Executive dysfunction following a sport-related concussion is independent of task-based symptom burden

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Abstract

The present work examined whether oculomotor deficits associated with a sport-related concussion (SRC) reflect an impairment to executive-based planning mechanisms or a task-based increase in concussion symptomology (e.g., headache, vertigo). Therefore, I employed a standardized measure of SRC symptom severity (SCAT-5), antisaccade performance and pupillometry metrics in persons with a SRC during early (i.e., initial assessment: ≤12 days post-SRC) and later (i.e., follow-up assessment: 14-30 days post-SRC) stages of recovery. In the initial assessment, the SRC group yielded longer reaction times (RT) (p=0.001), increased directional errors (p=0.002) and larger task-evoked pupil dilations (TEPD) (p=0.004) than the control group. The follow-up assessment indicated that RTs did not reliably vary between groups (p=0.155); however, the SRC group demonstrated more directional errors and larger TEPDs (p<0.03). Moreover, SCAT-5 symptom severity indicated that the oculomotor assessment did not increase symptom burden (p=0.622). Accordingly, I propose that a SRC impairs executive-based oculomotor planning mechanisms.

Keywords

Antisaccade
Executive function
Oculomotor
Prosaccade
Pupillometry
Sport-related concussion
Summary for Lay Audience

Executive function is a component of cognition that supports our ability to process and respond to single and multiple stimuli, maintain task goals in working memory, and assert high-level inhibitory control. Indeed, executive dysfunction has been identified as a persistent issue in individuals who sustain a sport-related concussion (SRC). The antisaccade task (i.e., eye movement mirror-symmetrical to a target) may serve as an effective tool for the identification and management of executive dysfunction following a SRC. Convergent evidence indicates that persons with a SRC exhibit longer antisaccade reaction times and produce more directional errors than their age-matched healthy controls during their concussion recover – deficits that persist even when the clinical signs of a SRC resolve. It is, however, unclear whether antisaccade performance deficits directly relate to impaired executive control or reflect a task-based increase in symptom burden (e.g., difficulty concentrating, headache, vertigo) associated with the administration of the antisaccade task. Therefore, the current study employed a standardized SRC concussion symptom checklist (i.e., Sport Concussion Assessment Tool: SCAT-5) in combination with antisaccade performance and pupillometry measures in persons with a SRC – and their age- and sex-matched controls – during the early (≤12 days post-SRC) (i.e. initial assessment) and later (14-30 days post-SRC) (i.e. follow-up assessment) stages of recovery. I included a measure of pupil dilation during antisaccade planning because some work has suggested that increased pupil dilation provides a proxy for increased executive demands in response preparation. At the initial assessment, the SRC group exhibited longer antisaccade reaction times, increased directional errors and larger pupil dilations than the control group. At the follow-up assessment, the SRC and control groups demonstrated comparable reaction times; however, the former continued to demonstrate increased directional errors and larger pupil dilations. SCAT-5 symptom scores indicated that the oculomotor assessment did not influence task-based symptom burden. The results therefore demonstrate that antisaccade performance deficits following a SRC relate to executive dysfunction in the planning mechanisms supporting antisaccades, and further suggest that the antisaccade task may serve to support SRC diagnosis and management.
Co-Authorship Statement

The author, under the supervision and mentorship of Dr. Matthew Heath and Dr. Lisa Fischer, conducted the work in this master’s thesis. Dr. Lisa Fischer provided valued guidance during conceptualization of this project and participant recruitment, and Dr. Matthew Heath provided valued guidance during conceptualization of this project, participant recruitment, data collection, data analyses, and manuscript writing.
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Chapter 1

1 Literature Review

The goal of my thesis was to determine whether acute and longer-term oculomotor changes arising from a sport-related concussion (SRC) reflect an executive dysfunction in movement planning and/or an increase in task-based symptom burden. I recruited a corpus of individuals with a SRC (and their age-, and sex-matched controls) and assessed SRC symptomology via a standardized scale (Sport Concussion Assessment Tool: SCAT-5) (McCrory et al., 2017) prior to and after an oculomotor assessment via the antisaccade task. The antisaccade task was evaluated via traditional performance metrics (i.e., reaction time, directional errors, endpoint accuracy) and a measure of pupil dilation (i.e., pupillometry). In developing my thesis document, I first provide a general review of: 1) the mechanisms, (neuro)pathophysiology, behavioural and clinical consequences of a SRC, 2) executive control, 3) the neural mechanisms associated with the production of an antisaccade (and prosaccade), and 4) the neural mechanisms, behavioural properties and interpretation of pupillometry. Subsequent to the general review, I provide the manuscript version of my thesis document.

1.1 Sport-Related Concussions (SRC)

A sport-related concussion (SRC) is a mild traumatic brain injury (mTBI) resulting from biomechanical forces transmitted to the head that imparts shear-related damage to the brain’s neural and glial networks (Meaney & Smith, 2011). Evidence has shown that SRCs are associated with extensive neuropathological changes, elicit a range of clinical signs and symptoms that may – or may not – involve a loss of consciousness (LOC), and produce rapid- or delayed-onset of transient impairments to neurological function that may resolve spontaneously (McCrory et al., 2017).

The diffuse nature of symptom presentation and the diverse mechanisms associated with a SRC has led to the well-recognized view that no concussion is the same. In spite of this, one feature common to all SRCs is the involvement of the near instant transfer of kinetic energy (Shaw, 2002). Normally, the brain floats within a
protective shield filled with cerebrospinal fluid (i.e., the subarachnoid space). During normal movement the brain is secured within the skull by the rough, irregular contours of the inner skull, which act as ‘hooks’, in combination with the three cranial fossa (Bigler, 2007). Notably, however, when the brain is subjected to a larger than normal load of kinetic energy following an impact, it contacts the skull causing deformation, distortion, and compression of neural and glial tissue (Meaney, Smith, Shreiber et al., 1995; Sumer, Atasoy, Unal, Kalayci, Malhmutyazicioglu, & Erdem, 2003). Moreover, it has been proposed that frontal cortical regions are most susceptible to concussive injury due to the region’s proximity to the convexity of the anterior cranial fossa. Indeed, impact models have shown that anterior brain structures are associated with greater deformation than other cortical regions (Bigler, 2007; Gurdjian, 1975). As will be discussed in more detail below, this is an important factor in developing tools to identify the short- and long-term cognitive, motor and sensory deficits arising from a SRC.

When a force is transmitted to the head there are three possible kinematic responses (Meaney et al., 1995). First, if contact is directed through the center of mass of the brain (i.e., centroidal) there is a linear acceleration without concomitant head rotation. Animal studies have shown that such a contact produces little brain motion or deformation (Hardy, Foster, Mason, Yang, King, & Tashman, 2001); that is, a linear acceleration does not impart a SRC. Second, if a contact force occurs at a non-centroidal area without linear acceleration then a rotational acceleration of the head results in a shearing force to the brain’s neural and glial networks, and imparts deformation to the brain’s vasculature. Third, and more commonly, a force transmitted to the head at a non-centroidal area with linear acceleration then imparts a linear and rotational acceleration of the head. These inertial (i.e., accelerative/decelerative) forces contribute to microscopic shearing and stretching of system-wide brain structures that initiate a cascade of molecular events disrupting normal cellular function.

The bulk of neuropathological changes associated with concussion have been studied in animal models using the fluid percussion model of brain injury (see Giza & Hovda, 2001; Giza & Hovda, 2014; Lindgren & Rinder, 1969). In this model, a percussion instrument delivers a brief mechanical insult to the skull resulting in the
transmission of a pressure pulse throughout the cranial cavity. The consequences following the percussive force include elastic deformation, displacement, distortion of neural tissue, loss of responsiveness, flaccidity, the abolition of reflexes, as well as disturbances in cerebrovascular, metabolic, respiratory, and cognitive functions (Jenkins, Moszynski, Lyeth et al., 1989). Notably, with advances in neuroimaging and bioassay techniques these findings have been extended to humans and the result of this work is a systematic model asserting that a SRC results in a “neurometabolic cascade” of bioenergetic challenges, cytoskeletal and axonal alterations, neurotransmitter dysfunction and vulnerability, and chronic dysfunction and cell death (Giza & Hovda, 2014). In particular, and as outlined by Giza and Hovda, the immediate cellular consequence of a SRC is an abrupt and indiscriminant cellular efflux of potassium and glutamate and an influx of calcium within the hippocampus, frontal, parietal, and occipital cortices (Katayama, Becker, Tamura, & Hovda, 1990; Osteen, Giza, & Hovda, 2004). Figure 1 shows that following a concussion there is an immediate increase in the activity of ionic-specific pumps (i.e., sodium-potassium) to restore cellular homeostasis. Because sodium-potassium pumps require adenosine triphosphate (ATP) to function, there is an associated increase in ATP demands, which in turn requires increased glucose metabolism (i.e., glycolysis). The accelerated glycolysis leads to the accumulation of lactate, which results in neuronal dysfunction induced by acidosis, membrane damage, altered blood brain permeability, and cerebral edema (Kalimo, Rehncrona, & Soderfeldt, 1981; Kalimo, Rehncrona, Soderfeldt, Olsson, & Siesjo, 1981). Furthermore, concussion-related hypermetabolism occurs with diminished cerebral blood flow (CBF) and the disparity between glucose supply and demand triggers an energy crisis. The rapid exhaustion of glucose (~30 minutes post concussive impact) leads to a period of depressed metabolism (i.e., hypometabolism). In this stage, persistent increases in calcium are linked to mitochondrial dysfunction (Vagnozzi, Tavazzi, Signoretti et al., 2007), and diffuse axonal injury via microtubule breakdown (Tang-Schomer, Johnson, Baas, Stewart, & Smith, 2012), which indirectly triggers cell death (Johnson, Steward, & Smith, 2013). In addition to the aforementioned changes in cellular physiology, concussions are associated with dysfunctional excitatory neurotransmission with glutamatergic, adrenergic, and cholinergic systems (Kobori, Hu, & Dash, 2011; Osteen, Giza, & Hovda, 2004; Schmidt
Impairments in these systems have been tied to deficits in long-term potentiation (i.e., a measure of plasticity) (Sick, Perez-Pinzon, & Feng, 1998), inhibitory transmission (Giza, Maria, & Hovda, 2006; Osteen, Giza, & Hovda, 2004), and choline acetyltransferase activity and an associated loss of forebrain cholinergic neurons (Schmidt & Grady, 1995). It is important to note that the fluid percussion technique used in many of these findings produced the aforementioned cellular alterations without the presence of histopathological changes (DeFord, Wilson, Rice et al., 2002). This is crucial because the presence of histopathological changes in the brain would indicate that the brain injury being examined in animal studies are related to more severe brain injuries, and not concussions. Indeed, Figure 1 depicts the time course of the neurometabolic changes (as % increases or decreases from control levels) that are associated with the clinical signs and symptoms commonly associated with a SRC (see details below). All rapid cellular changes associated with hypermetabolism are shown to occur within the first hour of impact. This is followed by the more persistent hypometabolic phase in which reduced CBF and residual calcium levels are maintained for up to 10 days post-concussive event. Accordingly, the aforementioned cellular changes are thought to contribute to a constellation of functional, cognitive, motor and sensory impairments.
The neuropathologic changes associated with a concussion are linked to specific clinical signs and behavioural outcomes. In particular, in the first few minutes following a SRC an athlete may experience a wide range of symptoms that vary in intensity and duration. Traditionally, LOC was used as the primary measure of SRC diagnosis and severity; however, recent research has shown that LOC is not a determinant feature of a SRC and does not predict post-concussion outcome (McCrea, Kelly, Randolph, Cisler, & Berger, 2002). Instead, evidence suggests that more importance should be placed on the nature, burden, and duration of SRC symptoms (Lovell, Iverson, Collins, McKeag, & Maroon, 1999; McCrory, Ariens, & Berkovic, 2000). Currently, SRC diagnosis is based on the assessment of clinical symptoms, physical signs, and neurological, cognitive, motor and sensory impairment(s) (McCrory, Johnston, Meeuwisse et al., 2005). Clinical symptoms and physical signs can been classified into four clusters: (1) somatic (i.e., headache, pressure in head, neck pain, nausea/vomiting, dizziness, blurred vision, balance problems, sensitivity to light, sensitivity to noise), (2) cognitive (i.e., feeling slowed down, feeling “in a fog”, “don’t feel right”, difficulty concentrating, difficulty remembering, confusion), (3) arousal/sleep problems (i.e., fatigue/low energy,
drowsiness, trouble falling asleep), and (4) emotion (i.e. more emotional, irritability, sadness, nervous/anxious). All of these symptoms are included in the Post-Concussion Symptom Scale that has been incorporated in the Sport Concussion Assessment Tool (SCAT-5). The SCAT-5 is a brief neuropsychological test battery designed to detect deficits in any of these areas. In particular, the SCAT-5 assesses for signs of SRC (i.e., LOC, unresponsiveness, balance problems, convulsive activity); symptoms commonly associated with SRC (i.e. the 22 symptoms mentioned above); memory impairments (i.e., orientation questions and retrograde memory); cognitive impairments (i.e., episodic memory, impairments on both an immediate and a 5-minute delayed recall of five words, attentional regulation); and neurological impairments (i.e., neurological screen and balance/gain examination). The Consensus Statement on Concussion in Sport recommends that the SCAT-5 should be completed by a physician or licensed health care professional in a distraction-free environment. If an athlete presents with signs or symptoms associated with any component of the SCAT-5, it is recommended that a SRC be declared and the athlete removed from competition and practice (McCrory et al., 2017). Indeed, the ability to identify a SRC – even in the case of a false positive – represents an important issue because concussed athletes are at a heightened risk for a second and more severe injury. Cantu (1998) showed that athletes who return to play prior to SRC recovery are at a heightened risk for secondary impact syndrome and long-term neuro-cognitive impairment. The increased risk is associated with pre-existing cellular impairment producing neural vulnerability for a second – and less forceful – impact (Hovda, Lee, Smith et al., 1995; Fu, Smith, Thomas, & Hovda, 1992).

