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The Effect of a Single Bout of Sub-Symptom Threshold Aerobic Exercise on Executive Function During Early Sport-Related Concussion Recovery

Alma Rahimidarabad, *Western University*

Supervisor: Heath, Matthew, *The University of Western Ontario*

A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Neuroscience

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Abstract

Background: Impaired executive function (EF) is a primary sequela of sport-related concussion (SRC). Aerobic exercise below symptom exacerbation may improve post-SRC EF via increased cerebral blood flow (CBF). **Objectives:** To examine the impact of a single bout of sub-symptom threshold aerobic exercise on CBF and EF during SRC recovery. **Methods:** SRC participants (n = 16) and age- and sex-matched healthy controls (HC) completed 20-min of aerobic exercise at 80% of their heart rate threshold (HRt). Pre- and postexercise EF was assessed via antisaccades. Transcranial Doppler ultrasound (TCD) estimated exercise-mediated CBF changes. **Results:** SRC and HC participants showed an exercise-mediated increase in CBF ($p < .001$) and an equivalent postexercise reduction in antisaccade reaction times (RT; $p < .001$); however, CBF and RT changes were not reliably related ($p = 0.62$). SRC symptom scores did not increase immediately and were significantly reduced 24 h postexercise. **Conclusions:** Sub-symptom threshold aerobic exercise increases CBF and improves inhibitory control following an SRC.

Keywords

Mild Traumatic Brain Injury

Cognitive Performance

Oculomotor

Physical Activity

Transcranial Doppler Ultrasound

Summary for Lay Audience

Executive function (EF) is a collection of cognitive processes that support our ability to plan, focus attention, remember instructions, and complete multiple tasks. A brief bout of aerobic exercise improves EF, and this is – in part – attributed to an exercise-based increase in blood flow to the brain. In turn, persons who have experienced a sport-related concussion (SRC) show an impairment in EF and a decrease in blood flow to the brain. Notably, however, no work to date has examined whether a single bout of aerobic exercise improves EF in persons in the early stages of SRC recovery and whether the benefit is related to an increase in brain blood flow. Accordingly, my thesis investigated whether a single session of aerobic exercise, below a level that increases concussion symptoms, improves EF during early SRC recovery. I also explored if improvements in EF were related to increased blood flow to the brain during exercise. On an initial visit, 16 participants recovering from SRC performed an exercise test (via a stationary bike) to determine the heart rate threshold (HRt) at which their symptoms increased, or they voluntarily stopped due to exhaustion. On a separate day, SRC participants and healthy individuals of similar age and sex exercised on a stationary bike for 20 min at 80% of HRt. Blood flow to the brain was estimated by measuring its velocity in the middle cerebral artery. Participants completed an eye movement task (i.e., oculomotor assessment) before and after exercise that required them to “look away” from a target that appeared suddenly on a computer screen (i.e., antisaccade task). The antisaccade task was used because it provides a reliable basis to assess subtle changes in EF. SRC and healthy participants showed increased brain blood flow during exercise and demonstrated improved performance on the antisaccade task following exercise; however, the increase in brain blood flow and improvement in antisaccade performance were not related. As well, concussion symptoms in the SRC group did not increase immediately after exercise and were reduced 24 hours later. The results suggest that a personalized aerobic exercise program may help improve EF following an SRC.

Co-Authorship Statement

The author conducted the work in this master's thesis under the supervision and mentorship of Dr. Matthew Heath, Dr. Darryl Putzer, and Dr. Michael Robinson. Dr. Putzer and Dr. Robinson provided valued guidance during the conceptualization of this project and participant recruitment. Dr. Heath provided valued guidance during the conceptualization of this project, participant recruitment, data collection, data analyses, and manuscript writing. The author gratefully acknowledges the invaluable assistance provided by fellow lab members in participant recruitment and data collection for Chapter Two. Alma Rahimi served as the first author, with Azar Ayaz, Chloe Edgar, Gianna Jeyarjan, Lian Buwadi, and Dr. Matthew Heath contributing as co-authors in the manuscript version of the work.

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Chapter 1

1 Literature Review

The goal of my thesis was to investigate whether a single bout of sub-symptom threshold aerobic exercise improves executive function (EF) in individuals with a sport-related concussion (SRC) and determine if this potential benefit is associated with an exercise-mediated increase in cerebral blood flow (CBF). In developing my thesis document, I first begin with a literature review outlining (1) the neuropathophysiological mechanisms and behavioural and clinical consequences of an SRC (sections 1.1-1.4), (2) the core components of EF (section 1.5), (3) the behavioural and neurophysiological mechanisms supporting pro- and antisaccades (section 1.6), (4) the behavioural changes and neurophysiological mechanisms associated with a single bout postexercise EF benefit (sections 1.7-1.8), and (5) the role of exercise in SRC symptom resolution (section 1.9) and the evolution of SRC treatment to more active rehabilitation (section 1.10). Following this literature review, I present the manuscript version of my thesis document.

1.1 Sport-Related Concussions (SRC)

Sport-related concussion (SRC) is a significant concern, with approximately 1 in 450 Canadians aged 12 years and older reporting an SRC as their most significant injury associated with disability in the previous year (Gordon & Kuhle, 2022). The 2022 Amsterdam International Consensus Statement defines an SRC as “A traumatic brain injury caused by a direct blow to the head, neck or body resulting in an impulsive force being transmitted to the brain that occurs in sports and exercise-related activities. This initiates a neurotransmitter and metabolic cascade, with possible axonal injury, blood flow change and inflammation affecting the brain.” (Patricios et al., 2023, p. 697). The prevalence of SRCs increased nearly 2.5 times from 2005 to 2013, with higher rates among youth (12-19 years old) compared to adults (>19 years old) (Gordon & Kuhle, 2022). In Ontario, between 2008 and 2016, there was an average incidence of 1,153 concussions per 100,000 residents (Langer et al., 2020), and between 1990 and 2009, hockey accounted for the greatest number of SRCs (44.3%), followed by soccer (19.0%) and football (12.9%) (Cusimano et al., 2013).

SRC symptoms (e.g., headache, nausea, vertigo) typically resolve within 14 days for adults and 30 days for children and adolescents (McCrory et al., 2017). Persistent symptoms beyond this timeline are referred to as post-concussion syndrome (PCS). Risk factors for PCS include young age, biological sex (i.e., females at a higher risk for PCS), severity of early symptoms, history of repetitive concussions, and comorbidities such as migraine and psychiatric disorders (Broshek et al., 2015; Guskiewicz et al., 2003; Harmon et al., 2013; Makdissi et al., 2013; Reid et al., 2018). A recent study of 1,751 male and female collegiate athletes with SRC across various sports found that 80% of athletes recovered and returned to sports within 24 days (McAllister et al., 2023). Factors influencing recovery time include injury severity, pre-existing neurological or psychological conditions, and adherence to prescribed rest and recovery protocols (Harmon et al., 2019).

The long-term prognosis for athletes with a history of SRCs is a topic of ongoing research. Although studies suggest that athletes with multiple SRCs may be at increased risk for developing neurodegenerative conditions such as chronic traumatic encephalopathy (CTE) (McKee et al., 2013), the link between SRCs and these long-term outcomes remains unclear (Asken et al., 2016). Given the potential short-term and long-term consequences of SRCs, it is crucial for athletes, coaches, and healthcare professionals to be aware of signs and symptoms and follow appropriate protocols for diagnosis, management, and return to play (Harmon et al., 2019). This includes a gradual, stepwise approach to resuming physical and cognitive activities and ongoing monitoring for persistent or recurrent symptoms (McCrory et al., 2017; Patricios et al., 2023). Moreover, it is important that continuing research identify interventions that facilitate SRC symptom recovery and safe return to educational, occupational and sport-related activities.

1.2 Concussion Assessment

The assessment and management of SRCs have evolved into a comprehensive approach that considers symptom severity, duration, and cognitive, motor, and sensory functioning (McCrory et al., 2017; Patricios et al., 2023). Clinical assessments for SRCs can be broadly categorized as subjective or objective. Subjective assessments, such as symptom

checklists administered through questionnaires or standardized interviews, rely on the patient's report of their symptoms, but the consistency of this information has been debated. Current clinical SRC diagnosis relies on patient history and clinical assessment via a combination of patient-reported measures and clinical assessments (Kutcher & Giza, 2014). As well, emergent work is exploring objective biomarkers (Johnson et al., 2012; Slobounov et al., 2012) to diagnose and track SRC recovery.

In 2016, the Concussion in Sports Group created a sideline evaluation protocol involving a standardized diagnostic assessment following head trauma during competition or training (McCrory et al., 2013, 2017; Yengo-Kahn et al., 2016). The most frequently used diagnostic tool for detecting SRCs in real time is the Sport Concussion Assessment Tool (SCAT; Echemendia et al., 2017; McCrory et al., 2017; Patricios et al., 2023). The SCAT-5 provides a standardized method for evaluating the domains affected by SRCs, including immediate on-field assessment, symptom evaluation, cognitive screening, neurological screening, and delayed recall (Echemendia et al., 2017; Yengo-Kahn et al., 2016). The symptom evaluation sub-section assesses 22 symptoms on a 7-point Likert scale and has been shown to have clinical utility in identifying, diagnosing, and tracking recovery in patients (Dessy et al., 2017). Clinical symptoms and physical signs can be classified into four clusters: 1. Somatic: headache, pressure in the head, neck pain, nausea/vomiting, dizziness, blurred vision, balance problems, sensitivity to light, sensitivity to noise; 2. Cognitive: feeling slowed down, feeling "in a fog", "don't feel right", difficulty concentrating, difficulty remembering, confusion; 3. Arousal/sleep problems: fatigue/low energy, drowsiness, trouble falling asleep; and 4. Emotion: more emotional, irritability, sadness, nervous/anxious (Echemendia et al., 2017). Screening for symptoms such as neck stiffness, vomiting, double vision, motor or sensory deficits, and seizures distinguishes SRC from more severe conditions requiring immediate hospital care (McCrory et al., 2017). Baseline testing, while not essential, can improve diagnostic reliability if testing conditions are replicated (McCrory et al., 2017). The latest version of the SCAT—the SCAT-6—features updates such as an enhanced athlete demographic and red flags section, new coordination and ocular/motor screening, and a timed component in the months-in-reverse subtest. The symptom evaluation subsection remains unchanged (Echemendia et al., 2023).

1.3 Treatment and Rehabilitation

The complex nature of SRCs necessitates a multifaceted approach to treatment and rehabilitation, with the primary goal of promoting recovery while minimizing the risk of long-term sequelae and preventing further injury (Karton & Hoshizaki, 2018; McCrory et al., 2017; Patricios et al., 2023). Current evidence-based guidelines advise a comprehensive evaluation by a licensed healthcare provider and the immediate removal of the athlete from play (Harmon et al., 2019; McCrory et al., 2017; Schneider et al., 2017). To minimize academic and social disruptions during recovery, complete rest and isolation are generally not recommended, even for the first 24–48 hours. Instead, a period of relative rest is suggested to balance the need for recovery with the importance of maintaining some level of normal activity (Patricios et al., 2023). Following the initial period of relative rest, athletes are instructed to adhere to a graduated return to sport (RTS) protocol consisting of six stages: (1) symptom-limited activity, (2) Light and moderate aerobic exercise, (3) individual sport-specific exercise, (4) non-contact training drills, (5) full-contact practice, and (6) RTS (Patricios et al., 2023). Progression through each stage is guided by the athlete's symptoms, cognitive function, clinical examination findings, and the healthcare provider's clinical judgment. Each stage usually lasts at least 24 hours, and athletes can start symptom-limited activity within 24 hours post-injury. If symptom exacerbation exceeds mild levels (i.e., >2 points on a 0–10 scale), the athlete is instructed to repeat the current stage instead of returning to the previous one (Patricios et al., 2023).

Vestibular and oculomotor impairments are common following SRC and can contribute to prolonged symptoms and delayed recovery (Mucha et al., 2014). Vestibular rehabilitation exercises, such as gaze stabilization and balance training, and oculomotor rehabilitation, which targets impairments in eye movements and visual processing, have been shown to reduce symptoms and improve outcomes in athletes with SRC (Schneider et al., 2014, 2017, 2018; Thiagarajan & Ciuffreda, 2015). Neurocognitive testing, such as the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT™) battery, plays a crucial role in SRC management by assessing cognitive functions such as attention, memory, processing speed, and reaction time (RT) (Allen & Gfeller, 2011).

Unlike the SCAT-5, ImPACT™ does not include a physical examination component and is administered pre-season for baseline and post-injury for comparison and recovery tracking. ImPACT™ serves as a complementary tool to monitor neurocognitive recovery and guide RTS decisions (Allen & Gfeller, 2011). Psychological factors, such as anxiety and depression, can contribute to prolonged symptoms and delayed recovery following SRC (Broshek et al., 2015). Providing psychological support and education to athletes and their families is essential, and interventions such as cognitive-behavioural therapy (CBT) have been shown to reduce symptoms and improve outcomes in patients with persistent post-concussion symptoms (Potter et al., 2016). In summary, the treatment and rehabilitation of SRC require a comprehensive, individualized approach that addresses the physical, cognitive, and psychological aspects of the injury. By following evidence-based guidelines and incorporating vestibular, oculomotor, and neurocognitive rehabilitation strategies, healthcare providers can optimize recovery and minimize the risk of long-term sequelae in athletes with an SRC.

