been validated as a strong tool for indexing MF and deficits to cognitive performance (Basner et al., 2018; Evans et al., 2019; Loh et al., 2004). Further, it is often used as a tool for MF induction given that PVT RTs increase as a function of the time spent on the task, and poorer performance is an indicator of MF onset (Darnai et al., 2023; Lim et al., 2010, 2012). Moreover, the PVT has been implemented concurrently with HRV, EEG, and neuroimaging tools, providing convergent psychophysiological measures of MF (Chua et al., 2012; Gorgoni et al., 2014; Lim et al., 2010; Molina et al., 2019; Nogueira et al., 2022).

1.5.2 Mental fatigue and neuroimaging studies

A paucity of work has evaluated MF-based brain activity and blood flow changes. For example, Drummond et al. (2005) employed fMRI to evaluate the neural correlates of PVT performance and reported that shorter RTs were associated with increased activity within the frontoparietal attentional networks (i.e., right middle frontal gryus, left and right inferior parietal lobes), whereas longer RTs were associated with a 'default' attentional mode involving the medial frontal, superior frontal, and ventral anterior cingulate gyri. The default mode entails brain regions associated with cognitive disengagement (Drummond et al., 2005). When an individual directs their attention to executing a cognitively demanding task, resources are allocated towards attention networks responsible for executing those tasks, and away from the default network (Greicius et al., 2003). In turn, Ishii et al.'s (2014) review provides support for a "dual regulation system" of MF. The authors assert that the brain alternates between two networks supporting task engagement or disengagement. Their model consists of two systems: the mental facilitation system and the mental inhibition system. The mental facilitation system is activated by cognitive workload and is responsible for maintaining or enhancing cognitive performance. The facilitation system consists of the thalamo-cortical loop that connects the limbic system, basal ganglia, thalamus and frontal cortex. The mental inhibition system is also activated by cognitive workload; however, activation impairs cognitive performance. The inhibition system consists of the insular cortex and posterior cingulate cortex. When mental workload reaches levels that impair cognitive performance, the dual regulation system theory states that impairments to the facilitation

system results in overactivation of the mental inhibition system and an MF-based impairment in cognitive performance. In support of the decreased activity of the facilitation system owing to MF, Lim et al.'s (2010) findings reported that engaging in the PVT activates a frontoparietal attention network, which becomes less active after the task. Their results also demonstrated decreased CBF within the frontoparietal network and longer RTs as a function of the time spent on the task. However, there is evidence contradicting the findings of Drummond et al. (2005) and Ishii et al. (2014). For example, Darnai et al. (2023) report that decreased performance as a function of time during the PVT is associated with reduced activation of the right middle frontal gyrus, right insula, and right anterior cingulate gyrus. The decreased activation of the right middle frontal gyrus supports the dual regulation system; however, the decreased activation of the right insula contradicts it (Drummond et al., 2005; Ishii et al., 2014). Thus, the literature regarding the neural correlates of MF remains ambiguous, and more work is warranted to further investigate this.

1.5.3 Mental fatigue and acute aerobic exercise

There is limited research investigating the effects of a single bout of aerobic exercise on MF mitigation. Loy et al.'s (2013) systematic review and meta-analysis sought to examine the effects of acute exercise on self-reported energy and fatigue levels. They reported that energy (i.e., defined as "potential to execute a task") is enhanced following acute exercise, whereas reduced fatigue levels are present only when energy increases are "moderately large" following low-to-moderate exercise of a duration greater than 20 minutes.

González-Fernández et al. (2017) had participants complete the PVT for 45 min while engaging in either a control condition of low-effort movement or an exercise condition at 75% of ventilatory anaerobic threshold (VAT). Their results show that those in the 75% VAT group had shorter RTs when compared to the control group over the 45-min period. Furthermore, Hwang et al. (2016b) had participants complete one of four conditions: (1) low-level laser stimulation of the prefrontal cortex, (2) a 20-min single bout of high-intensity exercise (85-90% VO_2max) (3) laser treatment and exercise together, or (4) a control group that did not exercise or receive laser therapy. The laser stimulation was

implemented as it has been proposed to stimulate prefrontal cortex stimulation and increase BDNF levels (Hwang et al., 2016b). The PVT was administered prior to and post-treatment. The exercise and laser therapy condition reduced PVT RTs; however, the combined laser therapy and exercise condition resulted in the greatest magnitude reduction in PVT RTs.

Some research suggests exercise may have no influence on vigilance. In Slutsky et al.'s (2017) study, participants were randomized into either a light-intensity exercise (40% HRR) or non-exercise control group following sleep deprivation, after which they performed the PVT. They reported no difference in PVT performance between the control and exercise groups. In turn, Saner et al. (2024) investigated the effects of high-intensity interval exercise (HIIE) following sleep deprivation on alertness through the PVT and compared a non-exercise control group to a group that completed HIIE. They reported there was no reliable difference in PVT performance between the two groups, and the detriments to MF were not mitigated by exercise. The aforementioned studies, however, did not focus on the effects of exercise on MF mitigation.

In the context of EF, Ahn et al.'s (2023) work examined whether passive exercise (and a non-exercise control condition) performed concurrent with the PVT ameliorates MF and mitigates an MF-induced EF deficit. This question was motivated by evidence showing that passive exercise benefits EF and because passive exercise served as a viable platform for examining exercise induced cognitive benefits during the SARS CoV-2 pandemic (i.e., a time when protocols involving an increase in ventilation were contraindicated). Results showed that PVT performance declined as a function of time; however, the magnitude of the decline did not vary between passive and control conditions. Regarding EF, control condition antisaccade RTs were longer following the intervention when compared to baseline values. In contrast, the passive exercise condition demonstrated shorter antisaccade RTs following the intervention when compared to baseline. Thus, passive exercise mitigated the EF deficit resulting from MF. To my knowledge, however, there is no research investigating the effects of active or passive exercise completed prior to MF induction on MF mitigation.

1.6 Research predictions

Chapter 2 of my thesis examined whether a single bout of passive and active exercise differentially affect EF and MF. Further, I sought to evaluate MCA changes during a MF task. Accordingly, participants completed three 20-min conditions of: (1) active exercise via cycle ergometer, (2) passive exercise via a mechanically driven cycle ergometer flywheel, and (3) a non-exercise control. EF was evaluated pre- and post-condition via the pro- and antisaccade tasks. Following the postexercise EF assessment a 20-min PVT was performed, and RT changes from the first to last five minutes of the protocol were used to assess for potential condition-specific changes in the magnitude of MF. Throughout the protocol, TCD was used to measure MCAv and estimate condition-specific changes in CBF. In terms of research predictions, I posit that active and passive exercise will result in a postexercise EF benefit linked to an exercise-mediated increase in CBF. Further, I predict that active and passive exercise will result in a smaller magnitude increase in RTs from the first to last five minutes of the PVT protocol. More directly, I predict that a prior exercise condition will ameliorate MF induction associated with the PVT. Last, I predict that the decreased objective measure of MF during the PVT will be associated with a decreased reduction in CBF.