Recent studies examining CBF (Churchill, Hutchison, Graham, & Schweizer, 2017), axonal integrity (Grossman, Inglese, & Bammer, 2010), and electroencephalographic activity (DeBeaumont, Brisson, Lassonde, & Jolicoeur, 2007) have shown specific links to SRC-induced behavioural impairments. More notably, convergent evidence has shown that a deficit in executive function represents the most persistent and common sequela associated with a SRC (Lezak, 1982; Heitger, Jones, Dalrymple-Alford, Frampton, Ardagh, & Anderson, 2007a). Broadly defined, executive function represents the ability to plan and control voluntary actions, process single and multiple stimuli, update and monitor working memory, and assert high-level inhibitory
control (Norman & Shallice, 1986). In the acute stage of SRC recovery (i.e., <7 days) there is robust evidence revealing SRC-induced deficits in reaction time (RT), processing speed, visual and verbal memory, executive control, and learning (Iverson, Lovell, & Collins, 2003; Johnson, Zhang, Hallett, & Slobounov, 2015b). Specifically, Lipton and colleagues (Lipton, Gulko, Zimmerman et al., 2009) examined executive function in 20 concussed individuals within two weeks of their injury. Participants completed two computer-based executive function tasks (i.e., the Continuous Performance task and the Executive Maze task) and diffusion tensor imaging (DTI) was used to determine whether frontal white matter abnormalities were related to executive dysfunction. The authors found that concussed individuals achieved lower executive function scores than their age-matched controls and that this was associated with multiple clusters of lower frontal white matter fractional anisotropy (FA: a measure of connectivity) within the dorsolateral prefrontal cortex (DLPFC) (for details on the cortical structures associated with executive function see Section 1.2: Executive function). Based on these findings the authors concluded that impaired executive function following a concussion is associated with diffuse DLPFC axonal injury.

In the later stages of concussion recovery (i.e., >10 days), lab-based measures have provided evidence of SRC-related executive dysfunction without associated impairment on traditional neuropsychological measures. In a seminal study, De Beaumont et al. (2007) included individuals with no history of a SRC (i.e., control group), as well as individuals with a history of a single (i.e., single-SRC group) or multiple (i.e., multiple-SRC group) SRCs. Notably, individuals in the SRC groups were at least 9-months removed from their most recent injury and all groups achieved comparable scores on a traditional battery of neuropsychological tests. De Beaumont et al. had participants complete an executive-demanding oddball search task (Brisson & Jolicoeur, 2007) and examined concurrent event-related brain potentials (ERP). Results showed that groups did not reliably differ in terms of the speed or accuracy of their performance on the oddball task; however, the amplitude of the P300 ERP for the control group was larger than the single-SRC group, which in turn was larger than the multiple-SRC group. The P300 has been interpreted to reflect a measure of executive function (Lai, Lin, Liou, Yang, Liu 2013; for review see Donchin, 1988) and as such, De
Beaumont et al. concluded that a SRC elicits long-term dysfunction to executive control networks that is not detected by standardized neuropsychological tests. Moreover, a series of lab-based studies examining dual-task gait training have observed persistent executive dysfunction following a SRC (Catena, Van Donkelaar, & Chou, 2007; Howell, Osternig, & Chou, 2013; Sosnoff, Broglio, & Ferrara, 2008; Van Donkelaar, Osternig, & Chou, 2006). For example, Parker, Osternig, Van Donkelaar, & Chou (2006) showed that multiple aspects of gait (i.e., decreased gait velocity and stride length) were compromised in individuals with a SRC for up to 4 weeks post-injury when they performed a concurrent cognitive/executive task (i.e., walking while spelling five-letter words in reverse, subtracting by sevens, and reciting the months of the year in reverse). The authors concluded that lab-based measures of dual-task gait training provide a tool for identifying long-term executive and motor dysfunction arising from a concussion.

One of the limitations of dual-task gait training studies is that they require considerable space and time to set up (i.e., placing markers on limb position for biomechanical recording). A potential paradigm for addressing these limitations is the assessment of an executive-based oculomotor task. In particular, two studies have used the antisaccade paradigm to examine executive dysfunction following the early and later stages of SRC recovery (Johnson, Hallett, & Slobounov, 2015a; Johnson et al., 2015b; Webb, Humphreys, & Heath, 2018). As will be described in more detail below (see Section 1.3, The control of antisaccades), antisaccades are an executive task requiring that an individual complete a goal-directed eye-movement (i.e., a saccade) mirror-symmetrical to a target. Johnson et al. (2015a; 2015b) found that individuals with a SRC produced longer antisaccade RTs than their age- and sex-matched healthy controls at acute (i.e. <7 days post-SRC) and subacute (i.e. 30 days post- SRC) stages of SRC recovery. This was found to be associated with an increase in neural activity across a range of frontoparietal and subcortical structures. Second, Webb, Humphreys and Heath (2018) demonstrated that antisaccade RTs in an SRC group were 97 ms longer than

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1 Johnson et al. (2015a; 2015b) involved the same participants – and methodology – and only differed in terms of the timing of post-concussion assessment.
healthy controls at an initial assessment (i.e., <7 days post-SRC); however, RTs for the SRC and control group did not reliably differ at the follow-up assessment (i.e., 14-20 days post-SRC). It is, however, important to note that at the follow-up assessment persons with a SRC continued to exhibit increased antisaccade directional errors (i.e., a prosaccade instead of an instructed antisaccade). Indeed, the fact that participants continued to exhibit increased directional errors is notable because all participants at this time point were medically cleared for safe return to play. As a result, convergent evidence indicates that executive dysfunction following a SRC persists even after clinical signs have resolved.

Although previous studies have concluded that a SRC results in impaired executive-based oculomotor planning mechanisms, it is entirely unclear whether such a deficit is independent of an increase in task-based symptom burden. This is a notable issue because increased cognitive demand has been shown to increase symptom severity (e.g., headache, vertigo) in concussed athletes and result in decreased attention and vigilance (Covassin, Crutcher, & Wallace, 2013). Accordingly, there is a need to establish whether impairments associated with oculomotor and other executive-based tasks are independent of an increase in task-based symptom burden.

1.2 Executive Function

Executive function is essential to activities of daily living as it underlies behavioural adaptations to our dynamic environment. For example, imagine operating a motor vehicle and being stopped at a red traffic signal. If your intention is to move straight through the intersection, then you must withhold a response (accelerating through the intersection) when a green left-hand turn signal is presented. Indeed, executive function permits you identify the nature of the stimulus and assert inhibitory control to avoid an inappropriate response (i.e., taking foot of the accelerator). Three core dimensions are proposed to underlie executive function: (1) cognitive flexibility (set-shifting, mental flexibility), (2) working memory, and (3) inhibitory control (behavioural inhibition, selective attention and cognitive inhibition) (Lehto, Juujärvi, Kooistra, & Pulkkinen, 2003; Miyake, Friedman, Emerson, Witzki, Howerton, & Wager, 2000). Convergent neuroimaging and lesion studies have revealed robust associations between
executive function and the prefrontal cortex (PFC). Notably, the PFC can be sub-divided into three regions that are relevant to components of executive function: DLPFC, orbitofrontal cortex (OFC), and the anterior cingulate cortex (ACC) (Royall, Lauterback, Cummings et al., 2002) (**Figure 2**). Lesions to the DLPFC impair higher-order cognition, including goal-setting, inhibitory control, planning, sequencing, response-set formation, task shifting, verbal and spatial working memory, self-monitoring, and self-awareness (Diamond, 2013). In turn, lesions to the OFC are associated with impairments to the initiation of social and internally driven behaviours, as well as the inhibition of inappropriate behavioural response (Truelle, Le Gall, Joseph, & Aubin, 1995). Last, ACC lesions have been shown to result in deficits in behavioural monitoring and error correction (Mansouri, Buckley, Fehring, Tanaka, 2019). In this literature review, I focus primarily on inhibitory control and the reported involvement of the prefrontal cortex (PFC) in this executive domain.

A number of behavioural tasks including the Wisconsin Card Sorting Test (WCST) (Grant & Berg, 1948), the Stroop Interference Task (Stroop, 1935), Tower of London (Norman & Shallice, 1980), and the Go/No-Go paradigm (Shue & Douglas,
1992) have been used to examine executive-mediated inhibitory control. The Stroop Interference Task is perhaps the most widely used measure of response inhibition and requires the selective allocation of attention to stimuli, while ignoring task-irrelevant stimuli. For instance, in a classic variant of the Stroop task (i.e., Stroop Colour-Word test) participants are presented with a word (i.e. a colour name) written in ink that is congruent (i.e., RED written in red text) or incongruent (RED written in green text) with the word meaning (Stroop, 1935). Results have repeatedly shown that RTs and response errors are increased when participants are asked to report the ink colour in the incongruent condition (for review see MacLeod, 1992). These behavioural results have been referred to as the “Stroop Interference Effect” and are suggested to reflect competing tendencies (i.e., the standard task of reading vs. the non-standard task of identifying ink colour) that require the selective attention to one stimulus and the inhibition of the other (Stroop, 1935).

Stuss, Floden, Alexander, Levine, & Katz (2001) examined the Stroop Interference Effect using the Stroop Colour-Word task in 51 patients with single focal brain lesions to frontal (i.e. DLPFC and superior medial frontal lobe) and posterior regions as well as 26 healthy controls. Their findings demonstrated that individuals with frontal lesions exhibited longer Stroop Interference Effect RTs and increased response errors compared to individuals with posterior lesions or healthy age-matched controls. Stuss et al. therefore concluded that the frontal cortex – in general – supports inhibitory control. In line with lesion studies, neuroimaging studies have linked the PFC to Stroop Interference Task inhibitory control. For example, MacDonald and colleagues’ (MacDonald, Cohen, Stenger, & Carter, 2000) fMRI study employed an AABB version of the Stroop Interference task and reported that the left DLPFC was more activated during the preparatory cue period for colour naming, as compared to word reading – a finding taken to evince the activation of different attentional sets based on task-demands. Additionally, the increase in DLPFC activation was found to correlate to reduced Stroop interference effects. Therefore, the aforementioned findings provide evidence that the DLPFC supports the executive mechanisms required for inhibitory control.
The Stroop Interference Task has also been used to examine executive dysfunction following traumatic brain injury (TBI) and, more germane to the current thesis, following a SRC. As mentioned above (see Section 1.1: *Sport-Related Concussions (SRC)*), a series of studies examined combined gait and the Stroop Inference performance (i.e., dual-task gait task) to examine executive dysfunction following a SRC (Catena et al., 2007; Howell et al., 2013; Parker et al., 2006; Sosnoff et al., 2008; Van Donkelaar et al., 2006). In one example, Howell & colleagues (2013) employed a dual-task paradigm to examine executive and motor performance in 20 adolescent athletes with a SRC and their sex-, age-, height-, and weight-matched health controls at five time points post-SRC (i.e., 72 hours, 1 week, 2 weeks, 1 month, and 2 months post-SRC). All participants completed two conditions: walking with undivided attention (single-task condition) and walking while concurrently performing an auditory Stroop Interference task. In the dual-task condition neither walking nor Stroop performance was prioritized. Results showed that the SRC group had decreased center of mass velocity and displacement (i.e. impairments in balance and gait control) as well as decreased Stroop task accuracy compared to the control group – a result that was observed across the 2-month testing period. The authors proposed that their results reflect that a SRC imparts a long-term impairment in attention reallocation and inhibition. Thus, evidence indicates that executive function tasks provide a critical tool for assessing PFC impairment.