1.4 The Neurometabolic Cascade

SRCs involve the near-instantaneous transfer of kinetic energy (Shaw, 2002), resulting in the brain contacting the skull and imparting morphological alterations in neural and glial tissue (Meaney & Smith, 2011). Three possible kinematic responses occur when a force is applied to the head: (1) Centroidal contact involves linear acceleration without head rotation, producing minimal brain motion or deformation (Hardy et al., 2001); (2) Non-centroidal contact without linear acceleration involves rotational acceleration, creating diffuse axonal injury (Meaney et al., 1995) and (3). Non-centroidal contact with linear acceleration involves both linear and rotational acceleration, causing microscopic shearing and stretching of brain structures (Holbourn, 1943). The above kinematic responses can trigger a cascade of molecular events that disrupt cellular function.

Neuropathological changes linked to an SRC have been investigated using the fluid percussion model of brain injury in animals (DeFord et al., 2002; Giza & Hovda, 2001, 2014; Lindgren & Rinder, 1969). These findings have been extended to humans, resulting in a systematic model asserting that SRCs lead to a "neurometabolic cascade" characterized by bioenergetic challenges, cytoskeletal and axonal alterations,

neurotransmitter dysfunction, and chronic dysfunction and cell death (Giza & Hovda, 2014). The immediate cellular consequences of an SRC include an abrupt and indiscriminate cellular efflux of potassium and glutamate and an influx of calcium within the hippocampus, frontal, parietal, and occipital cortices (Katayama et al., 1990; Osteen et al., 2004). This is followed by increased activity of ionic-specific pumps (sodium-potassium) to restore cellular homeostasis, requiring increased ATP and glucose metabolism (glycolysis). The accumulation of lactate due to increased ion pump activity results in neuronal dysfunction induced by acidosis, membrane damage, altered blood-brain permeability, and cerebral edema (Kalimo, Rehncrona, & Söderfeldt, 1981a; Kalimo, Rehncrona, Söderfeldt, et al., 1981b). Hypermetabolism occurs with diminished cerebral blood flow (CBF), triggering an energy crisis. The rapid exhaustion of glucose (~30 min post-concussive impact) leads to a period of depressed metabolism (hypometabolism). During this stage, persistent increases in calcium are linked to mitochondrial dysfunction (Vagnozzi et al., 2008), diffuse axonal injury via microtubule breakdown (Tang-Schomer et al., 2012), and indirect triggering of cell death (Johnson et al., 2013). The rapid cellular changes associated with hypermetabolism occur within the first hour of impact, followed by a more persistent hypometabolic phase with reduced CBF and residual calcium levels maintained for up to 10 days post-concussive event (Giza & Hovda, 2014). These cellular changes contribute to functional, cognitive, motor, and sensory impairments (Giza & Hovda, 2014), which underscore the importance of developing effective treatment and rehabilitation strategies to manage SRCs and mitigate their short- and long-term effects on brain health and function.

1.5 Executive Function (EF)

Executive function (EF) encompasses processing and focusing on single and multiple stimuli, updating and monitoring working memory, and exerting high-level inhibitory control (Norman & Shallice, 1986). Extensive research using lesion studies and neuroimaging techniques has identified that EF is primarily supported by four prefrontal cortical structures: the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC), and anterior cingulate cortex (ACC) (Delgado et al., 2016; Royall et al., 2002). The DLPFC is responsible for attention,

planning, emotional regulation, sequencing, and effortful cognitive decisions (Forbes et al., 2014). In contrast, the OFC is involved in motivational behaviours related to eating, drinking, and abstract behavioural reinforcers such as pain, taste, and smell (Rolls, 2004). The vmPFC plays a crucial role in emotional regulation and suppressing negative affect by inhibiting the amygdala (Myers-Schulz & Koenigs, 2012). Last, the ACC is involved in conflict monitoring/resolution and modulating activity in downstream brain regions to adapt to incorrect behaviours (Bush et al., 2000). Importantly, the DLPFC is a critical neural substrate that supports the top-down processes underlying the core components of EF: inhibitory control, working memory, and cognitive flexibility (Diamond, 2013). Research has extensively investigated these core components using a variety of well-established tasks. The following section provides an overview of these tasks.

In terms of inhibitory control, the Stroop task (Stroop, 1935) is a well-established paradigm wherein participants are presented with words in which the semantic meaning of the word and the colour of the ink in which it is printed can be congruent (standard task: e.g., the word "RED" printed in red ink) or incongruent (non-standard task: e.g., the word "RED" printed in blue ink). The Stroop Interference Effect, characterized by increased RT and errors during incongruent trials, is attributed to the time-consuming EF demands of inhibiting a standard word-naming response in favour of a non-standard colour-naming response (MacLeod, 1992). Neuroimaging and lesion studies have highlighted the DLPFC's role in facilitating response inhibition during the Stroop task (Milham et al., 2002; Vendrell et al., 1995). For example, Vendrell et al. (1995) found that patients with prefrontal lesions had slower RTs and made more errors on incongruent Stroop trials compared to matched controls. Similarly, Milham et al.'s (2002) functional magnetic resonance imaging (fMRI) work showed that longer Stroop RTs associated with older adults were correlated to decreased task-based activity within the DLPFC.

In terms of working memory, the n-back task (Kirchner, 1958) requires participants to report whether a current stimulus matches an exemplar from "n" steps earlier in the sequence. The complexity of the n-back task is increased by manipulating the number of steps required to match the exemplar, and results have shown that this leads to an increase in RT and less accurate responses (Kirchner, 1958). Neuroimaging

and lesion studies have provided evidence for the role of DLPFC in supporting n-back task performance (Tsuchida & Fellows, 2009; Yeung et al., 2021). For example, Yeung et al. (2021) used functional near-infrared spectroscopy (fNIRS) to show task-dependent increases in DLPFC activity during a 3-back task. Moreover, Tsuchida and Fellows (2009) reported longer RTs and more errors in individuals with bilateral DLPFC lesions than controls, with differences increasing with task complexity. Taken altogether these findings demonstrate that DLPFC activity supports n-back performance (i.e., working memory), with increased involvement as a function of task demands.

In terms of cognitive flexibility, the Wisconsin Card Sorting Task (WCST) (Milner, 1963) requires participants to sort cards based on changing rules (e.g., sort by colour vs. sort by number). Performance is determined by completion time and the number of errors, with a higher number of errors reflecting diminished cognitive flexibility. Studies using neuroimaging and lesion approaches have provided evidence for the role of DLPFC in task-switching performance (Arnett et al., 1994; Li et al., 2006). For example, Li et al. (2006) used fMRI to investigate the neural correlates of the WCST and found that DLPFC activity increased with more frequent task-switching instructions. Additionally, Arnett et al. (1994) compared WCST performance between individuals with frontal lobe lesions, including DLPFC, and those with non-frontal lesions. Results showed that the frontal lobe lesion group took longer to complete the task and made more errors compared to the non-frontal lesion group.

Recent research highlights significant deficits in inhibitory control, working memory, and cognitive flexibility in individuals affected by mTBI, as evidenced by findings from Stroop, n-back, and Wisconsin Card Sorting Test (WCST) studies (Ord et al., 2010; Sicard et al., 2018; Xu et al., 2017). Xu et al. (2017) investigated inhibitory control and sustained attention deficits in individuals with mTBI, with an average of 28 months post-injury. Using a variant of the Stroop task and concurrent fMRI, the authors found that mTBI patients exhibited significantly more errors and longer response times for non-standard Stroop trials compared to healthy controls – a finding taken to evince difficulty in suppressing a standard response for a volitional non-standard one in the mTBI population. Similarly, Sicard et al. (2018) examined long-term cognitive outcomes

in athletes with a history of sport-related concussion (SRC) an average of 24 months post-injury using the n-back task. The study demonstrated that athletes with a history of concussion had significantly slower response times and lower accuracy compared to controls, particularly under higher cognitive load conditions (2-back), with deficits being more pronounced in female athletes. Such findings demonstrate persistent working memory impairments post-concussion. Moreover, Ord et al. (2010) explored cognitive flexibility deficits using the WCST among patients with varying severities of TBI at least one year post-injury. The study revealed that patients with moderate-to-severe TBI showed substantial impairments across several WCST indices, such as total errors, perseverative responses, and percentage of conceptual-level responses, compared to those with mild TBI. The study also highlighted the critical role of effort during testing, as poor effort exacerbated cognitive impairments. Collectively, these studies underscore the persistent and severity-dependent impact of TBI on EF, emphasizing the need for targeted rehabilitation strategies.

1.6 Antisaccades: An Oculomotor Assessment of EF

Traditional measures of EF function (i.e., Stroop, n-back, WCST) entail not only EF but also the non-EF components of language and colour processing (Stroop and WCST), perception-based shape identification (Flanker task and WCST), and numerical processing (n-back and WCST). In contrast, antisaccades (see details below) provide a hands- and language-free basis assessment tool for EF and the resolution to detect subtle EF deficits (Kaufman et al., 2012; Peltsch et al., 2014). In particular, antisaccades are a non-standard task requiring a goal-directed eye movement (i.e., saccade) mirror-symmetric to an exogenously presented target and are characterized by longer RTs (Hallett, 1978), increased directional errors (Fischer & Weber, 1992), reduced accuracy, and less accurate and more variable endpoints (Dafoe et al., 2007; Gillen & Heath, 2014) than their prosaccade counterparts (i.e., a pre-potent response to veridical target location). The behavioural 'costs' of antisaccades reflect the two-component EF process of (1) evoking a task-set to suppress a pre-potent response (i.e., response suppression) and (2) the 180° spatial transposition of a target's coordinates (vector inversion) (Munoz & Everling, 2004). Antisaccades have been frequently used to examine EF deficits in

individuals with prodromal Alzheimer's disease (Heath et al., 2016, 2017; Kaufman et al., 2012), frontal lobe lesions (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991), and schizophrenia (Ettinger et al., 2005; Tu et al., 2006).

To the best of my knowledge, only three studies to date have investigated antisaccades in healthy young adults with SRC. Johnson et al. (2015a; 2015b) examined behavioural data and fMRI measures of antisaccades in athletes with an SRC and age- and sex-matched controls at two distinct time points: initially (<7 days post-injury) and at follow-up (30 days post-injury). The concussed group exhibited longer antisaccade RTs and more directional errors at both assessments, with fMRI data showing hypo- and hyperactivity patterns across cortical and subcortical structures in the concussed group; however, follow-up fMRI findings did not significantly differ between groups. More recently, Webb et al. (2018) investigated athletes with an SRC and age- and sex-matched controls at 2-6 days post-injury (initial assessment) and 14-20 days after the initial assessment (follow-up assessment). At the initial assessment, the SRC group exhibited longer antisaccade RTs and more directional errors, whereas follow-up RTs were comparable between groups. Notably, however, the SRC group demonstrated more directional errors at the follow-up assessment even though they had been medically cleared for RTS. These findings suggest that antisaccades are sensitive to executive-related concussive deficits in both early and later stages of recovery. Moreover, the increased frequency of antisaccade directional errors reflects a failure to engage the high-level EF task-set required to evoke non-standard responses (Everling & Johnston, 2013). Although often considered purely inhibitory control tasks (Munoz & Everling, 2004), antisaccades also require working memory and cognitive flexibility to maintain the goal of performing an antisaccade instead of a prosaccade. Only deliberate practice can reduce antisaccade directional errors, as they represent a nonstandard task-set (Dyckman & McDowell, 2005). Thus, the increased directional errors in the SRC group, despite RTS clearance, suggest an oculomotor EF deficit (Everling & Johnston, 2013).

Ayala and Heath (2020) investigated whether oculomotor deficits associated with SRC result from impaired EF planning mechanisms or task-based increases in SRC symptomology. The authors employed SCAT-5, antisaccade performance, and

pupillometry metrics in individuals with SRC during the early (≤ 12 days post-SRC) and later (14-30 days post-SRC) stages of recovery. The early assessment revealed longer RTs, more directional error, and larger task-evoked pupil dilations (TEPD) in the SRC group compared to controls. At the later stage of assessment, RTs did not significantly differ between groups; however, the SRC group continued to demonstrate increased directional errors and TEPDs. Notably, Ayala and Heath observed that SCAT-5 symptom scores at early and later assessments did not vary from pre- to post-oculomotor assessments; that is, oculomotor assessment did not result in an increase in task-based symptom burden. Taken as a whole, these studies highlight the potential of the antisaccade to serve as a valuable tool for detecting SRC EF deficits and monitoring recovery and safe RTS.