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Chapter 2

2 Introduction

Executive function (EF) entails the top-down cognitive processes supporting activities of daily living and includes the core components of inhibitory control, working memory and cognitive flexibility (Diamond, 2013; Miyake et al., 2000). In turn, mental fatigue (MF) is a psychophysiological state of tiredness arising from cognitively demanding tasks that reduce the efficiency (e.g., increased reaction time [RT]) and effectiveness (e.g., increased performance errors) of EF measures (for review see, Kunasegaran et al., 2023). The psychomotor vigilance task (PVT) is frequently used to induce and assess MF and is a sustained attention task requiring that participants input a response to a series of exogenous stimuli presented over a set period of time (Dinges and Powell, 1985). For example, Lim and colleagues (2010) evaluated the neural correlates of the "time-on-task" effect, and its association with subjective ratings of MF. Participants completed a 20-min PVT while arterial spin labeling perfusion functional magnetic resonance imaging (fMRI) was implemented to examine brain activation and cerebral blood flow (CBF) prior to and post-PVT. Results showed that RT and CBF increased and decreased, respectively, as a function of the time spent on the PVT task and these changes were related to increases in subjective MF. Furthermore, an extensive literature has demonstrated the negative effects of MF on EF (Ahn et al., 2023; Holtzer et al., 2011; Kato et al., 2009; van der Linden et al., 2003). Indeed, persons with executive dysfunction arising from mild traumatic brain injury (for review see, Zgaljardic et al., 2013) and negative internal- and externalizing behaviours (Krabbe et al., 2017) show more rapid and larger magnitude objective and subjective measures of MF when exposed to a sustained vigilance task. Beyond a clinical domain, it also is important to understand the relationship between EF and MF in occupations requiring sustained attention and MF resistance (e.g., air traffic controllers) to understand how to ameliorate MF-induced performance deficits.

In contrast to an EF decrement, an extensive literature has reported that a single bout of aerobic and/or resistance exercise elicits a postexercise EF benefit (for meta-analyses see, Chang et al., 2012; Ishihara et al., 2021; Lambourne and Tomprowoski, 2010; Ludyga et al., 2016). This benefit has been – in part – attributed to an exercise-based increase in

CBF that improves the efficiency of the local-neural circuits supporting EF networks (i.e., the hemo-neural hypothesis) (Moore and Cao, 2008). For example, Tari et al. (2020) had participants complete separate 10-min conditions involving: (1) a single bout of aerobic exercise, (2) the inhalation of a higher-than-atmospheric concentration of CO_2 (i.e., hypercapnic condition), and (3) a non-exercise and non-hypercapnic control condition. The hypercapnic condition was used because it increases CBF (via pH induced vasodilation) independent of the metabolic demands of exercise (Ainslie and Duffin, 2009; Hoiland et al., 2019). Results showed that exercise and hypercapnic conditions produced a reliable postexercise EF benefit that was linked to an intervention-based increase in CBF. Further, Shirzad et al. (2022) had participants complete separate 20-min bouts of passive exercise (i.e., participants' lower limbs were moved via a mechanically driven cycle ergometer), traditional active (i.e., volitional) exercise, and a non-exercise control to evaluate their effects on EF and CBF. Unlike traditional active exercise, passive exercise does not require agonist muscle activation and does not increase ventilatory or gas exchange variables associated with volitional exercise (Shirzad et al., 2022). In spite of the fact that passive exercise does not render an increase in metabolic demands, the protocol does elicit an increase in CBF via feedforward central commands and the activation of mechanosensitive type *III* muscle afferent activation that stimulate the primary and somatosensory cortices to increase cardiac output and stroke volume (Eldridge et al., 1985; Gladwell & Coote, 2002; Goodwin et al., 1972; Krogh and Lindhard, 1913; Matsukawa, 2012; Nobrega and Araujo, 1993; Nurhayati & Boutcher, 1998; Victor et al., 1995). Shirzad et al. (2022) demonstrated that passive and active exercise increased CBF, although the magnitude of the increase was smaller in the former condition. More notably, both conditions produced an equivalent magnitude postexercise EF benefit that was reliably related to an increase in CBF. Thus, an increase in CBF independent of the metabolic and energy costs of exercise provides a postexercise EF benefit.

To our knowledge only one previous study addressed the impact of an exercise intervention on EF and MF. In that study, Ahn et al. (2023) had participants complete a 20-min bout of passive exercise (via cycle ergometry at a pedaling frequency of 70 rpm) and a non-exercise control condition *simultaneous* with a PVT protocol. EF was assessed

prior to and immediately after the simultaneous exercise/control and PVT intervention via the pro- and antisaccade tasks. Prosaccades require a goal-directed eye movement (i.e., saccade) to the veridical location of a target and are mediated largely independent of EF via direct retinotopic projections to the superior colliculus (Wurtz and Albano, 1980). In contrast, antisaccades require a response mirror-symmetrical to a target and result in longer RTs (Hallett, 1978), increased directional errors (Fischer and Weber, 1982) and less accurate and more variable endpoints (Gillen and Heath, 2014) than their prosaccade counterparts. Extensive neuroimaging and lesions studies in humans, as well as electrophysiology and transient cooling studies in non-human primates, have attributed the behavioural 'costs' of antisaccades to the time-consuming EF demands of inhibiting a pre-potent prosaccade and the 180º spatial transposition of a target's coordinates (for review see Munoz and Everling, 2004). Moreover, the hands- and language-free nature of the antisaccade task has been shown to provide the resolution for detecting subtle EF changes following exercise (for extensive review see Zou et al. 2023). Ahn et al. (2023) showed that PVT RTs for exercise and control conditions showed an equivalent magnitude increase from the first to the last five minutes of the intervention; that is, results showed that the PVT was associated with an objective increase in MF. In turn, at the post-intervention assessment the control condition showed an increase in antisaccade RTs, whereas the passive condition showed a decrease in antisaccade RTs. In other words, passive exercise performed simultaneous with the PVT provided a neuroprotective mechanism that ameliorated a post-PVT EF deficit.

Three issues remain from Ahn et al.'s (2023) work. The first reflects that Ahn et al. employed a passive – but not active – exercise condition. Only a passive condition was employed by Ahn et al. because the protocol provided a safe environment to assess the potential link between exercise, EF and MF during the SARS CoV-2 pandemic. Thus, it is unclear whether active exercise may ameliorate a MF-induced EF deficit distinct from passive exercise. The second issue is whether a single bout of passive and/or active exercise completed in advance of the PVT renders decreased objective and subjective measures of MF; that is, does exercise offer a neuroprotective benefit from a MF-inducing protocol. The third issue is that Ahn et al. did not provide a neurophysiological measure (e.g., transcranial Doppler ultrasound, functional near infra-red spectroscopy) to

examine the link between exercise, EF and CBF. To that end, the present work had participants complete separate 20-min single bouts of passive and active cycle ergometry as well as a non-exercise control condition and evaluated pre- and immediate postexercise EF via the antisaccade task. Subsequently, and in all conditions, participants completed a 20-min PVT protocol and we examined whether the prior intervention (i.e., control, passive and active exercise) influenced the magnitude of objective and subjective measures of MF. MCAv was measured during each condition and the PVT to examine the potential relationship(s) between CBF and EF and performance-based changes on the PVT. In particular, we sought to determine whether the relationship between an exercise-based increase in MCAv and postexercise EF benefit influenced the magnitude of a PVT-based MCAv change and associated objective measure of MF. On a practical level, the present work provides a framework by which to determine whether exercise performed in advance of an occupational task requiring sustained attention (e.g., air traffic controller) provides an intervention that ameliorates MF. In terms of research predictions, it is hypothesized that passive and active exercise will increase CBF – albeit with a larger increase in the latter condition – and that this change will be linked to a postexercise reduction in antisaccade RTs. In other words, it is predicted that an exercise-mediated increase in CBF will be associated with a postexercise EF benefit. As well, it is hypothesized that the postexercise EF benefit associated with passive and active exercise conditions will provide a neuroprotective benefit decreasing objective and subjective measures associated with subsequent performance on the PVT. Moreover, it is predicted that the PVT will render a decrease in CBF; however, we hypothesize this reduction will be lessened by a previously performed passive and/or active exercise intervention.