1.3 The Control of Antisaccades

Although the Stroop Interference task has been extensively used to assess executive (dys)function it is important to recognize that a measure of oculomotor performance provides a measure of executive control that is hands- and language-free. In other words, oculomotor tasks can examine executive performance independent of non-executive impairments. In particular, antisaccades are a volitional response requiring that an individual complete a goal-directed eye movement (i.e., saccade) mirror-symmetrical to the location of an exogenously presented visual target (Hallett, 1978). Antisaccade performance is typically contrasted to a stimulus-driven and pre-potent saccade wherein a response is directed to veridical target location (i.e., prosaccades). The antisaccade task
has been used in one of two paradigms (i.e., overlap and gap). In the overlap paradigm a central fixation cross is presented for a period of time prior to and concurrent to target onset, whereas in a gap paradigm the fixation cross is occluded for a brief period of time (i.e., 200 ms) prior to target onset (Fischer & Weber, 1997; Forbes & Klein, 1996). A wealth of studies have shown that in both overlap and gap paradigms antisaccades result in longer RTs (Hallett, 1978) and movement times (Edelman & Goldberg, 2003), lower peak velocities (Edelman & Goldberg, 2003), increased directional errors (Fischer and Weber, 1992) and less accurate and more variable endpoints (Dafoe, Armstrong, & Munoz, 2007; Gillen and Heath 2014a; 2014b) than their prosaccade counterparts. These antisaccade behavioral ‘costs’ have been linked to the two-component executive control processes of inhibiting a pre-potent prosaccade (i.e., response suppression) and the 180° inversion of a target’s coordinates (i.e., vector inversion) (for review see Munoz & Everling, 2004). Moreover, the antisaccade task has been used to identify executive dysfunction in individuals with frontal lobe lesions (Pierrot-Deseilligny, Müri, Ploner, Gaymard, Demeret, & Rivaud-Pechoux, 2003), persons in the prodromal stages of Alzheimer’s disease (Heath, Shellungton, Titheridge, Gill, & Petrella, 2017; Heath, Weiler, Gregory, Gill, & Petrella, 2016), Parkinson’s disease (Chang, Armstrong, Pari, Riopelle, & Munoz, 2005; Wang, McInnis, Brien, Pari, & Munoz, 2016), schizophrenia (McDowell, Brown, Paulus et al., 2002; McDowell, Myles-Worsley, Coon, Byerley, & Clementz, 1999) and SRC (Johnson et al., 2015a; 2015b; Webb et al., 2018). For example, Pierrot-Deseilligny and colleagues (2003) had participants with DLPFC lesions complete antisaccades (as well as a series of other saccade tasks; i.e., visually and memory-guided prosaccades, predictive saccades, smooth pursuit movements) and demonstrated significantly more directional errors on the antisaccade task compared to control counterparts – a finding interpreted to reflect that the DLPFC plays a crucial role in decisional processes and preparing saccade circuitry for inhibition.

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2 The gap paradigm is associated with shorter antisaccade RTs and increased directional errors than the overlap paradigm. This result has been attributed to a respective decrease and increases in collicular fixation and saccade build-up neuron activity during the gap interval. (Everling, Dorris, Klein, & Munoz, 1999)
Neuroimaging and electrophysiological evidence from human and non-human primates has linked the constituent elements of the antisaccade task (i.e., response suppression and vector inversion) to increased activity in an extensive frontoparietal executive network. For example, Ford and colleagues (Ford, Goltz, Brown, & Everling, 2005) fMRI study had human participants complete an interleaved pro- and antisaccade task and reported that during the late saccade preparatory period (i.e., between the instructional cue and target onset) antisaccades were associated with increased cortical activity in the DLPFC, frontal eye fields (FEF), pre-supplementary eye fields (pre-SEF), ACC, parietal occipital sulcus (POS), and the intraparietal sulcus (IPS). Furthermore, Ford et al. observed increased activation in the right DLPFC, right ACC, and the pre-SEFs on correct antisaccade trials compared to erroneous trials. The authors concluded that the preparation of an antisaccade activates a large frontoparietal network that supports volitional planning mechanisms. Moreover, single-cell recording studies in non-human primates have shown that FEF, supplementary eye fields (SEF) and superior colliculus (SC) saccade and fixation neuron activity is differentially modulated during pro- and antisaccades (Amador, Schlag-Rey, & Schlag, 2004; Everling et al., 1999; Everling & Munoz, 2000). In particular, it has been reported that prior to stimulus presentation the production of directionally correct antisaccades is associated with an increase and decrease in fixation and saccade neuron activity, respectively. To more directly outline these findings, Figure 3 presents Munoz and Everling’s (2004) representation of single-cell activity of FEF and SC fixation and saccade neurons during the production of gap paradigm pro- and antisaccades. During the fixation/instruction period, fixation neurons are tonically activated and saccadic neurons have little-to-no activity. Approximately 100ms into the gap period there is a decrease in fixation neuron activity accompanied by a slow build up of saccade neuron activity in both the FEF and SC (in the overlap condition fixation neuron activity remains consistent up until target onset and there is no slow build up of saccadic neuron activity). For prosaccades, target onset is followed by a phasic increase and decrease in saccadic burst neurons and fixation neurons, respectively, contralateral to the target. For antisaccades, target onset is followed by the phasic inhibition of saccadic burst neurons contralateral to target and the subsequent activation of saccadic burst neurons (and a concomitant reduction in fixation
neuron activity) ipsilateral to the target. In particular, Munoz and Everling have proposed that correct antisaccade performance requires “…top-down inhibition of saccade neurons in the SC and FEF before the target appears” (p. 222).

The DLPFC has been recognized as a prime contributor to top-down inhibition in the antisaccade task; however, a more recent view holds that the DLPFC imparts top-down executive control via excitatory inputs to the SC that provide the task-set and task rules necessary for the production of a directionally correct antisaccade (Chan, Koval, Womelsdorf, Lomber, & Everling, 2015; Johnston, Koval, Lomber, & Everling, 2014; Koval, Lomber, & Everling, 2011). For example, Koval and colleagues (2011) showed that in monkey’s bilateral cyrogenic deactivation of the DLPFC resulted in longer antisaccade RTs, increased directional errors and reduced SC neuron preparatory activity. The authors proposed that such results indicate that the DLPFC provides excitatory inputs to saccade generating mechanisms that encodes the task rules necessary for the constituent elements of the antisaccade task (i.e., response suppression and vector inversion).
In regard to the use of the antisaccade task following a TBI, Kraus and colleagues’ (Kraus, Little, Donnell, Reilly, Simonian, & Sweeney, 2007) examined oculomotor function in concert with neuropsychological testing in chronic closed head injuries across mild to severe severities of TBI and healthy controls. Thirty-seven participants with a history of TBI were recruited and performed blocked pro- and antisaccades, and additionally completed standardized neuropsychological tests that were heavily weighted on measures of executive function (e.g., the Tower of London, Stroop Colour-Word test, Paced Auditory Serial Addition). The authors reported that

**FIG. 3.** Recorded activity of individual saccade (SN) and fixation (FN) neurons in the frontal eye field (top panels) and superior colliculus (bottom panels) when a monkey performs a prosaccade and antisaccade in the gap paradigm. Responses for correct prosaccades (blue trace) are compared to responses for correct antisaccades (red trace) (Reproduced with permission. Munoz & Everling (2004). *Nature Reviews Neuroscience*. 5, 218-228.).
neuropsychological measures did not differ between controls and persons with mTBIs to moderate TBIs; however, the mTBI group was distinguished from the other groups due to their selective prolonged RTs and increased directional errors during the antisaccade task. The authors proposed that the antisaccade task can be used to identify subtle executive dysfunction that may not be identified via traditional neuropsychological test batteries.

1.4 Pupillometry in Executive Control

Pupillometry is the study of pupil diameter changes and has a long tradition of being used as a measure of cognitive resource recruitment and attentional allocation in language comprehension (Beatty, 1982), working memory (Goldinger & Papesh, 2012; Kahneman & Beatty, 1966), long-term memory (Beatty & Kahneman, 1966), numerosity (Hess & Polt, 1964), and executive control (van der Wel & van Steenbergen, 2018) tasks.

The pupil is the transparent opening in the center of the eye that varies between 1.5 and 9 mm and therefore alters the amount of light that enters the eye. Pupil size is modulated by activity in the parasympathetic and sympathetic branches of the nervous system via the constriction and dilation pathways, respectively. The sympathetic nervous system is involved in the dilation pathway and operates subcortically beginning at the level of the hypothalamus and locus coeruleus (LC) and connecting to the iris dilator muscle. In contrast, the parasympathetic nervous system is involved in the constriction pathway that operates subcortically and connects the retina to the iris sphincter muscle (Figure 4) (for review see Mathôt, 2018). Sympathetic activation contracts the dilator muscle evoking pupil dilation, whereas inhibition of parasympathetic activity reduces constriction of the sphincter muscle and indirectly results in dilation (Beatty & Lucero-Wagoner, 2000). A well-known change in pupil diameter is the pupillary light reflex and involves pupil constriction following the onset of a visual stimulus. This change in pupil size is predominantly driven by constriction via the parasympathetic nervous system and follows a very specific temporal profile that helps distinguish this reflex from other processes that influence pupil dynamics (i.e. executive function) (Markwall, Feigle, & Zele, 2010). In particular, Markwall and colleagues demonstrated that the pupil remains relatively unresponsive for approximately 200ms following the presentation of a bright stimulus (i.e. light). This is followed by an abrupt pupil constriction response that can
take up to 1500ms to complete. Until the light is extinguished the pupil may remain constricted or undergo a slight unconstricting phase (i.e. pupillary escape). The potentially confounding influence of the pupillary light reflex on pupillometry measures of executive control is described in more detail below.

![Diagram of the neural circuitry involved in pupillary constriction and dilation pathways](image)

**FIG. 4.** The neural circuitry involved in: (a) the pupil constriction pathway and (b) the pupil dilation pathway (Reproduced from Mathôt (2018). *Journal of Cognition*. 1, 1-23.).

An increasing body of literature has shown that the interaction between the constriction and dilation pathways is crucial to our understanding of pupil dynamics. As depicted in Figure 4, a key contribution of the parasympathetic nervous system pathway on pupil size modulation is mediated by inhibition of the Edinger-Westphal nucleus (EWN) located in the midbrain (Steinhauer & Hakerem, 1992). First, LC activity not only supports pupil dilation via the dilation pathway, but also indirectly dilates the pupil by inhibiting the constriction pathway at the level of the EWN (Steinhauer, Siegle, Condray, & Pless, 2004). Second, the intermediate layers of the SC project directly and
indirectly to the EWN, which activate and suppress parasympathetic activity, respectively (Edwards & Henkel, 1978; Wang & Munoz, 2015). Notably, these structures receive input from cortical regions linked to executive control (see White & Munoz, 2011). The pupillometry literature reports that the LC receives direct and indirect input from the PFC (i.e., medial PFC, lateral PFC, ACC and OFC) and the insula, and that their efferent projections influence the level of neural gain throughout the cortex, including cortical (i.e., frontal and parietal) and subcortical (i.e. SC) regions important for cognitive control (Aston-Jones et al., 2002; Bush, Luu, & Posner, 2000; Foote & Morrison, 1987; Nieuwenhuis, DeGeus, & Aston-Jones, 2011; Mückschel, Chmielewski, Ziemssen, & Beste, 2017). Electrophysiological evidence has linked changes in activity to the aforementioned cortical and subcortical structures to changes in pupil dilation (Aston-Jones & Cohen, 2005; Gilzenrat, Nieuwenhuis, & Cohen, 2010; Lehmann & Corneil, 2016; Sara & Bouret, 2012; Wang, Boehnke, White, & Munoz, 2012). Specifically, in non-human primates it has been reported that microstimulation of the intermediate SC layers (SCi) – but not the superficial SC layers (SCs) – in monkeys results in transient and bilateral pupil dilation (Wang et al., 2012). Based on this result, it was concluded that the SC is not only involved in covert shifts of attention, but also in the modulation of cognitive-related pupil dynamics. This change in pupil diameter was also observed when the FEF was microstimulated and occurred in the absence of an obligatory saccade (Lehmann & Corneil, 2016). Therefore, the pupillometry literature supports the claim that a link exists between the frontoparietal network and the pupil control circuit via the oculomotor system (Hogervost, Brouwer, & van Erp, 2014; Lehmann & Corneil, 2016; Reinhard & Lachnit, 2002; Rondeel, van Steenbergen, Holland, & van Knippenberg, 2015; Wang et al., 2012).

