AN EXPLORATION OF SEX- AND HORMONE-RELATED DIFFERENCES IN COGNITIVE-MOTOR PERFORMANCE, BRAIN NETWORK INTEGRITY, AND RECOVERY METRICS FOLLOWING CONCUSSION.

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Abstract:

Concussion, a form of mild traumatic brain injury, presents itself differently in all who sustain them. This makes diagnosis, recovery tracking, and return to play decisions extremely difficult. Along with general individual differences, sex and sex hormones may have an impact on incidence, symptoms, and time to recovery. The purpose of these dissertation projects was to better understand the general effects of concussion and add to the literature informing clinicians of what to look for following injury. Within this, another focus was to explore the potential impact of aspects related to sex on current metrics for examining concussive injury. We collected data from varsity level university athletes with and without a previous history of concussion. Data included visuomotor performance on a standard and non-standard reaching task, sport concussion assessment tool measures including symptom scales and balance, resting state functional magnetic resonance imaging, and hormone levels (estradiol, testosterone, and progesterone) via salivary enzyme immunoassays. Results from the three studies add to the literature surrounding both individualized and sex-related differences in outcomes following concussion, as well as the impact of hormones on general visuomotor performance and resting state functional connectivity (rs-FC) in females. Sex-specific differences were noted in visuomotor performance and symptom presentation. Progesterone and testosterone both exhibited positive relationships with visuomotor performance, and progesterone also exhibited a positive relationship with rs-FC in the dorsal attention network and a negative relationship with rs-FC in the salience ventral attention network. Overall, these results provide more detailed insight into the heterogeneous nature of concussion, and support that it is important to consider individuality in all cases of return to play decisions.

To my Nana – For every time you called me *Doctor*.

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Chapter one: General Introduction

Concussion, a form of mild traumatic brain injury, is being increasingly recognized as a debilitating injury requiring immediate, suitable, and individualized attention. In the past, primarily in the world of sport, concussion was considered a minor head injury, with limited standards in place surrounding care of injury and return-to-play protocols. As of late, research surrounding concussion has provided insight into the potential mechanisms of injury (Delaney et al., 2014; Hinton-Bayre et al., 2004) the resulting consequences, (Covassin, Swanik et al., 2006; Covassin, Schatz & Swanik, 2007; Frommer et al., 2011; Iverson, Gaetz et al., 2004), and the necessity for appropriate care following injury to ensure a safe and efficient recovery (Collines, Kontos, et al., 2014; McCrory et al., 2013; McCrory et al., 2017).

While the research is progressing, there are still many aspects which require further investigation. Recently there has been increased interest surrounding sex-specific differences in the impact of and recovery from concussion. Specifically, does concussion impact males and females differently, and what, if any, are the underlying causes of these differences?

In our daily lives, most people unconsciously execute a range of actions, some very simple and some more complicated. Cognitive motor integration (CMI), the act of thinking and moving at the same time, is essential for many of these tasks. For example, driving a car, using a computer mouse to move the cursor on the vertical screen, and playing sports. Through research, the frontal-parietal network, a functional brain network, has been identified as essential for the successful execution of tasks requiring CMI. In healthy brains, the frontal-parietal network is active when individuals are required to execute tasks which require some form of thinking and moving at the same time (Gorbet, Staines, & Sergio, 2004; Sayegh et al., 2017; Gorbet & Sergio, 2019). Interestingly, sex-related differences in frontal-parietal network activation have been noted during

CMI tasks in healthy brains, despite no behavioural differences (Gorbet & Sergio, 2007). Additionally, difficulty with CMI has been seen in those with different forms of reduced brain health, including concussion history (Sergio, Dalecki, et al., 2017; Dalecki et al., 2016) dementia risk (Rogojin et al., 2019), and mild and moderate cognitive impairment (de Boer et al., 2018).

In most sports (and more generally in many lines of work and duty), CMI is a necessity to safely navigate the field of play, be aware of rules and regulations, and accurately respond to the fast-paced and continually changing environment. As well, the brain areas required for CMI have a large overlap with those commonly affected by concussion. Therefore, it is not surprising that research has noted lingering deficits in brain function through the use of a CMI task, despite current standards having deemed these athletes clear and ready to return to play (Sergio, Dalecki, et al., 2017; Dalecki et al., 2016). Additionally, previous research has shown a difference in the performance of elite-level athletes versus varsity-level athletes on the current diagnostic metrics for concussion (Hurtubise et al., 2016). As well, it has been noted that individuals who have played their sport for longer, recover faster from concussion (Dalecki et al., 2019). In addition to sex-related differences seen in healthy CMI network activation, sex-related differences in both symptoms (Covassin, Schatz, & Swanik, 2007; Frommer et al., 2011; Berz et al., 2013) and recovery trajectory (Berz et al., 2013; Ono et al., 2016) following concussion have been noted. Therefore, it is important to consider the implications of blanket protocols for all athletes irrespective of skill level or sex.

The objective of this research is to add to the literature regarding the potential sex-specific differences on current concussion metrics, and investigate underlying neurological connections with behavioural symptoms following concussive injury as a function of hormonal fluctuations.

The overall goal being to piece together a larger picture through the combination of the resulting evidence as insight into changes needed on diagnostic and recovery tracking metrics.

Included in this introduction is detailed information on sensorimotor transformation, concussion, resting state functional magnetic resonance imaging (rs-fMRI), and current literature on sex-specific differences in aspects of general cognition and concussion. Moving forward, Chapter Two investigates differences in visuomotor performance and emotionality between males and females. Chapter Three and Four are extensions of this research investigating the impact of hormones on current concussion metrics in females, and exploring the relationships between hormones, visuomotor performance, and resting state functional network connectivity.

Frontoparietal networks for sensorimotor transformation

Movements directed by vision require visual information from the environment to be transformed into programmed motor outputs, a process known as visuomotor integration. This integration is thought to involve a transformation between reference frames from extrinsic (based on external cues) to intrinsic (based on required joint and muscle activations) (Kakei et al., 2003; Kalaska et al., 1992; Kalaska et al., 1997). The combination of this information is required to create an appropriate plan of motor action in order for successful goal-directed reaching movements to occur (Kalaska et al., 1992; Sabes, 2000). Previous research has indicated that the visuomotor integration required for reaching relies heavily on the activation of the frontal-parietal network (Sabes, 2000; Wise et al., 1997) – a network that is organized both hierarchically and in parallel in order to produce coordinated movement (Kalaska et al., 1992; Sabes, 2000). Hierarchically, visual information enters through the primary visual cortex of the occipital lobe and is further processed through the extrastriate cortex. Reaching requires the visual information to pass through the parieto-occipital extrastriate cortex to the posterior parietal cortex (PPC). The

PPC includes the superior parietal lobule (SPL), the median dorsal parietal area, and areas of the intraparietal sulcus; including medial, lateral, and ventral intraparietal areas (Kalaska et al., 1992; Wise et al., 1997). It has been determined that these areas are responsible creating a spatial representation of both limb and stimulus by receiving information from both visual and motor areas (Kalaska et al., 1992; Kalaska et al., 1997; Sabes, 2000; Andersen & Zipser, 1988). The areas where motor plans are created – premotor cortex; including medial supplementary motor area, and cingulate motor area, as well as the lateral dorsal (PMd) and ventral (PMv) premotor areas – receive information from the PPC and provide output to the primary motor cortex in order to create motor execution (Kalaska et al., 1992; Wise et al., 1997). The activity within the frontal-parietal network is responsible for transforming extrinsic visuospatial information into motor commands for reaching. However, it is not as simple as described above. This processing required depends on local communication and extensive reciprocal corticocortical projections that act both serially and in parallel (Kalaska et al., 1992; Kalaska et al., 1997; Wise et al., 1997). Changes in the pattern of activity of the frontal-parietal network, specifically within the PMd (Sayegh et al., 2013) and SPL (Hawkins et al., 2013), have been noted during a non-standard mapping visuomotor task.

Recent studies have further investigated the specific brain areas involved in non-standard visuomotor transformation tasks, specifically considering strategic control (Gorbet & Sergio, 2016), and spatial recalibration (Gorbet & Sergio, 2018). Gorbet and Sergio (2016) investigated brain areas involved in a non-standard mapping task where saccades and reaches were spatially dissociated through an 180^o rotation of cursor feedback. In this study, the authors found that activity in the cuneus and medial premotor regions was significantly increased during the task preparation phase when comparing the standard to the non-standard task. Additionally, an increase in activity in the inferior parietal lobule and cerebellum was seen during the execution of the non-standard task. As a further investigation, Gorbet and Sergio (2018) examined brain areas involved in a non-standard mapping task where saccades and reaches were made in different spatial planes. Using fMRI and multi-voxel pattern analysis, the authors observed a difference in brain activation between the standard and non-standard task. Interestingly, the pattern of activation was not markedly different until the closer to the motor execution phase of the task, as opposed to the initial planning stages. The areas of the brain which discriminated between the two tasks via increased activation in the movement period included the medial and lateral premotor, primary motor, superior and inferior parietal lobule, middle occipital gyrus, fusiform gyrus, lingual gyrus and anterior lobe of the cerebellum. Overall, it is important to note the involvement of different brain areas not only in standard versus non-standard tasks, but also in non-standard tasks with different natures of dissociation.

The cerebellum – responsible for motor coordination, motor learning, and spatial attention (Gorbet & Sergio, 2016; Kandel et al., 2000), and often not accounted for in this field of research – plays an essential role in standard and non-standard reaching tasks (Gorbet & Sergio, 2009; Granek & Sergio, 2015; Miall et al., 2001). Functionally, the cerebellum can be divided into the vestibulocerebellum, the spinocerebellum, and the cerebrocerebellum. Lesions to the deep nuclei of the spinocerebellum result in accuracy, hand path, and timing errors in reaching movements; while lesions to the deep cerebellar nucleus of the cerebrocerebellum result in delays in initiating movements and irregularities in movement timing (Kandel et al., 2000). In particular, it has been shown that cerebellum function is important during the corrective movement stages, when sensory feedback is accessed and utilized (Sabes, 2000; Kandel et al., 2000; Wolpert er al., 1995). Accordingly, increased cerebellar activity has been noted in non-standard compared to standard visuomotor tasks, resulting from the need for corrective movements or possibly due to a role in the actual dissociation of eye and hand (Gorbet & Sergio, 2016).

CMI and visually guided reaching

In everyday life, we often require this integration of visual information from our environment with rules and motor commands to accurately and successfully execute tasks. The ability to perform these movements requires different forms of visuomotor integration (Wise et al., 1996). There are two main forms of visuomotor integration examined in this research: standard mapping (where the targets of eye and limb movements are spatially congruent), and non-standard mapping (where there is a spatial dissociation between movements of the eyes and limb (Wise et al., 1996). Research has shown that the brain concurrently processes information for the eye and hand, simplifying planning and allowing for quick and accurate movements; the network responsible has been referred to as the default reaching network (Wise et al., 1996; Gorbet & Sergio, 2009). This network is utilized in standard mapped visuomotor transformations. These transformations involve looking at the target with which we are directly interacting. For example, when picking up a coffee cup both our gaze and our reach occur towards the cup. However, if the visual information from the environment does not align with the required spatial location of the motor output, the brain must create rules to execute an appropriate motor response (Brown et al., 2015; Tippett & Sergio, 2006). This type of visuomotor integration requires non-standard mapping and therefore the integration of spatial and cognitive rules (Wise et al., 1996). This decoupling of hand and eye coordination requires cognitive-motor integration (CMI) (Hawkins et al., 2013) – where the rules signify the association between perception and action. Non-standard mapping can be decoupled in a number of ways; however, focus for this research will be given to the following two instances: 1) There is an arbitrary relationship between the stimulus and the action (ex. Red traffic light means step on the brake), 2) There is a transformational dissociation between gaze, spatial attention, or limb movements, and the target (ex. using a computer mouse when looking at a computer screen). This decoupling can then be further separated in two ways: spatial recalibration or strategic control. Spatial recalibration requires the adaptation of the brain to changes in spatial orientation in order to align motor output with sensory input (Redding & Wallace, 1996; Bock, 2005; Granek & Sergio, 2015). For example, when using a computer mouse your gaze is directed at the screen on a vertical plane, but you are interacting with the mouse on a horizontal plane. This adaptation is slower and occurs without conscious awareness and therefore, is considered to be implicit (Redding & Wallace, 1996; Bock, 2005; Granek & Sergio, 2015; Clower & Boussaoud, 2000). The implicit recalibration is thought to occur through movement inaccuracies signaling an internal error and resulting in correction (Clower & Boussaoud, 2000). Conversely, strategic control requires the integration of a rule that is task-dependent in order to align the motor response with the target (Redding & Wallace, 1996; Bock, 2005; Granek & Sergio, 2015; Clower & Boussaoud, 2000). For example, rotating computer mouse input 180^{o} such that you would need to move your hand in the opposite direction of the target in order to successfully complete the task. This adaptation is considered explicit in nature, given that it requires external feedback to overcome movement errors. These types of visuomotor dissociations requiring CMI provide a means of assessing the brain's ability to think and move at the same time.

CMI in different brain states

Further to the differences in activation within brain networks during non-standard visuomotor integration tasks (requiring CMI) as compared to standard visuomotor integration tasks, it has also been found that there are behavioural performance differences between the two forms of decoupling. This may be due to the required recalibration and strategic measures needed in order to perform these tasks. Specifically, when vision and action are dissociated, movements are less accurate and require more time due to the additional planning and cognitive rules required (Wise et al., 1996; Gorbet & Sergio, 2009). While these effects are generally well understood in healthy individuals, it is less known in those with altered brain function. This is important as many neurological disorders may impact networks and connections, leading to impaired performance of activities of daily living. Therefore, understanding how altered brain function affects our ability to perform these complex CMI tasks will assist with understanding the etiology, progression, prevention, and rehabilitation for individuals suffering from neurological disorders.

Previous work has looked at how CMI in non-standard tasks is affected in those with mild cognitive impairment (MCI) (Salek et al., 2011) and Alzheimer's disease (Tippett, Sergio, and Black, 2012; Hawkins et al., 2015; Hawkins & Sergio, 2014). In particular, they noticed no performance differences between both MCI and Alzheimer's patients and healthy aged-matched controls in the standard conditions, where vision and action are congruent; however, performance differences were seen in the decoupled conditions, in which CMI is required, with the patient population showing difficulty. Alzheimer's patients had difficulty in non-standard conditions requiring either spatial recalibration or strategic control, with some completely unable to perform the task when both were combined. Specifically, they had impaired timing, consistency, and accuracy. This reflects an insufficient ability in the planning of motor movements as well as in sustaining an effective motor plan after initiation. In comparison, those with MCI had impaired reaction time and movement time but only when there were two levels of dissociation, where both spatial recalibration and strategic control were required. Furthermore, Hawkins et al. (2015) observed that the impaired motor planning and execution is associated with decreased white matter integrity within the frontal-parietal network in those at an increased risk for Alzheimer's disease in males. Additionally, recent work with concussion has shown that those with a history of concussion, despite being asymptomatic and cleared to return to play, perform worse on a non-standard visuomotor transformation task when compared to healthy controls (Hurtubise et al., 2016; Dalecki et al., 2016; Dalecki et al., 2020; Brown et al., 2015).

Impaired CMI has been observed in youth and adolescent athletes who had experienced a concussion but were asymptomatic (using self-report) at the time of testing (Dalecki et al., 2016; Dalecki et al., 2020; Brown et al., 2015; Hurtubise et al., 2016). These individuals included children and adolescents who played sport at the recreational and select level (Dalecki et al., 2016; Dalecki et al., 2020; Brown et al., 2015), as well as adolescents who played at an elite level (Hurtubise et al., 2016). In all cases, when having to incorporate some form of cognition and non-standard mapping into their movement control during an eye-hand coordination task, there were significant behavioural performance deficits in either the timing, trajectory formation, or both relative to peers with no concussion history. Specifically, while Dalecki et al. (2016) found deficits in ballistic movement time, ballistic path length, and full path length in non-standard compared to standard tasks in children. Brown et al. (2015) found deficits in only movement time and precision in varsity university aged athletes, and Hurtubise et al. (2016) found deficits in only reaction time in elite university aged athletes. Interestingly, both Brown et al. (2015), and Dalecki et al. (2016) were able to discriminate between those with a history of concussion and healthy controls with 70-94% accuracy. These data suggest that the brain networks used for simultaneous cognition and motor control are affected by concussion along a timeline longer than for tasks typically used to assess symptom resolution and readiness to resume activity.

Concussion

Concussion, a form of mild traumatic brain injury, has gained momentum in research surrounding the diagnosis, tracking of recovery, and potential differences related to age, sex, and multiple injury events. In the past, primarily in the world of sport, concussion was considered a minor head injury, with limited standards in place surrounding care of injury and return-to-play protocols. As of late, sports related concussion has been more accurately referred to as one of the most complex injuries in sports medicine to diagnose, assess, and manage (McCrory et al., 2017). There is still much debate surrounding the use of the term 'concussion', with many physicians deeming it inappropriate due to its lack of diagnostic information (Verboon, Patel, & Greenhalgh, 2021; Smith & Stewart, 2020; Sharp & Jenkins, 2015). However, current research surrounding concussion has continued to provide insight into the necessity for sensitive diagnostic tools (McCrory et al., 2013; Scorza, Raleigh, & O'Connor, 2012), detailed recovery tracking standards and individualized care following injury to ensure a safe and efficient recovery (Collins et al., 2014; McCrory et al., 2013; McCrory et al., 2017), as well as preventative measures to avoid secondary and repetitive injury (Bowen, 2003; Weibe, Comstock, & Nance, 2011; Signoretti et al., 2011). The continual improvement of these measures is necessary to address the heterogenous nature of this injury and provide accurate measures and diagnostic criteria for all demographic considerations.

Concussions occur when linear and/or rotational forces are transmitted to the brain through either direct or indirect impulsive mechanisms (McCrory et al., 2017). Diagnosis of a concussion is based upon clinical judgment of a physician and requires a mechanism of injury in combination with at least one symptom, physical sign, behavioural change, cognitive impairment, or a sleep disturbance (McCrory et al., 2017). In the majority (80-90%) of those who sustain a concussion, the symptoms will resolve within 7-10 days; however, in some, the signs and symptoms persist longer than 10 days and may result in Post Concussion Syndrome (McCrory et al., 2013; Harmon et al., 2013) (now also referred to as persistent symptoms, or post-concussive syndrome - PCS).

PCS is defined by the DSM-5 as either major or mild neurocognitive disorder due to traumatic brain injury with a decline in cognitive ability and persistent past the acute post-injury period, and affects 10-15% of those who sustain a concussion (McCrory et al., 2013; Harmon et al., 2013). Concussion results in no abnormalities on standard diagnostic images such as computed tomography or anatomical magnetic resonance imaging (McCrory et al., 2013; McCrory et al., 2017); therefore, it has been suggested that a functional disturbance is the cause of the associated symptoms. This may reflect cellular or molecular neuropathological and neurophysiological changes including ionic shifts, metabolic changes, and impaired neurotransmission (Giza & Hovda, 2014). The biomechanical forces which cause concussion trauma initiate a ‘neurometabolic’ cascade. This results in an increased need of glucose in order to restore ion homeostasis, and a decreased supply of glucose through decreased cerebral blood flow, creating a state of energy crisis (Giza & Hovda, 2014; Giza & Hovda, 2001; Barkhoudarian et al., 2011). It has been suggested that during this time that the brain is more vulnerable to the effects of another concussion. If a second injury does occur during this time of energy crisis, it may result in prolonged symptoms and a longer recovery to normal metabolic levels (Prins et al., 2010). Simultaneously with the ionic shifts and metabolic changes, there may also be an alteration in neurotransmission. Specifically, the mechanical stretching of axons leads to its cytoskeletal breakdown and loss of structural integrity, and therefore interferes with axonal transport. This axonal dysfunction results in slowed conduction, damage to cerebral networks, or deficits in neurotransmission, and therefore, impaired functioning (Giza & Hovda, 2014). As well, it is believed that this may be an underlying cause of the persistent symptoms associated with PCS. Interestingly, imaging studies have found decreased white matter integrity in both the acute and chronic stages of concussion (Lancaster et al., 2016; Lancaster, Meier, Olson, et al., 2018; Toldeo et al., 2012; Choe & Giza, 2015).