1.7 Aerobic Exercise and EF

Chronic aerobic exercise (≥ 1 month) benefits EF (Colcombe & Kramer, 2003). Furthermore, previous research has reported that aerobic exercise provides greater benefits to EF compared to speeded responses, visuospatial tasks, or controlled processing tasks (Colcombe & Kramer, 2003). Recent meta-analyses have demonstrated that long-term exercise programs can improve all three components of EF in children (Amatriain-Fernández et al., 2021; Liu et al., 2020), young adults (Verburgh et al., 2014) and older adults (Chen et al., 2020). Moreover, Heath and colleagues have shown that 60-min sessions of moderate-to-heavy-intensity aerobic and resistance exercise performed thrice weekly for 6 months improved EF in older adults with an objective cognitive complaint (Heath et al., 2016) and those with prodromal Alzheimer's disease (Heath et al., 2017). In turn, fMRI work has shown that chronic exercise results in task-dependent changes in EF networks in healthy adults and those with cognitive and metabolic diseases. For example, Colcombe et al. (2004) found that participants who underwent a 6-month fitness training program showed improvements in EF and increased task-based activity in the middle and superior frontal gyri and superior parietal lobules, as well as reduced activation in the ACC compared to those in a stretching and toning group. In addition to the benefits of chronic exercise, a growing literature has shown that a single-bout exercise provides a transient (~ 60 min) EF benefit (for meta analyses see, Chang et

al., 2012; Etnier & Landers, 1995; Lambourne & Tomporowski, 2010; Ludyga et al., 2016). These meta-analyses have identified several primary moderators of the single-bout EF benefit, including the timing of EF assessment, exercise duration and intensity, and cardiorespiratory fitness.

When EF is assessed *during* longer bouts of exercise (>20 min), improvements are observed (Lambourne & Tomporowski, 2010), which may be driven by alterations in the brain's neurotransmitter systems (McMorris, 2021; McMorris et al., 2009). Specifically, the onset of physical activity triggers the synthesis of catecholamines within the sympathetic-adrenal-system axis, and epinephrine (Ep) and norepinephrine (NE) are released from the adrenal medulla as exercise duration increases (McMorris et al., 2009). The release of catecholamines during longer exercise bouts is thought to contribute to the improvement of information processing network efficiency, thus facilitating EF. When EF is assessed *following* a single bout of exercise, studies consistently demonstrate immediate and sustained benefits lasting up to 60 min postexercise (Heath & Shukla, 2020; Hung et al., 2013; Joyce et al., 2009; Shukla et al., 2020; Shukla & Heath, 2022). Although Chang et al.'s (2012) meta-analysis reported that a single-bout exercise improves EF immediately after exercise cessation for 11-20 min postexercise, more recent work has shown that the benefit arising from moderate intensity exercise can persist for up to 60-min (Hung et al., 2013; Johnson et al., 2016; Joyce et al., 2009; Shukla & Heath, 2022)

The duration of exercise has also been identified as a primary moderator of the postexercise EF benefit. Studies have found that even brief bouts of exercise can produce positive postexercise EF benefits. For example, Samani and Heath (2018) instructed participants to complete 10 min of moderate-to-heavy intensity aerobic exercise and included a non-exercise control condition. They assessed EF using the antisaccade task before and immediately after exercise and found that antisaccade RTs were shortened following 10 min of exercise but not after a rest period (see also Dirk et al., 2020; Heath et al., 2018; Heath & Shukla, 2020; Petrella et al., 2019; Shukla et al., 2020). The intensity of exercise is the third primary moderator of the postexercise EF benefit. Traditional active exercise manipulations require participants to voluntarily recruit

muscle groups to perform a specific movement, stimulating increased O₂ uptake, CO₂ production, ventilation, HR, blood pressure, venous return, cardiac output, and CBF in an intensity-dependent manner (Hoiland et al., 2019; Smith & Ainslie, 2017). These metabolic demands are met by alterations to sympathetic and parasympathetic nerve activity in response to a given intensity. To address the role of exercise intensity in the postexercise EF benefit, Heath et al. (2018) employed participant-specific measures of lactate threshold (LT). The calibration of exercise intensity based on LT is advantageous to others (e.g., $\dot{V}O_{2\text{peak}}/\text{max}$, maximum predicted heart rate) because it increases linearly with power output (Keir et al., 2018). Participants completed separate 10-min bouts of moderate (80% of LT), heavy (15% of the difference between LT and $\dot{V}O_{2\text{peak}}$), and very-heavy (15% of the difference between LT and $\dot{V}O_{2\text{peak}}$) intensity exercise, and EF was assessed before and after each session using the antisaccade task. The results from frequentist and Bayesian statistics demonstrated that EF improved by comparable magnitudes following each bout of exercise, indicating an intensity-independent effect.

Another proposed moderator of the single bout EF benefit is participant fitness level (Etnier et al., 2006). Dupuy et al. (2015) examined the association between cardiovascular fitness, EF, and prefrontal oxygenation in younger (18-28 years) and older (55-75 years) women. Cardiovascular fitness was assessed using a graded exercise test ($\dot{V}O_{2\text{max}}$), EF was evaluated using the Stroop task, and prefrontal oxygenation was measured using NIRS. In both age groups, higher cardiovascular fitness levels were associated with better Stroop task performance and increased prefrontal oxygenation, suggesting that fitness may enhance EF and oxygenation. Notably, however, the cardiovascular fitness hypothesis has been challenged by a more recent meta-analysis reporting that fitness level does not elicit a moderating effect on postexercise EF benefits (Ludyga et al., 2016). For example, Cui et al. (2020) separated participants into high- and low-fit groups before they were asked to complete a 30-min single bout of moderate-intensity (60-69% HR_{max}) aerobic exercise. fMRI data was recorded before and after exercise while participants completed the Stroop Interference task. Results indicated that fMRI activation during the Stroop task differed between groups such that the high-fit group demonstrated lower activation of the ACC and DLPFC following exercise. Notably, however, EF improved in the low-fit but not the high-fit group. These findings

indicate the equivocal nature of the moderating effect of participant fitness and that further investigation is required. In summary, aerobic exercise has been consistently shown to provide benefits to EF, both in chronic and single bouts of exercise.

1.8 Mechanisms Underlying a Postexercise EF Benefit

Research on chronic bouts of exercise has reported that hippocampal neurogenesis is a primary moderator associated with an EF benefit. For instance, van Praag et al. (2005) found that mice provided ad libitum access to exercise over 45 days exhibited improved memory and spatial learning (via the Morris water maze task) compared to sedentary controls and that enhanced memory performance was associated with hippocampal neurogenesis. In humans, Erickson et al. (2011) employed fMRI to evaluate hippocampal volume changes in older adults who completed a year-long exercise program (i.e., walking three times weekly at 60-75% of HR reserve) and an age-matched sedentary control group. At 12 months, results demonstrated that the exercise group exhibited a 2% increase in hippocampal volume, whereas over the same duration, a 1.4% reduction in hippocampal volume was observed in the sedentary controls. Therefore, compelling evidence suggests that chronic exercise promotes neurogenesis, prevents neural death, and supports improved EF. Although chronic exercise supports hippocampal neurogenesis, it is unlikely that such a change would support improved EF following a single bout of exercise (Ming & Song, 2011). As such, it has been proposed that a single bout of exercise improves EF via (1) increased biomolecule concentrations (e.g., brain-derived neurotrophic factor (BDNF) and catecholamines) (for review, see Knaepen et al., 2010; Zouhal et al., 2008) (2) increased resting state functional connectivity (Schmitt et al., 2019), and (3) increased CBF (Tari et al., 2020), that improve the efficiency and effectiveness of EF networks.

BDNF is a neuroprotective hormone that aids neuronal and glial survival and growth, modulates neurotransmitter levels/binding, and promotes neuronal plasticity (Bathina & Das, 2015). Hwang et al. (2016) investigated the impact that 20-min of high-intensity aerobic exercise (i.e., 85-90% of VO_{2max}) had on Stroop task performance and serum BDNF. Results showed the expected postexercise reduction in Stroop task RTs, which was linked to increased serum BDNF levels. In contrast, Ferris et al. (2007) had

participants perform the Stroop task prior to and following 30-min of aerobic exercise at 10% above the ventilatory threshold (i.e., the point when ventilation increases faster than the rate of VO_2 consumption demand). Results showed that although Stroop task performance improved postexercise, the magnitude of the benefit was not related to serum BDNF levels. Thus, BDNF's role in exerting a postexercise EF benefit remains equivocal. Indeed, it could be that individual differences in resting BDNF levels (Casey et al., 2009; Lommatzsch et al., 2005) and the genetic predisposition for BDNF release in response to exercise (Chen et al., 2008) contribute to these equivocal findings and support the need for further investigation.

Catecholamines are monoamine derivatives foundational to the production of epinephrine and norepinephrine and have been linked to improved EF. A meta-analysis by McMorris et al. (2011) states that an acute bout of moderate-intensity exercise (i.e., 50-75% $\text{VO}_{2\text{max}}$) improves working memory when compared to light- or heavy-intensity exercise and that this improvement is linked to increased catecholamine metabolite concentrations in the brain (i.e., increased norepinephrine and dopamine). In contrast, Ando et al. (2022) had participants complete a single bout of aerobic and resistance exercise for 30-min (53-58% of HR_{max}) and observed that a postexercise inhibitory control benefit was not linked to a pre- to postexercise change in catecholamine levels. Taken together, the literature does not demonstrate that changes in catecholamines are the sole mechanism by which postexercise EF is influenced.

Another proposed mechanism modulating postexercise EF benefits is increased functional connectivity in DLPFC networks (Verburgh et al., 2014). Functional connectivity measures how brain regions interact and is quantified via non-invasive imaging (i.e., fMRI). Schmitt et al. (2019) had participants complete 30-min single bouts of aerobic exercise at low- (i.e., 35% below lactate threshold) and high-intensities (i.e., 20% above lactate threshold) and showed improved connectivity within DLPFC regions for both intensities. In contrast, Voss et al. (2020) showed that a 20-min single bout of moderate-intensity exercise (i.e., 65% of HR_{max}) improved n-back task performance but did not alter functional connectivity with frontoparietal EF networks. Accordingly, it is

unclear whether enhanced functional connectivity is a primary moderator of a postexercise EF benefit.

An exercise-mediated increase in CBF is the fourth candidate mechanism related to a postexercise EF benefit. Exercise rapidly increases CO₂ (a by-product of cellular metabolism), HR, and systolic blood pressure, facilitating a systemic increase in perfusion (Smith & Ainslie, 2017). Byun et al. (2014) demonstrated that a 10-min single bout of light-intensity exercise (30% VO_{2peak}) improved Stroop task performance and was a result linked to increased cerebral oxygenation in the DLPFC as assessed via fNIRS. As well, Tari et al. (2020) investigated the relationship between CBF and EF by comparing separate conditions requiring: (1) 10-min of moderate- to heavy-intensity aerobic exercise (wattage determined via participant-specific incremental ramp test to volitional exhaustion) and (2) 10-min of hypercapnia (5% CO₂: higher-than-atmospheric concentration of CO₂). The hypercapnic condition was used because it increases CBF independent of the metabolic costs of exercise via chemoreceptor reflex-induced vasodilation (O'regan & Majcherczyk, 1982). Results showed that exercise and hypercapnic conditions provided an equivalent magnitude postexercise EF reduction in antisaccade RTs. In turn, disease states (e.g., cognitive decline) and age-related impairments to EF have been linked to cerebral hypoperfusion. For example, Bertsch et al. (2009) demonstrated that healthy young adults show increased resting-state CBF and improved cognitive performance compared to a healthy cohort of older adults (> 55 years of age). As such, the bidirectional relationship between CBF and EF suggests that CBF provides a strong candidate mechanism for a single-bout postexercise EF benefit.

1.9 Role of Exercise in Concussion Symptom Resolution

The traditional treatment for SRC is rest; however, recent research suggests that strict rest until all concussion-related symptoms have resolved is not the most effective approach for managing SRCs. Instead, relative rest, which involves engaging in activities of daily living and limiting screen time, is recommended for the first 1-2 days following the injury (Leddy et al., 2023). Convergent evidence indicates that carefully controlled exercise may be beneficial in promoting recovery and shortening the duration of symptoms associated with SRC (Kurowski et al., 2017; Leddy et al., 2013; Maerlender et

al., 2015; Schneider et al., 2017). For example, Maerlender et al. (2015) investigated the effects of immediate (median = 2 days) post-SRC exercise compared to a no-exercise control group in collegiate athletes. The study found that moderate physical activity did not significantly affect recovery time, and SRC symptoms following exercise were only present initially and dissipated over subsequent exercise sessions. These findings suggest that moderate physical activity is safe during the initial phase of SRC recovery. Kurowski et al. (2017) investigated the effects of a structured aerobic exercise program versus full-body stretching on recovery time and symptom burden in adolescents with mTBI experiencing persistent symptoms for 4-16 weeks. The aerobic exercise group demonstrated greater improvement in the Post-Concussion Symptom Inventory (PCSI) total score and the emotional and fatigue subscales compared to the stretching group, suggesting that structured aerobic exercise may be an effective treatment for adolescents with persistent post-mTBI symptoms. Leddy et al. (2013) compared fMRI activation patterns, exercise capacity, and symptoms in PCS patients and healthy controls at baseline and after approximately 12 weeks, during which they received either exercise treatment or placebo stretching. Exercise PCS patients showed similar fMRI activation to healthy controls after 12 weeks, whereas placebo-stretching PCS patients had significantly decreased resting-state cortical and subcortical activity. As well, Schneider et al.'s (2017) review of rest, treatment and rehabilitation techniques following SRC, reported that athletes in submaximal exercise groups reported fewer symptoms, exhibited shorter recovery times to baseline cognitive and balance scores, and demonstrated more efficient fMRI activation patterns compared to matched controls.