In terms of cognitive processing, recent work has employed pupillometry as a proxy measure of executive function. More specifically, work has shown that pupil dilation reflects the recruitment and utilization of task-related neural resources across the domains of working memory (Belayachi, Majerus, Gendolla, Salmon, Peters, Van der Linden, 2015), cognitive flexibility (Rondeel et al., 2015), and response inhibition (Brown, Kindermann, Siegle, Granholm, Wong, & Buxton, 1999). For example, pupil size on Stroop Interference Task incongruent trials are larger than their congruent trial.
counterparts (Laeng, Orbo, Holmlund, & Miozzo, 2011) and was a result interpreted to reflect increased inhibitory control and conflict monitoring during incongruent trials.

More germane to the present literature review, pupillometry has been used as a proxy for the preparatory planning and executive control underlying the antisaccade task. Wang, Brien, & Munoz (2015) had healthy participants complete an interleaved pro- and antisaccade paradigm and examined traditional saccade performance metrics (i.e., RT and directional errors) in conjunction with changes in pupil size. In their study, the colour of a fixation cross (green=prosaccade, red=antisaccade) cued participants as to the nature of an upcoming trial. Following a 1000ms foreperiod, the fixation cross was extinguished and a target was presented 200 ms thereafter (i.e., gap paradigm). Three specific epochs during the saccade preparatory period were examined to identify pupil dynamics in saccade preparation: 1) start of visual fixation epoch (100-300ms post-fixation onset), 2) when the pupil was maximally constricted (800-850ms post-fixation onset), and 3) end of gap epoch (150-200ms post-gap onset). The baseline epoch served as a general measure of tonic psychophysiological arousal, whereas the other epochs were used to calculate phasic change in pupil size thought to be related to the executive demands of saccade preparation (i.e. task-evoked pupil dilation: TEPD). The authors hypothesized that antisaccades would produce larger TEPDs because previous fMRI (Connolly et al., 2002; Ford et al., 2005) and single neuron recording studies (Everling et al., 1999; Everling & Munoz, 2000) have demonstrated increased antisaccade preparatory activity (compared to prosaccade preparatory activity) within structures supporting oculomotor control (i.e. FEF, SC) that are linked to the pupil control circuit (Lehmann & Corneil, 2016; Wang et al., 2012). As expected, antisaccade RTs were longer and were associated with more directional errors than prosaccades. In addition, TEPDs for antisaccades were larger than prosaccades, and TEPDs for directionally correct antisaccades were larger than erroneous antisaccades. In accounting for the pupil size findings the authors concluded: “…pupil size can be an effective proxy of neural activity related to saccade preparation” (p. 1108) and that pupil size is modulated “…by both types of preparatory signals (i.e., inhibitory control and motor preparation) associated with the antisaccade task” (p. 1107). In a subsequent study, Wang, McInnis, Brien, Pari, & Munoz (2016) employed the same methods to examine oculomotor planning deficits in persons with Parkinson’s disease.
(PD) and their healthy age-matched controls. Results showed that control participants exhibited larger TEPDs for antisaccades compared to prosaccades (see also Wang et al., 2015), whereas pro- and antisaccade TEPD changes in the PD group were significantly blunted. The authors proposed that the absence of a reliable change in pupil size across pro- and antisaccades in the PD group reflects an executive impairment in saccade planning and advocated that pupil size may assist in further identifying executive impairment in PD. As well, Karatekin, Bingham and White (2009) reported that adolescents with youth-onset psychosis demonstrate increased antisaccade directional errors compared to healthy controls and that such a finding was linked to decreased TEPDs. Accordingly, Karatekin et al. concluded that the use of antisaccade performance and pupillometry measures in persons with youth-onset psychosis revealed a decreased recruitment of cognitive and executive resources in volitional motor control.

As detailed above, some work has proposed that pupillometry serves as a proxy for the neural activity related to executive function. It is, however, well-known that pupillometry has a number of salient limitations. Indeed, test-related conditions (i.e., stimulus luminance, lighting conditions, and speed of stimulus presentation) and participant-related (i.e., age, arousal, anxiety level, and use of pharmacological drugs that affect norepinephrine and cholinergic levels) factors can influence pupil size. For example, using stimuli that have varying luminance levels will change the TEPDs produced during the performance of a cognitive paradigm. Indeed, stimuli with greater luminance (or greater contrast) will produce TEPDs that are larger and have shorter latencies than stimuli with reduced luminance or contrast levels (Wang, Boehnke, Itti, & Munoz, 2014). Additionally, general arousal can modulate TEPDs in a manner that resembles the classic Yerkes-Dodson inverted-U relationship (Aston-Jones & Cohen, 2005; Gilzenrat et al., 2010). If arousal is too high (task disengagement) or too low (inattentive/non-alarm), TEPDs will be suppressed and cognitive performance will decrease. In contrast, if the participant has an optimal level of arousal (task engagement), TEPDs will be augmented and cognitive performance will be enhanced. As well, it is important to establish an intertrial interval that is sufficiently long for pupil size to return to baseline following phasic dilation from a previous trial. Eckstein and colleagues (Eckstein, Guerra-Carrillo, Singley, & Bunge, 2017) recommended that such an interval
be of a duration between 2 and 3 seconds, and notes that most studies in the pupillometry literature do not report this important control variable. It is also necessary for pupillometry research to control for participant consumption of caffeine and tobacco use prior to study completion because they influence cognition, pupil dynamics and general arousal (Bowling & Donnelly, 2010; Lie & Domino, 1999; Winn, Wendt, Koelewijn, & Kuchinsky, 2018). Last, some authors have noted that pupil dilation provides only an indirect measure of task-based neural recruitment and activation (Aston-Jones & Cohen, 2005; Gilzenrat et al., 2010). This conclusion was provided on the basis that no direct pathway had been identified linking together the LC to nuclei subserving sympathetic tone (Nieuwehuis et al., 2011). That being said, the more recent microstimulation studies outlined above provide evidence that the SC (as well as the FEF) modulate pupil size (Lehmann & Corneil, 2016; Wang et al., 2012). Accordingly, it is recognized and advocated that pupillometry should be used only in conjunction with additional behavioural, electrophysiological or neuroimaging measures in addressing executive control.
Chapter 2

2 Introduction

A sport-related concussion (SRC) is a mild traumatic brain injury (mTBI) induced by biomechanical forces transmitted to the head that produce shear-related damage to the brain’s neural and glial networks (Meaney & Smith, 2011). The consequences of a SRC are transient and rapid (i.e. seconds to minutes), or delayed (i.e. hours to days), symptom presentation and concurrent cognitive, motor and sensory impairment(s) (McCrory et al., 2017). SRCs are the third leading cause of TBI-related visits to emergency departments in the USA (CDC, 2011). Notably, the frequency of SRCs is widely regarded as an underestimation due to a myriad of factors including: (1) lack of recognition by coaching and training staff and, (2) an athlete’s reluctance to report symptoms due to concern about being withheld from competition (McCrea, Guskiewicz, Marshall et al., 2003; Torres, Galetta, Phillips et al., 2013). This is a crucial consideration given that up to 50% of individuals who incur a SRC show long-term cognitive deficits that impact their return to educational, occupational and leisure activities (Ellis, Leddy & Willer, 2015; Heitger et al., 2007a; Heitger, Jones, MacLeod, Snell, Frampton, & Anderson, 2009; McInnes, Friesen, MacKenzie, Westwood, & Boe, 2017), and because persons with a SRC are at 3 to 6 times greater risk of sustaining a subsequent – and more severe – concussion (Covassin et al., 2013). As a result, there is continued need for SRC research to improve diagnosis, management and return to play guidelines.

A SRC results in pathophysiological changes to the brain not evident on standard neuroimaging (i.e., computerized tomography (CT) and magnetic resonance imaging (MRI)) (Clark & Guskiewics, 2016; Giza & Hovda, 2001; 2014; McCrory et al., 2017; Mittl, Grossman, Hiehle et al., 1994; Yuh, Mukherjee, Lingsma et al., 2014). These pathophysiological changes have been collectively referred to as the “neurometabolic cascade” (Figure 1) resulting in altered neurotransmitter activity (i.e., glutamatergic, adrenergic and cholinergic systems), and neural excitability (see Giza & Hovda, 2001; 2014). These changes are associated with increased glucose utilization and reduced regional cerebral blood flow contributing to an energy demand ‘crisis’ and neural dysfunction (Osteen, Giza, & Hovda, 2004; Yoshino, Hovda, Kawamata, Katayama, &
More directly, the earliest SRC-related neurometabolic change is a brief (i.e. within 24 hours) hypermetabolic state that is followed by a more persistent “diffuse depression-like” hypometabolic state characterized by mitochondrial dysfunction, reduced cerebral blood flow, decreased glycolysis, and neurotransmitter disturbance (Osteen, Giza, & Hovda, 2004; Pettus & Povlishock, 1996; Xiong, Peterson, Verweij, Vinas, Moizekar, & Lee, 1998; Yoshino et al., 1991). These changes in neuronal metabolism and “brain state” have been documented extensively in the SRC literature and are associated with significant neuropathological (Churchill et al., 2017; Grossman, Inglese, & Bammer, 2010; Grossman, Jensen, Babb et al., 2013), electrophysiological (De Beaumont et al., 2007; Dupuis, Johnston, Lavoie, Lepore, & Lassonde, 2000; Gosselin, Thériault, Leclerc, Montplaisir, & Lassonde, 2006), and functional changes to the brain (Johnson et al., 2015a; 2015b). For example, Churchill et al. (2017) found that higher cognitive symptom load following a SRC was associated with reduced cortical (i.e., orbitofrontal cortex: OFC, middle frontal cortex: MFC, supplementary motor area: SMA, insula, and anterior cingulate cortex: ACC) and subcortical (i.e., caudate) cerebral blood flow. Additionally, diffusion tensor imaging (DTI) studies have demonstrated dysfunction to frontal association pathways supporting executive function (i.e. executive control) (Bazarian, Zhong, Blyth et al., 2007; Lipton, et al., 2009; Salmond, Menon, Chatfield et al., 2006). In particular, reduced fractional anisotropy (FA: a measure of connectivity) in frontal white matter – specifically the dorsolateral prefrontal cortex (DLPFC) – was correlated with executive-related SRC dysfunction. Accordingly, the SRC literature demonstrates that post-concussive disruptions in pathophysiology are linked to structural alterations to the brain.

The most recently published Consensus Statement on Concussions in Sport advocates the fifth iteration of the Sport Concussion Assessment Tool (SCAT-5) and its variant for children (ChildSCAT) as a valid and reliable neuropsychological battery for SRC sideline assessment and clinical diagnosis. The SCAT-5 provides a battery of tests for assessing SRC signs (i.e., loss of consciousness, unresponsiveness, balance problems, convulsive activity), symptomology commonly associated with SRC (e.g., headache, nausea, vertigo), cognitive impairments (i.e., orientation questions, retrograde and episodic memory, immediate and a 5-minute delayed serial recall, attentional regulation),
and motor and sensory impairments (i.e., balance/gain examination). It is, however, important to recognize that the tool’s utility decreases significantly three to five days post-concussive event – a critical limitation given that many sport venues do not provide the opportunity for the timely administration of the SCAT-5 (McCrory et al., 2017; Torres et al., 2013). Similarly, the Immediate Post-Concussion Assessment and Cognitive Test (ImPACT) is a brief computer-administered neuropsychological test battery that has been employed among several professional sports organizations for concussion management (Covassin & Elbin, 2010; McKeithan, Hibshman, Yengo-Kahn, Solomon, & Zuckerman, 2019). The test battery consists of six individual modules (e.g., Colour Trails, Symbol Matching) that provide global measures of attention, memory, response variability, RT, and processing speed (Iverson, Lovell, & Collins, 2005). In line with the SCAT-5, the ImPACT is associated with reduced resolution for identifying subtle cognitive deficits (Iverson, Brooks, Collins, & Lovell, 2006; Servatius, Spiegler, Handy, Pang, Tsao, & Mazzola, 2018), and an identified limitation of the tool is that it parallels self-reported symptoms (Iverson, Brooks, Collins, & Lovell, 2006). In particular, when concussed individuals report clinical symptoms, the ImPACT reveals neurocognitive deficits; however, when symptoms resolve neurocognitive measures return to normal.