The heterogenous nature of concussion and lack of concrete understanding of underlying disturbances make diagnostic tools and recovery metrics extremely difficult to generalize. However, current research strives to improve these tools and metrics as more evidence is gathered surrounding commonalities of injury presentation and recovery. The sport concussion assessment tool (SCAT) (Echemendia et al., 2017) is one metric that has been continually updated in an effort to keep up with the changing knowledge surrounding concussion, and is widely used by clinicians and athletic therapists. The SCAT consists of multiple components designed to evaluate for the presence of concussion including a symptom inventory, cognitive and memory components, and a vestibular balance component. While the SCAT is a generally agreed upon tool for the sideline assessment and diagnosis of concussion, one flaw is the sequential testing of cognition and motor behaviour (Fueger et al., 2019; Locklin et al., 2010; Sergio et al., 2020), despite these domains often having to be concurrently controlled during sport. Many studies have noted behavioural performance differences during the simultaneous execution of cognition and motor tasks which require the integration of the two domains, despite the lack of difficulty on the cognition and motor performance alone (Buttner et al., 2020; Howell, Osterning, & Chou, 2017). More generally, lingering deficits on tasks that require CMI have been observed in different populations of individuals diagnosed with a concussion, but asymptomatic and cleared for return to play by current metrics (Brown et al., 2015; Dalecki et al., 2016; Hurtubise et al., 2016; Mitchell & Cinelli 2019; Howell et al. 2017; Catena et al. 2007; Baker & Cinelli 2014; Ventura et al. 2016). Therefore, the studies presented in this dissertation utilize aspects of both the SCAT and CMI performance.

The current literature surrounding concussion is widespread and focusses on many areas. In general, the main focus consists of understanding the impact of concussion, and using this information to inform diagnostic and recovery tracking measures. The beginning stages of concussion research brought to light the very individualized nature of the injury. Therefore, continuing topics of research in this area have included the impact of concussion on different age groups, different levels of play, sex and gender, behavioural performance, and brain network integrity. Within these areas the literature includes investigation of potential tools and benchmarks to assist in identifying these impacts in individuals and streamlining the recovery tracking process. Majority of the research surrounding concussion utilizes control participants of similar demographics to reduce potential confounding results. As such, caution is always advised when attempting to generalize results from a study to a patient population with different demographics.

For this reason, the studies within this dissertation focus specifically on varsity athletes with similar levels of experience. Additionally, in the first study males and females are examined as separate groups, and moving forwards only females are included (with the hopes of repeating the same studies in males in the future).

Neuroimaging – resting state fMRI and concussion

Resting-state functional magnetic resonance imaging (rs-fMRI) utilizes spontaneous low frequency blood-oxygenation-level-dependent (BOLD) fluctuations in brain activity that are correlated both within and across regions (Biswal, Yetkin, Haughton, & Hyde, 1995) even when the subject is instructed to not focus on a task. Through the discovery of these correlations common rs-fMRI common networks, often referred to as ‘resting-state networks’ (RSNs), have been uncovered (Smith, Vidaurre, Beckmann et al., 2013). Along with offering new information about the structure and function of the healthy brain, the variations in the functional connectome of RSNs has been shown to have clinical value, providing markers of disease (Castellanos, Di Martino, et al., 2013).

Recently, studies surrounding concussion have utilized rs-fMRI functional connectivity values (rs-FC) to investigate the impact of concussion on functional brain network connectivity in hopes of developing helpful diagnostic and recovery markers. As this focus is relatively new, there are still many mixed results. In a study using multivariate predictive modelling to investigate changes in brain connectivity associated with clinical factors of concussion (Churchill, Hutchison, et al., 2016) no differences were found between athletes with and without a history of concussion. However, the middle cingulum, superior occipital lobe, precuneus, and cerebellum showed significant fluctuation with number of concussions. Conversely, in a study comparing athletes with a history of concussion to control athletes on both rs-FC and neurocognitive measures, no differences were seen in the neurocognitive performance, but concussion history subjects had increased connectivity between the frontal lobe, parietal lobe, and anterior cingulate cortex; and between the left dorsolateral prefrontal cortex, left middle and inferior temporal gyrus, and the right inferior parietal lobule (Czerniak et al., 2015). A similar result was seen in a study investigating youth with a history of concussion, with the concussed group showing increased connectivity the in posterior parietal cortex, but decreased connectivity in frontal and parietal cortices (Borich et al., 2014).

As research in this area has progressed, most of the focus has fallen on correlations between resting state functional connectivity and symptom presentation and severity. Kaushal et al (2019) found a global increase in connectivity in male athletes at 8 days post-concussion with symptoms present, but asymptomatic athletes showed no differences from controls. These authors suggested that whole-brain rs-FC alterations are therefore associated with clinical recovery. Similarly, Churchill et al. (2018) noted that a network of frontal, temporal, and insular regions; and a network with anti-correlated elements of the default-mode network and sensorimotor system showed reliable covariation with symptom severity with males and females included in each group. Madhavan et al., (2019) not only showed associations between symptom severity and functional connectivity, but also that connectivity immediately after injury was capable of predicting symptoms severity up to 3 months later. One study even suggested that rs-FC could be used as a biomarker to monitor dynamic changes following concussion (Zhu et al., 2015). Interestingly, Shafi et al (2020) found significant differences in rs-FC in both salience and frontoparietal network nodes between individuals with post-concussion syndrome (now often referred to as postconcussive syndrome or persistent symptoms) and controls.

As rs-fMRI has become increasingly popular, one of the main challenges is to ensure optimal alignment of anatomical and functional data across participants (Anticevic et al., 2008). Traditionally, a volume-based registration of participants to an established atlas has been used to compensate for individual variability (Woods et al., 1998; Anticevic et al., 2008). However, due to high degrees of variability in the folding patterns of each individual, and the proximity of functionally separate structures in volume space (Anticevic et al., 2008), researchers are beginning to favour a surface-based alternative. Surface-based differs from volume-based analysis in two important ways. Firstly, voxels are restricted to grey matter only in order to reduce noise, and secondly, registration of the voxels in surface-space creates a more appropriate distance metric which takes into account cortical folding (Oosterhof et al., 2011). For this dissertation a surface-based method approach was used due to the improvement of alignment of areas (Coalson, Van Essen, and Glasser, 2018) and the reduced signal contamination (Brodoehl et al., 2020) found with surface-based methods compared to volume-based.

Sex-related differences

Sex-related differences are an aspect of research that has greatly been overlooked in most fields. However, recent studies of cognition and brain networks have shifted to include the comparison of, or at least the separation of, the two sexes (often mislabeled as gender). As a result of this shift, behavioural sex-related differences have been noted in multiple different aspects of cognition such as visual-spatial tasks (Weiss et al., 2003; Li, 2014; Satterthwaite et al., 2015), verbal tasks (Weiss et al., 2003; Li, 2014; Kimura, 2002), nonverbal reasoning (Satterthwaite et al., 2015), perceptual speed (Kimura, 2002), and dexterity (Kimura, 2002). Additionally, sex-specific differences have been noted in brain network activity during complex visuomotor tasks in healthy individuals (Gorbet & Sergio, 2007), and in general rs-FC in RSNs in both healthy individuals (Hjelmervik et al., 2014; Satterthwaite et al., 2015; Engman et al., 2016) and those with concussion history (Wang et al., 2018) or post-concussion syndrome (Shafi et al., 2020). Such observations create a clearer picture that male and female brains do, in fact, control aspects of cognitive and motor behaviour differently. It has been proposed that differences in hormones, and fluctuation of hormones in females may contribute to these sex-related differences. The following sections will discuss these sex differences in more detail.

CMI

Recent imaging research has found differences in brain activation between males and females when performing a similar multi-domain CMI task (Gorbet & Sergio, 2007) as utilized in these dissertation studies. Gorbet & Sergio (2007) noted increased bilateral activation in females compared to males. Interestingly, despite the differences in functional activity, the difference in behavioural performance between the sexes was not statistically significant. This finding suggests that there are sex-related differences in the brain networks responsible for the successful performance of CMI tasks which are not observable through behavioural tasks alone.

Resting-state functional connectivity

As mentioned previously, studies surrounding concussion are examining rs-FC in hopes of developing helpful diagnostic and recovery markers. In order to ensure the thoroughness of this research, many authors are beginning to include sex-specific investigations. In general, most of the current research in healthy individuals suggests differences in functional connectivity between males and females. Engman et al. (2016) found sex-specific differences in rs-FC in the laterobasal and centromedial amygdala with males and females showing increased connectivity in different regions. Specifically, females showed higher connectivity between the laterobasal amygdala and the cerebellum, inferior frontal gyrus, postcentral gyrus, precuneus, putamen, and supramarginal gyrus; whereas males showed higher connectivity to the ventromedial prefrontal cortex and the superior temporal gyrus in the temporal pole. Hjelmervik et al., (2014) found sex-specific differences in the right dorsal and anterior network. Specifically, in the dorsal network women showed higher connectivity in left cerebellum, and in the anterior network women showed higher functional connectivity in left middle frontal gyrus, bilateral precuneus, and right inferior parietal lobule. And Satterthwaite et al. (2015) found sex-specific differences in nodes of the default mode network, ventral attention network, auditory network, and memory retrieval network. Interestingly, this study also noted that stronger connections in females are more likely to be within-node, but stronger connections in males are more likely to be between-node (with nodes based on the parcellation scheme from Power et al. (2011)).

Studies of rs-FC differences in those with concussion are limited. In fact, only two studies were found with direct reporting of sex-specific differences in relation to concussion. Wang et al. (2018) investigated rs-FC in mTBI patients (under a definition which is comparable to concussion) recruited from the emergency department within 7 days post-injury and age-, education-, and sex-matched controls. They found that male patients showed increased intrinsic functional connectivity compared to females in the functional connectivity motor network, ventral stream network, executive function network, and cerebellum network. As well, they found that male patients showed decreased connectivity compared to female patients in the visual network. Interestingly, these authors also noted increased connectivity in the motor and ventral stream networks and decreased connectivity in the visual network in male patients compared to male controls, but no differences were noted in female patients compared to female controls. In a study looking at those with post-concussion syndrome, sex-related differences in rs-FC were seen in the right lateral prefrontal cortex, left superior temporal gyrus, central opercular cortices, planum temporale, and the left lateral sensorimotor network (Shafi et al., 2020).

Hormones

While there have been mixed findings and some difficulty generalizing across studies due to methodologies, previous research has shown differences in cognitive performance between males and females (Kimura 2002; Jancke, 2018; Gurvich et al., 2018), and also in females during different times their menstrual cycles (Scheuringer & Pletzer, 2017; Weis et al, 2019). Therefore, it has been proposed that hormone levels may have an impact on cognitive performance (Kimura, 2002; Gouchie & Kimura, 1991; Hausmann et al., 2000). Specifically, the sex hormones estrogen and testosterone have received the most focus. In a study done by Hampson, Levy-Cooperman and Korman (2014), low estrogen was linked with significantly better accuracy on a mental rotation task. In a similar fashion, a study looking a testosterone found that healthy young men with lower levels of the hormone performed better on a spatial task than those with higher levels (Gouchie & Kimura, 1991). In a review by Kimura (2002), cognitive sex-related differences were presented as favouring males or favouring females. Across ages and cultures, it was fairly consistent that males performed better on spatial orientation, visualization, and mathematical reasoning. In contrast, females performed better on object location memory, perceptual speed, verbal memory, numerical calculation, and dexterity.

Additionally, current research has moved in the direction of hormonal fluctuation and rs-FC. Out of the few human studies that have been conducted so far, mixed results have been noted. Using a group independent components analysis (ICA) approach, Hjelmervik et al. (2014), and De Bondt et al. (2015) found no significant impact of phase of menstrual cycle on rs-FC. De Bondt et al. (2015) did, however, note an increase in rs-FC in the precuneus in relation to estrogen levels. Petersen et al. (2014) and Pletzer et al. (2016) found an impact of the luteal phase on rs-FC, and Pletzer et al. (2016) and Weis et al. (2019) found an impact of the pre-ovulatory phase on rs-FC. Using a seed-based connectivity approach, Syan et al. (2017) found no significant impact of the luteal phase, while Engman et al. (2018), noted increases in the amygdala to dorsolateral prefrontal cortex, sensorimotor cortices, and cerebellum; and the dorsal anterior cingulate cortex to the dorsolateral prefrontal cortex, temporal gyrus, and sensorimotor cortices; and Hidalgo-Lopez et al. (2020) noted decreased connectivity of the right angular gyrus with the default mode network (see Hidalgo-Lopez et al., 2020 for an excellent summary table). Of particular interest is the idea that concussion may cause a dysregulation of the hypothalamic-pituitary-gonadal axis, resulting in a disruption of estrogen and progesterone (Duffy et al., 2021).

Concussion

Research has demonstrated sex-related differences following concussive head injury (Meritt et al., 2019), including incidence (Hannah, Li, & Spiera, 2021; Covassin, Swanik, & Sachs, 2003; Black, Sergio, & Macpherson, 2017; Barnes et al., 1998), symptoms (Hannah, Li, & Spiera, 2021; Covassin, Schatz, & Swanik, 2007; Frommer et al., 2011; Berz et al., 2013), and recovery trajectory (Hannah, Li, & Spiera, 2021; Berz et al., 2013; Ono et al., 2016; Ledoux et al., 2019;

Gallagher et al., 2018; Covassin, Moran, & Elbin, 2016). Specifically, it has been observed that females have a higher incidence of sport-related concussion than males (Hannah, Li, & Spiera, 2021; Covassin, Swanik, & Sachs, 2003; Black, Sergio, & Macpherson, 2017; Barnes et al., 1998), suggesting that there may be a difference in desire and ability to report symptoms or disclose injuries, or that there may be underlying factors putting females at an increased risk for injury. In terms of symptoms, Frommer et al. (2011) noted sex-related differences in the *nature* of symptoms reported following concussion. Men tended to report more cognitive symptoms including memory loss and confusion, while females tended to report more neurobehavioural and somatic symptoms including sensitivity to noise and fatigue. With respect to concussion recovery, there has been a mixture of results regarding sex-related differences in this process. For example, while Black et al. (2017) noted greater incidence in females, they found no differences in symptom and neurocognitive recovery. In contrast, Hannah et al. (2021) noted higher odds of concussion in youth female athletes (median age 15 years), as well as increased symptom severity and longer recovery time compared to males. Similarily, two other studies of collegiate athletes (Gallagher et al., 2018; Covassin, Moran, & Elbin, 2016) noted a longer time to recover in female collegiate athletes than males.

Additionally, recent work with rodent models of repeated concussion have noted similar sex-related differences in recovery (McCorkle et al., 2019; Wright et al., 2017). In one study, the authors found that adolescent male rats experienced working memory impairments relative to sham control male rats within two weeks after injury. Female injured rats showed no such working memory impairment. Rather, only the female rats displayed prolonged depressive-like symptoms relative to sham-injured female rats (Wright et al., 2017). Further, brain imaging revealed greater prefrontal cortex atrophy in female versus male rats who had experienced repeated concussive injury. Neuroimaging of these animals showed that male injured rats showed white matter integrity deficits in the corpus callosum, a structure known to have hormone-related sexual dimorphism in rats and humans (Hausmann, 2017; Bjornholm et al., 2017; Fitch et al., 1990). A second study replicated these behavioural findings when the animals were tested four weeks post-injury and noted that the females displayed the depressive-like symptoms during the estrus phase of their cycle (McCorkle et al., 2019). In a similar manner, a preliminary study with female mice exposed to concussive injury found that motor deficits recovered within two weeks, while spatial learning deficits were still present at four weeks despite neuroinflammatory markers returning to baseline levels (Emitt et al., 2019). These studies and others suggest that neurobiological and hormonal mechanisms (Martin-Jimenez et al., 2019; Gallagher et al., 2018; Umeano et al., 2017; Wunderle et al., 2014) may underlie such sex-related differences and emphasize the importance of accounting for sex when examining concussion outcomes.

In relation to multiple concussive events, differences in performance have been shown between males and females with a history of multiple concussions on a computerized test battery (Immediate Postconcussion Assessment Cognitive Testing) (Covassin et al., 2010) with females performing better than males on verbal memory and visual memory.

Interestingly, a recent study also found sex-related differences in cerebral blood flow (CBF) in association with a history of concussion (Hamer et al., 2020). Males with a history of concussion had lower CBF bilaterally than males without, whereas females with a history of concussion showed no significant differences to their control counterparts but had significantly higher variability than their male counterparts.

Previous research has also noted a possible impact of gender norms in the reporting of symptoms following concussion (Kroshus et al., 2017; Covassin & Elbin, 2011; Broshek et al., 2005). A study by Kroshus et al. (2017) utilizing the Conformity to Masculine Norms Inventory (Mahalik et al., 2003) on 328 college athletes noted that societal gender norms have an impact on the reporting of emotional symptoms whereby females were more likely to report symptoms emotional in nature. Covassin & Elbin (2011) found that female athletes were more concerned about their future health than male athletes, possibly contributing to the differences in symptom reporting.

Overview of dissertation projects

In summary, it has been shown that CMI performance is essential for sport performance, and the networks required for successful CMI performance show an overlap with the networks and nodes commonly impacted by concussion. Additionally, previous research using tasks which require CMI has revealed differences in performance between those with a history of concussion and those without. Specifically, behavioural research has noted difficulties in those with a history of concussion who were asymptomatic by current standards at the time of testing compared to asymptomatic controls (no history of concussion), suggesting that CMI may uncover lingering deficits in brain network connectivity not detected by current standards.

Concussion also results in the presentation of somatic and emotional symptoms, cognitive impairment, and/or sleep disturbances. Within many of these areas, differences between males and females have been noted. Specifically, sex-related differences have been noted in the type and severity of symptoms following concussive head injury and the recovery trajectory, with females typically reporting a higher number, and higher severity of symptoms, and taking longer to recover. It has been suggested that cycling hormones may have an impact on risk of sustaining concussive injuries, and/or recovery trajectory following concussive injury. If a correlation exists between behavioural (CMI) performance, menstrual cycle stage, and functional network connectivity, development of more accurate protocols to prevent head injuries and inform sport medicine professionals of risk of injury will be enhanced. Therefore, the overall intention of this dissertation is to investigate sex-related differences in CMI performance, and in recovery tracking metrics following concussive injury.

The first study, *Cognitive-motor performance and emotionality recover differently in males and females following concussive injury*, builds on previous research from the Sergio lab demonstrating the effects of concussion history on CMI performance in samples of males only, or males and females combined. Due to the increased literature on sex-related differences in cognition, and brain activation during CMI tasks in healthy individuals, in addition to symptom presentation and severity in concussed individuals, this study focused on comparing males and females on CMI performance and symptoms following concussion.

In response to the findings of study one, along with previous research indicating sex-related differences in cognition, hormones, and resting state functional connectivity, both study 2 and 3 included only females. Both of these projects explore hormones and their relationship with different aspects of concussion. Specifically, study 2, *Hormone levels impact concussion recovery assessment metrics in female varsity athletes – A preliminary study*, looks at the relationship between hormones, aspects of the SCAT including symptom severity, total symptoms, and balance, and visuomotor integration performance (both standard and non-standard conditions). Study 3, *An exploration into the relationship of hormones, CMI performance, and Concussion history with resting state functional brain network connectivity in female athletes,* builds on study 2 using rs-FC in hopes of furthering our understanding of underlying connections to behavioural differences shown following concussion.

In the final chapter of this dissertation, a summary of the results of each individual study will be discussed collectively within the framework of concussion recovery tracking metrics and sex-specific differences/impacts.

Summary and knowledge dissemination

The information discussed in this dissertation adds to the literature surrounding concussion diagnostic and recovery tracking metrics, and advances our understanding of the impact of sex and sex-specific characteristics on these measures. Preliminary results from Study one have been presented at the Research and Community Engagement 1st Annual Meeting hosted by the Canadian Concussion Network, and the 8th Annual Concussion Research Symposium hosted by the University Health Network. As well, preliminary results from study three have been presented at the Society for Neuroscience Global Connectome.

The findings of this dissertation are informative for future research directions through many preliminary observations and remaining questions to explore. Additionally, the information in this dissertation is informative for clinicians and practitioners through the knowledge of sex-related differences in measures used to track recovery from concussion, and the impact of hormones in females on these measures.

Chapter Two: Cognitive-motor performance and emotionality recovery differently in males and females following concussive injury

(under review, Canadian Journal of Sport Medicine)

Abstract

Objective: Examine the interaction between sex, concussion history, emotionality, and visuomotor skill.

Participants: University varsity athletes, 145 with concussion history (78 female), and 188 with no history (100 female). Sex/gender was categorized by athlete self-report. All participants were asymptomatic by current standards at the time of preseason baseline testing.