The 2022 Amsterdam Consensus Statement offers updated recommendations for post-SRC exercise, advising that individuals can resume light-intensity physical activities, such as walking or stationary cycling, within 24-48 hours after a concussion, provided that these activities do not exacerbate symptoms beyond mild levels. The statement encourages healthcare professionals to prescribe sub-symptom threshold aerobic exercise within 2-10 days post-injury, based on the individual's heart rate threshold (HRt) that does not exacerbate symptoms during the exercise test. Athletes may progress in both duration and intensity of physical activity or prescribed aerobic exercise, as long as any symptom exacerbation remains mild (no more than 2 points above pre-

exercise levels) and brief (<1 hour). The consensus statement emphasizes the effectiveness of prescribed sub-symptom threshold aerobic exercise within 2-10 days of concussion in reducing the incidence of persistent symptoms (lasting more than 1 month) and promoting recovery in athletes experiencing prolonged symptoms (Patricios et al., 2023). Taken altogether, controlled, sub-symptom threshold aerobic exercise may be a safe and effective intervention for promoting recovery and reducing symptom duration in individuals with SRC or mTBI.

1.10 The Buffalo Concussion Bike Test (BCBT)

The Buffalo Concussion Treadmill Test (BCTT) and the Buffalo Concussion Bike Test (BCBT) are graded aerobic exercise tests used to assess physiological recovery and guide RTS decisions following an SRC. Performed on a treadmill or stationary bike, respectively, these tests involve progressively increasing exercise intensity while monitoring HR and symptoms. The tests are terminated when the individual reaches their HRt, characterized by significant symptom exacerbation, or when they voluntarily stop due to exhaustion (Haider et al., 2019; Leddy et al., 2011). Several studies have investigated the safety, prognostic value, and effectiveness of the BCTT in managing SRC. Leddy et al. (2018) conducted a prospective, randomized, controlled trial to evaluate the safety and prognostic value of early provocative (i.e., eliciting symptoms) exercise testing using the BCTT in adolescents who had sustained a recent SRC (1-9 days post-injury). The study found that early provocative exercise testing using the BCTT is safe for recently concussed adolescents and has prognostic utility, with lower HRt being associated with a longer recovery time. In turn, Leddy et al. (2019) assessed the effectiveness of early sub-symptom threshold aerobic exercise in adolescents with a recent SRC diagnosis (<10 days postinjury) in a multicenter, prospective, randomized clinical trial. Participants were randomized to either an aerobic exercise group after completing the BCTT or a stretching placebo group. The study found that aerobic exercise safely accelerated recovery from SRC (i.e., improvements in symptoms and shorter return to activities of daily living) in adolescents compared to the placebo stretching intervention.

In addition to the prognostic value and effectiveness of BCTT, researchers have also investigated changes in exertion-related symptoms on the BCTT across different age groups. Rutschmann et al. (2021) conducted a retrospective study examining changes in exertion-related symptoms on the BCTT in adults (age ≥ 18 years; 8-129 days postinjury) and youth (age < 18 years; 9-101 days postinjury) following an SRC. The study found that exertion-related symptoms improved over time in both age groups, with adults having increased initial exertion-related symptoms compared to youth. Increased initial symptoms were associated with longer recovery times in both age groups. Furthermore, Leddy et al. (2019) reported that male adolescents with an SRC (1-9 days post-injury) who completed a 20-min bout of aerobic exercise at 80% of HRt on the BCTT recovered significantly faster compared to a standard care (i.e., rest) group when measuring the time from the initial clinic visit to recovery. Moreover, at the end of the 14-day symptom monitoring period, the exercise group had significantly fewer participants who remained symptomatic overall, and in the physical, cognitive, and sleep symptom clusters of the SCAT-3 symptom scale compared to the rest group. These findings support the use of the BCTT as a safe method for early assessment and as a useful prognostic tool for predicting recovery duration in acutely concussed adolescents.

As an alternative to the BCTT, the BCBT was developed to improve accessibility, safety, versatility, and precision in SRC symptom management and recovery (Haider et al., 2019; Janssen et al., 2022; Leddy, Haider, et al., 2018). Haider et al. (2019) conducted a study comparing the effectiveness of BCBT with BCTT in assessing exercise tolerance and HRt in adolescents following an SRC. The study found that the BCBT is a comparable alternative to the BCTT for evaluating exercise tolerance, with the HRt being equivalent between the two tests. This finding suggests that the BCBT is a valid physiological test for the clinical evaluation of exercise tolerance post-SRC. Furthermore, the study revealed that the BCBT could predict recovery time, with those exhibiting a lower symptom-limited threshold requiring a longer recovery period. These results highlight the potential of the BCBT as a valuable tool for assessing and predicting recovery in individuals with concussions, offering a more accessible and versatile alternative to the BCTT.

To my knowledge, no work has examined whether persons in the early stages of SRC recovery elicit a single bout postexercise EF benefit and whether such a benefit is linked to an exercise-mediated increase in CBF. Consequently, the purpose of my thesis was to investigate the impact of a single bout of sub-symptom aerobic exercise on EF among individuals with an SRC. Persons with an SRC 3-14 days post-injury underwent the BCBT to determine the HRt at which concussion symptoms worsened or voluntary exhaustion was reached. After a minimum of 24 hours, the SRC group performed a 20-min cycling exercise intervention at 80% of their HRt while their MCAv was measured via TCD to estimate CBF. The participants completed pro- and antisaccades before and immediately after the exercise to assess a putative postexercise EF benefit. The SRC group also completed the SCAT-5 symptom evaluation checklist at multiple time points to monitor changes in symptom severity mediated by the exercise and/or the oculomotor assessment. The performance of the SRC group was compared to that of an age- and sex-matched healthy control (HC) group who completed the same exercise, CBF, and EF assessments. In terms of research predictions, I expect that sub-symptom threshold aerobic exercise will increase CBF in SRC and HC groups, and I anticipate this increase to be associated with a decrease in antisaccade RTs following the exercise intervention. Furthermore, I hypothesize that the sub-symptom threshold exercise intervention will not elicit an exercise-related or task-based increase in SRC symptomology. Consequently, I predict that the exercise protocol employed will serve as a safe and effective means of inducing a transient EF improvement in individuals with SRC.

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Chapter 2

2 Study

2.1 Introduction

One in 450 Canadians aged 12 years and older report a sport-related concussion (SRC) as their most significant disability during the previous year (Gordon & Kuhle, 2022). An SRC is a mild traumatic brain injury resulting from an external force transmitted to the head or body that impairs the brain's neural and glial networks (Meaney & Smith, 2011; Menon et al., 2010). Following an SRC, there is a temporal window of a neurometabolic cascade that is independent of the resolution of subjective symptoms (Vagnozzi et al., 2008) and results in a reduction in cerebral blood flow (CBF) that typically persists 6-10 days post-injury (Giza & Hovda, 2014).

A primary behavioural sequela of concussion is an executive function (EF) impairment (Howell et al., 2013; Rabinowitz & Levin, 2014; Webb et al., 2018). EF includes the core components of inhibitory control, working memory, and cognitive flexibility (Diamond, 2013; Miyake et al., 2000) and is a cognitive construct essential for activities of daily living. Persons with an SRC exhibit deficits in each core component of EF throughout the early (i.e., <24 hours) and later stages (> 2 months) of recovery (for review see (Gallo et al., 2020) For example, Webb et al. (2018) assessed the inhibitory control component of EF in young adults via an oculomotor task (i.e., the antisaccade task) within 2–6 (i.e., initial assessment) and 14-20 (i.e., follow-up assessment) days post-SRC. Antisaccades require a goal-directed eye movement (i.e., saccade) mirror-symmetrical to an exogenously presented target and result in longer reaction times (RT) (Hallett, 1978), increased directional errors (Fischer & Weber, 1992) and less accurate and more variable endpoints (Dafoe et al., 2007; Gillen & Heath, 2014) than their prosaccade counterparts (i.e., saccade to veridical target location). Extensive neuroimaging in humans and electrophysiology and transient cooling studies in non-human primates have attributed the behavioural ‘costs’ of antisaccades to the time-consuming and EF demands of evoking a task-set to suppress a pre-potent response (i.e., inhibitory control) and invert a target’s coordinates (i.e., vector

inversion) (for review see, Munoz & Everling, 2004). At the initial assessment, Webb et al. reported that individuals with an SRC exhibited longer antisaccade RTs and increased directional errors (i.e., a prosaccade instead of an instructed antisaccade) compared to healthy age- and sex-matched control. In turn, at the follow-up assessment, individuals with an SRC continued to demonstrate increased directional errors in spite of medical clearance for a full return to play/practice (see also Johnson et al., 2015a; 2015b). In subsequent work, Ayala and Heath (2020) demonstrated that task-related symptom burden did not influence antisaccade performance deficits. Accordingly, our group (Ayala & Heath, 2020; Webb et al., 2018) and others (Johnson et al., 2015a; 2015b) proposed that the antisaccade task provides a valid tool for detecting SRC deficits related to inhibitory control efficiency (i.e., reaction time) and effectiveness (i.e., directional errors).

Physical and cognitive rest have historically been recommended to support SRC recovery (McCrorry et al., 2013); however, contemporary literature indicates that such an approach may result in an extended recovery period (Buckley et al., 2016; de Kruijk, 2002; DiFazio et al., 2016; Moor et al., 2015; Silverberg & Iverson, 2013; Thomas et al., 2015). For example, Leddy et al. (2019) found that male adolescents with an SRC (1-9 days post-injury) who performed a 20-min aerobic exercise at 80% of the heart rate associated with symptom exacerbation (HRt) on the BCTT recovered significantly faster than a standard care (i.e., rest) group. After 14 days of monitoring, the exercise group had significantly fewer participants with overall, physical, cognitive, and sleep symptoms on the SCAT-3 symptom scale compared to the rest group. What is more, a single bout of aerobic exercise in healthy adults provides a transient (i.e., ~60 min) EF benefit that has been linked to an exercise-mediated increase in CBF (Byun et al., 2014; Dirk et al., 2020; Heath & Shukla, 2020; Liu et al., 2023; Petrella et al., 2019; Samani & Heath, 2018; Shukla et al., 2020; Tari et al., 2020; Tari, Shirzad, Behboodpour, et al., 2021; Yanagisawa et al., 2010). For example, Shirzad et al. used transcranial Doppler ultrasound (TCD) to measure middle cerebral artery velocity (MCAv) and estimate CBF during a single 20-min bout of light-intensity aerobic exercise (via cycle ergometer) in healthy young adults. Results showed a pre- to postexercise reduction in antisaccade RTs, and this change was linked to the magnitude

of the exercise-mediated increase in MCAv (see also Bertsch et al., 2009; Byun et al., 2014). The link between an exercise-mediated increase in CBF and improved EF is thought to reflect improved oxygen and nutrient delivery to the brain, the elimination of cellular waste, and improved temperature regulation (Claassen et al., 2021) supporting EF network efficiency (Moore & Cao, 2008).

To our knowledge, however, no work has examined whether persons in the early stages of SRC recovery elicit a single bout postexercise EF benefit and whether such a benefit is linked to an exercise-mediated increase in CBF. Accordingly, we had persons with an SRC (3-14 days post-injury) complete the Buffalo Concussion Bike Test (BCBT) to identify participant-specific HRt associated with exercise-induced symptom exacerbation or voluntary exhaustion (Haider et al., 2019). The BCBT required volitional cycle ergometry at progressively increasing work rates based on a body weight to power/watt (W) conversion and was used here because it provides a safe tool for prescribing exercise intensity during SRC recovery. On a subsequent visit (> 24 h), the SRC group completed 20-min of cycle ergometry (80% of HRt) while a TCD-based measure of MCAv was concurrently recorded to estimate CBF. Pro- and antisaccades were assessed prior to (i.e., pre-exercise) and immediately following (i.e., postexercise) the exercise intervention. Pro- and antisaccades were used to determine whether the exercise intervention provided a general improvement in information processing (i.e., decrease in pro- and antisaccade RTs) or an EF-specific benefit (i.e., selective decrease in antisaccade RTs). The SRC group completed the Sport Concussion Assessment Tool (SCAT-5) symptom evaluation checklist: (1) before and after the exercise intervention, (2) prior to and after the oculomotor assessment, and (3) at 24-h follow-up to determine whether the exercise intervention and/or oculomotor assessment rendered an increase in symptom burden. The performance of the SRC group was contrasted to that of age- and sex-matched healthy controls (i.e., HC group) that completed the same exercise, CBF, and EF assessment.