The use of lab-based tasks that provide a specific measure of executive function has been proposed to improve SRC identification and determine a return to normative neurocognitive performance. Executive function is the ability to process and respond to single and multiple stimuli, maintain task goals in working memory, and assert high-level inhibitory control (Norman & Shallice, 1986). Moreover, the selective examination of executive function following a SRC is thought to provide an optimal platform for diagnosis and management because executive dysfunction has been identified as the most common and persistent sequela impairing recovery across all severities of TBIs (Heitger, et al., 2007b; Kraus et al., 2007; Lezak, 1982). For example, Kraus et al. (2007) reported that although persons with a mTBI showed language, arithmetic, memory and spatial processing similar to age-matched controls, they continued to demonstrate executive dysfunction that persisted up to seven years post-injury. Furthermore, Pontifex and colleagues (Pontifex, O’Connor, Broglio, & Hillman, 2009) showed that although
athletes with a history of SRC (i.e., 3 years post-SRC) and their age-matched controls exhibited comparable performance on the ImPACT, the former group showed longer RTs and less accurate performance on an executive-demanding flanker task. Thus, convergent evidence suggests that measures of executive function may provide increased resolution for detecting SRC impairment than other “general” measures of cognitive, motor and sensory function.

A number of studies have employed the dual-task gait paradigm as a means to detect subtle executive dysfunction during the early and later stages of SRC recovery (Catena et al., 2007; Sosnoff et al., 2008; Van Donkelaar et al., 2006). For example, Howell, Osternig, & Chou (2013) employed conditions in which 20 participants with a SRC completed a self-paced gait task under two conditions: (1) walking with undivided attention and (2) walking while concurrently performing the Stroop Interference task test (i.e., an executive task of response inhibition) wherein participants reported whether the word “high” or “low” matched an auditory cue (high tone vs. low tone). Participants with a SRC were compared to their sex-, age-, height-, and weight-matched controls at 72 hours, 1-week, 2-weeks, 1-month- and 2-months post-injury. Results demonstrated longer gait times for the SRC group and decreased Stroop accuracy compared to controls – a deficit that was observed across the 72-hrs to 2-month assessments. The authors concluded that a SRC imparts a long-term impairment in the executive function of attentional reallocation.

A salient limitation of gait studies is that they require considerable time and space to administer. As well, the inclusion of the Stroop Interference task in dual-task studies requires non-executive processing (e.g., tone discrimination). A more parsimonious evaluation of executive function in SRC is an oculomotor assessment. Indeed, and in

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3 The Eriksen Flanker task is a test of selective attention and inhibitory control. The participant completes a directional response (i.e., key press) corresponding to a central target while ignoring the directionality associated with flanking stimuli (e.g., << > >>). The interference effect is similar to that of the Stroop task wherein interference from irrelevant stimuli influence response selection timing and accuracy (Eriksen & Eriksen, 1974).
contrast to gait studies, oculomotor tasks require less time and space to administer and provide for a more direct measure of executive function than the Stroop task (Kaufmann, Pratt, Levine, & Black, 2010). Moreover, convergent neuroimaging work involving humans and electrophysiological evidence from non-human primates provides an exemplar model for understanding the executive control of volitional saccades (i.e., goal-directed eye movement). In particular, antisaccades are a volitional response requiring that an individual saccade mirror-symmetrical to an exogenously presented target. Antisaccades result in longer reaction times (RT) (Hallett, 1978), more directional errors (Fischer and Weber, 1992), and increased endpoint error and variability (Gillen and Heath, 2014a; 2014b) than their prosaccade (i.e. saccade directed to veridical target location) counterparts. The antisaccade behavioural ‘costs’ have been attributed to the two-component executive control processes of inhibiting a prepotent prosaccade (i.e. response suppression) and the 180° transposition of a target’s coordinates (i.e. vector inversion) (for review see Munoz and Everling, 2004). Neuroimaging evidence has linked the constituent elements of the antisaccade task to increased activity in an extensive frontoparietal network (i.e., DLPFC, frontal eye fields: FEF, pre-supplementary eye fields: pre-SEF, intraparietal sulcus: IPS, ACC, and parietal occipital sulcus: POS) (Ford et al., 2005). As a result, the antisaccade task has been used as a tool to examine executive function in healthy controls as well as identify executive dysfunction in a range of clinical and neuropsychiatric populations (Heath et al., 2017; Heath et al., 2016; McDowell et al., 2002; McDowell et al., 1999; Pierrot-Deseilligny, Rosa, Masmoudi, Rivaud, & Gaymard, 1991; Rodrigue, Schaeffer, Pierce et al., 2018; Wang et al., 2016).

To my knowledge, only two studies have employed the antisaccade task in a population with a SRC. In the first, Johnson and colleagues employed antisaccades and concurrent fMRI to examine executive function at acute (i.e., <7 days) (Johnson et al., 2015b) and subacute (i.e., > 30 days) (Johnson et al., 2015a) stages of SRC recovery. Results showed that persons with a SRC produced acute and subacute stage antisaccade RTs that were 50 ms and 15 ms longer, respectively, than counterparts without a SRC. Further, the authors reported that the longer antisaccade RTs were associated with hyperactivity across a range of frontal and posterior structures (cerebellum, visual cortex, DLPFC, and ACC). The authors proposed that the “…elevated activation and additional
recruitment is due to compensatory mechanisms” (p. 571); that is, the author proposed inefficient activation of oculomotor planning mechanisms. In the second study, Webb and colleagues (2018) contrasted pro- and antisaccade performance in persons with a SRC at an early (i.e., initial: <7 days post-injury) and later (i.e., follow-up: 14-20 days post-injury) stage of SRC recovery. Importantly, the follow-up assessment occurred immediately after (i.e., in most cases < 2 hours) athletes had been medically cleared for safe return to play. Results showed that antisaccade RTs for the SRC group were 97 ms longer than controls at the initial assessment; however, RTs for the SRC and control group did not reliably differ at the follow-up assessment. It is, however, important to note that at the follow-up assessment persons with a SRC continued to exhibit increased antisaccade directional errors (i.e., a prosaccade instead of an instructed antisaccade). As a result, the authors concluded that executive dysfunction following a SRC persists even after clinical signs have resolved.

An important consideration of the antisaccade task and other executive and cognitive tasks is that their ‘challenging’ nature may exacerbate SRC symptomology (Covassin et al., 2013). It is therefore possible that a task-induced increase in symptom severity engenders an implicit or explicit control strategy wherein concussed athletes decrease executive effort to prevent (or reduce) symptomology. Of course, in an antisaccade task such a strategy would result in longer RTs and increased directional errors independent of an executive impairment. To address this issue, I employed traditional antisaccade performance metrics (i.e., RT and directional errors) with measures of: (1) pupil size (i.e., pupillometry), and (2) pre- and post-oculomotor assessment symptom severity determined via the SCAT-5 total symptom severity score. In the first case, the inclusion of pupillometry was based on work in healthy controls showing that the preparatory phase (i.e., prior to saccade initiation) of directionally correct antisaccades is associated with larger pupil dilations than counterpart prosaccade trials (Wang et al., 2015; see also Karatekin et al., 2009) and that pro- and antisaccade pupil size changes are blunted in persons with Parkinson’s disease (Wang et al., 2016). Given these findings, Wang and colleagues proposed that pupil size is a representative proxy of neural activity related to the executive control of saccade preparation. In the second case, it is widely recognized that the number and severity of concussion
symptoms (e.g., anxiety, headache, nausea, vertigo) is increased when an individual with
a SRC is returned to a challenging environment (i.e., school, occupational or sport) prior
to their recovery (Majerske, Mihalik, Ren et al., 2008; McCrea, Guskiewicz, Marshall et
al., 2003). It is, however, unclear whether the evaluation of antisaccades contributes to
increased symptom burden and a resultant decrease in executive effort and performance.
Accordingly, I had participants complete pre- and post-oculomotor assessment SCAT-5
post- concussion symptom scales. The total symptom severity score involves the Likert
ratings of a 22-item list of concussion symptoms that measure quality of life following
SRC recovery (Morgan, Gerry Taylor, Rusin, et al., 2012).

To my knowledge, no studies have examined symptom burden in combination
with pro- and antisaccade performance and pupillometry measures in persons with a
SRC. This represents an important issue because such a study provides a basis to identify
whether a SRC imparts a dysfunction to executive planning processes and/or renders an
increase in task-based symptom burden. Accordingly, my thesis examined traditional
antisaccade (and prosaccade) performance metrics with pupillometry and SCAT-5
symptom scores in persons with a SRC as well as their age- and sex-matched controls.
Oculomotor assessments occurred at an early stage (≤12 days post-SRC) (i.e., the initial
assessment) and later stage (14-30 days post-SRC) (i.e., the follow-up assessment) of
SRC recovery. SRC symptom severity (as determined via the SCAT-5) was collected
prior to and after initial and follow-up oculomotor assessments. In terms of research
predictions, if the SRC group produces longer antisaccade RTs coupled with null
between- group differences in preparatory phase pupil dilations and increased symptom
severity post-oculomotor assessment then results would evince a task-based increase in
symptom severity. In contrast, if the SRC group exhibits longer antisaccade RTs and a
between-group difference in pupil size without a change in symptom severity then results
would provide convergent evidence of an executive impairment in oculomotor planning.
Further, the inclusion of acute and follow-up stages provided a framework to determine
the magnitude by which SRC symptom burden and/or executive impairment continues to
influence oculomotor performance.
Chapter 3

3 Methods

3.1 Participants

SRC participants were recruited through the *Sports Medicine Concussion Care Program* at the Fowler Kennedy Sports Medicine clinic, London, ON, CA. Participants in the SRC group were required to have been diagnosed with a SRC via the Sport Concussion Assessment Tool (ver 5.0: SCAT-5) and the combined clinical judgment of a sports physician and physician assistant, and be recruited into the program within 12 days of the concussive event. Additional inclusion criteria included: between 16-35 years of age; right-handed (self-report); normal or corrected-to-normal vision; no previous or current neurological or neuropsychiatric disorder (apart from the current concussion); no history of learning disorder, and no use of anticholinergic medication. Individuals with a previous history of concussion were included and account for 50% of the SRC sample. Twenty-five individuals were identified for inclusion into the study with recruitment occurring over a 6-month window. The rationale for not being enrolled included: expressed lack of interest (N=2); due to the length of time between injury and diagnosis being greater than 12 days (N=6); and self-reported history of learning or neuropsychiatric disorder (N=3). Accordingly, 14 individuals with a SRC (age range: 16-28 years; 5 male, 9 female) agreed to participate in the study and completed the full study protocol. One SRC participant was excluded from my results due to excessive blinking. Thus, the oculomotor and SCAT-5 symptom severity data for the SRC group are based on 13 participants (age range: 16-28 years; 5 male, 8 female). Fourteen healthy individuals (i.e., control group, age range: 16-28 years of age; 5 male, 9 female) were recruited from the Western University community and served as age- and sex- matched controls. Inclusion criteria for the control group were the same as SRC participants with the exception that they reported no previous concussion history. Participants were asked to refrain from consuming caffeine or tobacco eight hours prior to any study visit.

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, and the Research Quality and Compliance Board, Lawson Health Research Institute. This work was conducted according to the Declaration of Helsinki.

3.2 Experimental Overview

The SRC group completed their experimental sessions (see details below) at two different time points (i.e., initial and follow-up assessments). The initial assessment occurred 1-12 days post concussive event (average= 6 days, SD= 4), and in all cases occurred within one hour of a concussion diagnosis by a sports medicine practitioner (see details in Section 3.1). The follow-up assessment occurred 14-30 days post concussive event (average= 24 days, SD= 5), and was completed within one hour of participants seeing the Fowler-Kennedy clinical care team for their follow-up evaluation. For the control group, the duration between initial and follow-up assessments were matched as close as possible to the timing of their age- and sex-matched participant in the SRC group (average= 17 days, SD= 3).

3.3 Apparatus and Procedure

Prior to and after initial and follow-up oculomotor assessments (see details below) participants completed the self-report SCAT-54 symptom severity checklist that includes 22 typical concussion symptoms (e.g., headache, difficulty concentrating, vertigo) with each scored on a Likert scale (0= none; 6= severe) (McCrorry et al., 2017). We used the total symptom score (maximum=132) to evaluate for possible pre- to post-oculomotor assessment changes in symptomology. The administration of the symptom severity checklist required approximately five minutes.