Methods: Participants were tested on two visuomotor skill tasks – a standard slide-finger-to-target on a touchscreen and a decoupled gaze/hand location and reversed visual feedback – and the SCAT3/5 assessment.

Outcome measures: Kinematic variables, SCAT symptom inventory emotion-related measures.

Results: In males, concussion history significantly impacted visuomotor skill performance (accuracy, velocity, and pathlength, $p<0.05$). However, there was no such concussion history effect in females ($p>0.05$). As well, the only statistically significant effect observed in emotionality symptoms was a rise in number of males who subscribed to the Anxious symptom ($p<0.05$)

Conclusions: Males and females may recover differently from concussion, with females recovering more reliably on visuomotor skill. While both males and females with concussion history subscribed to more emotionality symptoms compared to non-concussed athletes, within concussion history group there remained significantly greater reporting of emotionality symptoms in females. Clinically, these data suggest that females and males may require different tools for post-injury monitoring, outcome projections, and recovery assessment.

Background

Sex-related differences are an aspect of research that have been overlooked in most biomedical fields, and this is especially apparent in concussion and mild traumatic brain injury (mTBI) research. Recent studies of general cognition and brain networks have shifted to include the comparison of, or at least the separation of, the two sexes (often mislabeled as gender). As a result of this shift, behavioural sex-related differences have been noted in multiple different aspects of cognition such as visual-spatial tasks (Weiss et al., 2003; Li, 2014; Satterthwaite et al., 2015), verbal tasks (Weiss et al., 2003; Li, 2014; Kimura, 2002), nonverbal reasoning (Satterthwaite et al., 2015), perceptual speed (Kimura, 2002), and dexterity (Kimura, 2002). Such observations create a clearer picture that male and female brains control aspects of cognitive and motor behaviour differently. More specifically, recent imaging research has found differences in brain activation between males and females when performing a multi-domain cognitive-motor integration (CMI) task (Gorbet & Sergio, 2007). Interestingly, despite the differences in functional activity in this study, the difference in behavioural performance between the sexes was not statistically significant. This finding suggests that there are sex-related differences in the brain networks responsible for the successful performance of CMI tasks which are not observable through behavioural tasks alone. Given the nature of sex-related differences seen in cognitive performance and network activation, there is a possibility that lack of findings in previous clinical research investigating brain networks and visuomotor performance could be due to a washout effect through the inclusion of both males and females in a single analysis.

The functional networks involved in complex visuomotor performance - whose activation varies with sex - comprise brain areas commonly affected by concussive injury. Concussion is a challenging injury to diagnose and monitor due to its heterogeneous nature. Recently, research has demonstrated sex-related differences following concussive head injury (Merritt, Padgett, & Jak, 2019), including incidence (Hannah, Li, & Spiera, 2021; Covassin, Swanik, & Sachs, 2003; Black, Sergio, & Macpherson, 2017; Barnes et al., 1998), symptoms (Hannah, Li, & Spiera, 2021; Covassin, Schatz, & Swanik, 2007; Frommer et al., 2011; Berz et al., 2013), and recovery trajectory (Hannah, Li, & Spiera, 2021; Berz et al., 2013; Ono et al., 2016; Ledoux et al., 2019) (Gallagher et al., 2018; Covassin, Moran, & Elbin, 2016). Specifically, it has been observed that females have a higher incidence of sport-related concussion than males (Hannah, Li, & Spiera, 2021; Covassin, Swanik, & Sachs, 2003; Black, Sergio, & Macpherson, 2017; Barnes et al., 1998), suggesting that there may be underlying factors putting females at an increased risk for injury. In terms of symptoms, Frommer et al. (2011) noted sex-related differences in the *nature* of symptoms reported following concussion. Men tended to report more cognitive symptoms including memory loss and confusion, while females tended to report more neurobehavioural and somatic symptoms including sensitivity to noise and fatigue. With respect to concussion recovery, there has been a mixture of results regarding sex-related differences in this process. For example, while Black et al. (2017) noted greater incidence in females, they found no differences in symptom and neurocognitive recovery. In contrast, Hannah et al. (2021) noted higher odds of concussion in youth female athletes (median age 15 years), as well as increased symptom severity and longer recovery time compared to males. Similarly, two other studies of collegiate athletes (Gallagher et al., 2018; Covassin, Moran, & Elbin, 2016) noted a longer time to recover in female collegiate athletes than males.

Lastly, recent work with rodent models of repeated concussion have noted similar sex-related differences in recovery (McCorkle et al., 2019; Wright et al., 2017). In one study, the authors found that adolescent male rats experienced working memory impairments relative to sham control male rats within two weeks after injury. Female injured rats showed no such working memory impairment. Rather, only the female rats displayed prolonged depressive-like symptoms relative to sham-injured female rats (Wright et al., 2017). Further, brain imaging revealed greater prefrontal cortex atrophy in female versus male rats who had experienced repeated concussive injury. Neuroimaging of these animals showed that male injured rats showed white matter integrity deficits in the corpus callosum, a structure known to have hormone-related sexual dimorphism in rats and humans (Hausmann, 2017; Bjornholm et al., 2017; Fitch et al., 1990). A second study replicated these behavioural findings when the animals were tested four weeks post-injury, and noted that the females displayed the depressive-like symptoms during the estrus phase of their cycle (McCorkle et al., 2019). In a similar manner, a preliminary study with female mice exposed to concussive injury found that motor deficits recovered within two weeks, while spatial learning deficits were still present at four weeks despite neuroinflammatory markers returning to baseline levels (Emitt et al., 2019). These studies and others suggest that neurobiological and hormonal mechanisms (Martin-Jimenez et al., 2019; Gallagher et al., 2018; Umeano et al., 2017; Wunderle et al., 2014) may underlie such sex-related differences, and emphasize the importance of accounting for sex when examining concussion outcomes.

Interestingly, a recent study also found sex-related differences in cerebral blood flow (CBF) in association with a history of concussion (Hamer et al., 2020). Males with a history of concussion had lower CBF bilaterally than males without, whereas females with a history of concussion showed no significant differences to their control counterparts but had significantly higher variability than their male counterparts. These results provide further evidence of differential impacts of concussive injury on males and females.

Despite the growing interest, majority of the current literature surrounding sport-related concussion has focused on males only, or a combination of males and females with no separation of the sexes for analytical purposes (Koerte et al., 2020). However, it is becoming more apparent that concussion affects males and females differently from risk to recovery (Koerte et al., 2020; McGroarty, Brown, & Mulcahey, 2020). Previous research from our lab, conducted with males and females as a single cohort (Dalecki et al., 2016; Dalecki et al., 2020; Brown et al., 2015) or with males only (Hurtubise et al., 2016), found decreased CMI performance in those with concussion history compared to those without. The imbalance in female to male ratio in these studies, however, makes it difficult to generalize these performance findings.

In order to gain a better understanding of the underlying processes related to concussion recovery, and to improve the diagnostic and recovery standards surrounding concussive injury, we applied a sex-based analysis to the effect of concussion history on complex skilled performance and emotionality symptoms in university varsity athletes. Based on previous research involving both human and animal models of concussion, we hypothesized that athletes with a history of concussion would display greater emotionality symptoms and cognitive-motor integration deficits despite being considered eligible for return to play by current standards. We further hypothesized that the nature of these lingering deficits would be different for females and males.

Methods

Participants:

A total of 178 female (Hx = 78) and 155 male (Hx = 67) participants were recruited through the Gorman Shore Sports injury clinic on York University Keele Campus in North York, Ontario, Canada. The mean age of participants was 20 $\pm$ 1.79 years, and time since concussion was >3 months for all participants in the Hx group. Note that on the SCAT3 forms, participants are presented with a category titled ‘Gender’, with two response options, ‘M’ and ‘F’. On the SCAT5 form, the section for 'Gender' provides three response options, 'M','F', and 'Other'. For this study, we refer to their choice as one of Sex given the binary nature of the version 3 form, and the lack of any 'Other' responses from our participants on the version 5 form. We recognize the limitations of the provided categories.

Participants were excluded if they were diagnosed with any neurological disorder or sustained their head injury due to a motor vehicle accident. Information on the injury, (including the number of previous concussions and length of time since the concussion), and other demographic information was collected through a questionnaire. The York University Research Ethics board human participants subcommittee approved the protocol used in the experiment. The experimental protocol was also in compliance with the Declaration of Helsinki. All participants provided informed written consent prior to data collection.

Procedure:

All participants completed either a standardized sideline concussion assessment tool (SCAT3 or SCAT5) and/or a computerized CMI task involving a standard and non-standard visuomotor transformation condition in a single session.

Symptom assessment

For all participants, symptoms were measured through the symptom inventory as part of a standardized Sport Concussion Assessment Tool (SCAT3 or SCAT5) (Echemendia et al., 2017). In both cases, the symptom inventory consisted of 22 commonly reported symptoms, which are self-rated on a 7-point Likert scale from 0 (no issue) to 6 (severe). Both the number of symptoms (max 22), as well as a symptom severity score (sum of all reported symptoms, max 132) are reported. The SCAT also incorporates other aspects of sideline testing such as delayed recall and balance. However, for the purpose of this study, only the symptom inventory was used in the analysis. All researchers were trained on the proper collection of SCAT prior to working with participants.

Cognitive-Motor Integration Tasks:

For the CMI task collection, participants completed two computer-based visuomotor transformation tasks, one standard (V) and one non-standard (HR) (where visual goal and required action were decoupled). Participants sat at a desk comfortably in front of a 10.1" ACER tablet connected to a 15" USB touchpad (Keytec™, TycoTouch, USA) allowing for a touch screen in both the horizontal and vertical planes. In both conditions, participants were instructed to slide their index finger of their preferred hand along the touch screen in order to displace a cursor from a central target to one of four peripheral targets (up, down, left, right) as quickly and as accurately as possible. Participants guided a crosshair cursor, viewed on a black background, to the yellow central (or home) target which, when reached successfully, changes to green. After 4000ms, a red peripheral target is presented and the central target disappears, which serves as the 'Go' signal for the participant to initiate movement. Once the participant successfully reaches the target and remains for 500ms, the peripheral target disappears, signaling the end of the trial. The next trial begins with the presentation of the central target after an inter-trial interval of 2000ms. Peripheral targets are located 55mm from the center target, and target diameters are 15mm. In order to ensure smooth movement of the finger during the task, participants wore a capacitive-touch glove on their preferred hand (FIG 1a & 1b).

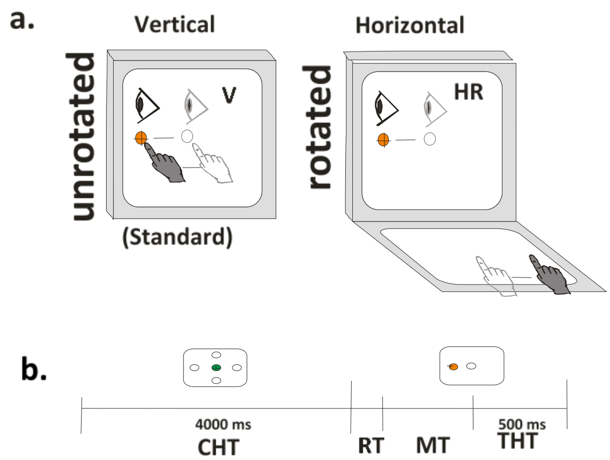


Fig. 1a & 1b. (A) Schematic drawing of both experimental conditions V (vertical, standard) and HR (Horizontal Rotated, non-standard). Visual stimuli were presented on the vertical monitor for all conditions. Green circle, light grey eye, and hand symbols denote the instructed eye and hand movements for each task. Red circles denote the peripheral (reach) target, presented randomly in one of four locations (left, up, right, and down). The dark crosshair denotes the cursor feedback provided during each condition. (B) Schematic drawing of time progression of task. centre hold time (CHT) indicates the 4000ms participants must hold in the centre target before a peripheral target appears, followed by reaction time (RT) of participant to respond to the stimulus, movement time (MT) of participant to successfully slide the cursor from the central target to the peripheral target, and target hold time (THT) signifying the 500 ms that participants must hold in the peripheral target until returning back to centre to start their next trial.

Participants completed the standard and non-standard conditions in a randomized block design. In the standard condition, participants both viewed the stimuli and slid their finger on the vertical screen, and thereby directly interacted with the targets. Movements for the non-standard visuomotor condition were made on the horizontally oriented Keytec touchpad. The touchpad was calibrated such that the distance of the finger movement path on the touchpad is equivalent to the distance the cursor moves on the tablet screen – making the required travel distance the same for both the standard and non-standard condition. The non-standard condition includes two levels of decoupling: (i) plane change; in which participants look at the vertical screen while moving on the horizontal screen, requiring spatial recalibration, and (ii) cue reversal; in which the feedback is rotated 180° (i.e. in order to move the cursor left, you slid your finger right), requiring strategic control. Six trials in each of the four directions were completed per condition for a total of 40 trials per participant (4 directions x 5 trials x 2 conditions). Eye movements were monitored by the experimenter to ensure participants looked at the correct target.

Behavioural data preprocessing:

Custom-written (C++) acquisition software sampled the finger's X-Y screen position at 60Hz. Custom analysis software (Matlab, Mathworks Inc.) was used to generate a computerized velocity profile of each trial's movement. Movement onsets and ballistic movement offsets (the initial movement prior to path corrections) were scored at 10% peak velocity, while total movement offsets were scored as the final 10% peak velocity point once the finger position is within the peripheral target. These profiles were then verified by visual inspection, and manually corrected if necessary. Trials were considered errors if the finger/cursor left the center target too early (< 4000ms), reaction time was less than 150ms or more than 8000ms, or total movement time was more than 10000ms. Trials in which the first ballistic movement exited the boundaries of the center target in the wrong direction (greater than 90° from a straight line to target) were coded as direction reversal errors, eliminated from further evaluation, and analyzed as a separate variable. The scored data was then processed to compute both movement timing and execution outcome measures.

The kinematic variables for movement timing were as follows: 1) Reaction Time (RT), the time interval (milliseconds) between the central target disappearance and movement onset; 2) Movement Time (MT), the time between movement onset and offset (millisecond), and 3) Peak Velocity (PV), the maximum velocity obtained during the ballistic movement. Kinematic variables for movement execution were: 1) Full Path Length (PLf), the total distance (resultant of the x and y trajectories) travelled between movement onset and offset (millimeters), 2) Absolute Error (AE, accuracy), the average distance from the individual ballistic movement endpoints ($\sum x/n$, $\sum y/n$) to the actual target location (millimeters); 3) Variable Error (VE, precision), calculated as the distance between the individual ballistic movement endpoints ($\sigma 2$) from their mean movement (millimeters); and 4) Percentage Direction Reversal errors (DR) were calculated as the number of trials with a deviation of greater than ±45° from the direct line between the midpoint of the central and peripheral targets compared to the number of successful trials.

***Data Analysis*:**

Participants were divided into four groups – Males with a previous history of concussion (M-Hx), males with no previous history of concussion (M-NoHx), females with a previous history of concussion (F-Hx), and females with no previous history of concussion (F-NoHx).

SCAT emotionality symptoms:

Of the 22 symptoms listed as part of the SCAT symptom scale, we selected the four which best reflected emotionality: More emotional, Irritability, Sadness, Nervous or anxious. If a participant selected greater than 0, the column was assigned a value of 1 to indicate the presence of the symptom. If they selected a 0, the column was assigned a value of 0 to indicate no presence of the symptom. Chi-Square tests were then run comparing groups M-Hx to M-NoHx, and F-Hx to F-NoHx. Additionally, individual t-tests were run comparing groups F-NoHx to M-NoHx, and F-Hx to M-Hx.

Cognitive motor integration measures:

For the seven of the dependent variables described above (RT, MT, PV, PLf, AE, VE, and DR), two-way ANOVAs were run using sex and concussion history as the independent factors. Following this, individual independent samples T-Tests were performed comparing the M-Hx to the M-NoHx, the M-Hx to the F-Hx, the F-NoHx to the M-NoHx, and the F-Hx to the F-NoHx.

Results

Measures of emotionality:

Chi-Square tests of independence were performed to examine the relationship between emotionality symptom reporting (More emotional, Irritability, Sadness, and Nervous or anxious) and concussion history in males. There were no significant differences in frequency of reporting between the two groups on More Emotional X^2(df = 1, N = 88) = 2.406, p = 0.121, Irritable X^2(df = 1, N = 88) = 1.462, p = 0.227, or Sadness X^2(df = 1, N = 88) = 0.557, p = 0.456. However, a significantly greater number of males with concussion history reported the presence of the Anxious symptom X^2(df = 1, N = 88) = 3.860, p = 0.049.

Chi-Square tests of independence were also performed to examine the relationship between emotionality symptom reporting (More emotional, Irritability, Sadness, and Nervous or anxious) and concussion history in females. There were no significant differences in frequency of reporting between the two groups on any of the symptoms measured. More Emotional X^2(df = 1, N = 86) = 0.195, p = 0.658, Irritable X^2(df = 1, N = 86) = 0.628, p = 0.428, Sadness X^2(df = 1, N = 86) = 1.323, p = 0.250, and Anxious X^2(df = 1, N = 86) = 2.604, p = 0.107.

Further Chi-Square tests of independence were performed to examine the relationship between emotionality symptom reporting (More emotional, Irritability, Sadness, and Nervous or anxious) and sex by comparing females with no history of concussion (F-NoHx) and males with no history of concussion (M-NoHx). See Table 1 for summary of percentages. There were no significant differences in frequency of reporting between the two groups on More Emotional X^2(df = 1, N = 174) = 1.952, p = 0.162, or Sadness X^2(df = 1, N = 174) = 0.475, p = 0.491. However, we saw a trend toward significance in reporting of Irritable X^2(df = 1, N = 174) = 3.376, p = 0.066. and a significant difference in Anxious X^2(df = 1, N = 174) = 4.030, p = 0.045.

Finally, Chi-Square tests of independence were performed to examine the relationship between emotionality symptom reporting (More emotional, Irritability, Sadness, and Nervous or anxious) and sex by comparing females with history of concussion (F-Hx) and males with history of concussion (M-Hx). See Table 1 for summary of percentages. There were no significant differences in frequency of reporting between the two groups on any of the symptoms measured. More Emotional X^2(df = 1, N = 117) = 0.431, p = 0.511, Irritable X^2(df = 1, N = 117) = 1.229, p = 0.268, Sadness X^2(df = 1, N = 117) = 0.379, p = 0.773, and Anxious X^2(df = 1, N = 117) = 1.640, p = 0.200.

TABLE 1: Summary of percentages of number of participants reporting symptoms in each group. *= significant at $p<0.05$

Variable	**Group**	**Percentage with Symptom**
Emotional	F-NoHx	11.6
	M-NoHx	5.7
	F-Hx	9.4
	M-Hx	13.2
Irritability	F-NoHx	14
	M-NoHx	5.7
	F-Hx	18.8
	M-Hx	11.3
Sadness	F-NoHx	7
	M-NoHx	4.5
	F-Hx	12.5
	M-Hx	7.5
Anxious	F-NoHx	19.8 } *
	M-NoHx	9.1 }
	F-Hx	31.3 } *
	M-Hx	20.8 }

In summary, males showed significant differences subscribing to Anxiety as a function of concussion history, while females showed no differences on any of the symptoms measured. Within the control group, however, a greater number of females subscribed to the Anxious symptom compared to males. Additionally, while not statistically significant, it is interesting to note the greater percentage of females subscribing symptoms in both the control group and concussion history group on all symptoms except More Emotional.

Measures of integrated visuomotor skill and cognition:

Two-way ANOVAs found a significant interaction of sex and concussion history on accuracy ($p<0.01$), precision ($p<0.05$), and peak velocity ($p<0.02$) in condition two, and full pathlength in both condition one ($p<0.001$) and two ($p<0.02$), with a trend towards significance in peak velocity in condition one ($p=0.060$).

Males compared to females

Post-hoc independent samples T-Tests revealed that males with no history of concussion (M-NoHx) had significantly worse performance than females with no history of concussion (F-NoHx) on reaction time ($p < 0.01$) in condition one, and significantly better performance on peak velocity ($p < 0.05$) in condition two.

Post-hoc independent samples T-Tests revealed that males with concussion history (M-Hx) had significantly worse performance than females with concussion history (F-Hx) on reaction time ($p < 0.01$), and peak velocity ($p < 0.05$) in condition one, and significantly better performance on full pathlength ($p < 0.001$) in condition one, and absolute error ($p < 0.01$), variable error ($p < 0.01$) and full pathlength ($p < 0.01$) in condition two. A comparison of means and indication of performance can be found in Table 2.