2.1 Methods

2.1.1 Participants

Twenty-two (13 female, 9 male) healthy young adults (average age: 22.4 years, SD = 3.3; range: 18 - 27) volunteered to participate in this study. The sample size was determined *a priori* via a power analysis based on Shirzad et al.'s (2022) work comparing pre- and postexercise antisaccade RTs ($\alpha = 0.05$, power = 0.80, $d_z = 0.60$). Inclusion criteria entailed: self-reported normal or corrected-to-normal vision; no history of neurological

impairment (including concussion), neuropsychiatric disorder, cardiovascular or metabolic disease; non-smoking; not taking medications affecting metabolic, hemodynamic, cardiac or respiratory responses to exercise. Participants were asked to refrain from alcohol and recreational drugs 12 h prior to a study session and were requested to get eight hours of sleep the night prior to each session. Participants were directed to drink 555 mL of water one hour before the session and consume a "normal" breakfast on the morning of each session. Participants were deemed "physically ready" to exercise via the Physical Activity Readiness Questionnaire (PAR-Q) (Warburton et al., 2021) and were "active" as determined by the Godin Leisure-Time Exercise Questionnaire (GLETQ) (Godin, 2011) (average GLETQ score = 50, SD = 22.7). The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) was used to evaluate participants' subjective rating of sleep quality, and participants were required to receive a score less than or equal to 7. The PSQI was to ensure that poor sleep habits did not influence day-to-day measures of subjective fatigue. The average PSQI score was 4 (SD = 1.6) and indicated that participants were "good" sleepers.

Participants provided informed written consent via a protocol approved by the Health Sciences Research Ethics Board, University of Western Ontario (HSREB #124382) and this study conformed to the most recent iteration of the Declaration of Helsinki with the exception that participants were not registered in a database.

2.1.2 Experimental Overview

Participants completed active and passive exercise and control conditions on separate days at the same time of day. The order in which conditions were completed was counterbalanced. Each session required approximately 120-min to complete. **Figure 1** provides a schematic of the timeline of study events and shows that for control, passive and active exercise conditions a baseline oculomotor assessment was first performed and followed by an associated intervention (i.e., 26-min of no-exercise (control) or same duration passive and active exercise intervention). Subsequently, a post-intervention oculomotor assessment was completed after which participants completed a 20-min PVT protocol. MCAv was recorded via TCD throughout each intervention and the PVT to estimate CBF. As well, subjective measures of MF were taken prior to and immediately

after the intervention and the PVT. Upon arrival to the lab, participants were provided a 20-min baseline period. The baseline period was used to account for the locomotor-based physiological costs of arriving to the lab.

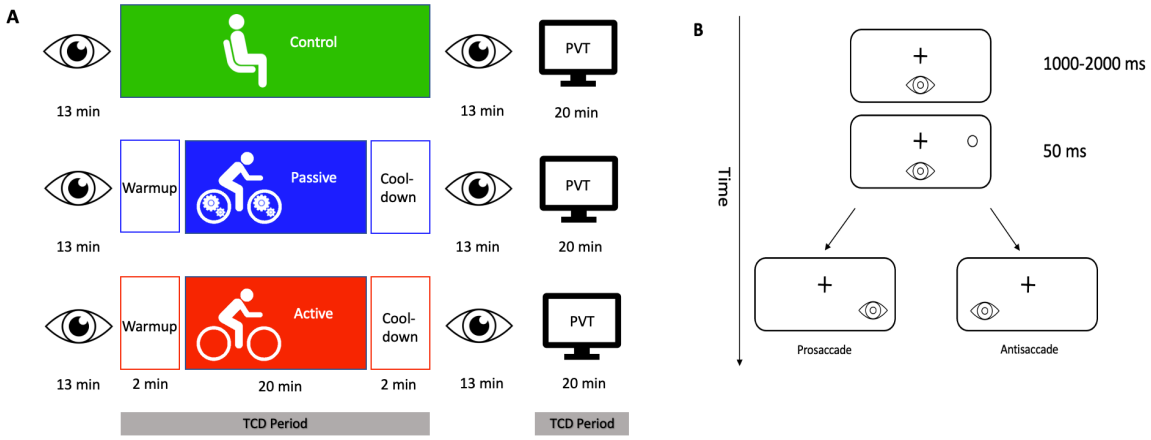

Figure 1. Panel A shows a timeline of experimental events for control (green), passive (blue) and active (red) exercise conditions. The eye icon represents when oculomotor EF assessments were conducted (i.e., prior to and post each condition). In the passive and active exercise conditions, following the baseline EF assessment and assessment of physiological measures (i.e., heart rate (HR) and middle cerebral artery velocity (MCAv)), participants completed a 2-min warmup (i.e., mechanically-driven pedaling at a cadence of 40 rpm and volitional pedaling at a cadence of 40 RPM and 15 W, respectively), followed by a 20-min intervention (i.e., mechanically-driven pedaling at a cadence of 70 rpm and volitional pedaling at a cadence of 70 rpm and 37 W, respectively), and a 2-min cooldown at the same intensity as the warmup. For the control condition, participants remained seated on the cycle ergometer without passive or active pedal movement. During the last minute of the intervention ('steady-state') HR and MCAv data were recorded. Following the second EF assessment, participants performed the PVT and HR and MCAv were continuously recorded during this timeframe. **Panel B** shows the timing and schematic of events for the prosaccade and antisaccade tasks.

2.1.3 Passive, active and control conditions

For the duration of control, active and passive conditions participants sat on an upright active-passive cycle ergometer (E-PAT AP; Healthcare International, Langley, WA,

USA). Participants feet were securely strapped to the pedals of the ergometer such that their legs achieved approximately 85% of full extension upon completion of a passive/active pedal stroke. Prior to each condition, participants sat for 2-min while baseline physiological measures were taken (i.e., MCAv and HR). Subsequently, during the passive exercise condition, participants completed a 2-min mechanically driven warm-up at 40 rpm, followed by a step-transition to 70-rpm for the 20-min intervention, after which a 2-min cool-down at 40 rpm took place. Further, we note that previous work employing electromyography has shown that the passive exercise protocol used here does not result in volitional muscle activity and does not elicit a baseline to steady-state change in cardiorespiratory measures (i.e., $\dot{V}O_2$, $\dot{V}CO_2$, ventilation, end-tidal CO_2 (Shirzad et al. 2022; Tari et al. 2023). The same timeline was followed for the active exercise condition; however, for the warm-up and cool-down, participants pedaled volitionally at a cadence of 40 rpm with a resistance of 15 W, and for the 20-min intervention participants pedaled at 70 rpm with a resistance of 37 W. For the control condition, participants were seated for 26-min (time-matched to the other conditions) without exercising. Throughout the 26-min timeline for all interventions participants were able to chat with the experimenters.