In terms of research predictions, sub-symptom threshold aerobic exercise is hypothesized to increase CBF in SRC and HC groups, and it is predicted that the increase will be linked to a postexercise reduction in antisaccade RTs. It is further predicted that the sub-symptom threshold exercise intervention will not elicit an increase

in exercise- or task-based SRC symptomology. As such, the exercise protocol used here is predicted to provide a safe and effective tool for eliciting a postexercise EF benefit in persons with SRC.

2.2 Methods

2.2.1 Participants

Participants diagnosed with an SRC (i.e., 3-14 days post-injury) were recruited through the *Sport Medicine Concussion Care Program* at the Fowler-Kennedy Sport Medicine Clinic, London, Ontario. SRC diagnosis was based on the clinical judgment of a sports medicine physician and physician assistant. To be eligible for the study, participants had to meet the following criteria: (1) 15 years of age or older; (2) normal or corrected-to-normal vision; (3) ability to read and write in English; (4) no history or current diagnosis of learning, neurological, or neuropsychiatric disorders (except for concussion); (5) not taking medication that may affect metabolic, cardiac, respiratory, or hemodynamic responses to exercise; (6) no current illness impacting daily activities (e.g., flu-like symptoms, cold, difficulty breathing); (7) no self-reported history of neck or cervical injury; (8) no self-reported history of drug or alcohol dependence (excluding caffeine); (9) full score on the Physical Activity Readiness Questionnaire (PAR-Q) (Warburton et al., 2011); (10) score equal to or greater than 14 on the Godin Leisure-Time Exercise Questionnaire (GLETQ) (Godin, 2011); (11) medical clearance for exercise obtained from a sports medicine physician and physician assistant. The inclusion criteria for the healthy control (HC) group paralleled the SRC group with two exceptions: (1) HC participants did not report a lifetime history of concussion, and (2) were exempt from the requirement to obtain exercise medical clearance from a sports medicine physician.

A total of 25 individuals with an SRC were approached for recruitment over a five-month period (September 2023 to January 2024). Of that number, 17 consented; however, one SRC participant completed Visit 1 but did not return for Visit 2, and this participant indicated that “a lack of time” served as the barrier for completing Visit 2. Thus, the final sample for the SRC group involved 16 participants (5 female, age range: 18 - 24 years,

average = 20.5, SD = 1.7) and all were varsity athletes at the University of Western Ontario (see **Table 1** for details). In addition, 16 age- and biological-sex-matched individuals without a concussion (i.e., HC group) were recruited (5 female age range: 17 - 26 years, average = 20.7, SD = 2.4). Participants were instructed to avoid alcohol, recreational drugs and strenuous exercise 24 hours prior to each session. Participants were instructed to arrive at the lab in a rested and hydrated state (i.e., ~500 mL of water consumed 1 h before a study session) and to have consumed a standard breakfast and/or lunch. All study sessions occurred between 9:00 am and 1:00 pm. Prior to data collection, participants read a letter of information and signed a consent form approved by the Health Sciences Research Ethics Board, University of Western Ontario (Study ID: 122653), and the Research Quality and Compliance Board, Lawson Health Research Institute. This study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2.2 Experimental Overview

The SRC group completed two separate visits. Visit 1 occurred 4–13 days post-injury (8.3 days, SD = 3.3), whereas Visit 2 occurred 5–14 days post-injury (10.1 days, SD = 3.0), with a 1–4-day gap between Visit 1 and 2 (1.8 days, SD = 1.0). Visit 1 required that participants complete the BCBT (see details below) to determine the appropriate work rate for the exercise intervention administered at Visit 2. In contrast, the HC group completed a single visit. All participants completed a demographics questionnaire (i.e., age, sex, height, weight, concussion history, type of sport engaged in, and duration of sports participation).

2.2.3 Apparatus and Procedures

2.2.4 Exercise Protocol

At Visit 1, the SRC group completed the BCBT on a recumbent cycle ergometer (Life Fitness 95R Inspire Lifecycle Bike, Rosemont, IL, USA) with a pedal cadence of 60 rpm and workload adjustments every 2 mins based on a body weight to power/watt (W) conversion (see supplemental materials for Haider et al., 2019). Prior to the BCBT, baseline heart rate (HR) and blood pressure (BP) were measured using a Wahoo Fitness

TICKR X Heart Rate Monitor (Wahoo Fitness, Atlanta, Georgia, USA) and an Omron Blood Pressure Monitor (Omron Healthcare Inc., Lake Forrest, IL, USA), respectively. HR and BP were subsequently recorded at 2-min intervals throughout the BCBT. In addition, symptomatology and perceived physical exertion were evaluated every 2 min using a visual analogue scale (VAS) (0 = "Feeling Good", 10 = "Worst Ever Felt") and the Borg Rating of perceived exertion (RPE) (6 = "No Exertion", 20 = "Maximum Effort"), respectively. The BCBT was terminated if VAS symptoms were exacerbated by ≥ 3 points from pre-BCBT or the participant reached voluntary exhaustion (RPE ≥ 17). If neither criterion was met, participants exercised for up to 30 mins. Participants were encouraged to report symptoms and avoid "pushing through discomfort". Two experienced experimenters were present during the BCBT to monitor for signs of distress. The BCBT has been shown to provide a safe and reliable means to determine exercise intensity for individuals within 10 days of sustaining an SRC (Haider et al., 2019; Leddy et al., 2018).

At Visit 2 (i.e., <14 days post-injury), the SRC group engaged in a 20-min single bout of supervised sub-symptom threshold aerobic exercise as 80% of the HR achieved during the BCBT (i.e., HR_t at symptom exacerbation/self-reported voluntary exhaustion, or the 30-min mark). The protocol for Visit 2 included a 2-min baseline (i.e., participants sat on the recumbent bike without exercising), 2.5-min warm-up (50 W at 45 rpm), 15-min exercise intervention at 80% of participant-specific HR_t (60 rpm), and 2.5-min cool-down at (50 W, 45 rpm). HR, BP, RPE and VAS scores were collected at baseline and 2-min intervals throughout the exercise protocol, at the onset of the cool-down period and 2-min thereafter. Following the warm-up period, the workload was manually adjusted throughout the intervention until the target HR (i.e., 80% HR_t) was reached and reasonably maintained (85-100% range), and then step-transitioned to 50 W for the cool-down period. The HC group completed their exercise intervention in a single visit, cycling at 80% of the HR_t value determined by their age-and sex-matched SRC counterpart's BCBT performance.

2.2.5 Middle Cerebral Artery Velocity (MCAv)

During the exercise intervention, a TCD probe (Neurovision 500 M, Neurovision TOC2M; Multigon Industries, Elmsford, CA) was applied with an aqueous ultrasound gel (Aquasonic Clear, Parker Laboratories Inc., Fairfield, NJ) and affixed to the participants' left anterior temporal window using a headband. This setup facilitated MCAv recording at baseline (i.e., prior to the exercise intervention) and steady-state (i.e., the last 2 min of exercise at the prescribed intensity). The TCD protocol used here provides a valid proxy for a direct measure of CBF (i.e., Xenon 133 tracing; see Bishop et al., 1986).

2.2.6 Oculomotor Assessment

Prior to and following the exercise session, participants sat on a height-adjustable chair in front of a table with their head placed on a head-chin rest. A 30-inch liquid crystal display (LCD) monitor (60 Hz, 8 ms response rate, 1280×960 pixels; Dell 3007WFP, Round Rock, TX, USA) was located at the participants' midline and 550 mm from the front edge of the tabletop. The gaze position of the participants' left eye was sampled at 1000 Hz (EyeLink 1000 Plus; SR Research Ltd, Ottawa, ON, Canada). Two additional monitors, visible only to the experimenter, provided real-time point-of-gaze information, trial-by-trial saccade kinematics, and information related to the accuracy of the eye-tracking system. Stimulus presentation and data acquisition were controlled via MATLAB (R2018b, TheMathWorks, Natick, MA, USA) and the Psychophysics Toolbox extensions (v. 3.0; Brainard, 1997; Kleiner et al., 2007) including the EyeLink Toolbox (Cornelissen et al., 2002). Prior to data collection, a nine-point calibration of the viewing space was completed and was followed by an immediate verification to determine that no point in the calibration space contained more than 1° of error.

Visual stimuli were presented on a high-contrast black background (1 cd/m^2) and included a white fixation cross (1° : 132 cd/m^2) that appeared at participants' eye level and open white 'target' circles (2.7° : 132 cd/m^2) located 13.5° (i.e. proximal target) and 16.5° (i.e., distal target) to the left and right of fixation and in the same horizontal axis. The different target eccentricities were used to prevent participants from adopting stereotyped responses. A trial began with the appearance of the fixation cross for 1000

ms, after which it was extinguished, and a target appeared 200 ms thereafter (i.e., gap paradigm). Targets were presented for 50 ms, and the brief presentation served to equate pro- and antisaccades for the absence of extraretinal feedback regarding response accuracy. Target onset cued participants to pro- (i.e., saccade to veridical target location) or antisaccade (i.e., saccade mirror symmetrical to target location) "quickly and accurately". Pro- and antisaccades were performed in separate and randomly ordered blocks, and stimulus location (i.e., left and right at proximal and distal eccentricities) was pseudorandomized within a block of 60 trials. A block of pro- and antisaccade trials required approximately 10 min to complete. For both the exercise intervention and oculomotor assessments, the lights in the experimental suite were dimmed to an ambient light level of 39 cd/m².

Once participants entered the lab, they sat for 20 min and chatted with the experimenter regarding the upcoming protocol. This “rest” period ensured that HR, BP, and MCA_v were not elevated due to the locomotor demands of arriving at the lab. The last two minutes of this period were used to record physiological baseline. After the 20-min “rest”, the pre-exercise oculomotor assessment was initiated and was followed immediately by the exercise intervention. The postexercise oculomotor assessment was initiated 5 min after cessation of the exercise intervention and occurred only if participants' HR and BP had returned to baseline levels (see **Figure 1** for a schematic of the timing of experimental events).

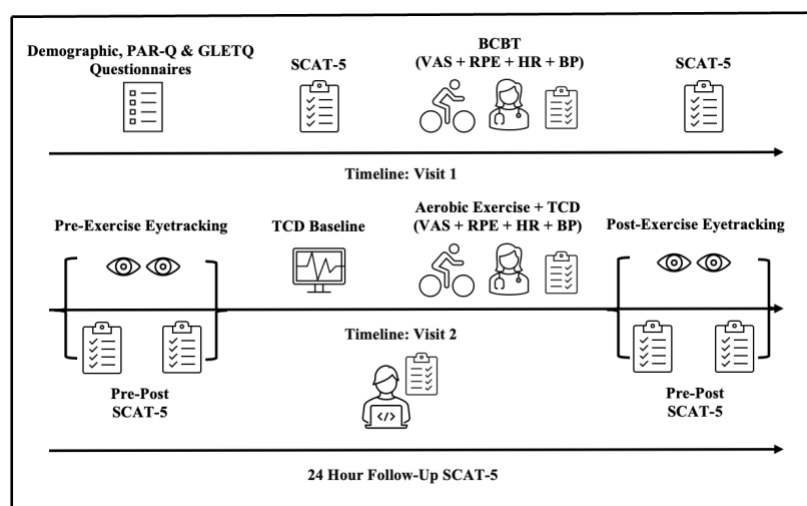


Figure 1: Schematic of the timeline (left to right) of experimental events associated with Visit 1 (top panel: sport-related concussion (SRC) group only), Visit 2 (middle panel: SRC and healthy control (HC) groups) and 24-h follow-up (bottom panel SRC group only).

2.2.7 Symptom Assessment

The Sport Concussion Assessment Tool (SCAT-5) symptom evaluation checklist assessed the frequency (i.e., number of separate symptoms) and severity of 22 symptoms on a scale from 0 (i.e., none) to 6 (i.e., severe) (total symptom severity = 132) (Echemendia et al., 2017; McCrory et al., 2017). The administration of the symptom checklist required approximately 5 min. The SRC group completed the checklist: (1) before and after the BCBT (i.e., Visit 1), (2) before and after the exercise intervention and each oculomotor assessment (Visit 2), and (3) at 24 hours after the exercise intervention (i.e., 24-h follow-up) (see **Figure 1**).