Concussed compared to non-concussed within sex

Post-hoc independent samples T-Tests revealed that males with concussion history (M-Hx) had significantly impacted performance on peak velocity ($p<0.05$) in standard condition one (the basic visuomotor skill condition), accuracy ($p<0.001$) in non-standard condition two (the CMI condition) and full pathlength in both conditions one and two ($p<0.001$) when compared to their non-concussed counterparts. Additionally, a trend towards significance was seen in both variable error ($p=0.060$) and peak velocity ($p = 0.055$) in the non-standard condition two. This visuomotor performance decrement was not observed between females with and without a history of concussion ($p>0.05$, all measures). A comparison of means and indication of performance can be found in Table 3.

TABLE 2. Mean and Standard deviation (SD) for each significant kinematic outcome variable (full pathlength - PLf; Peak Velocity - PV; Reaction time – RT; Absolute Error – AE; Variable Error – VE) in the M-Hx to F-Hx and M-NoHx to F-NoHx t-tests prior to Bonferroni correction for multiple comparison. Reported by sex (M – male, F – female) and concussion history (Hx) and standard condition (Cond1) or non-standard condition (Cond2). Including an indication of interpretation of performance

Variable	**Sex**	**Hx**	**Mean**	**SD**	**Hx Performance**	**NoHx Performance**
PLf Cond1	M	No	53.91	1.02	M-Hx better than F-Hx	M-NoHx better than F-NoHx (non-significant)
	M	Yes	44.43	6.06		
	F	No	54.40	1.28		
	F	Yes	54.11	1.24		
PV Cond1	M	No	172.41	53.28	M-Hx worse than F-Hx	M-NoHx better than F-NoHx
	M	Yes	142.49	44.46		
	F	No	166.19	46.50		
	F	Yes	167.39	34.21		
RT Cond 1	M	No	377.30	41.71	M-Hx worse than F-Hx	M-NoHx worse than F-NoHx
	M	Yes	367.45	39.60		
	F	No	341.59	32.08		
	F	Yes	331.17	34.97		
AE Cond2	M	No	4.34	0.90	M-Hx better than F-Hx	M-NoHx worse than F-NoHx
	M	Yes	3.15	0.94		
	F	No	4.19	1.03		
	F	Yes	4.20	0.66		
VE Cond2	M	No	3.31	0.81	M-Hx better than F-Hx	M-NoHx worse than F-NoHx
	M	Yes	2.59	0.97		
	F	No	3.20	1.09		
	F	Yes	3.43	0.61		
PLf Cond2	M	No	55.13	2.71	M-Hx better than F-Hx	M-NoHx better than F-NoHx
	M	Yes	44.83	6.23		
	F	No	56.38	7.32		
	F	Yes	56.24	4.14		
PV Cond2	M	No	110.57	40.69	M-Hx worse than F-Hx	M-NoHx better than F-NoHx
	M	Yes	94.54	34.23		
	F	No	89.10	28.93		
	F	Yes	104.93	42.27		

TABLE 3. Mean and Standard deviation (SD) for each significant kinematic outcome variable (full pathlength - PLf; Peak Velocity - PV; Absolute Error – AE; Variable Error – VE) in the M-NoHx to M-Hx and F-NoHx to F-Hx t-tests prior to Bonferroni correction for multiple comparison. Reported by sex (M – male, F – female) and concussion history (Hx) and standard condition (Cond1) or non-standard condition (Cond2). Including an indication of interpretation of performance.

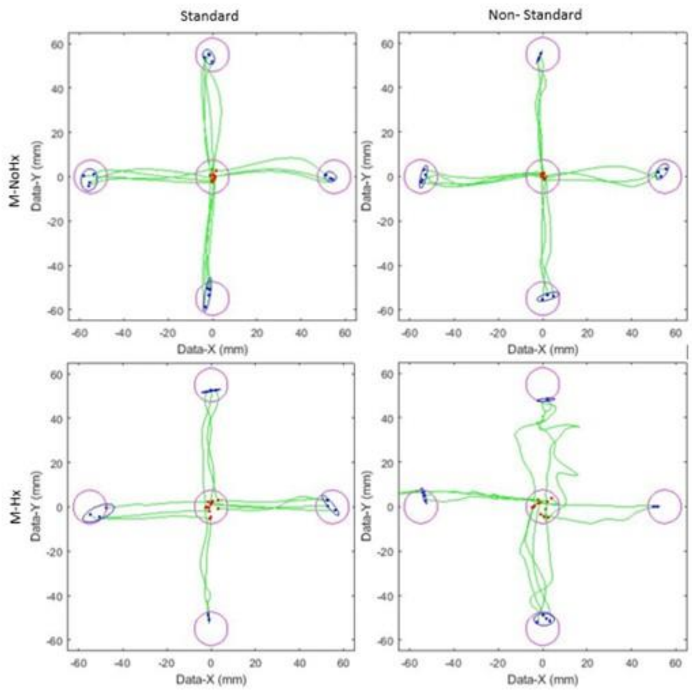
Variable	**Sex**	**Hx**	**Mean**	**SD**	**Males Performance**	**Females Performance**
PLf Cond1	M	No	53.91	1.02	NoHx worse than Hx	NoHx same as Hx
	M	Yes	44.43	6.06		
	F	No	54.40	1.28		
	F	Yes	54.11	1.24		
PV Cond1	M	No	172.41	53.28	NoHx better than Hx	NoHx same as Hx
	M	Yes	142.49	44.46		
	F	No	166.19	46.50		
	F	Yes	167.39	34.21		
AE Cond2	M	No	4.34	0.90	NoHx worse than Hx	NoHx same as Hx
	M	Yes	3.15	0.94		
	F	No	4.19	1.03		
	F	Yes	4.20	0.66		
VE Cond2	M	No	3.31	0.81	NoHx worse than Hx (trend)	NoHx same as Hx
	M	Yes	2.59	0.97		
	F	No	3.20	1.09		
	F	Yes	3.43	0.61		
PLf Cond2	M	No	55.13	2.71	NoHx worse than Hx	NoHx same as Hx
	M	Yes	44.83	6.23		
	F	No	56.38	7.32		
	F	Yes	56.24	4.14		
PV Cond2	M	No	110.57	40.69	NoHx better than Hx (trend)	NoHx worse than Hx (non-significant)
	M	Yes	94.54	34.23		
	F	No	89.10	28.93		
	F	Yes	104.93	42.27		

Following a Bonferroni correction for multiple comparisons ($p = 0.05/4 = 0.0125$), reaction time in condition one ($p < 0.0125$) remained significant when comparing M-NoHx to F-NoHx. Reaction time ($p < 0.0125$) and full pathlength ($p < 0.0125$) in condition one, and absolute error ($p < 0.0125$), variable error ($p < 0.0125$) and full pathlength ($p < 0.0125$) in condition two remained significant when comparing M-Hx to F-Hx. And full pathlength in standard condition one ($p<0.0125$), and absolute error in standard condition two ($p<0.0125$) remained significant when comparing M-NoHx to M-Hx. Cohen's *d* was calculated for each variable, and the following effect sizes were noted (Table 4).

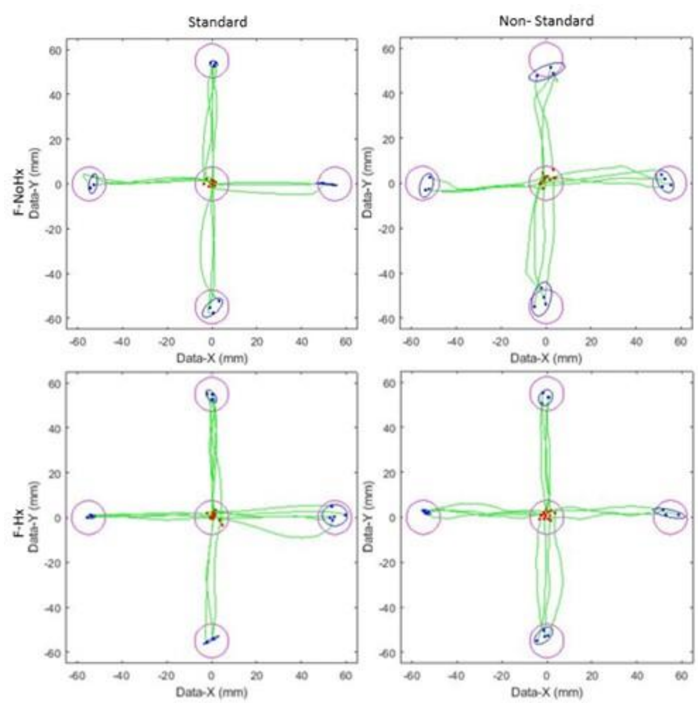
TABLE 4. Cohen's *d* value reported for all significant interactions between sex and concussion history on kinematic outcome variables (full pathlength, PLf; peak velocity, PV; Accuracy – Absolute error, AE; & Precision – Variable error, VE).

Condition	**Variable**	**Cohen's *d***	**Effect Size**
1 (standard)	PLf	1.143	Large
	PV	0.249	Moderate
2 (non-standard; CMI)	Accuracy (AE)	0.406	Moderate
	Precision (VE)	0.498	Moderate
	PLf	0.251	Small - Moderate
	PV	0.626	Large

Additionally, the trajectory traces in figure 2 a & b give a visual representation of the difficulties that can be seen in performance on the CMI task. Figure 2a. shows sample trajectories of one M-NoHx and one M-Hx participant on both the standard and non-standard condition. Figure 2b. shows sample trajectories of one F-NoHx and one F-Hx participant on both the standard and non-standard condition. It is interesting to look at both the trajectory differences of the sliding of the finger (green lines), and the number off successful trials to each target (blue dots). Trials are coded as unsuccessful if the participant does not hold in the external target or if the participant exits the centre target greater than 45^{o} in the wrong direction. These errors may provide insight into performance along with trajectory paths and kinematic variables.



2a.



2b.

Figure 2a. & 2b. Successful trajectories (green lines) from finger start position (red dot) in the central target (purple circle) to finger end position (blue dot) in the peripheral target (purple circle) for A) One M-NoHx and one M-Hx participant on both the standard (left) and non-standard (right) condition. And B) One F-NoHx and one F-Hx participant on both the standard (left) and non-standard (right) condition.

Discussion

We examined the effect of concussion history on emotionality and CMI performance, and how this performance differs between the sexes. We examined self-reported emotionality symptoms, and performance on a computer CMI task between males and females with and without a history of concussion. Based on animal models and past research looking at symptom reporting following concussion (Covassin, Schatz, & Swanik, 2007; Frommer et al. 2011; Berz et al., 2013; McCorkle et al., 2019; Wright et al., 2017), we predicted that males would not show a difference in emotionality despite a history of concussion and instead would show difficulty with visuomotor skill recovery, while females would show a difference in emotionality despite a history of concussion, but would have recovered visuomotor skill. Instead, we found that males with a history of concussion significantly differed on both the reporting of emotionality symptoms and visuomotor skill recovery, while females showed no differences on either measures.

The current literature has mixed results regarding the nature and reliability of self-reported symptoms as an indicator of concussion recovery. Of particular interest is the possible impact of gender norms in the reporting of symptoms following concussion (Kroshus et al., 2017; Covassin & Elbin, 2011; Broshek et al., 2005). A study by Kroshus et al. (2017) on 328 college athletes noted that societal gender norms have an impact on the reporting of emotional symptoms whereby females were more likely to report symptoms emotional in nature. Covassin & Elbin (2011) found that female athletes were more concerned about their future health than male athletes, possibly contributing to the differences in symptom reporting. Due to the cross-sectional nature of this study, we suggest that gender norms are not playing a role in the reporting of emotionality symptoms. Contrary to previous studies looking at symptom presentation between males and females after concussion (Hannah, Li, & Spiera, 2021; Covassin, Schatz, & Swanik, 2007;

Frommer et al., 2011; Berz et al., 2013) whereby females reported more symptoms than males throughout the recovery process, our results suggest that males struggle more with emotionality as the result of concussion than females. In this study, the only statistically significant effect was a rise in Anxiety for males. Additionally, significantly more males with a history of concussion reported Anxious symptoms than their control counterparts, which was not seen in females. Interestingly, though not statistically significant, a greater percentage of females with no history of concussion subscribe to all symptoms except More Emotional when compared to their male counterparts. As well, when looking at the percentages, it appears that a history of concussion in males brings the percentages of those subscribing to symptoms to a similar level of females without a history of concussion. These results may imply that concussion is responsible for a greater impact on male's general emotionality, given that females are reporting both before and after a concussion, whereas males are increasingly reporting after a concussion. It is important to note that this study is cross-sectional; while this adds support to the notion that the reporting of symptoms in males in this cohort is not due to gender norms, it also means these results may not only reflect the impact of concussion but also the nature of the individuals, and caution should be taken when generalizing to other samples. While it is not entirely clear from this dataset what may be the cause of the differences in emotionality symptoms, it is an important addition to the literature regarding the presence of sex-specific differences in response to concussive injury.

The results of the CMI performance are somewhat more expected. Earlier studies which used a CMI task and included both females and males (Dalecki et al., 2016; Dalecki et al., 2020; Brown et al., 2015) or males only (Hurtubise et al., 2016) found significant impact of concussion history on CMI performance. However, recent research from our lab has indicated that these differences may have been driven by males. In order to investigate whether these earlier results were repeatable in a female sample, we had a subset of both male and female participants perform a standard and non-standard visuomotor task with the same mechanics and data output as the ones used in previous studies. We were not able to repeat the finding of significant differences on CMI performance in females with and without a history of concussion. This provides support that the previous differences were driven by males given the significant difference in visuomotor performance of males but not females when analyzed as two separate groups. More importantly, given that these males were cleared by current standards to return to play but appear to be showing lingering difficulties on visuomotor performance, this also provides evidence that even objective measures to track recovery following concussion should have different thresholds for male and female athletes. As well, while significance was lost after correcting for multiple comparisons, we also find it interesting that there is a potential speed-accuracy compensation in behavioural performance in males with a history of concussion. Referring to Table 4., the M-Hx group had increased performance on variables relating to accuracy (AE, VE, and PLf), but decreased performance on peak velocity when compared to their NoHx counterparts, and while no differences in performance were seen in females. Additionally, males with a history of concussion performed better than females with a history concussion on all accuracy variables, but worse on peak velocity. Similar to the implication that elite level athletes are able to pass current metrics despite still have lingering damage (Hurtubise et al., 2016), the ability for these male athletes to pass this metric with what we are suggesting is a compensation tactic suggests that they may actually be at risk of secondary injury (Bowen, 2003; Weibe, Comstock, & Nance, 2011; Signoretti et al., 2011). Given the contact nature of the sports assessed in this study, the need for high level CMI performance in order to play safely, and the fact that all athletes were cleared by current standards at the time of testing, a trend such as this may indicate the need for more specific testing and tracking methods following concussion, with particular emphasis on different compensations in males versus females.

While very limited research has been done looking separately at female athletes with concussion; one previous study looked at the difference in effect of no concussions, one concussion, or multiple concussions. They found a difference in performance between males and females with a history of multiple concussions on a computerized test battery (Immediate Postconcussion Assessment Cognitive Testing) (Covassin et al., 2010) with females performing better than males on verbal memory and visual memory. Interestingly, in conjunction with the results of the current study showing recovered cognitive-motor integration in females but not in males, this not only provides support for adjusted testing measures for males and females, but may suggest further adjustments are needed based on previous number of sustained concussions. While we did not have a large enough sample size to compute correlations of CMI performance and emotionality across groups of number of previous concussions, we are looking to investigate this in our future work.

No previous studies have used CMI to investigate sex-related differences in performance following concussion despite the overlap of the brain areas involved in CMI and the brain areas commonly impacted by concussion. However, it is interesting to note that brain imaging research has found differences in brain activation between healthy (no concussion history) males and females when performing a CMI task (Gorbet & Sergio, 2007). An increased bilateral activation in females compared to males was observed. Given the results of this current study, with females showing recovery of visuomotor skill following concussion, it is possible that this bilateral activation pattern has a protective effect on visuomotor skill following injury such as concussion. Indeed, it may be that such visually-guided skill retention and recovery in females is related to a more resilient motor control network that is supported by both bilateral brain activation and corpus callosum structural differences (Albines et al., 2016; Liu et al., 2010; Bjornholm et al., 2017). Further research observing functional network connectivity in females and a comparison to males is necessary to determine whether there is a resiliency or compensation happening following concussion.

Similarly, it has been proposed that hormone levels may have an impact on cognitive performance (Kimura, 2002; Gouchie & Kimura, 1991; Haussman et al., 2000). Specifically, sex hormones estrogen and testosterone have received the most focus. In a study done by Hampson, Levy-Cooperman and Korman (2014), low estrogen was linked with significantly better accuracy on a mental rotation task. In a similar fashion, a study looking a testosterone found that healthy young men with lower levels of the hormone performed better on a spatial task than those with higher levels[41.] In a review by Kimura (2002), cognitive sex-related differences were presented as favouring males or favouring females. Across ages and cultures, it was fairly consistent that males performed better on spatial orientation, visualization, and mathematical reasoning. Whereas females performed better on object location memory, perceptual speed, verbal memory, numerical calculation, and dexterity. Given the significant difference between males and females with a history of concussion on a CMI task and emotionality, it would be interesting to investigate the potential impact of hormones in this area. Hormones, and particularly the fluctuation of hormones through the menstrual cycle, have been shown to impact cognitive performance (Weiss et al., 2003; Li, 2014; Satterthwaite et al., 2015; Jancke, 2018; Gurvich et al., 2018). Therefore, further investigation into the impact of hormones on CMI performance may reveal a protective effect accounting for the lack of performance difference noted in females with and without a history of concussion, and may provide insight into the differences in expression of emotionality symptoms.

In addition to adding to the literature surrounding concussive injury, such an understanding of sex-related differences in symptom reporting and visuomotor performance could assist clinicians in making return-to-play decisions through improved diagnostic and recovery tracking standards. Current international protocols require athletes to be evaluated by a physician and meet baseline measurements of both cognitive and motor assessments prior to beginning return-to-play progressions (McCrory et al., 2017). However, these assessments are identical for both males and females. This study shows that males and females are impacted differently following concussion and may require more tailored testing to ensure the safety of all athletes. Additionally, this study brings up the importance of baseline testing measures. Having a comparison available of symptoms following concussion to symptoms prior to receiving a concussion on an individual basis would strengthen the diagnostic and recovery tracking nature of sideline assessments.

Feasibility/Limitations

The sample size is small and consists of only varsity level athletes. Therefore, caution must be taken when generalizing the results to the larger population.

Because we did not compare the emotionality of each athlete to a personal baseline symptom scale, we cannot definitively attribute the differences in number of participants who subscribe to emotionality symptoms to concussion. It may be that these individuals had higher emotionality to begin with, even though both males and females had higher emotionality symptom reporting post-concussion. Lastly, we used standardized forms that constrained our participants' classification to binary self-reported sex, rendering the role of gender on concussion recovery beyond the scope of the current study. Future work will address this important consideration.

Chapter three: Hormone levels impact concussion recovery assessment metrics in female varsity athletes – A preliminary study

Abstract

Objective: Investigate the relationship between levels of estradiol, testosterone and progesterone and aspects of the sport concussion assessment tool along with a visuomotor transformation task in female varsity athletes.

Participants: University varsity athletes, 30 females (16 with a history of concussion). The mean age of participants was 19.9 +/- 1.5 years. All participants were asymptomatic by current standards at the time of preseason baseline testing.

Methods: Participants were tested on two visuomotor skill tasks, one of which was a standard slide-finger-to-target on a touchscreen and the other had a decoupled gaze/hand location and reversed visual feedback. They also completed the SCAT3/5 assessment, and a saliva sample was collected.

Outcome measures: Kinematic timing and trajectory variables, SCAT symptom inventory, SCAT modified balance error scoring system, estradiol, testosterone, progesterone.

Results: No significant group differences were found on any of the metrics - with and without the controlling for levels of estradiol, testosterone, or progesterone. When collapsed into a single group, progesterone was moderately positively correlated with overall performance on a visuomotor transformation task, and testosterone was moderately positively correlated with the cognitive-motor integration trials (two levels of dissociation) of the visuomotor transformation task.

Conclusions: We suggest that these hormones may therefore have an impact on the sensitivity of current metrics and clinicians should take into account these impacts when making return to play decisions.