2.1.4 Oculomotor assessment

Oculomotor assessments of EF were completed prior to (i.e., pre-intervention) and immediately following (i.e., post-intervention) control, passive and active exercise conditions. For each assessment, participants sat on a chair in front of a table upon which an LCD monitor (60 Hz, 8 ms response rate, 1280×960 pixels; Dell 3007WFP, Round Rock, TX) was placed 550 mm from the table's front edge. Participants rested their chin on a head-chin rest and the gaze location of their left eye was monitored using a video-based eye tracking system (EyeLink 1000 Plus; SR Research, Ottawa, ON, Canada) sampling at 1000 Hz. Before the start of an oculomotor assessment, a nine-point calibration and validation (i.e., $<1^{\circ}$ of error) of the participant's viewing space was completed. MATLAB and the Psychophysics Toolbox extension (v. 3.0) (Brainard, 2004; Kleiner et al., 2007), including the EyeLink Toolbox (Cornelissen et al., 2002) were used

to control all computer events. For all experimental sessions, the lights in the experimental suite were dimmed to produce an ambient luminance of 8 cd/m^2.

Visual stimuli were displayed on a high-contrast black screen (0.1 cd/m^2) and included a white fixation cross (1˚ in diameter: 127 cd/m^2) and open "target" circles (1º in diameter: 127 cd/m^2). The fixation cross was displayed for a randomized and uniformly distributed foreperiod (1000 to 2000 ms) after which the target circle was displayed for 50 ms 13.5˚ (proximal target) and 16.5˚ (distal target) left and right of the fixation and in the same horizontal plane. The fixation cross was presented throughout a trial (i.e., overlap paradigm) and onset of the target served as the imperative to pro- (i.e., saccade to target) or antisaccade (i.e., saccade mirror-symmetrical to target). For each oculomotor assessment, pro- and antisaccades were completed in separate and randomly ordered blocks involving 60 trials pseudo-randomly ordered to each target location (i.e., proximal, distal) and visual space (i.e., left and right of fixation). Each oculomotor assessment (including calibration time) required approximately 13 min to complete.

2.1.5 Psychomotor vigilance task (PVT)

Following the post-intervention oculomotor assessment, participants completed a 20-min PVT protocol (PC-PVT, Biotechnology HPC Software Applications Institute, Frederick, MD, USA) to induce and assess MF. The PVT was presented on the same monitor set-up as the oculomotor assessment. The protocol required that participants direct their gaze towards the center of a high-contrast black screen (0.1 cd/m^2). Following a random and uniformly distributed interval between 2 and 10 s, a target stimulus (i.e., a timer counting the ms lapsing since the onset of its presentation) (2°, 127 cd/m^2) appeared on the screen. Participants used their dominant hand to complete a left "click" on a computer mouse in response to stimulus onset "as quickly as possible". Participants were provided on-screen feedback regarding the speed of their response for 500 ms before the screen was "blanked" for a subsequent trial. As per the control, active and passive exercise conditions, MCAv and HR were continuously measured during the PVT protocol.

2.1.6 Middle cerebral artery velocity (MCAv) and heart rate (HR) collection

A TCD probe (Neurovision 500 M, Neurovision TOC2M; Multigon Industries, Elmsford, CA) covered in aqueous ultrasound gel (Aquasonic Clear, Parker Laboratories Inc., Fairfield, NJ) was placed on the right anterior temporal window and secured via an adjustable headband to measure MCAv and estimate CBF. Notably, the TCD technique used here has been shown to provide a reliable proxy for a direct measure of CBF (i.e., Xenon 133 tracing: see Bishop et al., 1986). HR was measured using a wearable heart rate monitor secured to the participant's sternum (Polar Electro T34; Polar Electro Oy, Kempele, Finland).

2.1.7 Subjective rating of mental fatigue

For each condition, a seven-point Likert scale asking, "How mentally fatigued do you feel right now?" (i.e., 1 indicated "not mentally fatigued at all", 7 indicated "very mentally fatigued") was provided to participants prior to and following each intervention and prior to and following the PVT.

2.1.8 Dependent variables, data reduction and statistical analyses

TCD data involving signal aliasing/loss (e.g., head shift) were excluded (Terslev et al., 2017) and peak systolic MCAv were analyzed (Clyde et al., 1996) given that it provides a valid proxy for a direct measure of CBF (i.e., Xenon 133 tracing: Bishop et al. 1986). For the intervention phase of this investigation, MCAv and HR were analyzed via separate 3 (condition: active, passive, control) by 2 (time: baseline [i.e., 1 min interval prior to warm-up], steady state [i.e., last min of the intervention]) fully repeated measures ANOVAs (α=0.05). For the PVT phase of this investigation, MCAv and HR were analyzed via a 3 (condition: active, passive, control) by 2 (time: first min of PVT, last min of PVT) fully repeated measures ANOVAs (α = .05).

For the oculomotor EF assessment, gaze position data were filtered via a dual-pass Butterworth filter with a low-pass cut-off frequency of 15 Hz. A five-point central-finite difference algorithm was used to determine instantaneous velocities and accelerations. Saccade onset was determined when velocity and acceleration were greater than 30°/s

and 8000°/s^2, respectively. Saccade offset was determined when velocity was less than 30°/s for 40 ms. Oculomotor dependent variables included RT (time from target onset to saccade onset), saccade duration (time from saccade onset to offset) and saccade gain (saccade amplitude/veridical target location). Trials were excluded for signal loss (i.e., eye blink), anticipatory responses (RTs < 50 ms), and RTs > 2.5 standard deviations from a participant-specific mean. Trials involving directional errors (i.e., prosaccade instead of antisaccade) were excluded because they are mediated via planning mechanisms distinct from their directionally correct counterparts (DeSimone et al., 2011). Based on the aforementioned criteria, not more than 12% of the trials for any participant were excluded. Oculomotor dependent variables were analyzed via 3 (condition: active, passive, control) by 2 (time: pre-, post-intervention) by 2 (task: prosaccade, antisaccade) fully repeated measures ANOVAs (alpha = .05).

HR, MCAv and oculomotor dependent variables were assessed for normality and mean values were subsequently used for their analyses. Significant main effects and interactions were decomposed via simple effects (i.e., reduced model ANOVA and/or paired-samples t-tests) and Hyunh-Feldt corrections for sphericity were included when appropriate (i.e., corrected degrees of freedom to one decimal place). In addition to frequentist statistics, Bayesian paired samples t-test contrasts (Cauchy distribution=0.707) were used to evaluate the null hypothesis (i.e., BF_{01}). Jeffreys' (1961) nomenclature of "anecdotal" (i.e., 1 to <3), "moderate" (i.e., 3 to <10), "strong" (i.e., 10 to <100) and "very strong" (i.e., >100) was used to contextualize Bayes factor robustness.

For the PVT, RTs (i.e., time from stimulus appearance to mouse click) were analyzed via 3 (condition: active, passive, control) by 2 (time: first and last five minutes of the protocol) repeated measures ANOVA. Median RTs were used given the positive skew of the RT distribution (see Figure 5). In line with previous work, we did not remove any RT values from the PVT data set given that longer values have been shown to indicate a lapse of attention in a sustained vigilance task (Rupp, 2013). Subjective ratings of MF were analyzed via 3 (condition: active, passive, control) by 4 (time: pre-intervention, post-intervention, pre-PVT, post-PVT) repeated measures ANOVA.