2.2.8 Data Reduction

TCD data affected by signal aliasing or loss (i.e., sudden head movement) were excluded from the analysis (Terslev et al., 2017) and peak systolic MCAv was examined because it provides a reliable proxy for an exercise-mediated change in CBF (Clyde et al., 1996; Duschek et al., 2018; Rosengarten & Kaps, 2002; Tari et al., 2020). Mean

values for HR and MCAv were determined from the last two minutes of rest (i.e., baseline) and the last two minutes of the exercise intervention (i.e., steady-state). For the oculomotor task, gaze position data were filtered offline using 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 compute instantaneous velocities and accelerations. Saccade onset was determined when velocity and acceleration exceeded $30^\circ/\text{s}$ and $8000^\circ/\text{s}^2$, respectively. Saccade offset was determined when velocity fell below $30^\circ/\text{s}$ for 40 ms. Trials involving a signal loss (e.g., an eyeblink) were removed, as were anticipatory responses (RTs < 50 ms) (Wenban-Smith & Findlay, 1991) and RTs > 2.5 standard deviations from a participant- and task-specific mean (Gillen & Heath, 2014). Less than 11% of trials for any participant were removed due to these criteria. Trials with a directional error (e.g., a prosaccade instead of an instructed antisaccade or *vice versa*) were omitted from the analysis of RT because they are mediated via planning mechanisms distinct from their directionally correct counterparts (DeSimone et al., 2014).

2.2.9 Dependent Variables and Statistical Analyses

MCAv and HR data were examined via 2 (group: SRC, HC) by 2 (time: baseline, steady-state) split-plot ANOVAs. For the oculomotor assessment, dependent variables included RT (i.e., time from target onset to saccade onset), saccade duration (i.e., time from saccade onset to saccade offset), saccade gain variability (i.e., within-participant standard deviation of saccade amplitude/veridical target location), and the percentage of directional errors. Oculomotor dependent variables were analyzed via 2 (group: SRC, HC) by 2 (time: pre-, postexercise) by 2 (task: pro-, antisaccade) split-plot ANOVAs. RPE data were examined via 2 (group: SRC, HC) by 11 (time: warm-up, 2-min iterative time points during the exercise, and at both cool-down time points) split-plot ANOVA (see **Figure 1** for a schematic of the timeline). SCAT-5 symptom frequency and severity (SRC group only) were contrasted via planned comparison paired-sample t-tests (i.e., pre-BCBT vs. post-oculomotor task, pre-BCBT vs. 24-hour follow-up). Data were evaluated for violations of sphericity (Mauchly's $p > 0.05$) and where appropriate, Huynh-Feldt corrected degrees of freedom are reported. Significance was determined

based on $\alpha = 0.05$, and significant interactions were decomposed via simple effects or power polynomials (i.e., trend analysis) (Pedhazur, 1997). Pearson's r was used to examine MCAv and HR baseline to steady-state changes and associated pre- to postexercise differences in antisaccade RTs.

2.3 Results

2.3.1 Demographic Characteristics

Table 1 provides SRC and HC group demographic and health characteristics, with the SRC group reporting an average of two concussions ($SD = 1.1$). Independent samples t -tests revealed no reliable between-group difference in height ($t(30) = 1.06$, $p = 0.30$, $d_z = 0.38$), systolic and diastolic BP at baseline ($t(30) = 0.53$ and 0.77 , $ps < 0.60$, $d_z = 0.19$ and 0.27), nor systolic and diastolic BP postexercise ($t(30) = -0.15$ and 0.81 , $ps < 0.88$, $d_z = -0.06$ and 0.29). Furthermore, no reliable between-group difference was observed in HR at baseline or postexercise ($t(30) = 0.21$ and -1.48 , $ps > 0.15$, $d_z = 0.07$ and -0.52). In contrast, the SRC group had a greater body weight and GLETQ score, exercised at a more intense workload, and maintained a higher steady-state HR than the HC group ($t(30) = 2.39$, 2.74 , 2.48 , and 2.18 , $ps < 0.04$, $d_z = 0.85$, 0.97 , 0.88 , and 0.77). No adverse events were observed. One SRC participant completed Visit 1 but did not return for Visit 2, and this participant indicated that “a lack of time” served as the barrier for completing Visit 2. A new participant was recruited, and all SRC participants ($n = 16$) ultimately achieved a 100% follow-up completion rate (i.e., Visits 1 and 2 and 24-hour symptomology follow-up).

Table 1

Participant demographics and health information

Variable	Mean (SD)	
	SRC (n = 16)	HC (n = 16)
Age	20.5 (1.7)	20.9 (2.4)
Sex, n (% Female)	5.0 (31.3)	5.0 (31.3)

BMI	26.5 (5.5)	22.5 (2.5)
Height (cm)	177.2 (6.6)	174.6 (7.0)
Weight (kg)	84.1 (22.9)	68.9 (11.3)
HR_{Baseline} (bpm)	73.1 (11.4)	72.3 (12.2)
HR_{Steady-State} (bpm)	127.2 (17.9)	114.6 (14.6)
HR_{Post} (bpm)	83.1 (11.9)	90.9 (17.6)
SBP/DBP_{Rest} (mmHg)	117.3 (9.2) / 76.5 (7.9)	115.8 (7.5) / 74.3 (8.1)
SBP/DBP_{Post} (mmHg)	121.4 (9.9) / 77.4 (8.3)	121.9 (8.4) / 74.6 (10.8)
HR_t (bpm)	120.0 (18.2)	120.0 (18.2)
Workload (W)	93.3 (33.2)	69.5 (19.2)
GLETQ Total Score	84.4 (18.2)	65.1 (21.5)
VAS Score Visit 1	1.6 (1.1)	-
RPE Score Visit 1	11.1 (3.5)	-
VAS Score Visit 2	0.5 (0.7)	0.0 (0.0)
RPE Score Visit 2	9.2 (2.5)	9.3 (2.3)
Concussion History	2 (1.1)	-
Days Since Injury to Visit 1	8.3 (3.3)	-
Days Since Injury to Visit 2	10.1 (3.0)	-
Days Since Visit 1 to Visit 2	1.8 (1.0)	-

Note. SRC = sport-related concussion; HC = healthy control; BMI = body mass index; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR_t = heartrate threshold; GLETQ = Godin Leisure-Time Exercise Questionnaire; VAS = visual analogue scale; RPE = rating of perceived exertion

2.3.2 Heart Rate (HR) and MCAv

HR and MCAv produced main effects of **time**, $F_s(1, 30) = 290.08$ and 262.99 for HR and MCAv, respectively, $p_s < .001$, $\eta_p^2 = 0.91$ and 0.90 , and **group** by **time** interactions, $F_s(1, 30) = 4.26$ and 6.32 , $p_s = .048$ and $.018$, $\eta_p^2 = 0.12$ and 0.17 . The main panel of **Figure 2** shows participant-specific and group mean HR and MCAv for SRC and HC groups and demonstrates that values for both variables increased from baseline to steady-state (all $t_s(31) > 16.20$ and 14.98 , $p_s < .001$, $d_z > 2.65$); that is, both variables produced the expected impact of the exercise intervention. To uncover the nature of the interaction, we computed HR and MCAv difference scores (steady-state minus baseline) and found that values were greater for the SRC (HR: 44 bpm, $SD = 17$; MCAv: 38 cm/s, $SD = 13$) compared to the HC (HR: 42 bpm, $SD = 14$; MCAv: 28 cm/s, $SD = 10$) group ($t_s(30) = 2.06$ and 2.51 , $p_s = .04$ and $.02$, $d_z = 0.73$ and 0.89).

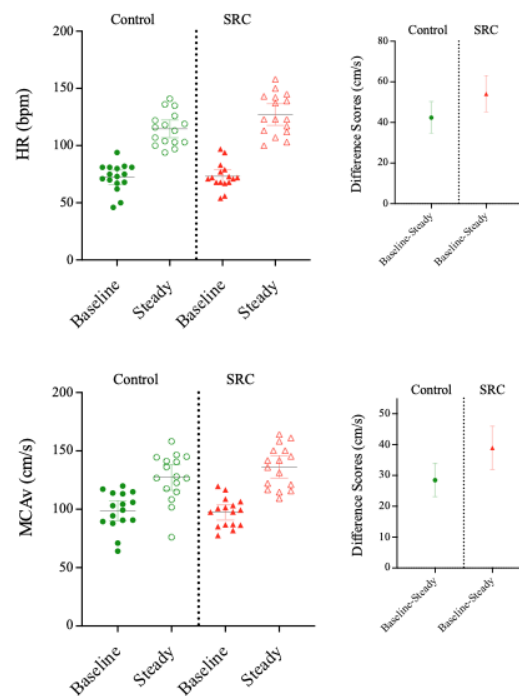


Figure 2: The left panels show participant-specific and group mean (and associated 95% confidence interval) heart rate (HR: top panel) and peak systolic middle cerebral artery velocity (MCAv: bottom panel) at baseline and steady-state for sport-related concussion

(SRC) and healthy control (HC) groups. The smaller offset panels show the SRC and HC HR and MCAv group mean difference scores (steady-state minus baseline) and 95% confidence interval. The absence of overlap between the error bar and zero indicates a reliable difference inclusive of a test of the null hypothesis.

2.3.3 Oculomotor Performance

RT yielded main effects for **time**, $F(1, 30) = 39.34$, $p < .001$, $\eta_p^2 = 0.57$, **task**, $F(1, 30) = 114.24$, $p < .001$, $\eta_p^2 = 0.79$, and **group**, $F(1, 30) = 5.03$, $p = .03$, $\eta_p^2 = 0.14$, as well as interactions involving **time** by **task**, $F(1, 30) = 13.89$, $p < .001$, $\eta_p^2 = 0.32$, **time** by **group**, $F(1, 30) = 5.59$, $p = .03$, $\eta_p^2 = 0.16$, and **group** by **time** by **task**, $F(1, 30) = 4.21$, $p = .04$, $\eta_p^2 = 0.12$. In general, prosaccade RTs (235 ms, $SD = 35$) were shorter than antisaccades (292 ms, $SD = 38$). In decomposing the highest-order interaction, pre- and postexercise prosaccade RTs did not vary between SRC and HC groups ($t(30) = -1.17$ and -1.21 , $ps > 0.23$, $d_z = -0.41$ and -0.43). In turn, pre-exercise antisaccades RTs were longer for the SRC than the HC group ($t(30) = -3.56$, $p < .001$, $d_z = -1.26$); however, postexercise RTs did not differ between groups ($t(30) = -1.04$, $p = .31$, $d_z = -0.37$) (**Figure 3**). Moreover, given this work's primary objective, we computed pro- and antisaccade RT difference scores (postexercise minus pre-exercise) separately for SRC and HC groups and examined via single-sample t-statistics. Results showed prosaccade values for SRC and HC groups did not reliably differ from zero ($t(15) = 1.27$ and 1.08 , $ps > .22$, $d_z = 0.32$ and 0.27), whereas antisaccade values for SRC and HC groups were less than zero ($t(15) = 6.05$ and 4.37 , $ps < .001$, $d_z = 1.51$ and 1.09). In other words, antisaccade – but not prosaccade – RTs for SRC and HC groups decreased from pre- to postexercise.

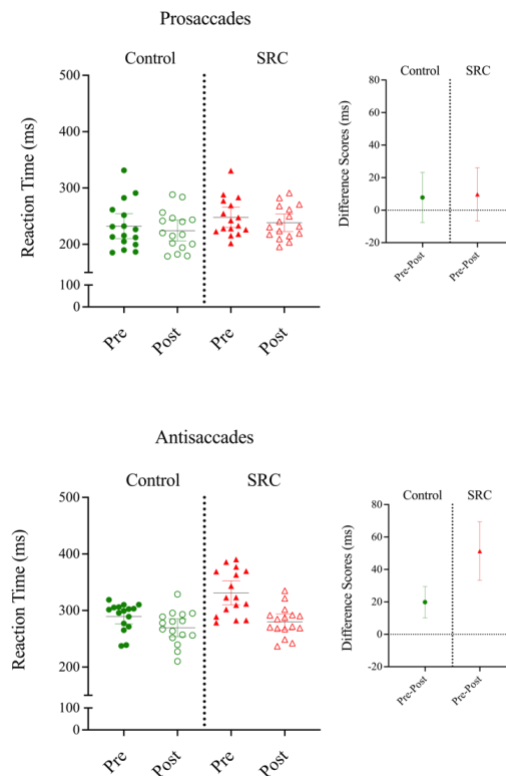


Figure 3: The left panels show participant-specific and group mean reaction times (RT) for pro- (top panel) and antisaccades (bottom panel) at pre- and postexercise assessments for sport-related concussion (SRC) and healthy control (HC) groups. The smaller offset panels show SRC and HC group mean RT difference scores (post minus pre-exercise) and 95% confidence intervals. The horizontal dashed lines for these panels represent zero, and the absence of overlap between the error bar and zero indicates a reliable difference inclusive of a test of the null hypothesis.

2.3.4 Directional Errors

Directional errors produced main effects for **task**, $F(1, 30) = 59.77$, $p < .001$, $\eta_p^2 = 0.67$, and **group**, $F(1, 30) = 10.93$, $p = .002$, $\eta_p^2 = 0.27$. **Figure 4** shows that prosaccades (3%, $SD = 2$) produced fewer errors than antisaccades (8%, $SD = 5$), and the HC group (6%, $SD = 4$) produced fewer errors than the SRC group (11%, $SD = 6$). We did not observe a main effect for **time**, $F(1, 30) = 0.40$, $p = .53$, $\eta_p^2 = 0.01$, nor **group** by **time** nor **group** by **time** by **task** interactions, $F(1, 30) < 0.01$, $p > .92$, $\eta_p^2 < .001$ – results indicating the

exercise intervention did not modulate the percentage of directional errors for SRC or HC groups.