Background

Concussion has been deemed one of the most complicated injuries of which to diagnose and manage recovery in sports medicine (McCrory et al. 2017). The heterogenous nature of the injury and increasingly wide range of confounding factors such as age, sex, previous incidence of concussion, experience in sport, and level of play, make diagnostic tools and recovery metrics extremely difficult to generalize. However, current research strives to improve these tools and metrics as more evidence is gathered surrounding commonalities of injury presentation and recovery. The sport concussion assessment tool (SCAT) (Echemendia et al., 2017) is one metric that has been continually updated in an effort to keep up with the changing knowledge surrounding concussion, and is widely used by clinicians and athletic therapists. The SCAT consists of multiple components designed to evaluate for the presence of concussion including a symptom inventory, cognitive and memory components, and a vestibular balance component. Notably, sex-related differences in both symptoms (Covassin, Schatz, Swanik, 2007; Frommer at al., 2011; Berz et al., 2013) and recovery trajectory (Berz et al., 2013; Ono et al., 2016) have been observed following concussion, with females reporting an increased number of symptoms and longer recovery times compared to males. Additionally, it has been noted that females have a higher incidence of sport-related concussion than males (Covassin, Swanik, Sachs, 2003; Black, Sergio, & Macpherson, 2017; Barnes et al., 1998), suggesting that there may be underlying factors putting females at an increased risk for injury and longer recovery.

While the SCAT is a generally agreed upon tool for the sideline assessment and diagnosis of concussion, one flaw is the sequential testing of cognition and motor behaviour (Fueger et al., 2019; Locklin et al., 2010; Sergio et al., 2020), despite these domains often having to be concurrently controlled during sport. Many studies have noted behavioural performance differences during the simultaneous execution of cognition and motor tasks which require the integration of the two domains, despite the lack of difficulty on the cognition and motor performance alone (Buttner et al., 2020; Howell, Osterning, & Chou, 2017). More generally, lingering deficits on tasks that require cognitive-motor integration (CMI) have been observed in different populations of individuals diagnosed with a concussion, but asymptomatic and cleared for return to play by current metrics (Brown et al., 2015; Dalecki et al., 2016; Hurtubise et al., 2016, Mitchell & Cinelli 2019; Howell et al. 2017;Catena et al. 2007;Baker and Cinelli 2014;Ventura et al. 2016).

Behavioural sex-related differences have also been noted in multiple aspects of cognition alone, such as visual-spatial tasks (Weiss et al., 2003; Li, 2014), verbal tasks (Weiss et al., 2003; Li, 2014; Kimura, 2002), perceptual speed (Kimura, 2002), and dexterity (Kimura, 2002). It has been proposed that these differences in cognition may be as a result of hormone levels (Kimura, 2002; Gouchie & Kimura, 1991; Hausmann et al., 2000). In this area, sex hormones estrogen and testosterone have received the most focus. In a study done by Hampson, Levy-Cooperman and Korman (2014), low estrogen was linked with significantly better accuracy on a mental rotation task. In a similar fashion, a study looking at testosterone found that healthy young men with lower levels of the hormone performed better on a spatial task than those with higher levels (Gouchie & Kimura, 1991). In a review by Kimura (2002), cognitive sex-related differences were presented as favouring males or females depending on the task. Specifically, across ages and cultures, it was fairly consistent that males performed better on spatial orientation, visualization, and, mathematical reasoning. In contrast, females performed better on object location memory, perceptual speed, verbal memory, numerical calculation, and dexterity. Much of the research surrounding the impact of hormones on cognition has been done using the natural fluctuation of hormones inherent with the female menstrual cycle. The results of most of these studies suggest that females performed better on “male dominant” cognitive tasks during periods of low estrogen, and on “female dominant” cognitive tasks during periods of higher estrogen (Kimura, 2002; Hausmann et al., 2000). Some studies have also noted the importance of progesterone in cognition in animal models (Yousuf et al., 2014; Roof et al., 1994; Wali et al., 2014; Frye & Walf, 2008) and human cognition (Henderson, 2018; Sofuoglu, Mouratidis, & Mooney, 2011). Given the importance of cognition in CMI, it is plausible that estrogen, testosterone, and progesterone may have an impact on overall CMI performance.

Difference have also been noted in postural sway and balance between those with a previous history of concussion and those without (Guskiewicz, Perrin, & Gansneder, 1996; Guskiewicz et al., 1997; Riemann & Guskiewicz, 1997; Purkayastha et al., 2019; Cavanaugh et al., 2005). Research in this area led to the inclusion of the modified Balance Error Scoring System (mBESS) in concussion diagnosis and recovery metrics such as the SCAT. Interestingly, sex-differences have also been noted in this area but are slightly mixed. For example, Hurtubise et al. (2018) found no sex-related differences on performance of BESS following concussion in university athletes. However, Covassin et al., (2012) found worse performance on the BESS in female athletes following concussion than males in college athletes. Studies using BESS following concussion have been investigated in multiple different age groups and levels of experience in sport which add to the inconsistent results. Interestingly, research has investigated the effect of estradiol on postural balance in women (Naessen, Lindmark, & Larsen, 1997; Ekblad et al., 2000). However, the findings were similarly inconsistent. Nassen, Lindmark, & Larsen found that postmenopausal women using estradiol implants showed levels of postural sway significantly lower than non-users, and similar to those in young premenopausal women. In contrast, Ekblad et al. (2000) showed no significant differences in postmenopausal women using a transdermal estradiol patch compared to a transdermal placebo patch in dynamic posture over a period of 12 weeks. For this reason, we are particularly interested in the effect of estradiol levels on performance of the modified Balance Error Scoring System (mBESS) component of SCAT.

Study one explored sex-specific differences in performance on a CMI task following concussion. Males with a history of concussion showed significantly different levels of performance than their control counterparts on multiple kinematic variables – whereas no differences were seen in females. Additionally, this study found that males subscribed to an increased number of emotionality-related symptoms following concussion than their female counterparts. While little to no research has been done on hormones and concussion metrics directly, information presented in past research on cognition and motor performance suggests that levels of estrogen, testosterone, and progesterone may have some connection with the sex-specific differences found in the reporting of symptoms, vestibular performance, and CMI performance following concussion.

As a first step to address this issue directly, this study investigated whether levels of estradiol, testosterone and progesterone measured through saliva in female varsity athletes were correlated with scores on the total SCAT5 symptom inventory, the SCAT5 symptom severity, the modified Balance Error Scoring System (m-BESS) included in the SCAT5, and a cognitive-motor integration task. On a basic behavioural level, we hypothesized that there would be no significant differences between those with a previous history of concussion and those without on the CMI task, but that those with a history of concussion would show an increased number of total symptoms and symptom severity compared to controls in this group of female athletes. In terms of sex hormones, given the potential protective effects of estrogen on postural sway and balance we hypothesized that there would be no significant differences in mBESS performance between concussion history groups, but that levels of estrogen would positively correlate with overall mBESS scores. As well, we hypothesized that there would be a relationship between levels of estrogen, testosterone, and progesterone with performance on the CMI task, regardless of history of concussion. Specifically, lower estrogen and/or higher testosterone, and higher progesterone would result in better visuomotor performance. An exploratory aspect to this study was the effect of sex hormone levels on SCAT symptom number and severity scores at the time of testing, particularly in those athletes with a concussion history.

Methods

Participants

A total of 35 participants were initially recruited through the Gorman Shore Sports injury clinic on York University Keele Campus in North York, Ontario, Canada. Out of them, we obtained saliva samples from 30 participants (16 with a history of concussion – asymptomatic and cleared for play). The mean age of participants was 19.9 +/- 1.5 years (Table 1). Age and years of experience did not differ between groups.

Table 1. Demographic information regarding sport, age, years of experience playing specific sport listed, previous history of concussion, number of previous concussion, and time since last concussion in months.

Sport	Age	Years Experience	Concussion History	Number Previous Concussions	Months Since Last Concussion
volleyball	21	9	0	0	N/A
volleyball	21	16	0	0	N/A
hockey	20	15	0	0	N/A
soccer	18	14	0	0	N/A
soccer	21	17	0	0	N/A
basketball	18	12	0	0	N/A
hockey	19	12	0	0	N/A
hockey	18	14	0	0	N/A
soccer	21	11	0	0	N/A
hockey	20	15	0	0	N/A
hockey	19	14	0	0	N/A
hockey	19	15	0	0	N/A
hockey	18	13	0	0	N/A
hockey	20	16	0	0	N/A
soccer	24	21	1	5	12
hockey	18	15	1	1	24
basketball	19	13	1	2	11
volleyball	21	14	1	3	36
soccer	21	13	1	1	9
basketball	19	15	1	3	24
volleyball	21	14	1	4	6
hockey	18	5	1	1	36
hockey	20	15	1	1	36
volleyball	22	15	1	2	3
volleyball	19	10	1	1	11
hockey	20	13	1	3	36
volleyball	19	16	1	2	24
hockey	19	9	1	1	12
basketball	22	16	1	1	3
soccer	21	8	1	2	12

All participants included in the study were asymptomatic and had no other injury preventing them from practicing and playing their sport at the time of testing. The York University Research Ethics board human participants subcommittee approved the protocol used in the experiment. The experimental protocol was also in compliance with the Declaration of Helsinki. All participants provided informed written consent prior to data collection.

Procedure

Participants completed a CMI task, SCAT5, and saliva collection in a single session.

Behavioural-Visuomotor:

Participants completed two computer-based visuomotor transformation tasks, one standard and one non-standard (vision and action decoupled, CMI). Participants sat at a desk comfortably in front of a 10.1" ACER tablet (60Hz refresh rate) connected to a 15" Keytec^{TM} touchpad allowing for a touch screen in both the horizontal and vertical planes. In both conditions, participants were instructed to slide their index finger of their preferred hand along the touch screen in order to displace a cursor from a central target to one of four peripheral targets (up, down, left, right) as quickly and as accurately as possible. Participants guided a crosshair cursor, viewed on a black background, to the yellow central (or home) target which, when reached successfully, changes to green. After 4000ms, a red peripheral target is presented and the central target disappears, which serves as the 'Go' signal for the participant to initiate movement. Once the participant successfully reaches the target and remains for 500ms, the peripheral target disappears, signaling the end of the trial. The next trial begins with the presentation of the central target after an inter-trial interval of 2000ms. Peripheral targets are located 55mm from the center target, and target diameters are 15mm. In order to ensure smooth movement of the finger during the task, participants wore a capacitive-touch glove on their preferred hand (FIG1a & 1b).

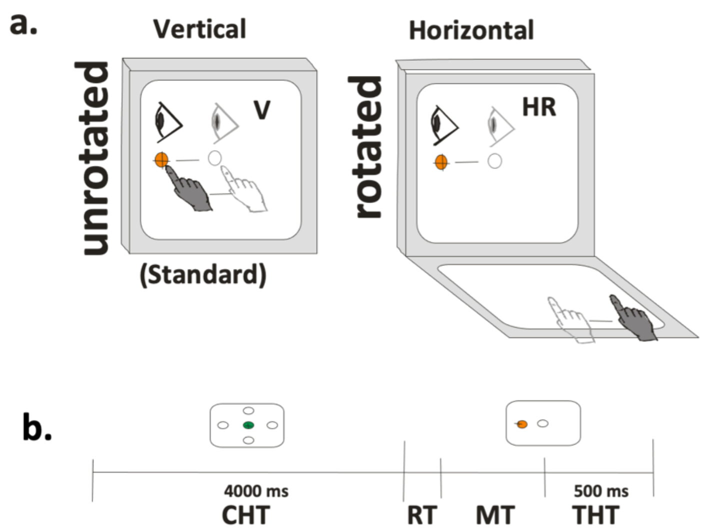


Fig. 1a & 1b. (A) Schematic drawing of both experimental conditions V (vertical, standard) and HR (Horizontal Rotated, non-standard). Visual stimuli were presented on the vertical monitor for all conditions. Green circle, light grey eye, and hand symbols denote the instructed eye and hand movements for each task. Red circles denote the peripheral (reach) target, presented randomly in one of four locations (left, up, right, and down). The dark crosshair denotes the cursor feedback provided during each condition. (B) Schematic drawing of time progression of task. centre hold time (CHT) indicates the 4000ms participants must hold in the centre target before a peripheral target appears, followed by reaction time (RT) of participant to respond to the stimulus, movement time (MT) of participant to successfully slide the cursor from the central target to the peripheral target, and target hold time (THT) signifying the 500 ms that participants must hold in the peripheral target until returning back to centre to start their next trial.

Participants completed the standard and non-standard conditions in a randomized block design. In the standard condition, participants both look and move on the vertical screen, and thereby directly interacted with the targets. Movements for the non-standard visuomotor condition are made on the horizontally oriented Keytec^{TM} touchpad. The touchpad was calibrated such that the distance of the finger movement path on the touchpad is equivalent to the distance the cursor moves on the tablet screen. The non-standard condition includes two levels of decoupling: (i) plane change; in which participants look at the vertical screen while moving on the horizontal screen, requiring spatial recalibration, and (ii) cue reversal; in which the feedback is rotated 180° (i.e. in order to move the cursor left, you slid your finger right), requiring strategic control. Six trials in each of the four directions were completed per condition for a total of 40 trials per participant (4 directions x 5 trials x 2 conditions). Eye movements were monitored by the experimenter to ensure participants look at the correct target.

Behavioural – SCAT5:

Symptoms were measured through the symptom inventory as part of the SCAT5 and balance was measured through the modified Balance Error Scoring System (m-BESS) as part of the SCAT5. The symptom inventory consists of 22 commonly reported symptoms, which are self-rated on a 7-point Likert scale from 0 (no issue) to 6 (severe). Both the number of symptoms (max 22), as well as a symptom severity score (sum of all reported symptoms, max 132) are reported. Balance is measured through the m-BESS, incorporating three 20sec tests of different stances (feet together, single leg – non-dominant, tandem – non-dominant behind) on a firm ground. Specified deviation from the stance is counted as an error, up to a maximum of 10 errors per stance (max 30 total).

Saliva Acquisition:

Saliva collection was done using the passive drool method. Following set-up of the saliva collection aid and collection vial by the researcher, the participant was instructed to allow saliva to pool in their mouth with their head tilted down, and then slowly allow the saliva to pour from their mouth into the vial. Participants were asked to refrain from spitting or forcing saliva into the tube in order to avoid excess bubbles. Following instruction, participants were left alone in a quiet room in order to fill the tube with saliva. Participants were instructed to refrain from eating or drinking 30 minutes prior to saliva acquisition.

Data Pre-processing

Behavioural- CMI:

Custom-written (C++) acquisition software samples the finger's X-Y screen position at 60Hz. Custom analysis software (Matlab, Mathworks Inc.) was used to generate a computerized velocity profile of each trial's movement. Movement onsets and ballistic movement offsets (the initial movement prior to path corrections) were scored at 10% peak velocity, while total movement offsets were scored as the final 10% peak velocity point once the finger position is within the peripheral target. These profiles were then verified by visual inspection, and manually corrected if necessary. Trials were considered errors if the finger/cursor left the center target too early (< 4000ms), reaction time was less than 150ms or more than 8000ms, or total movement time was more than 10000ms. Trials in which the first ballistic movement exited the boundaries of the center target in the wrong direction (greater than 90° from a straight line to target) were coded as direction reversal errors, eliminated from further evaluation, and analyzed as a separate variable. The scored data was then processed to compute both movement timing and execution outcome measures.

The kinematic variables for movement timing were as follows: 1) Reaction Time (RT), the time interval (milliseconds) between the central target disappearance and movement onset; 2) Movement Time (MT), the time between movement onset and offset (millisecond), and 3) Peak Velocity (PV), the maximum velocity obtained during the ballistic movement. Kinematic variables for movement execution were: 1) Full Path Length (PLf), the total distance (resultant of the x and y trajectories) travelled between movement onset and offset (millimeters), 2) Absolute Error (AE, accuracy), the average distance from the individual ballistic movement endpoints ($\sum x/n$, $\sum y/n$) to the actual target location (millimeters); 3) Variable Error (VE, precision), calculated as the distance between the individual ballistic movement endpoints ($\sigma 2$) from their mean movement (millimeters); and 4) Percentage Direction Reversal errors (DR) were calculated as the number of trials with a deviation of greater than ±45° from the direct line between the midpoint of the central and peripheral targets compared to the number of successful trials.

Saliva:

The High Sensitivity Salivary 17β-Estradiol Enzyme Immunoassay Kit, Salivary Progesterone Enzyme Immunoassay Kit, and Expanded Range Salivary Testosterone Immunoassay Kit from Salimetrics were used for analysis of the saliva samples. Full assay protocols can be found on the Salimetrics website (https://salimetrics.com/assay-kits)

Data Analysis:

Initial independent samples T-Tests were conducted to ensure there were no statistically significant differences between age and years of experience in the concussion history group versus the control group.

For the seven kinematic variables described above (RT, MTf, PV, PLf, CE, VE, %DR) an overall score was calculated to reflect summarized performance on the visuomotor (VM) task for both the standard condition (S-VM), the non-standard condition (CMI-VM) and the overall visuomotor performance (OA-VM). A smaller value on all variables except Peak Velocity indicates better performance. Therefore, peak velocity was multiplied by a value of -1 prior to calculation. Related variables were added together and weighted 20% of the final score. This resulted in the following equation:

$$(RT+MTf)*0.2+(PV)*0.2+(CE+VE)*0.2+(PLf)*0.2+(\%DR)*0.2$$

For ease of understanding, the final S-VM, CMI-VM, and OA-VM scores were multiplied by a value of -1 such that a higher score on these variables indicated better performance, and a lower score indicated worse performance. Total number of symptoms reported on the SCAT symptom inventory were totalled for each participant, and symptom severity was calculated using the 7-point Likert scale values for each of the reported symptoms. An overall balance score was calculated by totalling all errors made across each of the three stances for each subject. Estradiol, Testosterone, and Progesterone were each included as their own variables.

Statistically, data were analyzed in three ways. First, a one-way ANOVA was conducted with concussion history as the independent variable, and S-VM, CMI-VM, Symptom total, Symptom severity, mBESS, Estradiol, Testosterone, and Progesterone as the dependent variables.

Following this, one-way ANCOVAs were run with S-VM, CMI-VM, Symptom total, Symptom severity, and mBESS as dependent variables and Estradiol as a covariate; S-VM, CMI-VM, Symptom total, Symptom severity, and mBESS with Testosterone as a covariate; and S-VM, CMI-VM, Symptom total, Symptom severity, and mBESS with Progesterone as a covariate.

Lastly, due to the asymptomatic nature of the concussion history participants, the two groups were then collapsed, and Spearman's correlations were run between Estradiol and S-VM, CMI-VM, OA-VM, Symptom total, Symptom severity, and mBESS; Testosterone and S-VM, CMI-VM, OA-VM, Symptom total, Symptom severity, and mBESS; and and Progesterone and S-VM, CMI-VM, OA-VM, Symptom total, Symptom severity, and mBESS. Additional Spearman's correlations were then run between a calculated Estradiol:Testosterone ratio and S-VM, CMI-VM, OA-VM, Symptom total, Symptom severity, and mBESS based on previous research by Sherwin (2009) suggesting that the balance between the two may be more important in sex-specific cognitive differences than the impact of each hormone alone.

Results

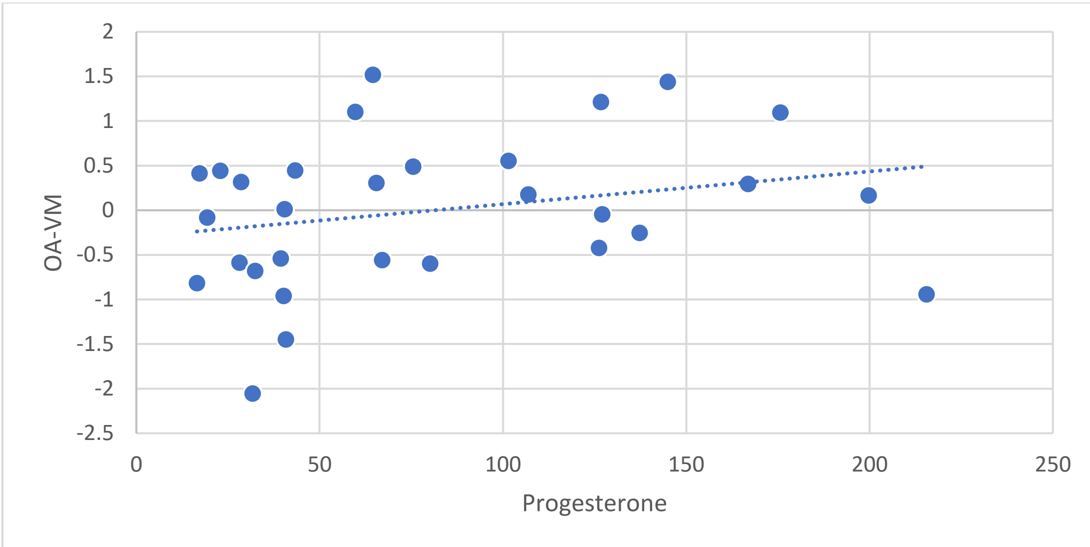
Group Analyses

We initially examined the data for differences on factors which typically affect visuomotor performance and balance. We found that age and years of experience did not significantly differ between the concussion history group and the control group (independent samples t-test, p>0.05 for both).