For the oculomotor assessment, participants sat in a height-adjustable chair with their head placed on a head/chin rest. A 30-inch LCD monitor (60 Hz, 8 ms response rate, 1280x960 pixels; Dell 3007WFP, Round Rock, TX, USA) located at participants’ midline and 550 mm from the front edge of the tabletop and was used to present visual stimuli. The gaze position and pupil size of participants’ left eye was sampled (EyeLink

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4 The SCAT-5 is available for download at http://www.sportphysio.ca/wp-content/uploads/SCAT-5.pdf
1000 Plus; SR Research Ltd, Ottawa, ON, Canada) at 1000 Hz. Two additional monitors visible only to the experimenter provided real-time point of gaze information, trial-by-trial saccade kinematics (i.e., displacement and velocity), and information related to the accuracy of the eye-tracking system (i.e., to perform a recalibration when necessary). Stimulus presentation and data acquisition were controlled via MATLAB (R2018b, The MathWorks, Natick, MA, USA) and the Psychophysics Toolbox extensions (ver 3.0; Brainard, 1997; Kleiner, Brainard, & Pelli, 2007) including the Eyelink Toolbox (Cornelissen, Peters, & Palmer, 2002). Prior to data collection the eye-tracker was calibrated using a nine-point calibration and was followed by an immediate verification to determine that no point in the calibration space contained more than 1° of error.

Stimuli were presented on a high-contrast black background (0.1 cd/m²) and included a centrally presented fixation cross (1°) that appeared as green or red and was luminance matched (42 cd/m²). The colour of the fixation indicated the nature of a to-be-completed response (i.e., prosaccade=green; antisaccade=red). As well, open white circles served as target stimuli (2.7° diameter: 132 cd/m²) and were located at 13.5° (i.e. proximal target) and 16.5° (i.e. distal target) to the left and right of the fixation cross and in the same horizontal axis. The different eccentricities were used to prevent participants from adopting stereotyped responses. A trial began with the appearance of a fixation cross for 1000 ms after which the fixation was extinguished and a target stimulus appeared 200 ms thereafter (i.e., gap paradigm) (Figure 5). A gap paradigm was used because its duration provided a timeframe to examine task-based changes in pupil dynamics (Wang et al., 2015). In line with Wang et al. (2015), target stimuli were presented for 50 ms and this brief presentation – in part – served to equate pro- and antisaccades for the absence of extraretinal feedback (Heath, Weiler, Marriott & Welsh, 2011). Target onset cued participants to pro- (i.e. saccade to veridical target location) or antisaccade (i.e. saccade mirror-symmetrical to target location) as “quickly and accurately” as possible. Pro- and antisaccades, as well as stimulus location (i.e., left and right of fixation at proximal and distal eccentricities) were pseudo-randomly interleaved for a total of 120 trials. Data collection – including calibration time – required approximately 12 minutes for control and SRC participants and the intertrial interval was set to 2.5 s (Eckstein et al., 2017).
3.4 Data Reduction and Pupil Preprocessing

Gaze position data were filtered offline via a dual-pass Butterworth filter employing a low-pass cut-off frequency of 15 Hz. Filtered displacement data were used to calculate instantaneous velocities via a five-point central-finite difference algorithm. Acceleration data were similarly obtained from the velocity data. Saccade onset was determined when velocity and acceleration exceeded 30°/s and 8000°/s, respectively. Saccade offset was marked by velocity less than 30°/s for 42 consecutive frames (i.e., 42 ms). Trials with missing data (i.e., loss of signal >25% of fixation period) (Winn et al., 2018), RT less than 100 ms (Wenban-Smith & Findlay, 1991), and/or an amplitude less than 2° or greater than 26° (Gillen & Heath, 2014a; 2014b) were excluded from the analyses and accounted for less than 6% of trials. In addition, pro- and antisaccades with a directional error (i.e., a prosaccade instead of an instructed antisaccade and vice versa) were excluded from the analyses of RT, movement time, saccade gain and pupillometry (see details below) because they are mediated by planning mechanisms distinct from their directionally correct counterparts (DeSimone, Weiler, Aber & Heath, 2014).

Pupil data were filtered separately offline via a 10 Hz low-pass filter. Trials missing more than 30% of data or an eye position deviation of more than 2° from the fixation cross during the initial fixation period (i.e., 0-1200 ms after fixation cross onset) were excluded from analyses. A blink correction algorithm was incorporated that involved linear interpolation beginning 50 ms before the blink and ending 150 ms after the blink in order to avoid task-uncorrelated high-frequency changes in pupil size (Winn et al., 2018). Furthermore, outliers greater than 2.5 standard deviations from the participants’ mean were removed (less than 18% of total data were removed). Because video-based tracking can distort pupil size following changes in gaze location I restricted measurement of this variable to epochs involving central fixation and prior to saccade initiation (i.e., when gaze was located at the center of the screen). Specifically, and in line with Wang et al. (2015), three epochs were selected: (1) the start of the visual fixation (FIXst: 100-300 ms after fixation onset), (2) maximal pupil constriction (CONmax: 650-750 ms after fixation onset), and (3) end of gap (GAPend: 150-200 ms following gap onset) (see Figure 5).
3.5 Dependent Variables and Statistical Analyses

Dependent variables were: reaction time (RT: time from stimulus onset to saccade onset), the coefficient of variation (CV) of RT (i.e. standard deviation/mean x 100), movement time (MT: time between movement onset and movement offset), percentage of directional errors (i.e. a prosaccade instead of an instructed antisaccade or **vice versa**), and amplitude gain (i.e. saccade amplitude/target amplitude) in the primary (i.e. horizontal) movement direction. Dependent variables for pupillometry included: baseline pupil diameter (ABS: average pupil diameter during FIX epoch), and task evoked pupil dilation (TEPD: GAP end epoch minus the CON max epoch) (see **Figure 5**). The aforementioned pupil measures were based on relative diameter and are in accord with an extensive literature (e.g., Karatekin et al., 2009; Wang et al., 2012; 2015; 2016). Notably, pupil responses reported in previous work consist of a sharp constriction component in response to fixation onset (i.e., the pupillary light response) followed by a dilation component (i.e., TEPD). The dilation component is reported to represent a measure of cognitive and neural processing related to saccade preparation in the locus coeruleus (LC), superior colliculus (SC), and frontal eye fields (FEF) (Aston-Jones & Cohen, 2005; Lehmann & Corneil, 2016; Wang et al., 2012; 2015). For the pupillometry data, values were converted from arbitrary units to millimeters using the algorithm provided by Hayes and Petrov (2016). The SCAT-5 total symptom severity score (maximum =132) also served as a dependent variable.

Dependent variables related to oculomotor measures were analyzed via 2 (group: SRC, control), by 2 (assessment: initial, follow-up), by 2 (task: pro-, antisaccade) split-plot ANOVAs. For the symptom score on the SCAT-5, the variable **time** (pre-assessment, post-assessment) was included in the ANOVA model to account for the fact that symptom scores were examined prior to and after an oculomotor assessment. An alpha level of 0.05 was used for statistical significance and simple-effects were employed to decompose main effects and interactions. Pearson correlation coefficients were used to examine putative relationships between saccade metrics and SCAT-5 symptomology scores.
FIG. 5. The timeline of visual and motor events for pro- and antisaccades (A). Three selected epochs for pupil analysis: FIX$_{st}$ (fixation start), 100-300ms after fixation onset; CON$_{max}$ (maximal pupil constriction), 650-750ms after fixation onset; GAP$_{end}$ (gap end), 150-200ms after gap onset (B). The solid black line indicates time course changes of absolute pupil diameter in response to stimuli.
Chapter 4

4 Results

4.1 Symptom Scores

Symptom Burden

The SCAT-5 symptom severity score revealed a main effect for group, $F(1,25)= 39.27$, $p<0.001$, $\eta_p^2=0.61$, assessment, $F(1,25)= 30.41$, $p<0.001$, $\eta_p^2=0.55$, and an interaction involving group by assessment, $F(1,25)= 30.41$, $p<0.001$, $\eta_p^2=0.55$. Figure 6 shows that the SRC group had greater symptom scores than the control group at initial and follow-up assessments (all $t(25)= -5.85$ and $-2.301$, $p<0.001$ and $p=0.030$, respectively). In addition, within-groups comparisons indicated that the control group reported equivalent values at initial (3, SD=3) and follow-up assessments (3, SD=3) ($t(13)= 0.00$, $p=1.0$), whereas the SRC group showed a decrease from initial (38, SD=19) to follow-up assessments (10, SD=10) ($t(12)= 5.33$, $p<0.001$). Notably, the symptom severity score did not produce a main effect of time nor any higher-order interaction involving that variable, all $F(1,25)<1.25$, ps>0.27, all $\eta_p^2<0.04$. Further, and given the nature of our research question, we employed the two one-sided tests (TOST) statistic (i.e., equivalence tests) to contrast SRC group pre- and post-oculomotor SCAT-5 scores at initial and follow-up assessments (Lakens, Scheel, & Isager, 2018). At the initial assessment, pre- and post-oculomotor values were not within an equivalence boundary ($t(12)= 1.4$, $p=0.094$), whereas follow-up assessment values were ($t(12)=1.92$, $p=0.041$). Although initial assessment values were not within an equivalence boundary, values decreased from the pre- (40, SD=21) to post-oculomotor (35, SD=21) time points. Thus, null hypothesis, equivalence testing and interpretation of descriptive statistics indicate that the oculomotor task used here did not increase symptom severity.
FIG. 6. The left panels show SCAT-5 participant-specific symptom severity scores (maximum score = 132) at initial and follow-up assessments and prior (i.e., pre-) and after (i.e., post) each oculomotor time point. The smaller offset panel shows group mean SCAT-5 symptom severity difference scores (i.e., post- minus pre-oculomotor time points) with a negative valence indicating decreased symptom severity from pre- to post- time points. Error bars represent 95% between-participant confidence intervals.

4.2 Oculomotor data

Reaction time (RT) and coefficient of variation (CV of RT)

The main panels of Figure 7 present control and SRC group pro- and antisaccade RT frequency histograms at acute and follow-up assessments with the light and dark grey rectangles in each panel highlighting anticipatory (<100 ms) and short-latency (100-200
ms) responses, respectively. The figure qualitatively demonstrates the expected finding that RTs for prosaccades were shorter than antisaccades. In addition, the histograms demonstrate that pro- and antisaccades were associated with a low frequency of anticipatory responses and that the former produced a greater percentage of short-latency responses. Further, Figure 7 shows that pro- and antisaccade RTs decreased from the initial to follow-up assessment for the SRC group – but not the control group. Moreover, Figure 9 presents exemplar SRC (bottom panels) and control group (top panels) participants’ time by position traces for pro- and antisaccades at initial and follow-up assessments. The figure demonstrates that the SRC participant produced markedly longer and more variable RTs than the control participant at the initial assessment and that this difference was decreased at the follow-up assessment. In term of quantitative analyses, RT yielded main effects of group, F(1,25)= 7.05, p=0.014, $\eta^2_p=0.22$, assessment, F(1,25)= 115.67, p= 0.010, $\eta^2_p=0.24$, and task, F(1,25)= 115.67, p< 0.001, $\eta^2_p=0.82$, and an interaction involving group by assessment, F(1,25)= 5.40, p= 0.029, $\eta^2_p=0.18$.

Figure 7A presents participant-specific pro- and antisaccade RTs at initial and follow-up assessments and shows that RTs for antisaccades were longer than prosaccades. In decomposing the two-way interaction, Figure 7A and 7B show that initial assessment RTs were longer for the SRC than the control group (t(25)= -4.14, p= 0.001); however, follow-up assessment RTs did not reliably vary between groups (t(25)= -1.47, p=0.155). Additionally, I computed within-groups comparisons and found that the SRC group had larger initial than follow-up assessment values (t(12)=2.77, p=0.017), whereas control group initial and follow-up assessment values did not reliably differ (t(13)= 0.51, p=0.622).
FIG. 7. The top and bottom panels show control and sport-related concussion (SRC) group histograms depicting the percent frequency pro (right panels; green traces) and antisaccade (left panels; red traces) RTs at initial and follow-up assessments. The light and dark grey rectangles in each histogram highlight anticipatory (<100 ms) and short-latency (100-200 ms) responses, respectively. The left inset panel (A) shows participant-specific mean pro (green) and antisaccade (red) RTs for control and SRC groups at initial and follow-up assessments. The right inset panel (B) shows group mean pro- and antisaccade RTs for control and SRC groups at initial and follow-up assessments. Error bars represent 95% within-participant confidence intervals.
The CV of RT revealed main effects of group, $F(1,25)= 6.83$, $p= 0.015$, $\eta^2_p =0.21$, assessment, $F(1, 25)= 7.18$, $p= 0.013$, $\eta^2_p =0.22$, and task, $F(1,25)= 27.06$, $p<0.001$, $\eta^2_p =0.52$. Values were larger for the SRC (23, SD=10) than the control group (18, SD=6), were larger at the initial 22, SD=9) than follow-up (19, SD=8) assessment, and were larger for prosaccades (24, SD=8) than antisaccades (17, SD=7).