2.2 Results

2.2.1 Control, active and passive interventions: physiological and oculomotor measures:

HR and MCAv: Results generated main effects for **condition**, *Fs*(2, 42) = 78.13 and 14.70 for HR and MCAv, respectively, ps <.001, η_p^2 = 0.79 and 0.41, **time**, *F*(1, 21) = 116.12 and 248.89, *p* <.001, η_p^2 = 0.85 and 0.92, and their interactions, *F*(2, 42) = 143.23 and 154.34, *p* <.001, η_p^2 = 0.87 and 0.88. In terms of HR, control and passive exercise condition values did not reliably vary from baseline (control: 76 bpm, SD = 10, passive: 81 bpm, SD = 8) to steady state (control: 76 bpm, SD = 11, passive: 82 bpm, SD = 9) (ts[21] = -0.61 and -1.28, *p*s =.55 and.21, d_z = -0.13 and -0.27 respectively), whereas for the active exercise condition values increased from baseline (81 bpm, SD = 12) to steady state (123 bpm, SD = 18) (t[21] = -12.25, *p* <.001, d_z = -2.61). In terms of MCAv, **Figure 3** shows that control condition values did not reliably vary from baseline to steady state (t[21] = 0.83, *p* = .42, d_z = 0.18), whereas values for active and passive exercise conditions increased during the same time period (ts[21] = -15.12 and -10.83, *p*s <.001, d_z = -3.22 and -2.31). As well, we computed participant-specific MCAv difference scores (steady state minus baseline) and observed that values were greater in the active (28 cm/s, SD = 9) than the passive exercise (8 cm/s, SD = 4) condition (t[21] = 11.49, *p* <.001, d_z = 2.45).

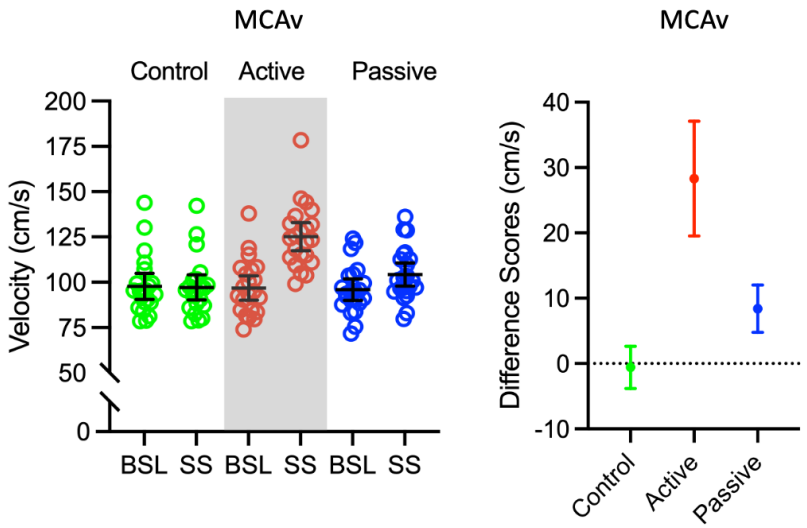

Figure 2. The left panel shows control, active, and passive exercise condition participant-specific and group mean systolic middle cerebral artery velocity (MCAv) at baseline (BSL) and steady state (i.e., SS). The right panel depicts the group mean MCAv difference scores (i.e., SS – baseline). Error bars indicate 95% between-participant confidence intervals.

Participant-specific percentages of predicted maximum heart rate (%HRmax) were computed for the active exercise condition and produced a mean value of 62% (SD = 9: range: 44-74%) and thus indicates that participants exercised at a moderate-intensity (for classification of exercise intensity see, Warburton et al., 2006).

Oculomotor performance: RT yielded a main effect for **time**, $F(1, 21) = 25.43$, $p < .001$, $\eta_p^2 = 0.55$, and **task**, $F(1, 21) = 70.51$, $p < .001$, $\eta_p^2 = 0.77$, and interactions involving **time** by **task**, $F(1, 21) = 16.15$, $p < .001$, $\eta_p^2 = 0.44$, and **condition** by **time** by **task**, $F(2, 42) = 5.58$, $p = .007$, $\eta_p^2 = 0.21$. **Figure 4** demonstrates the general finding that RTs for prosaccades (204 ms, SD = 23) were shorter than antisaccades (267 ms, SD = 51) – a result independent of time of assessment and condition. In decomposing the highest-order interaction, we contrasted pre- and post-intervention pro- and antisaccade RTs separately for each condition. As shown in **Figure 4**, prosaccade RTs did not reliably change from pre- to post-intervention across control, passive and active conditions (ts[21] < 2.07, *p*s >.05, $d_z < 0.45$). For antisaccades, RTs decreased from pre- to post-intervention across

each condition (ts[21] = 2.41, 3.90, 4.30, p =.03, <.001 and <.001 d_z = 0.51, 0.83, 0.92). Further, and given the primary objective of this work, we computed antisaccade RT difference scores (post-intervention minus pre-intervention) and found that the magnitude of the RT benefit did not reliably differ between passive (-16 ms, SD = 19) and active (-14 ms, SD = 15) exercise conditions (t[21] = -0.49, p =.63, d_z = 0.10) and both produced a larger difference score than the control condition (-5 ms, SD = 11) (ts[21] = 2.49 and 2.36, ps =.02 and .03, d_z = 0.53 and 0.50). Additionally, a Bayesian paired samples t-test contrasting RT difference scores for passive and active conditions produced a BF_{01} value of 4.03 and thus provided moderate support for the null hypothesis. In other words, passive and active exercise conditions produced an equivalent magnitude postexercise reduction in antisaccade RTs.

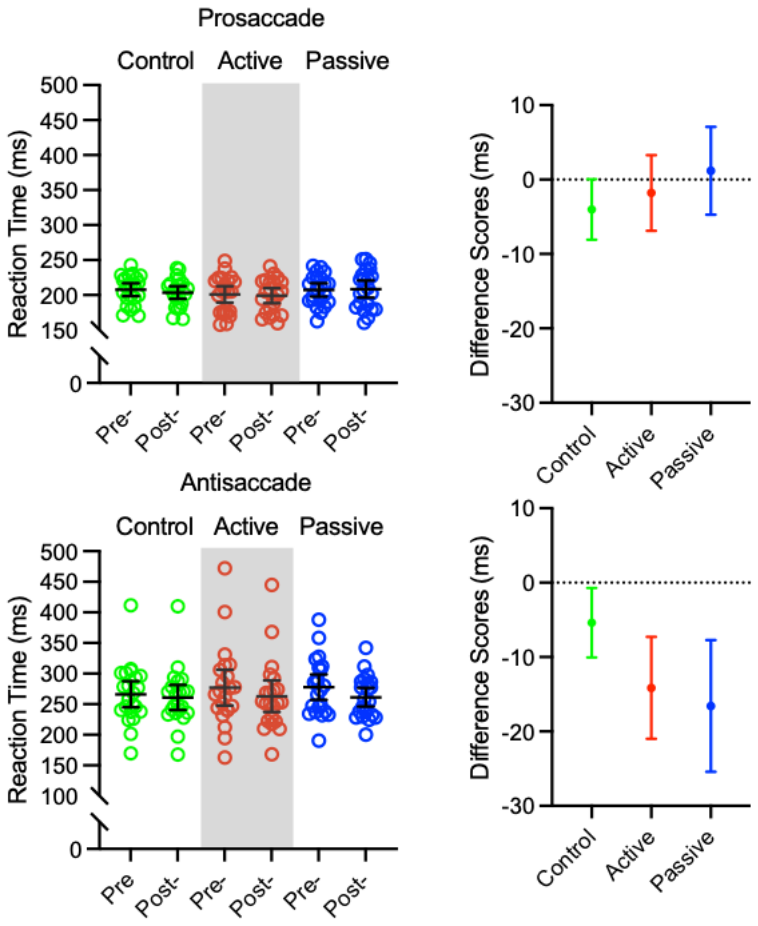

Figure 3. The left panels show participant-specific and group mean pro- and antisaccade reaction times (RTs) pre- and post-intervention for control (green), active (red) and

passive exercise (blue) conditions. The right panel shows condition-specific group mean pro- and antisaccade RT difference scores (post-intervention minus pre-intervention). Error bars represent 95% between-participant confidence intervals.