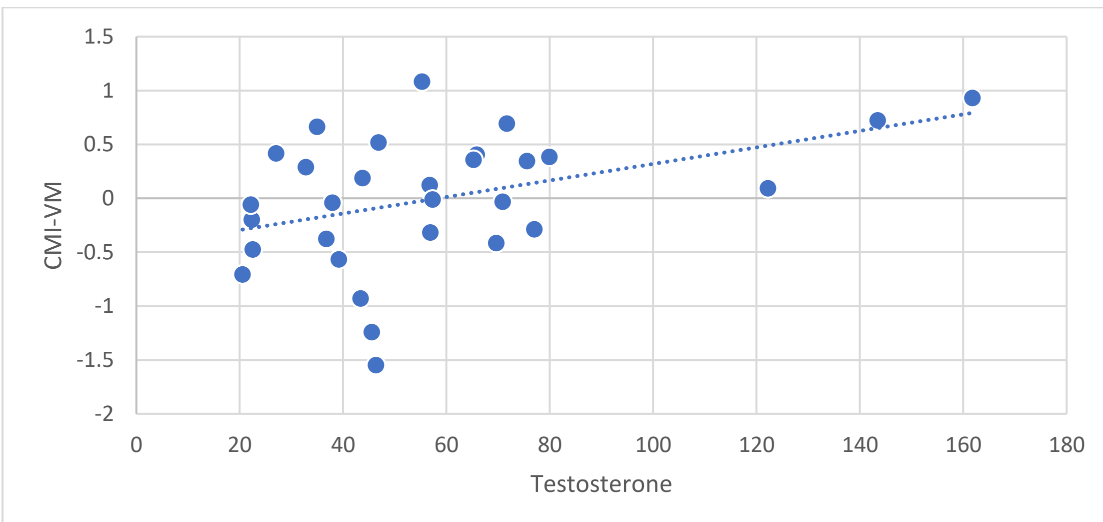
We then performed two analyses on the data divided into concussion history/no concussion history groups. The one-way ANOVA revealed no significant differences on any of the dependent variables (S-VM, CMI-VM, Symptom total, Symptom severity, mBESS, Estradiol, Testosterone, and Progesterone) between the concussion history group and the control group (p>0.05 for all). Next, using the sex hormones as covariates, a one-way ANCOVAs revealed no significant differences in S-VM, CMI-VM, Symptom total, Symptom severity, or mBESS (p>0.05 for all).

Correlation analysis on combined data

Lastly, we combined the data to examine for any relationships between our variables of interest and sex hormones. We observed two significant correlations: Progesterone levels were positively correlated with the overall visuomotor performance score (OA-VM, r = .390, p=0.033, and Testosterone levels were positively correlated with performance on the cognitive-motor integration task (CMI-VM, r = .407, p = 0.025), both of which can be seen in Figure 2. All other correlations were non-significant (p>0.05). The results of the Spearman's correlations can be found in Table 2.



A.



B.

Figure 2a&b. A) Progesterone levels were positively correlated with the overall visuomotor performance score (OA-VM, $r = .390$, $p=0.033$, and B) Testosterone levels were positively correlated with performance on the cognitive-motor integration task (CMI-VM, $r = .407$, $p = 0.025$).

Table 2. Correlation Coefficient and p-value for Spearman's Rho correlations. *significant at ($p<0.05$)

Correlation	Correlation Coefficient (rho)	Strength	*p-value*
Progesterone & S-VM	.112	Weak	0.554
Progesterone & CMI-VM	.268	Weak	0.152
Progesterone & OA-VM	.390*	Moderate	0.033
Progesterone & mBESS	-.214	Weak	0.255
Progesterone & Symptom Total	-.161	Weak	0.395
Progesterone & Symptom Severity	-.151	Weak	0.425
Estradiol & S-VM	.045	Very Weak	0.814
Estradiol & CMI-VM	.222	Weak	0.238
Estradiol & OA-VM	.347	Moderate	0.060
Estradiol & mBESS	-.220	Weak	0.243
Estradiol & Symptom Total	-.287	Weak	0.124
Estradiol & Symptom Severity	-.276	Weak	0.140
Testosterone & S-VM	.204	Weak	0.281
Testosterone & CMI-VM	.407*	Moderate	0.025
Testosterone & OA-VM	.107	Weak	0.575
Testosterone & mBESS	-.209	Weak	0.267
Testosterone & Symptom Total	-.291	Weak	0.119
Testosterone & Symptom Severity	-.283	Weak	0.130
ET-ratio & S-VM	-.281	Weak	0.132
ET-ratio & CMI-VM	-.320	Moderate	0.085
ET-ratio & OA-VM	.305	Moderate	0.101
ET-ratio & mBESS	.047	Weak	0.804
ET-ratio & Symptom Total	.068	Weak	0.720
ET-ratio & Symptom Severity	.071	Weak	0.710

Discussion

This study investigated whether levels of estradiol, testosterone, and progesterone measured through saliva in female varsity athletes were correlated with scores on the total SCAT5 symptom inventory, the SCAT5 symptom severity, the m-BESS included in the SCAT5, and a visuomotor task with both standard eye-hand coordination and cognitive-motor integration components. Initially examining group-based differences on our behavioural measures, we hypothesized that there would be no significant differences between those with a previous history of concussion and those without on the CMI task but those history of concussion would show an increased number of total symptoms and symptom severity compared to controls. With respect to hormones, behaviour, and concussion history, we hypothesized that there would be no significant differences in mBESS performance between groups (given their ‘recovered’ status), but that levels of estrogen would correlate with overall mBESS scores. As well, we hypothesized that there would be a relationship between levels of sex hormones and performance on the CMI task, regardless of history of concussion. Specifically, lower estrogen and/or higher testosterone, and higher progesterone would result in better visuomotor performance.

Our hypothesis surrounding the behavioural data was partially supported. We observed no significant differences on CMI performance in those with a history of concussion compared to controls. This study was in part done as an extension to study one which saw significant differences in CMI performance in males with a history of concussion compared to their control counterparts, but no such differences in females. The current study was able to repeat these findings in a different group of female athletes. Additionally, the current study did not find significant differences in symptom total or symptom severity between the concussion history and the control group. Previous research surrounding self-reported symptoms as a measure of concussion recovery has been mixed. Most studies focused on whether there was a difference between males and females, as opposed to a difference between those with a history of concussion and those without. As well, studies of pre- to post-injury symptom reporting have a confounding difficulty regarding what definition of post-concussion syndrome (or persistent symptoms) is used (Iverson et al., 2021). Many studies defined the absence of persistent symptoms as being completely asymptomatic and reporting no symptoms of any severity on a symptom questionnaire (Miller et al., 2016; Corwin et al. 2014; Erlanger et al., 2003; Gibson et al, 2013; Meehan et al., 2013). Others allowed for some symptoms with mild severity (Baker et al., 2015) or symptom improvement allowing for return to play (Heyer et al., 2016). This unclear definition results in mixed findings regarding symptom total and symptom severity following concussion. For this reason, it is hard to determine the underlying reason for a lack of differences in symptoms between the two groups, although this has been observed in previous studies (Zimmer at al., 2015; Valovich et al., 2012; Hurtubise et al., 2018). Here, we suggest that the lack of difference may also be due, in part, to recruitment methods. This study was conducted as part of a larger imaging study in which participants completed the tasks mentioned here as well as brain imaging in a two-hour session. The ability and desire to participate in this type of research may be a reflection of the participants' overall symptom total and severity to begin with, in that those who are experiencing higher levels of emotionality most likely would not extend themselves to voluntarily complete such a study. The lack of differences noted in this case may be due to the nature of those who volunteered to participate.

Additionally, in support of our hypothesis, we found no significant differences between groups on the performance of the mBESS. While previous differences have been noted in postural sway and balance between those with a previous history of concussion and those without using BESS (Guskiewicz, Perrin, & Gansneder, 1996; Guskiewicz et al., 1997; Riemann & Guskiewicz, 1997; Purkayastha et al., 2019; Cavanaugh et al., 2005), arguments have been made that when administered on its own, sensitivity is very low (Buckley, Oldham, & Caccese, 2016; Hurtubise et al., 2018). As well, much of the research surrounding BESS indicates that deficits tend to recover anywhere from 3 – 10 days post injury (Valovich McLeod & Hale, 2015; Caccese, Buckley, & Kaminski, 2016). Therefore, it is not surprising that we did not find group differences in performance in this case.

In contrast to what we predicted, we did not find a correlation between estradiol levels and performance on the mBESS. Nassen, Lindmark, & Larsen (1997) found that postmenopausal women using estradiol implants showed levels of postural sway significantly lower than non-users, and similar to those in young premenopausal women. However, very little research has been done on the effects of estradiol on vestibular measures in young premenopausal women. We suggest that the lack of correlation found in this study indicates that there is a potential threshold amount of estradiol with which differences in vestibular performance are observed. Previous studies findings may also have to do with other aging factors that our participants do not have, given the small age range of our group.

We did not find any significant differences between groups (concussion versus controls) on any variables, and this null finding was retained when the analysis used sex hormones as a covariate. However, in support of our hypothesis, we did note a significant correlation between higher levels of progesterone and better performance on the overall visuomotor task. In line with previous research indicating the importance of progesterone in cognition across different populations (Henderson, 2018; Sofuoglu, Mouratidis, & Mooney, 2011), we suggest that levels of progesterone at the time of testing may have partially promoted a difference in performance. Also, in line with our hypotheses, we found a significant relationship between testosterone and rule-based visuomotor performance, such that higher levels of testosterone correlated with better performance on the CMI component of the visuomotor task. Figure 2b. shows this relationship, however, it is important to note the three data points driving the positive correlation. These data points together with the relationship noted when observing progesterone may suggest that ratios of these hormones have more of an impact than individual hormones. Further investigation in this area is needed. However, previous studies have found that females tend to perform better on "male dominant" cognitive tasks, such as spatial orientation and visualization, during periods of low estrogen, and higher testosterone (Kimura, 2002; Hausmann et al., 2000; Pintzka et al 2014). Hence, the female athletes in our study with higher testosterone and progesterone levels at the time of testing may have had an advantage on our CMI task given the nature of the visual and spatial dissociation required to successfully perform the movements. We suggest that these sex hormones may therefore have an impact on performance on current metrics that involve skilled performance and cognitive testing. Therefore, levels of these sex hormones may impact performance on baseline measures of these metrics, and result in a discrepancy when attempting to use these metrics for diagnostic and recovery tracking purposes. In the future, it is important to longitudinally observe the impact of sex hormones on skilled performance and cognitive testing metrics.

It is important to note that majority of participants in this study were taking an oral contraceptive (n=21) at the time of testing. The number of participants taking an oral contraceptive did not differ between groups ($p>0.05$), but it is important to take this into account when interpreting the results of this study. Different forms of birth control exist including different hormones, different dosages, and different timelines of dosage. Additionally, previous research has noted an impact of birth control on symptom severity whereby females taking birth control exhibited lower symptoms severity than those not (Gallagher et al., 2018). Therefore, further research is necessary to investigate whether oral contraceptives have an impact on the variables examined, and whether different types of oral contraceptives result in different impacts.

Overall, these findings emphasize the value of accounting for sex-related differences in assessment metrics. It is important for those charged with evaluating competitive athletes for participation in sport consider these impacts when making their decisions.

Chapter four: The effect of concussion history, rule-based skilled performance, and sex hormone levels on neural network connectivity.

Abstract

Objective: Investigate the effect of 1) levels of estradiol, testosterone, and progesterone, 2) behavioural performance on a cognitive-motor integration (CMI) task, and 3) previous concussion history, on alterations in resting state functional connectivity (rs-FC) in brain networks.

Participants: University varsity athletes, 30 females (16 with a history of concussion).

Methods: Participants were tested on two visuomotor skill tasks – a standard slide-finger-to-target on a touchscreen, and a decoupled gaze/hand location and reversed visual feedback. They also completed the SCAT3/5 assessment, and a saliva sample was collected.

Outcome measures: Performance on a visuomotor task was assessed between the concussion history group and the control group. Rs-FC within the nodes of the Visual network, Somatomotor network, Dorsal Attention network, Salience Ventral Attention network, Limbic network, Frontoparietal Control network, and Default Mode network was assessed against visuomotor performance scores, levels of hormones, and concussion history.

Results: Visuomotor performance alone indicates no differences between those with concussion history and those without. In addition, no difference in rs-FC was noted in correlation with behavioural performance scores. Concussion history showed a moderate negative correlation with rs-FC in the Visual network ($r = -.447$, $p = 0.008$), while Progesterone level showed a moderate negative correlation with rs-FC in the DAN ($r = -.378$, $p = 0.022$) and SVA ($r = -.344$, $p = 0.034$).

Conclusions: These findings suggest sex hormone-related differences in rs-FC and performance on a CMI task, and support the need for further investigation into the impact of hormones on this performance.

Background

Concussive injury has been shown to induce an altered metabolic state in the brain following injury (Musumeci et al., 2019; Banks & Dominguez, 2019). The length of time for complete recovery from this state is not completely understood. The vulnerability to subsequent concussive injury during the recovery period indicates an increased danger of returning an athlete to sport too soon after a concussion, and an increased potential for second impact syndrome (Muscumeci et al., 2019; McCrory et al., 2013; McCrory et al., 2017; Prins et al., 2010), chronic traumatic encephalopathy (McKee et al. 2015; Saffary, Chin, & Cantu, 2012) and even death (Musumeci et al., 2019; McCrory et al., 2013; Harmon et al., 2019; Barkhoudarian, Hovda, & Giza, 2011). By understanding the behavioural and neurological effects of concussion in athletes and others who are highly motivated to return to activity following injury, we can improve current diagnostic and recovery tracking measures to ensure the safety and health of these individuals.

Generally, athletes are required to maintain a high level of cognition while executing precise movements in order to play their sports well and to play them safely. Movements must be made in the context of game-related rules, various aspects of attention, spatial information regarding the locations of other players, and prior knowledge of how to best accomplish a given task. While there has been a great deal of research into the effects of concussion on cognition alone (Gallo et al., 2020; Cook et al., 2020), there has been considerably less research into these effects on cognition integrated with movement in the context of sport and on-field performance (Tan et al., 2019). Combining thought and action is a process known as cognitive-motor integration (CMI). CMI is essential for the completion of skilled activities that involve non-standard mappings, which are relationships used when the visual information guiding the motor task does not come from the location of object one is interacting with (Wise, Di Pellegrino, & Boussaud, 1996; Granek &

Sergio, 2015). These mappings rely on different neural computations, requiring the central nervous system to ignore the routine connections among visuospatial stimuli, gaze, attention, and reaching movements compared to standard, direct mapping (the spatial location of the viewed object is the same as the motor goal) (Wise, Di Pellegrino, & Boussaoud, 1996; Granek & Sergio, 2015; Gorbet & Sergio, 2016). CMI is often required for complex skills, making it crucial for work, duty, sport, and daily life. Importantly, we have observed impaired CMI in youth and adolescent athletes who had experienced a concussion but were asymptomatic (using self-report) at the time of testing (Dalecki et al., 2016; Dalecki et al., 2020; Brown et al., 2015; Hurtubise et al., 2016). These individuals included children and adolescents who played sport at the recreational and select level (Dalecki et al., 2016; Dalecki et al., 2020; Brown et al., 2015), as well as adolescents who played at an elite level (Hurtubise et al., 2016). Notably, in a previous behavioural study of varsity athletes, we observed impaired CMI performance in a sample of primarily males (16/18 participants) with a history of concussion who were asymptomatic at testing, relative to peers with no history (Brown et al., 2015). In all cases, when having to incorporate some form of cognition and non-standard mapping into their movement control during an eye-hand coordination task, there were significant behavioural performance deficits in either the timing, trajectory formation, or both relative to peers with no concussion history. These data suggest that the brain networks used for simultaneous cognition and motor control are affected by concussion along a timeline longer than for tasks typically used to assess symptom resolution and readiness to resume activity.

While the post-concussion CMI studies focused on movement control impairments at a behavioural level, recent studies have investigated the specific brain areas involved in cognitive-motor integration during skilled performance in healthy young adults. Gorbet and Sergio (2016) investigated brain areas involved in a non-standard mapping task performed using an MRI compatible touch screen where saccades and reaches were spatially dissociated through a 180^{o} rotation of cursor feedback, requiring the participant to slide their hand in the opposite direction of the goal. In this study, the authors found that activity in the cuneus and medial premotor regions was significantly different during the task preparation phase when comparing the standard to the non-standard task. Additionally, an increase in activity in the inferior parietal lobule and cerebellum was seen during the execution of the non-standard task. In a related study, Gorbet and Sergio (2018) examined brain areas involved in a non-standard mapping task where saccades and reaches were made in different spatial planes. Using functional magnetic resonance imaging (fMRI) and multi-voxel pattern analysis, the authors observed a difference in brain activation between the standard and non-standard task. Interestingly, the pattern of activation was not markedly different until closer to the motor execution phase of the task, as opposed to the initial planning stages. The areas of the brain which discriminated between the two tasks in the movement period included the medial and lateral premotor, primary motor, superior and inferior parietal lobule, middle occipital gyrus, fusiform gyrus, lingual gyrus and anterior lobe of the cerebellum.

A difference in CMI-related brain activation has also been shown between high-performance individuals and less-experienced individuals during rule-based skill execution (Gorbet & Sergio, 2018; Granek, Gorbet, & Sergio, 2010), and skilled performance more generally (Lotze et al, 2003). Elite performers typically show reduced neural activation relative to non-elite performers during motor performance, often in sensorimotor cortices involved in skill execution (Haslinger et al., 2004; Jancke et al., 2000; Krings et al., 2000; Petrini et al., 2011). Such reduced activity is thought to reflect ‘neural efficiency’ developed in the control networks underlying enhanced performance. When examining the brain activity of elite performers - in this case video gamers - during an integrated cognitive-motor task, Granek et al. (2010) found additional prefrontal cortex activity during the planning stages of movement, as well as a later onset of preparatory activity (Gorbet & Sergio, 2018). In the context of concussion recovery in experienced performers, our group has observed that number of years of sport experience is correlated with recovery, such that those who have been playing their sport longer demonstrated faster behavioural recovery relative to less-experience athletes (Dalecki et al., 2019). These data suggest that sport experience mitigates concussion-related skilled behavioural impairment, putatively related to 'neural efficiency'. However, even with the improvement in recovery and reduced neural activations, elite athletes with concussion have still shown a deficit in CMI performance when compared to elite athletes without a history of concussion (Hurtubise et al., 2016).

Recently, resting state functional connectivity (rs-FC) has also been of interest in relation to concussive injury. Most of the focus has fallen on correlations between resting state functional connectivity and symptom presentation and severity. Kaushal et al (2018) found a global increase in connectivity in male athletes at 8 days post-concussion with symptoms present, but asymptomatic athletes showed no differences from controls. These authors suggested that whole-brain rs-FC alterations are therefore associated with clinical recovery. Similarly, Churchill et al (2018) noted that a network of frontal, temporal, and insular regions; and a network with anti-correlated elements of the default-mode network and sensorimotor system showed reliable covariation with symptom severity with males and females included in each group. One study even suggested that rs-FC could be used as a biomarker to monitor dynamic changes following concussion (Zhu et al., 2015). Interestingly, Shafi et al (2020) found significant differences in rs-FC between individuals with post-concussion syndrome (now often referred to as postconcussive syndrome or persistent symptoms post-concussion:PPCS) and controls; and they noted sex-related differences in rs-FC in the right lateral prefrontal cortex, left superior temporal gyrus, central opercular cortices, planum temporale, and the left lateral sensorimotor network.

Given the ability to detect lingering difficulty with a CMI task, and the suggestion that rs-FC can be indicative of clinical recovery following concussion, we were particularly interested in the relationship between CMI performance and rs-FC in athletes with and without a previous history of concussion. Specifically, due to the sex-related differences noted in brain activation during a CMI task, and the lack of literature observing female athletes in both CMI performance and rs-FC following concussion, we chose to focus this investigation on only females.