*Directional errors*

Directional errors yielded main effects of group, $F(1,25)= 11.86$, $p=0.002$, $\eta^2_p =0.27$, assessment, $F(1,25)= 9.18$, $p= 0.006$, $\eta^2_p = 0.27$, and task, $F(1,25)=18.57$, $p<0.001$, $\eta^2_p = 0.43$. Directional errors were greater for the SRC (17%, SD=15) than the control (7%, SD=7) group, were greater in the initial (14%, SD=14) than follow-up (10%, SD=11) assessment and were greater for anti- (17%, SD=14) than prosaccades (7%, SD=9) *(Figure 8)*.

**FIG. 8.** The left panel shows participant-specific percentage of pro- and antisaccade directional errors for control and sport-related concussion (SRC) groups at initial and follow-up assessments. The right panel shows group mean pro- and antisaccade directional errors for control and SRC groups at initial and follow-up assessments. Error bars represent 95% within-participant confidence intervals.
Movement time and amplitude gain

The main panels of Figure 9 present control and SRC group pro- and antisaccade MT percent frequency histograms at initial and follow-up assessments. The analysis of MT revealed a main effect for group, F(1,25)= 4.94, p=0.035, $\eta^2=0.17$: values were longer for the SRC than the control group.
FIG. 9. The top and bottom panels show control and sport-related concussion (SRC) group percent frequency histograms for pro (right panels; green traces) and antisaccade (left panels; red traces) MTs at initial and follow-up assessments. The left inset panel (A) shows participant-specific mean pro (green) and antisaccade (red) MTs for control and SRC groups at initial and follow-up assessments. The right inset panel (B) shows group mean pro- and antisaccade MTs for control and SRC groups at initial and follow-up assessments. Error bars represent 95% within-participant confidence intervals.
The inset panels of Figure 10 show a SRC and control participant’s pro- and antisaccade endpoint dispersions – and associated 95% confidence ellipses – at initial and follow-up assessments. The figure shows that the endpoints were more dispersed for the SRC than the control participant and were more dispersed for anti- than prosaccades. Additionally, the main panels of Figure 11 present control and SRC group pro- and antisaccade gain frequency histograms at acute and follow-up assessments. As expected, the figure qualitatively demonstrates prosaccade gains were larger than antisaccades. In terms of quantitative analysis, saccade gain results revealed a main effect for task, F(1,25)= 16.90, p<0.001, $\eta^2_p=0.40$, as well as interactions involving assessment by task, F(1,25)= 8.87, p=0.006, $\eta^2_p=0.26$, and group by assessment by task, F(1,25)= 6.05, p=0.021, $\eta^2_p=0.20$. As expected (see Harris, 1995), prosaccades produced larger gains than antisaccades, and Figure 11B shows that at the initial assessment the SRC group produced smaller prosaccade gains compared to the control group (t(25)= 2.46, p=0.021), whereas antisaccade gains did not vary between groups (t(25)=0.63, p=0.532). At the follow-up assessment, pro- and antisaccade gains did not vary between SRC and control groups (all t(25)= 0.75 and 1.05, ps= 0.46 and 0.30, respectively). Within-group comparisons revealed that control group pro- and antisaccade gains did not vary between initial and follow-up assessments (prosaccade: t(13)=0.18, p=0.863; antisaccade: t(13)=1.18, p=0.259). Similarly, SRC group pro- and antisaccade gains did not vary between initial and follow-up assessments (prosaccade: t(12)=-1.92, p=0.079; antisaccade: t(12)=2.12, p=0.055).
FIG. 10. The large panels show position (horizontal movement direction: in °) by time pro- (green traces) and antisaccade (red traces) trajectories for an exemplar control (top panels) and sport-related concussion (SRC) (bottom panels) participant at initial (left panels) and follow-up (right panels) assessments for the proximal (13.5°) and distal (16.5°) targets. Direction error trials are depicted by negative and positive deflection pro- and antisaccade trajectories, respectively. For the same participants, the inset panels show horizontal and vertical pro- and antisaccade endpoints (in °) and associated 95% confidence ellipses (solid line= prosaccade; dashed line= antisaccade). The inset figures display endpoints only for the proximal target.
FIG. 11. The top and bottom panels show control and sport-related concussion (SRC) group histograms for the frequency of pro (right panels; green traces) and antisaccade (left panels; red traces) gain (i.e., saccade amplitude/target amplitude) at initial and follow-up assessments. The left inset panel (A) shows participant-specific mean pro (green) and antisaccade (red) gains for control and SRC groups at initial and follow-up assessments. The right inset panel (B) shows group mean pro- and antisaccade gains for control and SRC groups at initial and follow-up assessments. Error bars represent 95% within-participant confidence intervals.
4.3 Pupillometry metrics

Baseline pupil diameter for correct pro- and antisaccade trials

Baseline pupil diameter produced an interaction involving group by assessment, F(1,25)= 8.64, p= 0.007, \eta_p^2=0.26. **Figure 12** shows that SRC and control group baseline pupil diameters did not vary at the initial (t(25)= -0.93, p=0.361) or follow-up assessment (t(25)=0.27, p=0.790). Within-group comparisons indicated that control group initial and follow-up assessment values did not reliably vary (t(13)= -0.88, p=0.40), whereas SRC group values were larger at the initial than the follow-up assessment (t(12)=3.04, p=0.01).

**FIG. 12.** The left panel (A) demonstrates baseline corrected pro- (red line) and antisaccade (green line) pupil size by time values averaged over multiple trials for an exemplar control (solid line) and sport-related concussion (SRC) (dotted line) participant during the period following fixation onset. The first shaded grey rectangle represents the FIXst epoch and highlights absolute pupil diameter. The second shaded grey rectangle represents the CONmax epoch and highlights maximal pupil constriction. The right panels (B) show mean pro- and antisaccade absolute pupil diameter (i.e., average pupil diameter 100-300 ms after fixation onset; FIXst epoch 100-300ms) for control and sport-related concussion (SRC) groups at initial and follow-up assessments. Error bars represent 95% within-participant confidence intervals.
Pupil dynamics before stimulus appearance

**Figure 13A** presents exemplar SRC (dashed lines) and control group (solid lines) participants’ task-evoked pupil dilation (TEPD) by time traces averaged over multiple trials for pro- and antisaccades at the initial assessment. The figure demonstrates that the SRC participant produced larger TEPDs than the control participant. In terms of quantitative analysis, TEPDs yielded significant main effects of group, F(1,25)= 9.29, p=0.005, \( \eta^2_p = 0.27 \), and task, F(1,25)= 27.63, p<0.001, \( \eta^2_p = 0.53 \), and a group by assessment interaction, F(1,25)= 4.46, p=0.045, \( \eta^2_p = 0.15 \). As expected, antisaccade values were larger than prosaccades and SRC group values were larger than control values. **Figure 13B** demonstrates that the SRC group produced larger values than the control group at initial and follow-up assessments (all t(25)= -3.17 and -2.33, ps= 0.004 and 0.029, respectively). In turn, within-group contrasts indicated that control group TEPDs did not vary from initial to follow-up assessment (t(13)= -0.35, p=0.734), whereas SRC values decreased from the initial to follow-up assessment (t(12)= 2.53, p=0.027).

**FIG. 13.** The left panel (A) demonstrates baseline corrected changes in pupil size from maximal pupil constriction (i.e. CON\text{max} epoch -550ms from target onset) to the end of the gap interval (i.e. GAP\text{end} epoch -50ms from stimulus onset) for exemplar control (solid line) and sport-related concussion (SRC) (dashed line) participant pro- (red line) and antisaccades (green initial) at the initial assessment. The shaded grey rectangle in this panel represents the gap interval where no fixation cross is present. The right panel (B) shows mean pro- and antisaccade task-evoked pupil dilations (TEPDs) computed by examining the difference in pupil size from the CON\text{max} to GAP\text{end} epochs for control and SRC groups at initial and follow-up assessments. Error bars represent 95% within-participant confidence intervals.
4.4 Correlations between oculomotor measures and SCAT-5 symptomology

Karatekin, Bingham, & White (2009) reported that a “strong positive” correlation between antisaccade RT variability and directional errors provides an index of task-based “fluctuations of attention”; that is, the correlation determines whether attentional dysfunction relates to antisaccade performance deficits. Accordingly, for the SRC group I computed the correlation coefficient involving the aforementioned variables and found that the metrics did not reliably relate at either initial (r=0.48, p=0.09) or follow-up (r=0.26, p=0.39) assessments (Figure 14A). In addition, I examined if SRC group antisaccade RTs and TEPD values observed at the initial assessment were related to pre- and/or post-assessment symptom burden as determined by the SCAT-5 (Figure 14B). Antisaccade RTs were not reliably related to either pre- (r=0.24, p=0.43) or post-assessment (r=0.39, p=0.19) symptom scores. Additionally, Figure 14C demonstrates that antisaccade TEPDs were not reliably related to either pre- (r=0.04, p=0.89) or post-assessment (r=0.20, 0.52) symptom scores. Last, I computed correlations between antisaccade RT and TEPD values for both SRC and control groups and found that the relationship between both variables approached – but did not attain – a conventional level of statistical significance (r=-0.26, p=0.06) (Figure 14 D).
FIG. 14. Scatterplots for the relationship between: A) sport related concussion (SRC) reaction time variability (RTvar) and the percentage of directional errors at initial and follow-up assessments, B) SRC antisaccade reaction times (RT) and SCAT-5 symptom severity scores (max=132) at pre- and post-oculomotor assessments, C) SRC antisaccade task-evoked pupil dilations (TEPD) and SCAT-5 symptom severity scores at pre- and post-oculomotor assessments, and 4) SRC (open symbols) and control (closed symbols) group antisaccade TEPD and antisaccade RT at initial (blue) and follow-up (dark grey) assessments.
5 Discussion

The present investigation examined saccade performance and pupillometry as well as SCAT-5 symptom severity to determine whether oculomotor dysfunction following the initial and later stages of a SRC relates to impaired executive-related motor preparation and/or increased task-based symptom burden. In outlining my results, I first discuss the general differences between pro- and antisaccade performance and pupillometry measures, and then discuss how such measures and SCAT-5 symptom severity scores varied between the SRC and control groups at initial and follow-up assessments.

Pro- and antisaccades exhibit distinct performance and pupillometry properties

Antisaccades produced longer RTs, increased directional errors and reduced gains compared to prosaccades. The prosaccade findings have been taken to reflect that a prepotent response entailing overlapping stimulus-response (SR) spatial relations is mediated via retinotopic motor maps in the SC (Wurtz & Albano, 1980) that operate with minimal top-down executive control (Pierrot-Deseilligny et al., 1991). In turn, the antisaccade RT and directional error findings reflect that the task’s constituent processes of response suppression and vector inversion are time-consuming and executive demanding processes (Munoz & Everling, 2004; Olk & Kingstone, 2003). Furthermore, that antisaccades produced smaller gains is in line with evidence that decoupling SR spatial relations results in increased uncertainty about target location (Edelman, Valenzuela, & Barton, 2006) and renders motor output supported via visual information (i.e., relative) functionally distinct from the direct (i.e., absolute) visual information mediating prosaccades (Gillen and Heath, 2014a; 2014b). The antisaccade performance metrics have been interpreted as providing a biomarker for executive dysfunction following a SRC (Johnson et al., 2015a; 2015b; Webb et al., 2018) as well as a number of other neurological and neuropsychiatric impairments (Heath et al., 2016; 2017; McDowell et al., 1999; 2002; Pierrot-Deseilligny et al., 1991; 2003; Rodrigue et al., 2018). Importantly, however, antisaccade RTs reflect a constellation of cognitive, motor and sensory demands and it is therefore not possible to assert that RT changes directly
relate to executive dysfunction (Schluter, Rushworth, Mills, Passingham, 1998). For example, an increase in SRC symptom severity arising from the executive demands of antisaccades may result in a decrease in effort and a general increase in antisaccade RT and directional errors. To account for this potential limitation, the present work employed traditional antisaccade performance metrics and pupillometry in combination with a pre- and post-oculomotor assessment of SRC symptom severity to provide a framework to determine whether antisaccade deficits following a SRC reflect: 1) impaired executive-based oculomotor planning, and/or 2) increased task-based symptom burden.