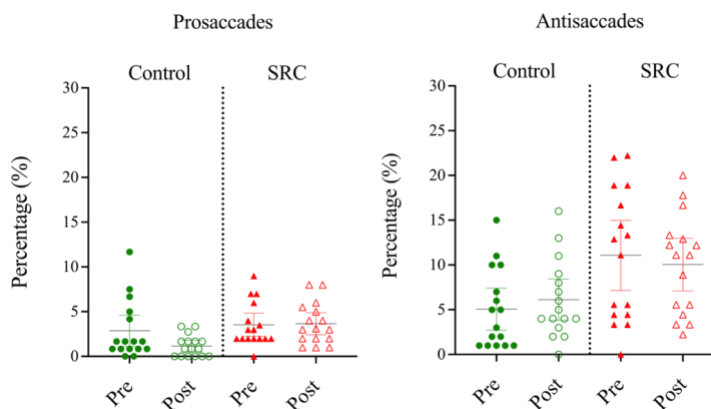


Figure 4: Participant-specific and group mean (with 95% between-participant confidence intervals) percentage of directional errors for sport-related concussion (SRC) and healthy controls (HC) at pre- and postexercise.

2.3.5 Saccade Duration and Gain Variability

Saccade duration and gain variability yielded main effects for **task**, $F_s(1, 30) > 56.07$, $p_s < .001$, all $\eta_p^2 > 0.65$), such that prosaccades produced shorter durations (57 ms, $SD = 9$) and less variable endpoints (0.12, $SD = 0.04$) than antisaccades (saccade duration: 61 ms, $SD = 10$; gain variability: 0.23, $SD = 0.05$). As well, neither the main effect of **group** nor any higher-order interaction involving **group** was significant, $F_s(1, 30) < 1.36$, $p_s > .25$, all $\eta_p^2 < 0.04$.

2.3.6 Correlation Between Physiological and Performance Variables

A Pearson r correlation involving pooled HC and SRC MCAv difference scores (steady-state minus baseline) and antisaccade RT difference scores indicated that the variables were not reliably related ($r(31) = -0.09$, $p = .59$). As well, pooled HR difference scores were not reliably related to antisaccade RT difference scores ($r(31) = -0.27$, $p = .13$). In turn, pooled MCAv and HR difference scores were reliably related to steady-state

exercise workload ($r(31) = 0.55$ and 0.36 , $p_s < 0.01$ and 0.04); that is, MCAv and HR increased with prescribed exercise intensity.

2.3.7 Perceived Exertion and Symptomology

Recall the BCBT (i.e., Visit 1) was completed by the SRC group (but not the HC group), and perceived exertion was measured via a visual analogue scale (VAS) at 2-min increments during the test. Notably, no participant in the SRC group reported a VAS score ≥ 3 above their self-reported baseline, with 15/16 participants completing the BCBT to their maximal permitted exertion (RPE = 17) and one participant completing the entire protocol (i.e., 30 min) without attaining their exertion threshold (**Table 2**). For the exercise intervention (i.e., Visit 2), RPE scores for SRC and HC groups were collected every 2 min, and these data were examined via 2 (group: HC, SRC) by 11 (time: warm-up, 2-min iterative time points during the exercise, and at both cool-down time points) split-plot ANOVA. Results produced a main effect for **time**, $F(3.0, 97.1) = 42.34$, $p < .001$, $\eta_p^2 = 0.57$, such that values increased linearly from baseline throughout the exercise intervention and then decreased during the first and second cool-down time points (i.e., significant quadratic polynomial: $F(1,30) = 83.77$, $p < .001$, $\eta_p^2 = 0.72$). Notably, RPE did not produce a reliable effect for **group**, $F(1, 30) = 0.12$, $p = .91$, $\eta_p^2 < 0.1$, nor a **group** by **time** interaction, $F(3.0, 85.6) = 1.08$, $p = .37$, $\eta_p^2 = 0.03$. Accordingly, perceived exercise intensity was comparable between SRC and HC groups (**Figure 5**).

SCAT-5 total symptom frequency and severity (SRC group only) evaluated at pre-BCBT (Visit 1) were contrasted to values following the postexercise oculomotor assessment (i.e., end of Visit 2) and at the 24-hour follow-up (**Table 3**). Results showed that the total frequency and severity of symptoms did not reliably differ between pre-BCBT and the end of Visit 2 ($t_s(15) = 1.93$ and 1.84 for frequency and severity, respectively, $p_s > .07$, $d_z = 0.48$ and 0.46), whereas at the 24-h follow-up, total symptom frequency and severity were less than the pre-BCBT assessment ($t_s(15) = 2.87$ and 2.56 , $p_s < .01$, $d_z = 0.72$ and 0.64). As well, SCAT-5 symptom frequency and severity did not

reliably differ between pre- and postexercise oculomotor assessments ($t_s(15) = 0.52$ and 0.13 , $p_s > .61$, $d_z = 0.13$ and 0.03).

Table 2

Visual analogue scale and Borg Rating of Perceived Exertion group means and ranges for the sport-related concussion group at incremental time points during the 30-minute Buffalo Concussion Bike Test

Time	Participants (n)	VAS Mean	VAS Range	RPE Mean	RPE Range
0	16	0.8	0-2	6.3	6-8
2	16	0.8	0-2	7.2	6-9
4	16	0.9	0-3	7.8	7-10
6	16	1.1	0-3	8.4	7-10
8	16	1.4	0-3	9.6	8-13
10	16	1.6	1-4	10.5	8-14
12	16	1.9	1-4	11.9	9-15
14	16	2.2	1-4	12.8	9-16
16	16	2.1	1-4	14.2	10-17
18	13	2.2	1-4	14.5	11-17
20	11	2.2	1-3	15.2	12-17
22	8	2.0	1-3	15.5	13-17
24	5	2.2	2-3	15.6	14-17
26	3	2.0	2-2	16.0	15-17
28	2	2.0	2-2	16.5	16-17
30	1	2.0	-	17.0	-

Note. Not all participants completed the BCBT for the same duration, and as a result, the number of participants associated with the group mean and range data decreases after the 16-min timepoint.

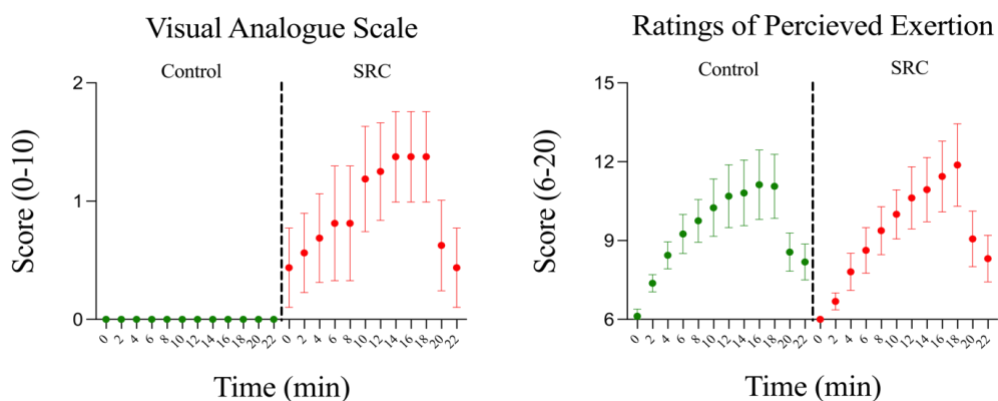


Figure 5: The left and right panels show visual analogue scale (VAS) and Borg Rating of Perceived Exertion (RPE) scores, respectively, for the sport-related concussion (SRC) and healthy controls (HC) during the 20-minute aerobic exercise intervention (i.e., Visit 2). The timeline for the aerobic exercise session includes baseline (minute 0), warm-up (minutes 1-3), exercise at prescribed intensity (minutes 4-19), and cool-down (minutes 20-22).

Table 3

SCAT-5 Symptom frequency and severity in sport-related concussion participants

Variable M (SD)	Values	
	Symptom Frequency	Symptom Severity
Pre-BCBT	8.9 (6.8)	16.1 (15.9)
Post-BCBT	7.5 (5.6)	12.9 (13.8)
Pre-Oculomotor Task	6.0 (5.4)	8.9 (10.3)
Post-Oculomotor Task	5.6 (5.0)	8.8 (11.5)
Pre-Exercise	5.6 (5.7)	8.9 (11.2)
Postexercise	5.0 (5.5)	7.3 (9.3)
24-h Follow-up	4.4 (4.9)	6.0 (7.7)

Note. SCAT-5 = Sport Concussion Assessment Tool 5th edition; BCBT = Buffalo Concussion Bike Test

2.4 Discussion

The current study investigated the effects of a single bout of sub-symptom threshold aerobic exercise on CBF and EF in individuals with an SRC. In the sections below, we first outline the HR and cerebral hemodynamic response to exercise before discussing pre-to-postexercise changes in EF across SRC and HC groups. Subsequently, we discuss whether the exercise protocol influenced SRC symptom burden.

2.4.1 SRC and HC Groups Exhibit an Exercise-Mediated Increase in Cerebral Blood Flow (CBF)

SRC and HC groups exhibited a baseline to steady-state increase in HR and MCAv. These well-documented findings reflect exercise-mediated changes in central command, biomolecule levels, serum pH, arterial and venous CO₂ and oxidative phosphorylation that increase HR and produce an associated increase in CBF (Querido & Sheel, 2007). Notably, the SRC group demonstrated a larger baseline to steady-state increase in HR and MCAv, and this finding is attributed to the former group exercising at an increased workload. In particular, the weight of individuals in the SRC group was greater than the HC group, and given that BCBT-prescribed power outputs are based on participant weight (Haider et al., 2019), the larger increase in HR and MCAv is expected. In further support of this view, HR and MCAv were reliably related to exercise intensity and thus evince a dose-dependent relationship accounting for the between-groups difference (Smith & Ainslie, 2017).

A neurophysiological consequence ascribed to an SRC is a CBF reduction within 24 hours post-injury that persists for 6-10 days (i.e., the neurometabolic cascade; see, Giza & Hovda, 2014). In the present study, SRC and HC groups showed equivalent baseline MCAv, and is a finding that may reflect that the exercise intervention (i.e., Visit 2) for the former group occurred between 5-14 days post-injury (average = 10.1 days; SD = 3.0); that is, the exercise-intervention occurred during a post-injury period beyond the timeframe of the neurometabolic cascade CBF reduction. In line with this view, MRI-based arterial spin labelling has shown that individuals more than 6 days post-SRC

exhibit baseline CBF levels similar to healthy controls (Churchill et al., 2020; Militana et al., 2016). Moreover, that the present work did not observe a group difference in baseline CBF is advantageous because it provides the basis to directly examine the degree to which exercise-mediated changes in CBF impact the magnitude of putative postexercise EF benefits.

2.4.2 Pro- and Antisaccades Exhibit Distinct Performance Metrics

Prosaccades produced shorter RTs and saccade durations, decreased directional errors, and less variable endpoints than antisaccades. The RT findings reflect that prosaccade planning is mediated via direct retinotopic maps in the superior colliculus that operate with minimal top-down EF (Wurtz & Albano, 1980). In turn, the antisaccade planning times reflect the time-consuming EF demands of inhibitory control and vector inversion (Munoz & Everling, 2004), and the increased frequency of antisaccade directional errors is related to a failure to evoke the high-level EF task-set supporting a non-standard response (Everling & Johnston, 2013). Further, that antisaccades were associated with longer saccade durations and greater endpoint variability reflects visuomotor uncertainty arising from decoupling the normally direct spatial relations between stimulus and response (Edelman et al., 2006). Accordingly, the distinct performance metrics of antisaccades provide a basis to evaluate whether an SRC and/or single bout of exercise selectively impact an oculomotor index of inhibitory control efficiency and effectiveness.

2.4.3 Pre-Exercise Oculomotor Performance Reveals an SRC-Induced EF Impairment

A number of studies have reported that the most common and persistent behavioural sequelae of an SRC is an EF impairment (Howell et al., 2013; Rabinowitz & Levin, 2014; Webb et al., 2018). In addition, oculomotor work by our group (Ayala & Heath, 2020; Webb et al., 2018) and others (Johnson et al., 2015a; 2015b) has demonstrated that individuals with an SRC exhibit longer antisaccade RTs and/or more directional errors compared to age- and sex-matched healthy controls within 7 days and 14–30 days post-injury. In the present work, pre-exercise RTs for prosaccades did not differ between SRC

and HC groups, and this represents an expected finding given that such responses are pre-potent and implemented independent of top-down EF (Johnson et al., 2015a; 2015b; Webb et al., 2018). In contrast, pre-exercise RTs for antisaccades were longer for the SRC than the HC group, and the former group exhibited an increased number of antisaccade directional errors. The magnitude of the between-group antisaccade RT difference (i.e., 42 ms) is similar to the 40 ms and 44 ms differences reported by Johnson et al. (2015b; <7 days post-injury) and Ayala and Heath (2020; <12 days post-injury), respectively. Moreover, the SRC group's longer antisaccade RTs and increased directional errors provide convergent evidence that the early stages of SRC render decreased planning efficiency (i.e., increased RTs) and effectiveness (i.e., increased directional errors) for an oculomotor index of inhibitory control.