Saccade duration and gain variability produced main effects for **task,** $Fs(1, 21) \geq 25.50$, $p < .001$, $\eta_p^2 \geq 0.55$, such that prosaccades had shorter durations (52 ms, SD=8) and less variable endpoints (0.13, SD=0.05) than antisaccades (saccade duration: 60 ms, SD=14; gain variability: 0.25, SD=0.08).

2.2.2 Psychomotor vigilance task (PVT): physiological and behavioural measures

HR and MCAv: HR yielded a main effect of **condition**, $F(2, 42) = 4.61$, $p = .02$, $\eta_p^2 = 0.18$, such that values for the active exercise condition (79 bpm, SD = 12) were greater than control (75 bpm, SD = 10) ($t[21] = 3.97$, $p < .001$, $d_z = 0.85$) and passive exercise (74 bpm, SD = 8) conditions ($t[21] = 3.11$, $p = .003$, $d_z = 0.66$), and the former two conditions did not reliably differ ($t[21] = 0.12$, $p = .91$, $d_z = 0.03$). Notably, neither a reliable main effect of **time** nor a **time** by **condition** interaction was observed, $Fs < 0.67$, $ps > .52$, all $\eta_p^2 < 0.04$, and thus indicates that HR across the different experimental conditions did not change from the first to last min of the PVT.

MCAv yielded a main effect of **time**, $F(1, 21) = 32.56$, $p < .001$, $\eta_p^2 = 0.61$, such that values decreased from the first (98 cm/s, SD = 15) to last (94 cm/s, SD = 13) minute of the PVT. Notably, we did not observed a main effect of **condition**, $F(2, 42) = 0.13$, $p = .88$, $\eta_p^2 = 0.006$, nor a **condition** by **time** interaction, $F(1.62, 34.10) = 0.009$, $p = .98$, $\eta_p^2 < .001$, indicating that the time-based decrease in MCAv was consistent across conditions.

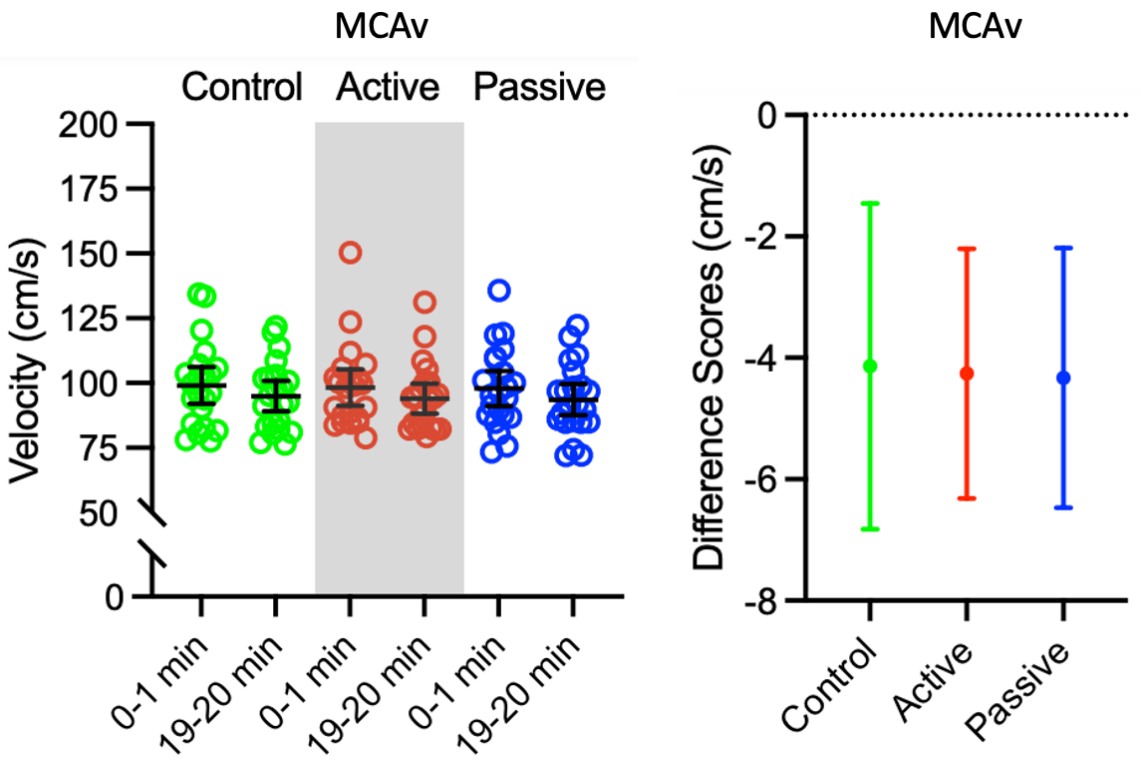

Figure 4. The left panel shows participant-specific and group mean peak systolic middle cerebral artery velocity (MCAv) during the first and last minute of the PVT for the control (green), active (red), and passive exercise (blue) conditions. The right panel shows group mean MCAv difference scores for each condition (i.e., last min minus first min). Error bars represent 95% between-participant confidence intervals.

Objective measure of mental fatigue during the PVT: **Figure 5** presents frequency histograms for the first and last 5-min of the PVT protocol separately for control, active and passive exercise conditions and graphically demonstrates a time-based increase in RT across all conditions. In terms of quantitative analyses, RT elicited a main effect of **time**, $F(1, 21) = 49.64$, $p < .001$, $\eta_p^2 = 0.70$, indicating that values increased from the first (262 ms, IQR = 5) to the last (304 ms, IQR = 9) 5-min of the PVT (**Figure 5**). Notably, a null **condition** by **time** interaction, $F(2, 42) = 0.73$, $p = .48$, $\eta_p^2 = 0.03$, indicated that the magnitude of the PVT change did not vary across control, passive and active exercise conditions. In addition, we computed participant-specific PVT difference scores (last 5-min minus first 5-min) separately for each experimental condition and examined them via

one-way repeated measures Bayesian ANOVA and observed a value (BF_{01} = 4.40) providing moderate support for the null hypothesis.

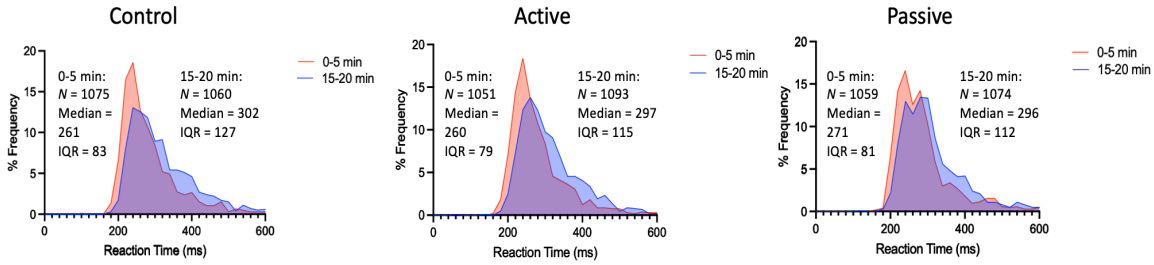

Figure 5. Psychomotor vigilance task (PVT) reaction time (RT) (ms) percent frequency histograms for control, active, and passive exercise conditions for the first (red) and last (blue) five minutes of the protocol. The figure includes PVT RTs under 600 ms. Distribution summary statistics are displayed within each histogram.