It has been demonstrated that pupil size is modulated by saccade preparation and neural activity in the SC (Wang et al., 2012) and FEF (Lehmann & Corneil, 2016) – structures that support the production of pro- and antisaccades. As such, it has been proposed that task-evoked pupil dilations (TEPD) preceding saccade initiation provide a measure of executive-related preparatory activity (Lee & Dan, 2012; Wang et al., 2012; 2015). In the present work, TEPDs for antisaccades (across SRC and control groups) were larger than prosaccades and is a result directly in line with Wang et al. and one that I attribute to increased fixation-related activity (associated with top-down inhibitory control of saccade activity) required to suppress a reflexive prosaccade prior to target presentation. As a result, I propose that the observed differences in pupil dynamics coupled with the traditional antisaccade performance metrics provides a framework to address the nature of oculomotor dysfunction in persons with a SRC.

Concussion symptomology did not vary from pre- to post-oculomotor assessments

A growing number of studies have asserted that impaired antisaccade RTs following a SRC provide a measure of executive dysfunction (Johnson et al., 2015a; 2015b; Webb et al., 2018). As mentioned previously, an alternative account is that RT and directional error differences between SRC and control participants reflect a task-based increase in symptom-burden and cognitive disengagement in an executive demanding task (Covassin et al., 2013). To address that issue, I measured the severity of concussion symptoms prior to and after each oculomotor assessment. As expected,
symptom severity for the SRC group was greater than the control group at both initial and follow-up assessments and the SRC group showed reduced symptomology from initial to follow-up assessments. More germane to the present results, symptom severity for the SRC group did not vary from pre- to post-oculomotor assessment at initial or follow-up sessions. In fact, Figure 6 shows that group mean data for SRC symptom severity decreased – albeit not reliably – from pre- to post-oculomotor times points. In addition, I computed correlation coefficients relating antisaccade RTs to symptom severity and antisaccade RT variability to directional errors. In both cases, the variables did not reliably relate; that is, symptom severity did not reliably predict antisaccade RT or TEPD measures, and symptom severity did not relate to the ability to maintain task-based focus of attention (Karatekin et al., 2009). Accordingly, the oculomotor assessment used here did not contribute to a task-based increase in symptom burden.

**Pro- and antisaccades: Initial and follow-up assessments**

Figure 7 shows that at the initial assessment, the SRC group produced pro- and antisaccade RTs that were 71ms and 51 ms longer than the control group, respectively, and the SRC group produced more directional errors than the control group (Figure 8). In terms of the prosaccade RT findings, I was initially surprised by the magnitude of the difference between SRC and control groups given that previous work by my group (Webb et al., 2018) found no group differences in RTs. In accounting for my finding, I note that Webb et al. employed a blocked pro- and antisaccade design, whereas my study involved an interleaved trial design. The random presentation of pro- and antisaccades introduces an additional executive component of task-switching (Allport, Styles, & Hsieh, 1994) and the oculomotor task-switching literature has found that RTs for a prosaccade preceded by an antisaccade are increased compared to when a prosaccade is followed by its same task-type5, whereas the converse switch does not influence RT (Tari, Fadel, & Heath, 2019; Weiler & Heath 2012a; 2012b; 2014; Weiler, Hassal,

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5 Control prosaccade switch trials (255ms, SD=58) produced longer RTs than their task-repetition counterparts (225ms, SD=57). Similarly, SRC prosaccade switch trials (331ms, SD=76) produced longer RTs than their task-repetition counterparts (273ms, SD=76).
This unidirectional prosaccade switch-cost has been interpreted to reflect that the constituent elements of the antisaccade task require an executive-mediated task-set that persists inertially and proactively delays the planning time for a subsequent prosaccade. What is more, support for this explanation is garnered by a recent study by Clough et al. (2018) reporting that asymptomatic persons with a history of a SRC elicit longer prosaccade switch-costs than their non-concussed controls – a result the authors interpreted in the context of Weiler and Heath’s (2014) oculomotor task-set inertia hypothesis. Accordingly, I propose that the longer initial assessment prosaccade RTs for the SRC group reflect executive dysfunction in task-switching (i.e., prosaccades). In terms of initial assessment antisaccade RTs, that the SRC group produced longer values than the control group is in line with previous work (Johnson et al., 2015a; 2015b; Webb et al., 2018), and the magnitude of the group difference observed here (51 ms) is roughly in accord with the previous 53 and 93 ms differences reported by Johnson et al. and Webb et al., respectively. As a result, the RT and directional error findings coupled with the observation that concussion symptomology did not increase from pre- to post-oculomotor assessments (see Concussion symptomology did not vary from pre- to post-oculomotor assessments) lends further support for the view that a SRC imparts a dysfunction to executive-related oculomotor planning mechanisms.

At the follow-up assessment, pro- and antisaccade RTs for the SRC group did not reliably differ from the control group. The RT finding is consistent with Webb et al. (2018) who showed that between 14 and 20 days following a concussion diagnosis – and when athletes were medically cleared for return to play – antisaccade RTs for SRC and controls did not reliably differ (see also Johnson et al. 2015a). Further, I note that the improved follow-up assessment RTs cannot be attributed to a speed-accuracy trade-off (Fitts, 1954) given that the SRC group showed reduced directional errors and improved saccade gains. In other words, the SRC group did not increase their pro- and antisaccade RTs at the cost of increased directional errors and decreased endpoint accuracy. It is, however, important to note that in spite of the improved follow-up assessment RTs, the SRC group demonstrate more pro- and antisaccade directional errors than the control group at the follow-up assessment. This is consistent with Webb et al. and supports the
finding that persons with a SRC demonstrate persistent executive deficits relating to saccade inhibition and the maintenance of task rules.

*Pupillometry in oculomotor planning*

Antisaccades have been used to examine executive impairments stemming from prodromal Alzheimer’s disease (Heath et al., 2016; 2017), neuropsychiatric disease (Karatekin et al., 2009; McDowell et al., 1999; 2002; Rodrigue et al., 2018; Wan, Thomas, Jarvis, & Boutros, 2017), and TBI (Covassin, Petit, & Anderson, 2019; Webb et al., 2018). As indicated above, the SRC literature has shown that antisaccades produce longer RTs and increased directional errors compared to healthy controls – a pattern of results interpreted to reflect a high-level deficit in oculomotor planning (Heitger et al., 2007a; 2004; Johnson et al., 2015a; 2015b; Webb et al., 2018). Wang et al. (2015) have proposed that an additional reporter variable for understanding antisaccade planning demands is the incorporation of pupillometry during movement preparation. To that end, I measured TEPDs in concert with pro- and antisaccade performance and found that individuals with a SRC produced larger pro- and antisaccade TEPDs compared to healthy controls. Notably, this occurred in the absence of any increase in task-based symptom burden. I believe that this finding indicates the inefficient recruitment and allocation of executive resources required for inhibitory control and the effective maintenance of an antisaccade task-set. Such a conclusion is in accord with Wang et al.’s (2016) work involving pro- and antisaccades in participants with Parkinson’s disease, and is a view consistent with Johnson et al.’s (2015a; 2015b) fMRI finding indicating that a SRC imparts inefficient neural activity across a constellation of cortical and subcortical structures. That said, I note that pupil size, in and of itself, does not provide a criterion for SRC diagnosis or management; rather, I propose that antisaccade performance, pupillometry and SCAT-5 symptomology together evince an oculomotor executive deficit following a SRC.

*Pupil dynamics: initial and follow-up assessments*

At the initial assessment, the onset of the fixation-cross resulted in comparable SRC and control group absolute pupil size. Absolute pupil size is modulated by activity
in the locus coeruleus–norepinephrine (LC-NE) system and this is thought to be mediated via an arousal mechanism (Aston-Jones & Cohen, 2005; Wang, Baird, Huang, Coutinho, Brien, & Munoz, 2018) based on findings showing a robust correlation between absolute pupil size and LC neural activity (Gilzenrat et al., 2010). That the SRC and control group exhibited comparable absolute pupil size suggests a similar level of LC activity between SRC and control groups and thus an equivalent level of psychophysiological arousal. In other words, results suggest that executive-related performance deficits and accompanying cognitive-related pupil responses in individuals with a SRC are not a reflection of impairments in LC activity and psychophysiological arousal. In contrast to the null absolute pupil size findings, initial assessment pro- and antisaccade TEPDs for the SRC group were larger than the control group (Figure 13). Recall that TEPDs in the pro- and antisaccade task have been interpreted to reflect saccade motor preparation and executive-related fixation activity in the SC and FEF (Lehmann & Corneil, 2016; Wang et al., 2015; 2016). My TEPD results – in combination with the abovementioned saccade performance metrics – suggest that the SRC group presented with a deficit in task preparation for the executive demands of the pro- and antisaccade trials used here.

At the follow-up assessment, the SRC group yielded absolute pupil diameters that were on par with their control counterparts. In contrast, follow-up assessment pro- and antisaccade TEPDs for the SRC group continued to be larger than the control group – a result I propose to be indicative of persistent executive dysfunction in movement planning. Further, I emphasize that this conclusion is supported by the finding that the SRC group continued to demonstrate increased directional errors at the follow-up assessment.

Limitations

My results are constrained by at least four methodological limitations. First, the SRC group included single- and multiple-concussed athletes and given the sample size used here it was not possible to determine whether the magnitude of an oculomotor dysfunction varies among persons with a single versus multiple concussions. Future work should therefore examine whether concussion history differentially influences
oculomotor performance and pupillometry metrics. This idea is illustrated by
DeBeaumont et al.’s (2007) electroencephalographic study demonstrating a significant
attenuation in the amplitude of ERP waveforms as a function of single and multiple
SRCs. Second, the evaluation of oculomotor performance, pupillometry and SCAT-5
symptomology should be examined in a longitudinal design (i.e., acute, subacute, and
early and late chronic stages) to determine whether or not subtle executive deficits are
resolved and hence determine whether the antisaccade task represents a reliable tool for
SRC management. Third, initial and follow-up oculomotor assessments were completed
at a range of times post-concussion (i.e., from 7 to 27 days), and in this study is a factor
attributed to patient scheduling at the Sports Medicine Concussion Care Program at the
Fowler Kennedy Sports Medicine clinic. In future work, I aim to involve varsity athletic
trainers and complete oculomotor assessment prior to the beginning of in-season
competition and then again immediately (i.e., within 1 day) following training staff
indication of a suspected SRC. Such a framework would provide for a within-person
control to address the magnitude and duration of executive-related oculomotor planning
dysfunction. Last, pupil size on its own does not provide a diagnostic criterion for
determining a SRC because such a measure is influenced by an array of cognitive and
sensory processes (i.e., arousal, motivation, attention, and cognitive processes). That
being said, my work as well as other studies (Wang et al., 2016; Karatekin et al., 2009)
indicate that measures of pupillometry when accompanied by additional metrics (e.g.,
behavioural, electroencephalographic, neuroimaging) provide a platform for assessing
temporally specific changes in the executive control of saccades.

Conclusion

The initial and follow-up stage oculomotor assessments used here did not result in
a pre- to post-assessment increase in SCAT-5 symptom severity. In terms of oculomotor
performance, the initial oculomotor assessment showed that persons with a SRC
produced longer pro- and antisaccade RTs, increased directional errors and larger TEPDs.
At a follow-up assessment, SRC and control group RTs did not reliably differ; however,
the former group continued to exhibit increased directional errors and larger TEPDs.
Taken as a whole, the present results indicate that SRC changes in oculomotor
performance are independent of a task-based increase in symptom burden and thus reflect impaired executive-related oculomotor planning. Furthermore, these results highlight the utility of implementing *combined* oculomotor performance, symptom evaluation and pupillometry measures in SRC diagnosis, management, and recovery.
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Research, Institute of Education Sciences, U.S. Department of Education.
Appendices

Appendix A: Initial Health Science Research Board Approval

Dear Dr. Matthew Heath,

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

Documents Approved:

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

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

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCP 2), the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

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

Sincerely,

[Signature]

Ethics Officer on behalf of Dr. Philip Jones, HSREB Vice-Chair
Appendix B: Sport Concussion Assessment Tool- 5th Edition

The SCAT-5 is available for download at http://www.sportphysio.ca/wp-content/uploads/SCAT-5.pdf
Curriculum Vitae

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