When observing cognition related measures in females, it is also important to note the potential impact of hormone level fluctuations. While there have been mixed findings and some difficulty generalizing across studies due to methodologies, previous research has shown differences in cognitive performance between males and females (Kimura 2002; Jancke, 2018; Gurvich et al., 2018), and also in females during different times their menstrual cycles (Scheuringer & Pletzer, 2017; Weis et al, 2019). In general, it has been suggested that females perform better than males on verbal abilities, and males perform better than females on spatial abilities (Gurvich et al., 2018). In a study done by Hampson, Levy-Cooperman and Korman (2014), low estrogen was linked with significantly better accuracy on a mental rotation task. In a similar fashion, a study looking a testosterone found that healthy young men with lower levels of the hormone performed better on a spatial task than those with higher levels (Gouchie & Kimura, 1991). Additionally, current research has moved in the direction of hormonal fluctuation and rs-FC. Out of the few human studies that have been conducted so far, mixed results have been noted. Using a group ICA approach, Hjelmervik et al. (2014), and De Bondt et al. (2015) found no significant impact of phase of menstrual cycle on rs-FC. But De Bondt et al. did note an increase in rs-FC in the precuneus in relation to estrogen levels. Petersen et al. (2014) and Pletzer et al. (2016) found an impact of the luteal phase on rs-FC, and Pletzer et al. and Weis et al (2019) found an impact of the pre-ovulatory phase on rs-FC. Using a seed-based connectivity approach, Syan et al. (2017) found no significant impact of the luteal phase, while Engman et al. (2018), noted increases in the amygdala to dorsolateral prefrontal cortex, sensorimotor cortices, and cerebellum; and the dorsal anterior cingulate cortex to the dorsolateral prefrontal cortex, temporal gyrus, and sensorimotor cortices. However, Syan et al., (2017) did note a negative correlation between estradiol and the bilateral entorhinal cortices in the mid-follicular phase; and a positive correlation between estradiol the left amygdala, bilateral somatosensory cortices, and right motor cortex in the late luteal phase. Additionally, they found negative correlations between progesterone and MPN regions during the mid-follicular phase, and positive correlations with the FPN in the late luteal phase. Hidalgo-Lopez et al. (2020) also noted decreased intrinsic connectivity of the right angular gyrus with the default mode network in the luteal phase (see Hidalgo-Lopez et al., 2020 for excellent summary table). Of particular interest for this study is the idea that concussion may cause a dysregulation of the hypothalamic-pituitary-gonadal axis, resulting in a disruption of estrogen and progesterone (Duffy et al., 2021). Together with the differences in cognition and rs-FC in, we are interested in the impact of concussion history on the relationship between hormones and these variables.

The purpose of the present study is to investigate the relationship between CMI performance, concussion history, hormones, and functional network connectivity in female varsity athletes. This study uses female athletes only, due to the previously noted sex-related differences in brain activation during equivalent CMI skill performance in healthy individuals (Gorbet & Sergio, 2007). Therefore, this study is meant to be a first-step in exploring potential sex hormone-related differences surrounding CMI performance, concussion, hormones, and functional brain network connectivity. We expect a relationship between concussion history and resting-state functional connectivity with a history of previous concussion resulting in decreased functional connectivity. However, we also expect this relationship to be impacted by levels of estrogen, testosterone, and progesterone at the time of testing.

Methods

Participants

The same 35 participants as study two were initially recruited through the Gorman Shore Sports injury clinic on York University Keele Campus in North York, Ontario, Canada. Three were excluded due to excessive head motion in the MRI scanner, and two were excluded due to the detection of excessive susceptibility artifacts in the images. Therefore, a remaining total of the same 30 participants as study two were finally included in the study (16 with a history of concussion – asymptomatic and cleared for play). The mean age of participants was 19.8 +/- 1.5 years (Table 1.)

TABLE 1. Demographic information on the 30 female varsity athletes included in analysis, including the varsity sport they play at York University (sport), their age, the number of years they have been playing said sport (years of experience), whether they have sustained a concussion previously (Concussion History – 0 = no, 1 = yes), and how many previous concussions they have sustained throughout their life obtained through self-report (Number Previous Concussions) and the number of months since their last concussion (time since last concussion).

volleyball	21	9	0	0	-
volleyball	21	16	0	0	-
hockey	20	15	0	0	-
soccer	18	14	0	0	-
soccer	21	17	0	0	-
basketball	18	12	0	0	-
hockey	19	12	0	0	-
hockey	18	14	0	0	-
soccer	21	11	0	0	-
hockey	20	15	0	0	-
hockey	19	14	0	0	-
hockey	19	15	0	0	-
hockey	18	13	0	0	-
hockey	20	16	0	0	-
hockey	18	15	1	1	24
soccer	21	13	1	1	9
hockey	18	5	1	1	36
hockey	20	15	1	1	36
volleyball	19	10	1	1	11
hockey	19	9	1	1	12
basketball	22	16	1	1	3
basketball	19	13	1	2	11
volleyball	22	15	1	2	3
volleyball	19	16	1	2	24
soccer	21	8	1	2	12
volleyball	21	14	1	3	36
basketball	19	15	1	3	24
hockey	20	13	1	3	36
volleyball	21	14	1	4	6
soccer	24	21	1	5	12

All participants included in the study had no other injury preventing them from practicing and playing their sport. No participant experienced multiple concussions within a year of each other; time between concussions ranged from 1 – 13 years. Additionally, all participants were screened using MRI safety protocols to ensure they were cleared to enter the MRI scanner. Participants were reimbursed for their time at a rate of $50 for one two-hour session. The York University Research Ethics board human participants subcommittee approved the protocol used in the experiment. The experimental protocol was also in compliance with the Declaration of Helsinki. All participants provided informed written consent prior to data collection

Procedure

Participants completed a single data collection session consisting of an imaging protocol, a visuomotor task that included a basic eye-hand coordination component and a cognitive-motor integration (CMI) component, SCAT5 assessment, and saliva collection. To help ensure consistent resting state data between individuals, the imaging protocol was completed prior to behavioural data collection for all participants.

Participants were scanned in a supine position with a 3T Siemens Magnetom Trio scanner at York University. For the resting state functional magnetic resonance imaging scan (rs-fMRI) each participant was instructed to rest (but remain awake) with their eyes open, focus on a fixation cross, and not to think of anything in particular. The participants were scanned in the sagittal plane, using a 32-channel head coil.

Anatomical images were acquired using a T1-weighted MPRAGE sequence. Field of View (FOV) = 256 mm, flip angle (FA) = 9 degrees, repetition time (TR) = 2.3s, 192 slices, 1.0 x 1.0 x 1.0 mm voxel resolution. Functional images (rs-fMRI) were acquired using multi-echo echo-planar imaging (EPI) using the following parameters: FOV = 216 mm, FA = 83 degrees, slice thickness

3.0 mm (no gap) 3.4 x 3.4 x 3.0 voxel resolution, TR=3.0s, and echo times (TEs)=14, 30, 46 ms. One 12-minute resting functional run consisting of 240 images was acquired for each participant.

Participants completed two computer-based visuomotor transformation tasks, one standard and one non-standard (vision and action decoupled, CMI). Participants sat at a desk comfortably in front of a 10.1" ACER tablet (60Hz refresh rate) connected to a 15" Keytec™ touchpad allowing for a touch screen in both the horizontal and vertical planes. In both conditions, participants were instructed to slide their index finger of their preferred hand along the touch screen in order to displace a cursor from a central target to one of four peripheral targets (up, down, left, right) as quickly and as accurately as possible. Participants guided a crosshair cursor, viewed on a black background, to the yellow central (or home) target which, when reached successfully, changes to green. After 4000ms, a red peripheral target is presented and the central target disappears, which serves as the 'Go' signal for the participant to initiate movement. Once the participant successfully reaches the target and remains for 500ms, the peripheral target disappears, signaling the end of the trial. The next trial begins with the presentation of the central target after an inter-trial interval of 2000ms. Peripheral targets are located 55mm from the center target, and target diameters are 15mm. In order to ensure smooth movement of the finger during the task, participants wore a capacitive-touch glove on their preferred hand (Fig. 1a & 1b).

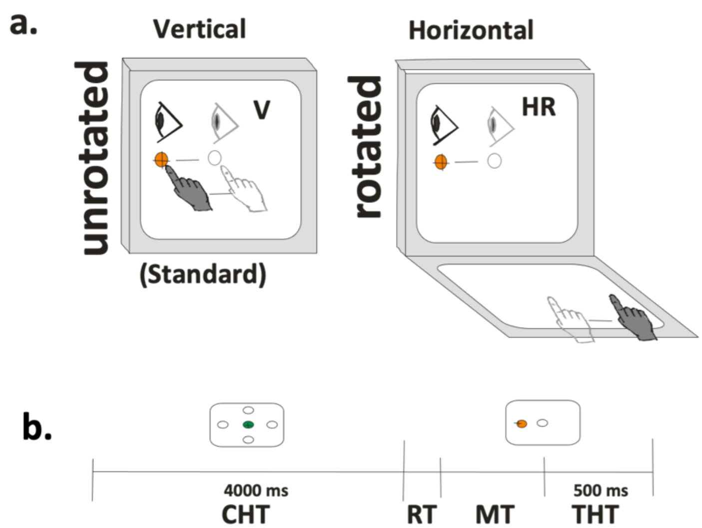


Figure 1a & 1b. (A) Schematic drawing of both experimental conditions V (vertical, standard) and HR (Horizontal Rotated, non-standard). Visual stimuli were presented on the vertical monitor for all conditions. Green circle, light grey eye, and hand symbols denote the instructed eye and hand movements for each task. Red circles denote the peripheral (reach) target, presented randomly in one of four locations (left, up, right, and down). The dark crosshair denotes the cursor feedback provided during each condition. (B) Schematic drawing of time progression of task. centre hold time (CHT) indicates the 4000ms participants must hold in the centre target before a peripheral target appears, followed by reaction time (RT) of participant to respond to the stimulus, movement time (MT) of participant to successfully slide the cursor from the central target to the peripheral target, and target hold time (THT) signifying the 500 ms that participants must hold in the peripheral target until returning to centre to start their next trial.

Participants completed the standard and non-standard conditions in a randomized block design. In the standard condition, participants both look and move on the vertical screen, and thereby directly interacted with the targets. Movements for the non-standard visuomotor condition are made on the horizontally oriented Keytec™ touchpad. The touchpad was calibrated such that the distance of the finger movement path on the touchpad is equivalent to the distance the cursor moves on the tablet screen. The non-standard condition includes two levels of decoupling: (i) plane change; in which participants look at the vertical screen while moving on the horizontal screen, requiring spatial recalibration, and (ii) cue reversal; in which the feedback is rotated 180° (i.e. in order to move the cursor left, you slid your finger right), requiring strategic control. Six trials in each of the four directions were completed per condition for a total of 40 trials per participant (4 directions x 5 trials x 2 conditions). Eye movements were monitored by the experimenter to ensure participants look at the correct target.

Saliva collection was done using the passive drool method. Following set-up of the saliva collection aid and collection vial by the researcher, the participant was instructed to allow saliva to pool in their mouth with their head tilted down, and then slowly allow the saliva to pour from their mouth into the vial. Participants were asked to refrain from spitting or forcing saliva into the tube in order to avoid excess bubbles. Following instruction, participants were left alone in a quiet room in order to fill the tube with saliva. Participants were instructed to refrain from eating or drinking 30 minutes prior to saliva acquisition.

fMRI data Preprocessing

Multi-echo rs-fMRI data preprocessing and denoising was performed using the Multi-Echo Independent Components Analysis (ME-ICA) pipeline in AFNI (Analysis of Functional NeuroImages). In order to preprocess the data using ME-ICA, files were converted from Dicom to .BRIK and .HEAD file format. Images were visually inspected at this stage to ensure proper conversion. Preprocessing of the functional data included motion correction (AFNI 3dvolreg), removal of large signal transients via interpolation (AFNI 3dDespike), and slice time correction (AFNI 3dTshift). Co-registration of functional and T1-weighted anatomical images was performed (AFNI 3dAllineate). TE-dependent denoising (ME-ICA) was implemented in AFNI as described in Kundu et al., 2013. Images were kept in native subject space and no spatial smoothing or scaling were applied at this stage of the analysis. After preprocessing, quality control steps included verification that scans did not include excessive head motion, confirmation that functional data were accurately aligned to anatomical data, and verification that data were not excessively noisy (a minimum of 10 independent components classified as BOLD signal by ME-ICA).

Using FreeSurfer version 6.0 (2012), we then parcellated T1 images into anatomical regions for each subject using the recon-all pipeline. To run this pipeline we first converted raw T1 dicom files to .nii files, and then converted these to FreeSurfer .mgz volume format files. Briefly, the recon-all pipeline performs motion correction, non-parametric non-uniformity intensity normalization, skull stripping, cortical and subcortical segmentation and labelling, minimization of distortion so that distances and areas are preserved, removal of topological defects, inflation of the original surface into a sphere while minimizing metric distortion, and creation of a summary table of cortical parcellation statistics for each structure. A quality check was done to ensure proper segmentation and characterization of the white matter and pial matter borders.

The denoised functional data were registered to the corresponding FreeSurfer anatomical images for each subject, converted to surface space, resampled to the surface-based fsaverage template, and spatial smoothing was applied using a 6-mm full-width half-maximum (FWHM) Gaussian kernel. The result of this process was smoothed surface data that have been aligned to the fsaverage template for both the right hemisphere and left hemisphere. A quality check was done to ensure proper coregistration. Following this, medial wall vertices data values were added back to the surface data in order to perform Group Prior Individual Parcellation (GPIP, see below). Finally, functional time-series data was normalized by scaling to a mean value of 0 and standard deviation of 1.

Behavioural data preprocessing:

Custom-written (C++) acquisition software samples the finger's X-Y screen position at 60Hz. Custom analysis software (Matlab, Mathworks Inc.) was used to generate a computerized velocity profile of each trial's movement. Movement onsets and ballistic movement offsets (the initial movement prior to path corrections) were scored at 10% peak velocity, while total movement offsets were scored as the final 10% peak velocity point once the finger position is within the peripheral target. These profiles were then verified by visual inspection, and manually corrected if necessary. Trials were considered errors if the finger/cursor left the center target too early (< 4000ms), reaction time was less than 150ms or more than 8000ms, or total movement time was more than 10000ms. Trials in which the first ballistic movement exited the boundaries of the center target in the wrong direction (greater than 90° from a straight line to target) were coded as direction reversal errors, eliminated from further evaluation, and analyzed as a separate variable. The scored data was then processed to compute both movement timing and execution outcome measures.

The kinematic variables for movement timing were as follows: 1) Reaction Time (RT), the time interval (milliseconds) between the central target disappearance and movement onset; 2) Movement Time (MT), the time between movement onset and offset (millisecond), and 3) Peak Velocity (PV), the maximum velocity obtained during the ballistic movement. Kinematic variables for movement execution were: 1) Full Path Length (PLf), the total distance (resultant of the x and y trajectories) travelled between movement onset and offset (millimeters), 2) Absolute Error (AE, accuracy), the average distance from the individual ballistic movement endpoints ($\sum x/n$, $\sum y/n$) to the actual target location (millimeters); 3) Variable Error (VE, precision), calculated as the distance between the individual ballistic movement endpoints ($\sigma 2$) from their mean movement (millimeters); and 4) Percentage Direction Reversal errors (DR) were calculated as the number of trials with a deviation of greater than ±45° from the direct line between the midpoint of the central and peripheral targets compared to the number of successful trials.

Saliva preprocessing:

The High Sensitivity Salivary 17β-Estradiol Enzyme Immunoassay Kit, Salivary Progesterone Enzyme Immunoassay Kit, and Expanded Range Salivary Testosterone Immunoassay Kit were used for analysis of the saliva samples (Salimetrics, Inc. CA, USA). Standard assay protocols were followed in processing the samples (c.f. https://salimetrics.com/assay-kits).

Data Analysis:

Initial independent samples T-Tests were conducted to ensure there were no statistically significant differences between age and years of experience in the concussion history group versus the control group.

Imaging analysis:

The normalized time-series data for each participant were used in the GPIP analysis (Chong et al., 2017) to investigate functional brain network differences. This approach creates a participant-specific estimation of individual functional areas allowing for improved accuracy (Chong et al., 2017) and is more sensitive to detecting rs-FC associations with behavior (Kong et al., 2019; Mwilambwe-Tshilobo et al., 2019). Using the Schaefer et al. (2018) atlas to define parcellation regions, each participant's parcel boundaries were refined relative to their resting-state fMRI data. The concentration (inverse covariance/partial correlation) matrices were then jointly estimated using a group sparsity constraint. GPIP iterates between these two steps to continuously update the parcel labels until convergence (Setton et al., 2021). MEDN data was extracted from each vertex and the above parcellation was conducted on each participant's data. The iterative process was repeated 20 times to produce a final parcellation with optimal segmentation with respect to the entire cortical surface (An example of parcellation can be seen in Figure 2). Homogeneity was calculated using the average correlation coefficient of all pairs of vertices in a given parcel and averaging across all parcels. Homogeneity was calculated first at the participant level and then averaged across the entire cohort for a group estimate. Using each participant's GPIP parcellation annotation and the 7-network model from Yeo et al. (2011), we calculated the product-moment correlation between the mean timeseries from each pair of nodes in each network to obtain network connectivity matrix. We then applied a Fisher's r-to-z transformation to normalize the distribution of correlation r-values for each subject and then took the mean of the resulting z-values for each participant as measure of overall within network functional connectivity. Specifically, a mean Fisher Z-transformed rs-FC value from the Visual network (VN), Somatomotor network (SMN) Dorsal Attention network (DAN), Salience Ventral Attention network (SVAN), Limbic network (LN), Frontoparietal Control network (FPCN), and Default Mode network (DMN) was created for each subject and used in the statistics analyses described below.

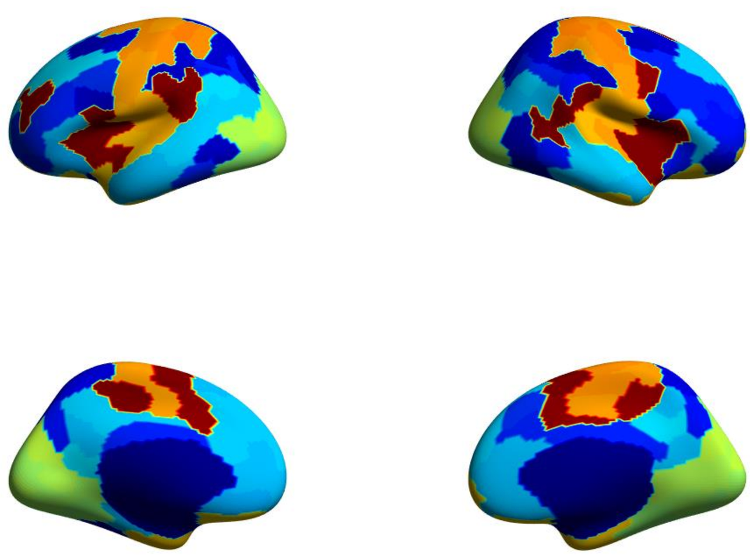


Figure 2. Example parcellation from a single subject using the Schaefer et al. (2018) atlas.

Behavioural data analysis:

For the seven kinematic variables described above (RT, MTf, PV, PLf, CE, VE, %DR) an overall score was calculated to reflect summarized performance on the visuomotor (VM) task for both the standard condition (S-VM), the non-standard condition (CMI-VM) and the overall visuomotor performance (OA-VM). A smaller value on all variables except Peak Velocity indicates better performance. Therefore, peak velocity was multiplied by a value of -1 prior to calculation. Related variables were added together and weighted 20% of the final score. This resulted in the following equation:

$$(RT+MTf)*0.2+(PV)*0.2+(CE+VE)*0.2+(PLf)*0.2+(\%DR)*0.2$$

For ease of understanding, the final S-VM, CMI-VM, and OA-VM scores were multiplied by a value of -1 such that a higher score on these variables indicated better performance, and a lower score indicated worse performance.

Multiple Linear Regression and Correlations:

Separate multiple linear regression models were performed for functional connectivity measures from each of the 7 networks with S-, CMI-VM, OA-VM, Estradiol, Progesterone, Testosterone, and Concussion history as explanatory variables.

Additionally, Correlations between all variables (rs-FC of each network, S-VM, CMI-VM, OA-VM, Estradiol, Progesterone, Testosterone, and Concussion history) were conducted.