Subjective ratings of mental fatigue: Results revealed a main effect of **time**, $F(3, 63)$, = 30.87, p <.001, η_p^2 = 0.60, such that values did not change across pre-intervention (2, SD = 1), and post-intervention (2, SD = 1); however, values increased from pre-PVT (2, SD = 1) to post-PVT (4, SD = 2). A null **condition** by **time** interaction, $F(6, 126)$ = 0.53, p =.78, η_p^2 = 0.03, indicated that the time-based change in subjective MF did not vary across the different conditions.

2.2.3 Relationship between antisaccade performance and middle cerebral artery velocity (MCAv)

We computed correlation coefficients involving participant-specific MCAv (i.e., steady-state minus baseline) and antisaccade RT (i.e., post- minus pre-intervention) difference scores and found that the variables were not related across control, passive and active exercise conditions (rs(21) = -0.32, -0.08, 0.28 for control, passive and active exercise conditions, respectively, ps =.15, .74, .21).

2.2.4 Relationship between antisaccade performance and mental fatigue (MF)

Participant-specific antisaccade RT (i.e., post- minus pre-intervention) and PVT RT (last 5-min minus first 5-min of protocol) differences scores were not reliably correlated

across control, passive and active exercise conditions (rs(21) = 0.05, -0.01 and -0.17, *p*s =.84, .98, and .45).

2.2.5 Relationship between MCAv and MF

Participant-specific MCAv (i.e., last min minus first min) and PVT RT (last 5-min minus first 5-min of protocol) differences scores were not reliably correlated across control, passive and active exercise conditions (rs(21) = 0.24, -0.11 and 0.10, ps =.28, .64, and .66).

2.3 Discussion

We sought to determine whether increased CBF and an associated postexercise EF benefit (passive and active exercise) provides a neuroprotective mechanism ameliorating a performance deficit associated with a subsequent MF task. In outlining the current findings, we first discuss intervention-based HR and CBF and post-intervention performance, and then describe physiological and behavioural data from arising from the PVT.

2.3.1 Passive and active exercise increase CBF and decrease antisaccade RTs

Active exercise produced a baseline to steady state increase in HR and MCAv consistent with a moderate-intensity work rate (Tari et al. 2021b; Warburton et al., 2006). In particular, the increase in HR is attributed to the increased cardiac output required to meet the O_2 requirements of working muscles (for review see, Radak et al., 2013). The increase in HR is additionally accompanied by an increase in stroke volume, nitric oxide (NO), vascular deformation, and CO_2, which leads to an increase in CBF (Lavie et al., 2015; Smith and Ainslie, 2017). In turn, the passive exercise condition did not produce a reliable baseline to steady state increase in HR; however, it was associated with a steady state increase in MCAv – albeit at a magnitude less than the active exercise condition. The MCAv increase independent of a change in HR is in line with previous work reporting that passive exercise stimulates type *III* muscle afferent and feedforward-based central command signals that activate primary somatosensory and motor cortices to

increase cardiac output and stroke volume (Amann, 2012; Eldridge et al., 1985; Gladwell and Coote, 2002; Goodwin et al., 1972; Krogh and Lindhard, 1913; Matsukawa, 2012; Nobrega and Araujo, 1993; Nurhayati and Boutcher, 1998; Victor et al., 1995). In turn, the control condition did not produce a baseline to steady-state change in HR or MCAv. Accordingly, the active and passive exercise conditions provide a framework to determine whether active and passive exercise-mediated increases in CBF are linked to a postexercise EF benefit.

In terms of the oculomotor assessment, antisaccades had longer RTs, saccade durations, and increased endpoint variability when compared to prosaccades. These well-documented antisaccade behavioural findings have been shown to reflect the time-consuming and EF demands required to inhibit a pre-potent prosaccade and invert a target's coordinates (vector inversion components of the task) (Gillen and Heath, 2014; Hallett, 1978; Heath et al., 2010; Munoz and Everling, 2004). Accordingly, the antisaccade task provided a framework by which to examine intervention-based changes in EF.

In terms of the interventions used here, prosaccade RTs did not vary from pre- to post-intervention across all conditions. In contrast, antisaccades showed a pre- to post-intervention RT reduction. That the control condition produced a post-intervention RT benefit is inconsistent with a large number of previous studies by our group (e.g., Dirk et al. 2020; Heath et al. 2016; 2017; 2018; Samani and Heath 2018; Shirzad et al., 2022; Shukla and Heath 2022; Tari et al., 2023) and others (for extensive review see Zou et al. 2023) reporting that antisaccades are refractory to a practice-related performance benefit. Hence, the pre- to post-intervention benefit observed here might reflect that participants developed an improved antisaccade task-set that supported post-intervention response efficiency (Everling and Johnston 2013). In spite of the post-intervention benefit in the control condition it is important to recognize that the magnitude of the post-intervention antisaccade RT benefit was larger in passive and active exercise conditions. Moreover, the antisaccade RT benefit for exercise conditions could not be attributed to an implicit or explicit strategy designed to decrease planning times at the cost of decreased movement accuracy (i.e., speed-accuracy trade-off; Fitts 1954) given that saccade duration and

endpoint variability did not reliably vary across conditions. Further, that antisaccades – but not prosaccades – showed a post-intervention EF benefit indicates that an exercise-intervention (or any associated practice benefit) did not result in a general increase in information processing speed and/or psychological/physiological arousal (Ayala and Heath, 2021). Indeed, if that were the case then both pro- and antisaccades would have demonstrated a post-intervention RT benefit. Instead, results are consistent with the view that a single bout of passive and active exercise provides a selective EF benefit (for meta-analyses see Chang et al., 2012; Lambourne & Tomproroski, 2010; Ludyga et al., 2016; see also Renke et al., 2022).

An important issue to address is that the magnitude of the passive and active exercise increase in MCAv was not related to antisaccade RT difference scores; that is, results did not show a relationship between an exercise-mediated increase in CBF and a postexercise EF benefit. On the one hand, this represented a surprising result given previous work reporting a link between the two variables (Shirzad et al. 2022; Tari et al. 2020). On the other hand, the present findings support some work reporting that an exercise-based change in CBF does not directly mediate a postexercise EF benefit (Ogoh et al. 2014). This latter view is bolstered by a most recent study by our group employing event-related TCD to examine pre- to postexercise (active exercise only) changes in antisaccade preparatory phase cerebral hemodynamics (Jeyarajan et al. 2024). In that study, the preparatory phase response for antisaccades was greater than prosaccades and was a result taken to evince the aforementioned tasks increased computation demands (see also Duschek et al. 2018; Tari et al. 2021). Notably, however, the preparatory phase hemodynamic response did not vary from pre- to postexercise in spite of an observed decrease in antisaccade RTs. Accordingly, it may be that an EF benefit is accrued from interdependent exercise-based adaptations that include – but is not limited to - CBF (Shirzad et al. 2022) and pressor response (Washio et al. 2023) changes as well as increased biomolecule availability (e.g., nitric oxide, brain-derived neurotrophic factor, catecholamines) (Perwiti et al., 2015; Knaepen et al. 2010; Zouhal et al. 2008) and functional connectivity within EF networks (Schmitt et al., 2019).