2.4.4 A Single Bout of Exercise Improves Antisaccade Reaction Times in SRC and HC Groups

The exercise intervention produced a pre- to postexercise reduction in antisaccade – but not prosaccade – RTs for the SRC and HC groups. The null pre- to postexercise change for prosaccade RTs is accounted for by their pre-potent nature (Wurtz & Albano, 1980) and demonstrates that an exercise intervention does not result in a general improvement in information processing. In contrast, the postexercise antisaccade RT reduction supports a number of studies by our group (Dirk et al., 2020; Heath et al., 2018; Petrella et al., 2019; Samani & Heath, 2018; Shukla & Heath, 2022) and others (Zhou & Bai, 2023; Zhou & Zhuang, 2023) reporting that healthy adults (young and older) and persons at risk for cognitive decline (Heath et al., 2016, 2017) elicit a selective postexercise EF benefit (for an extensive review, see Zou et al., 2023). The antisaccade RT reduction has been shown to be independent of a practice-related performance benefit, given that frequentist and Bayesian analyses report that antisaccade RTs are equivalent when interspersed by a non-exercise control interval (Dirk et al., 2020; Dyckman & McDowell, 2005; Klein & Berg, 2001; Samani & Heath, 2018; Shukla & Heath, 2022; Tari et al., 2020, 2023). Moreover, that antisaccade durations and gain variability did not vary across pre- to postexercise assessments indicates that the postexercise RT reduction was not related to an implicit – or explicit – control strategy designed to decrease RT at the cost of decreased endpoint

accuracy (i.e., speed-accuracy trade-off) (Fitts, 1954). As such, our findings accord an expansive literature reporting that a single bout of exercise provides a selective EF benefit (for meta-analyses, see Chang et al., 2012; Lambourne & Tomporowski, 2010; Ludyga et al., 2016; Zou et al., 2023). Most notably, we believe our results add importantly to the literature inasmuch as they provide a first demonstration that persons with an SRC exhibit an EF benefit following a single bout of sub-symptom threshold aerobic exercise.

At least three issues require addressing. The first relates to whether the EF benefit observed in the SRC group was associated with an exercise-based increase in symptom burden. In addressing this issue, symptomology as assessed via the SCAT-5 did not reliably vary from pre-BCBT to postexercise assessments, and showed a reduction at a 24-hour follow-up. These findings align with mounting evidence supporting the safety and potential benefits of sub-symptom threshold exercise for SRC management and recovery (Leddy, Hinds, et al., 2018; Leddy, Wilber, et al., 2018). The second issue pertains to the finding that the exercise intervention did not modulate the frequency of antisaccade directional errors in the SRC group. This finding may be accounted for by the fact that a single bout of exercise does not provide a sufficient stimulus to improve the computational demands associated with adopting the task-set, or task rules, necessary to evoke a directionally correct antisaccade (Everling & Johnston, 2013). Moreover, these findings suggest that the frequency of antisaccade directional errors provides the resolution to detect persistent SRC-related EF deficits. The third issue to address is the observation that baseline to steady changes in MCAv did not impact the magnitude of a postexercise EF in either the SRC or HC groups. One possible explanation is that the relationship between CBF and EF is not dose-dependent; that is, only a small change in CBF is necessary to induce an EF benefit (i.e., the hemo-neural hypothesis) (Moore & Cao, 2008). There is some support for this view, given that equivalent magnitude postexercise EF benefits have been observed across the continuum of metabolically sustainable power outputs (Petrella et al., 2019; Tari et al., 2021). An alternative explanation, and one supported by an increasing literature, is that a postexercise EF benefit is accrued from interdependent processes that include – but are not limited to – CBF (Shirzad et al., 2022) and pressor response changes (Washio & Ogoh, 2023) as well as increased biomolecule availability (e.g., nitric oxide, brain-derived

neurotrophic factor, catecholamines) (Knaepen et al., 2010; Maiorana et al., 2003; Zouhal et al., 2008) and functional connectivity within EF networks (Schmitt et al., 2019).

2.5 Study Limitations

The current study is limited by several methodological traits. First, TCD does not quantify vessel diameter when assessing changes in MCAv. This represents a potential limitation given that the MCA is capable of dilation and constriction in response to hypercapnic environments (Coverdale et al., 2015). It is, however, important to recognize that such changes have not been shown to influence the validity of TCD in evaluating exercise-related changes in MCAv. Second, the SRC group consisted of varsity athletes who may have had a higher exercise tolerance and associated exercise-induced symptomology. As such, our findings may not be generalizable to a broader population of individuals with SRC (i.e., non-varsity/recreational athletes and/or older adults). Third, the SRC group included single- and multiple-concussed athletes, and given the sample size, it was not possible to determine whether pre- and postexercise EF may have varied with SRC history. Fourth, participants exercised for a single 20-min bout, and we evaluated EF at only one timepoint immediately postexercise. Future work by our group is aimed at exploring how exercise duration and intensity influence EF and the persistence of EF benefits in the SRC population. Fifth, we evaluated an inhibitory control index of EF, and it is unclear whether a single bout of exercise benefits other core EF components (i.e., working memory, cognitive flexibility) in persons with an SRC. Last, we did not assess the menstrual cycle phase of female participants. This could be considered a potential limitation given that basal CBF is elevated during the luteal phase of the menstrual cycle (Adkisson et al., 2010; Peltonen et al., 2016; Skinner et al., 2023). In accounting for this limitation, it has been reported that the menstrual cycle phase does not impact postexercise EF benefits (Dirk et al., 2020) and thus evinces that knowledge of menstrual cycle status should not limit female participants' participation in exercise neuroscience research.

2.6 Conclusion

Persons with an SRC demonstrated a baseline impairment in an oculomotor index of EF. Notably, our results provide the first demonstration that the impairment was improved following a single bout of sub-symptom threshold aerobic exercise and that this result was unrelated to the magnitude of an exercise-mediated increase in CBF. Moreover, that the EF benefit occurred without a concomitant increase in SRC symptomology suggests that single and chronic exercise sessions with tailored exercise intensities may serve as a safe and effective intervention for SRC recovery.

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Appendices

Appendix A 1: Health Science Research Ethics Board (HSREB) Approval Letter



Date: 7 August 2023
To: Dr. Matthew Heath
Project ID: 122653
Review Reference: 2023-122653-42407
Study Title: The Effect of a Single Bout of Sub-Symptom Threshold Aerobic Exercise on Executive Function at the Acute Phase of Sport-Related Concussion Recovery
Application Type: HSREB Initial Application
Review Type: Delegated
Full Board Reporting Date: 23/Aug/2023
Date Approval Issued: 02/Aug/2023 14:12
REB Approval Expiry Date: 02/Aug/2024

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 WREEM 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
Eye Tracking Tool	Other Data Collection Instruments	11/Apr/2023	01
YCD Tool	Other Data Collection Instruments	11/Apr/2023	01
Blood Pressure Tool	Other Data Collection Instruments	12/Apr/2023	01
Visual Analogue Scale (VAS)	Paper Survey	24/May/2023	01
Borg Rating of Perceived Exertion (RPE)	Paper Survey	24/May/2023	01
Demographics Questionnaire	Online Survey	01/Jun/2023	01
Godin Leisure Time Exercise Questionnaire (GLTEQ)	Online Survey	01/Jun/2023	01
SCAT-5 Symptom Checklist	Online Survey	01/Jun/2023	01
Heart Rate Tool	Other Data Collection Instruments	01/Jun/2023	01
Recruitment Advertisement_V2	Recruitment Materials	14/Jul/2023	02
In-Clinic Recruitment Advertisement_V2	Recruitment Materials	14/Jul/2023	02
Rebatesurvey Email_V2	Email Script	14/Jul/2023	02
Follow-Up Email Script	Email Script	01/Jun/2023	01
Potential Participant Email Script_V2	Email Script	14/Jul/2023	02
BCBT Program Paper_V1	Online Survey	14/Jul/2023	01
BCBT Weight to Power/Win Conversion Table_V1	Online Survey	14/Jul/2023	01
REDCap LOI Links_V2	Other	14/Jul/2023	02
Protocol_V3	Protocol	01/Aug/2023	03
PARQ ₊ _2017_Shortened_V3	Online Survey	01/Aug/2023	03
Mass Email Recruitment Script_V3	Email Script	01/Aug/2023	03

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Document Name	Document Type	Document Date	Document Version
LOI-C-HEC_V3	Written Consent/Assent	01/Aug/2023	03
LOI-C-SRC_V3	Written Consent/Assent	01/Aug/2023	03

Documents Acknowledged:

Document Name	Document Type	Document Date	Document Version
Revised Study Budget_V2	Study Budget	14/Jul/2023	02

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 Harmonization Good Clinical Practice Consolidated Guideline (ICH GCP), Part C, Division 3 of the Food and Drug Regulations, Part 4 of the Natural Health Products Regulations, Part 1 of the Medical Device 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 0000094.

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

Electronically signed by:

...Nicola Georgegas-Morphy, Ethics Officer on behalf of Dr. Norman Posner, HSREB Chair, 02/Aug/2023 14:12

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

Name: Alma Rahimi

Post-secondary Education and Degrees:

The University of Western Ontario
London, Ontario, Canada
2022-2024 MSc. Neuroscience

York University
Toronto, Ontario, Canada
2014-2020 B.A. Hons. Psychology

Honours and Awards:

Ontario Graduate Scholarship (OGS); [Declined in 2024]
Canadian Graduate Scholarship (CGS-M); [Accepted in 2023]
Ontario Graduate Scholarship (OGS); [Declined in 2023]
Ontario Graduate Scholarship (OGS); [Accepted in 2022]
xYU Entrance Scholarship; [Accepted in 2014]

Related Work Experience:

Centre for Addiction and Mental Health (CAMH); 2018–2024
Position: Research Assistant II
Supervisors (s): Dr(s). Peter Selby, Laurie Zawertailo & Nadia Minian

University of Western Ontario; 2022–2024
Position: Teaching Assistant [Courses in Kinesiology]
Course: KINSIOL 1070A/1080B; Instructors: Dr(s). Harry Prapavessis & Matthew Heath

York University; 2018–2019
Position: Teaching Assistant [Courses in Statistics]
Course: GL/PSYC 2530 & GL/PSYC 2531; Instructors: Dr(s). Genevieve Quintin & Agnieszka Kopinska

Publications:

Rahimi, A., Roberts, S. D., Baker, J. R., & Wojtowicz, M. (2022). Attention and executive control in varsity athletes engaging in strategic and static sports. *Plos one*, 17(4), e0266933.

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Echlin, H. V., **Rahimi, A.**, & Wojtowicz, M. (2021). Systematic review of the long-term neuroimaging correlates of mild traumatic brain injury and repetitive head injuries. *Frontiers in neurology*, 1691.

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- DeRuiter, W. K., Barker, M., **Rahimi, A.**, Ivanova, A., Zawertailo, L., Melamed, O. C., & Selby, P. (2022). Smoking cessation training and treatment: Options for cancer centres. *Current Oncology*, 29(4), 2252-2262.
- Minian, N., Wong, M., Hafuth, S., Rodak, T., **Rahimi, A.**, Gjomema, D., ... & Selby, P. (2024). Identifying determinants of varenicline adherence using the Theoretical Domains framework: a rapid review. *BMC Public Health*, 24(1), 679.

Conferences:

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- Rahimi, A.**, Ayaz, A., Buwadi, L., Jeyarajan, G., & Heath, M. (2023, March 25-28). Cerebral blood flow and executive function changes in response to active and passive exercise. Poster Presentation, Cognitive Neuroscience Society, San Francisco, USA.
- Rahimi, A.**, Gicas, K., Kozloff, N., Wong, A., (2022, June 17-19). Characterization of methamphetamine-related psychiatric emergency department use and COVID-19 impact. Oral Presentation, Canadian Psychological Association Annual National Convention, Calgary, Alberta, Canada.
- Rahimi, A.**, Roberts, S., Baker, J., & Wojtowicz, M. (2021, October 20-22). Performance variability in alerting, orienting and executive control between varsity athletes in strategic and static sports. Oral Presentation, Canadian Society for Psychomotor Learning and Sport Psychology, Toronto, Ontario, Canada.
- Rahimi, A.**, Daskalo, C., Gardner, A., & Wojtowicz, M. (2020, July 6-August 28). Systematic video analysis of head impacts among female hockey players. Oral Presentation, Canadian Psychological Association Annual National Convention, Montréal, Quebec, Canada.