2.3.2 A postexercise EF benefit from increased CBF does not ameliorate a MF-based performance reduction

Recall that the PVT is a sustained vigilance task that in the present study was used as a way to induce and provide an objective measure of MF. For all conditions, the PVT increased RTs from the first to the last five min of the protocol and this objective performance change was associated with a reduction in MCAv and an increase in a subjective measure of MF. As noted previously, the decrease in MCAv during the PVT has been posited to reflect the negative effects of MF on the frontoparietal network and provides evidence for the role of this network in mediating cognitive performance (Lim et al., 2010). Thus, results evince that the PVT protocol used here reliably induced MF (Basner et al., 2018; Lim et al., 2010; see also Smith et al., 2019).

The primary objective of this work was to determine whether a preceding passive and/or active exercise intervention and associated EF benefit would ameliorate the magnitude of MF objectively and subjectively assessed during the PVT. Results showed that the performance on the PVT was not influenced by the preceding control, active or passive exercise interventions – a finding supported by frequentist and Bayesian statistics. Such a result counters our a priori hypothesis that a postexercise EF benefit would provide a neuroprotective benefit to a MF-inducing paradigm. The absence of an exercise benefit is not likely attributed to the transient nature of a postexercise EF benefit given that the 20-min PVT protocol was completed within the timeframe by which a postexercise EF benefit is observed (~60 min) (Hung et al. 2013; Joyce et al. 2009; Shukla and Heath 2022; for meta-analysis see Ludyga et al. 2016). Hence, one explanation for the absence of an exercise benefit is that the PVT is not directly mediated via EF. In particular, the PVT is a sustained vigilance task that evaluates sustained attention (Dinges & Powell, 1985; Evans et al., 2019) and although executive control is required to execute the task (i.e., inhibiting external distractors, remembering what the task entails) it is not a singular mediator of task performance. Further, although the PVT and EF are mediated via overlapping cortical structures, it is important to recognize that these functions are also supported by non-overlapping structures (Drummond et al., 2005; Lim et al., 2010; Rossit et al., 2011; Royall et al., 2002). For example, the inferior parietal cortex is involved in

both sustained attention and EF tasks, however the superior parietal lobe is a non-overlapping structure supporting sustained attention in a PVT (Collette et al., 2005; Rossit et al., 2011). Thus, it may be the case that the degree of the EF benefit associated with exercise does not provide a large enough benefit to support sustained attention during the PVT.

In line with our exercise findings, we note that MCAv during the PVT and associated behavioral metrics were not reliably related. This finding counters Lim et al.'s (2010) fMRI study reporting that increased PVT RTs were related to a decrease in frontoparietal CBF. One explanation may be that the participants in the present study recruited a cognitive reserve to maintain performance in the face of a MCAv decline (Barulli and Stern, 2013). Thus, the divergent findings between Lim et al. (2010) and the present study indicates there is no concrete evidence that a PVT-based reduction in CBF is associated with decreased performance.

2.3.3 Limitations

We acknowledge the generalizability of our work is limited by several methodological constraints. First, we did not include a baseline measure of PVT performance prior to the intervention to evaluate how active and passive exercise affect PVT RTs post-intervention compared to pre-intervention. The goal of our study was to evaluate MF mitigation within a PVT session; however, we are unable to conclude how the exercise conditions affect pre- to post-intervention changes. Second, we did not employ an oculomotor EF assessment following the PVT and are thus unable to directly assert that a neuroprotective EF benefit extended throughout the PVT protocol. That said, and as mentioned previously, the timeline of the PVT protocol used here was within the window associated with a postexercise EF benefit (Hung et al. 2013; Joyce et al. 2009; Shukla and Heath 2022; for meta-analysis see Ludyga et al. 2016). Third, the present study investigated healthy young adults and as such it is unknown whether the findings apply to older populations, individuals with chronic fatigue syndrome, or those with altered chronic changes in CBF (i.e., cerebral hypoperfusion). Fourth, TCD does not measure changes in vessel diameter, and the MCA may dilate or constrict in response to changes in physiological conditions (Coverdale et al., 2015). To our knowledge, however, these

changes do not affect the validity of TCD in evaluating exercise-induced changes to MCAv.

2.3.4 Conclusion

A single bout of passive and active exercise increases CBF and provides a postexercise EF benefit. In spite of the neuroprotective effects to EF, the exercise did not mitigate objective and subjective MF or the magnitude of a CBF decline associated with the MF-inducing PVT.

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Appendix

Appendix A: Ethics approval notice from Western University's Health Sciences Research Ethics Board

Western Research

Date: 17 January 2024

To: Dr. Matthew Heath

Project ID: 124382

Review Reference: 2024-124382-88239

Study Title: An investigation into the effects of a single bout of passive and active exercise on executive function and mental fatigue

Application Type: HSREB Initial Application

Review Type: Delegated

Meeting Date / Full Board Reporting Date: 06/Feb/2024

Date Approval Issued: 17/Jan/2024 17:08

REB Approval Expiry Date: 17/Jan/2025

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
GLTEQ	Paper Survey		
PARQPlus 2020	Paper Survey		
PSQI	Paper Survey		
Heart Rate Tool	Other Data Collection Instruments	07/Mar/2023	1
TCD Tool	Other Data Collection Instruments	26/Aug/2019	1
Eye Tracking Tool	Other Data Collection Instruments	26/Aug/2019	1
Blood Pressure Tool	Other Data Collection Instruments	23/Aug/2022	1
Research Protocol	Protocol	13/Dec/2023	1
Recruitment Poster (In-Class)	Recruitment Materials	13/Dec/2023	1
Recruitment Poster	Recruitment Materials	13/Dec/2023	1
Mass Email Script	Email Script	13/Dec/2023	1
Mental Fatigue Likert Scale	Paper Survey	16/Jan/2024	1
Demographic Questionnaire v2	Paper Survey	16/Jan/2024	2
Email Script v2	Email Script	16/Jan/2024	2
LOI v2	Written Consent/Assent	17/Jan/2024	2

Documents Acknowledged:

Document Name	Document Type	Document Date	Document Version
Reference List	References	13/Dec/2023	1
Flow Diagram	Flow Diagram	13/Dec/2023	1
Thesis Itemized Study Budget	Study budget	13/Dec/2023	1

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, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Electronically signed by:

Patricia Sargeant, Ethics Officer [redacted] on behalf of Dr. Roberta Berard, HSREB Vice-Chair, 17/Jan/2024 17:08

Reason: I am approving this document

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations, See Electronic System Compliance Review)

Curriculum Vitae

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Honours and Awards:	Ontario Graduate Scholarship 2023-2024 Western Graduate Research Scholarship 2023-2024 CIHR Summer Program in Aging (SPA) Travel Award 2023
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Publications:

Jeyarajan, G., Ayaz, A., Herold, F., Zou, L. & Heath, M. (2024). A single bout of aerobic exercise does not alter inhibitory control preparatory set cortical hemodynamics: Evidence from the antisaccade task. *Brain and Cognition, 179*, 106182. https://doi.org/10.1016/j.bandc.2024.106182

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