Results

We initially examined the data for differences on factors which typically affect visuomotor performance and balance. We found that age and years of experience did not significantly differ between the concussion history group and the control group (independent samples t-test, $p>0.05$ for both).

Behavioural

T-tests were conducted comparing performance scores of the Concussion history group to the Control group on all raw behavioural output variables (RT, MT, PV, PLf, CE, VE, DR). No significant differences were found on any of the variables ($p>0.05$). A trend towards significance was seen in PLf ($p = 0.08$) and PV ($p = 0.09$) with the Concussion history group exhibiting longer pathlengths and slower peak velocities.

T-tests were conducted comparing the S-VM, CMI-VM, and OA-VM composite scores of the Concussion group to the scores of the Control group. No significant differences were found in any of the three score categories ($p>0.05$).

Multiple Linear Regression and Correlations:

None of the separate multiple linear regression models performed for functional connectivity measures from each of the 7 networks with S-, CMI-VM, OA-VM, Estradiol, Progesterone, Testosterone, and Concussion history as explanatory variables were significant ($p>0.05$ for all, see Table 2).

We first examined the relationships between resting state connectivity for all our defined brain networks, and our three factors (concussion history, hormone levels, and skilled performance). In terms of concussion history and resting state connectivity, Point Biserial Correlations demonstrated significant moderately negative association between concussion history and VN rs-FC ($r = -.447$, $p = 0.008$) (figure 3a) and close to significance with a weak-moderate association with FPCN rs-FC ($r = -.304$, $p = 0.054$) and DAN rs-FC ($r = -.288$, $p = 0.065$) (figure 3b & c). With respect to hormone levels and resting state connectivity, Pearson Correlations showed that progesterone had a significant moderately negative association with DAN rs-FC ($r = -.378$, $p = 0.022$) and SVAN rs-FC ($r = -.344$, $p = 0.034$) (figure 4 a & b). We also observed a close to significant relationship, with a weak-moderate association, between progesterone and FPCN rs-FC ($r = -.282$, $p = 0.069$) (figure 4c). Finally, Pearson Correlations between skilled performance and resting state connectivity revealed no significant relationships. However, we did observe that standard VM was close to significance with a weak-moderate positive association with DMN rs-FC ($r = .306$, $p = 0.053$), SMN rs-FC ($r = .270$, $p = 0.078$), and FPCN rs-FC ($r = .279$, $p = 0.071$) (figure 5 a, b, & c).

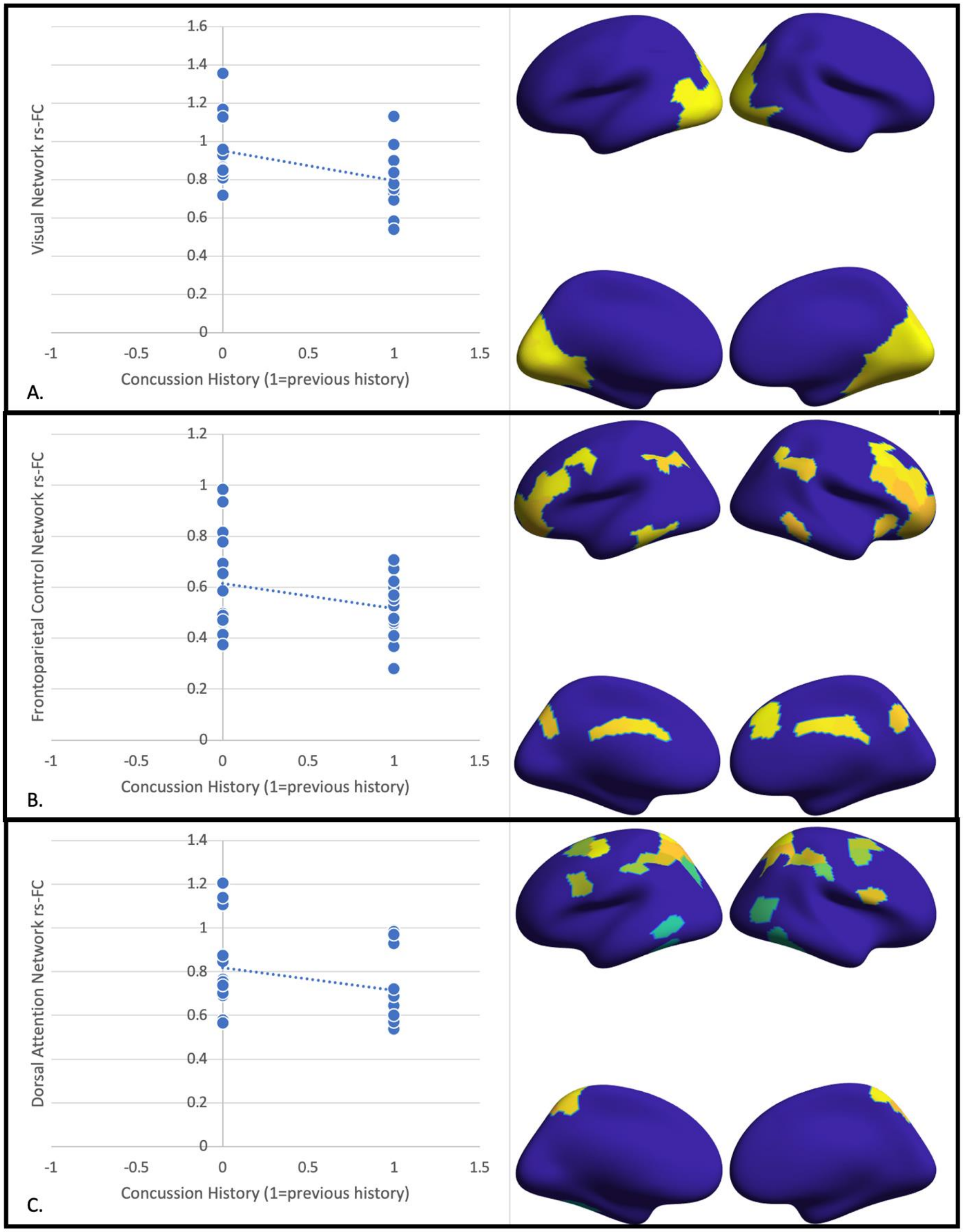


Figure 3. Scatterplot showing relationship between concussion history and mean rs-FC of the A) visual network, B) frontoparietal control network, and C) dorsal attention network for each subject (left panel) along with each corresponding GPIP network (right panel) top row = lateral, left and right hemisphere, bottom row = medial left and right hemisphere.

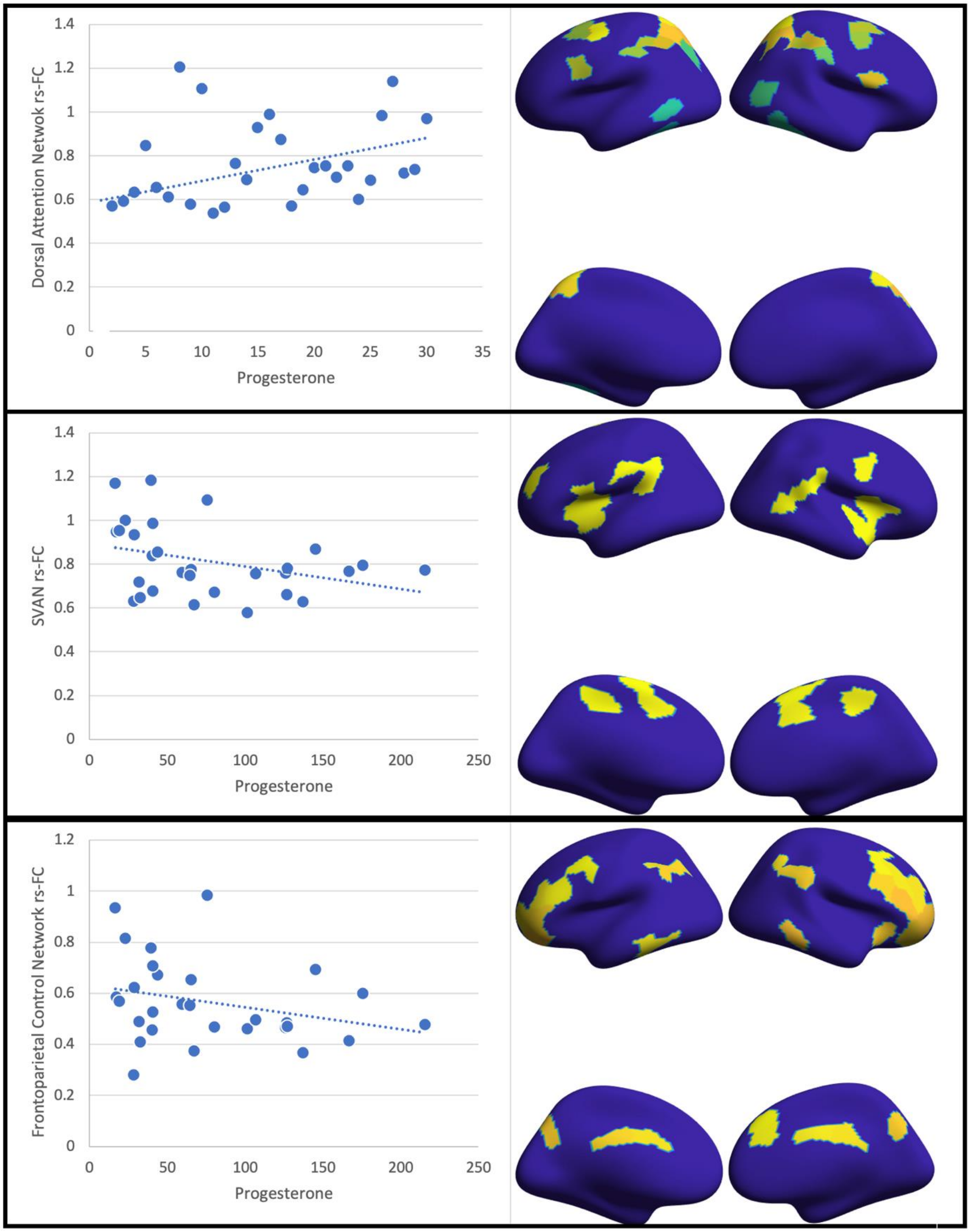


Figure 4. Scatterplot showing relationship between Progesterone and mean rs-FC of the A) dorsal attention network, B) salience ventral attention network (SVAN), and C) frontoparietal control network for each subject (left panel) along with each corresponding GPIP network (right panel) top row = lateral, left and right hemisphere, bottom row = medial left and right hemisphere.

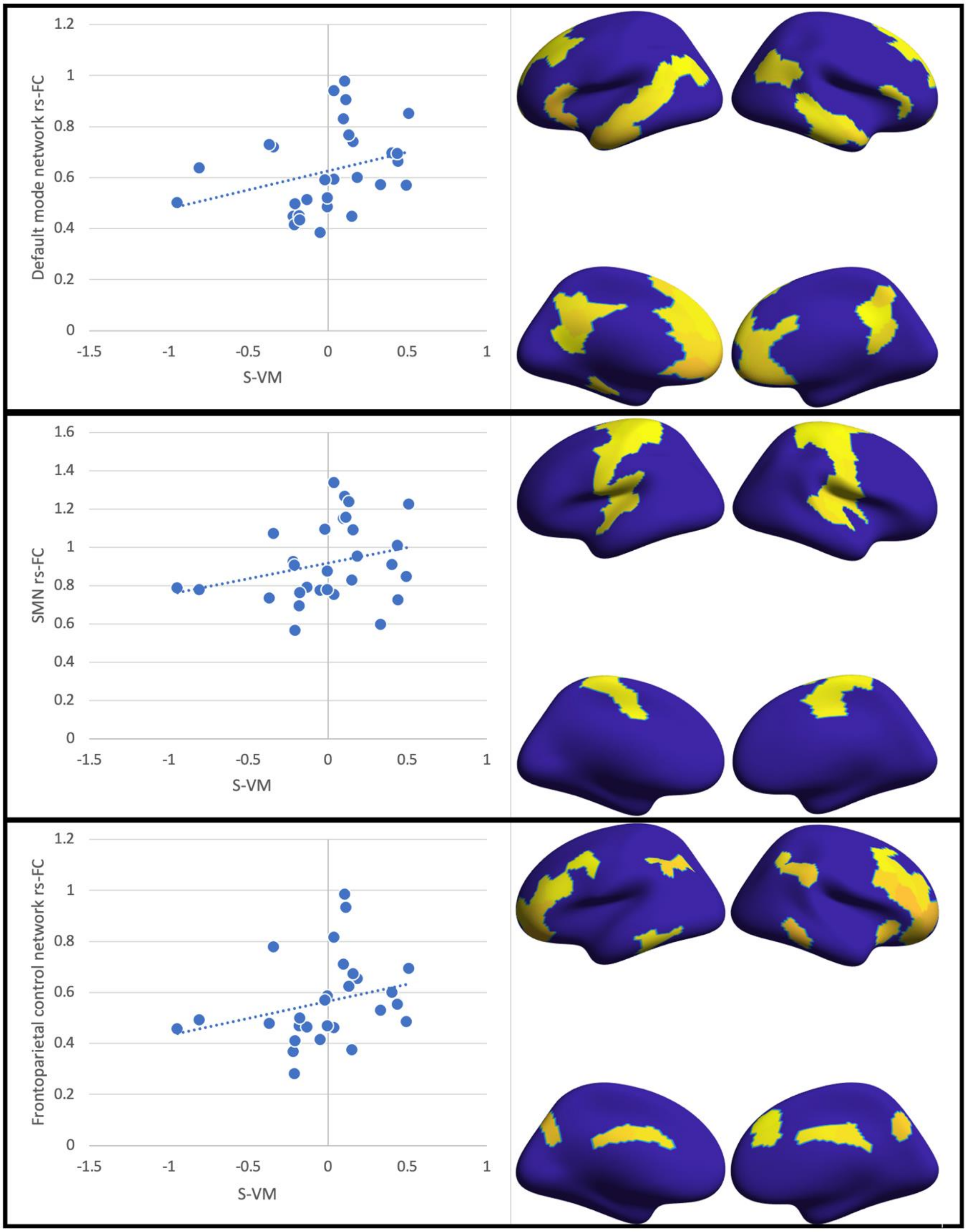


Figure 4. Scatterplot showing relationship between Standard visuomotor performance (S-VM) and mean rs-FC of the A) default mode network, B) somatosensory motor network (SMN), and C) frontoparietal control network for each subject (left panel) along with each corresponding GPIP network (right panel) top row = lateral, left and right hemisphere, bottom row = medial left and right hemisphere.

Next, we looked at the Pearson Correlations between skilled performance and sex hormone levels. Using 30 of the 35 participants included in study two, we observed the same significant moderate positive relationship between progesterone and the overall visuomotor performance composite score (r = -0.318, p<0.05), and significant moderate positive relationship between testosterone levels and performance on the cognitive-motor integration task (r = 0.441, p < 0.01). Different two study two we also observed a positive relationship between testosterone and the standard visuomotor task (r = 0.351, p<0.05).

Lastly, we did not observe any significant relationships between concussion history and either sex hormone levels or visuomotor performance. For all correlation values, see Table 3.

Table 2. Output for all separate multiple linear regression models for functional connectivity measures from each of the 7 networks with S-, CMI-VM, OA-VM, Estradiol, Progesterone, Testosterone, and Concussion history as explanatory variables.

				ANOVA				
Variable	**R**	**R^2**	**Adjusted R^2**	**Sum of Squares**	**df**	**Mean Square**	**F**	**Sig**
VN	.652	.425	0.233	.373	7	.053	2.213	0.075
SMN	.509	.260	0.013	.314	7	.045	1.051	0.427
DAN	.551	.303	0.071	.297	7	.042	1.305	0.296
SVAN	.435	.189	-0.081	.141	7	.020	0.699	0.672
LN	.321	.103	-0.196	.058	7	.008	0.345	0.924
FPCN	.574	.329	0.105	.250	7	.036	1.471	0.231
DMN	.457	.208	-0.055	.162	7	.023	0.790	0.603

Table 3. Correlation values. *(p<0.05) **(p<0.01)

	S-VM	**CMI-VM**	**OA-VM**	**Est.**	**Prog.**	**Tes.**	**ConcHx**
VN	0.247	-0.055	-0.1	0.224	-0.195	0.177	***-0.447*** ***
SMN	0.27	0.136	-0.191	0.209	-0.228	0.181	-0.136
DAN	0.146	-0.121	-0.178	-0.041	***-0.378****	-0.046	-0.288
SVAN	0.011	-0.068	-0.011	-0.107	***0.344****	-0.101	-0.236
LN	0.220	-0.003	-0.036	0.130	-0.005	0.171	0.082
FPCN	0.279	0.070	-0.101	0.001	-0.282	0.100	-0.304
DMN	0.306	0.054	-0.233	0.054	-0.172	0.156	-0.072
S-VM	1.00	***0.510*****	0.159	0.220	0.133	***0.351****	0.083
CMI-VM	***0.510*****	1.00	-0.106	0.299	0.280	***0.441*****	0.001
OA-VM	0.159	-0.106	1.00	0.246	***0.318****	0.126	-0.161
Est.	0.220	0.299	0.246	1.00	***0.456*****	***0.804*****	-0.190
Prog.	0.133	0.280	***0.318****	***0.456*****	1.00	***0.487*****	0.025
Tes.	***0.351****	***0.441*****	0.126	***0.804*****	***0.487*****	1.00	-0.069
ConcHx	0.083	0.001	-0.161	-0.190	0.025	-0.069	1.00

Discussion

We examined the effect of concussion history on CMI performance and how this performance relates to resting-state functional network connectivity and levels of estrogen, testosterone, and progesterone. Based on a recent study from our lab, we hypothesized that those with a previous history of concussion would show similar performance as controls on a CMI task. Additionally, we expected a history of previous concussion to result in decreased functional connectivity in networks with nodes commonly impacted by concussion. We predicted that this relationship would be modified by levels of estrogen, testosterone, and progesterone.

As expected, having a concussion history did not impact CMI performance as measured by our composite scores when compared to those with no concussion history. Contrary to our hypothesis, however, we observed no differences in connectivity regardless of performance on our CMI task in our group of female varsity athletes. Specifically, the visual network, somatomotor network, dorsal attention network, salience ventral attention network, limbic network, frontoparietal control network, and default mode network (as originally defined in Yeo et al. 2011) showed no changes in functional connectivity that correlated with our standard-, CMI-, or overall-

VM performance scores. Given previous work looking at neural connectivity impairments following concussion and mTBI which noted differences in white matter integrity (Wright et al., 2020; Churchill et al., 2017) and functional network strength and activation (Cook et al., 2020; Hristopolous et al., 2019; Czerniak et al., 2015) these results were unexpected. However, these previous studies included a mixture of mTBI and concussion patients (Cook et al., 2020), observed only males (Hristopulous et al., 2019; Czerniak et al., 2015) or included males and females in the same analysis (Churchill et al., 2017; Cook et al., 2020; Czerniak et al., 2015), and were done at the acute/subacute stage of concussion (Cook et al., 2020; Hristopulos et al., 2019; Czerniak et al., 2015). As noted previously, the CMI task used in this experiment has shown sex-related differences in activation in the healthy brain; therefore, there is a possibility that the functional network activity following concussion is impacted differently in females than in males. This study was conducted as a first step in exploring whether sex-related differences do in fact exist in resting state functional network connectivity, and whether this is impacted by a history of concussion. Interestingly, a decrease in these differences of network activation in those with concussion history and those without has been correlated with a decrease in symptoms (Czerniak et al., 2015), and with time since injury (Cubon et al., 2018; Murdaugh et al., 2018). Given that all of our participants were >3 months post-injury, and deemed asymptomatic and cleared to return to play, this may also provide us with a possible explanation as to why there are no differences in functional network connectivity between the two groups. Additionally, previous sex-related differences in CMI network activation were observed during task-based fMRI (Gorbet & Sergio, 2007), whereby the subjects were performing a CMI task during their scan. Perhaps, a task-based fMRI approach investigating potential correlations of CMI task performance and functional network connectivity would be more sensitive to any lingering effects of concussion on the neural networks related to behavioural control.

Previous studies investigating CMI performance with and without concussion history have shown an impact of concussion on CMI performance (Brown et al., 2015; Hurtubise et al., 2016) lasting up to two years (Dalecki et al., 2016). However, these previous studies were done with youth (Dalecki et al., 2016), included both males and females in a single group (Brown et al., 2015), or on males only (Hurtubise et al., 2016). Given the increased vulnerability of the developing brain in youth, we understand that these differences in performance may not be reflected at the varsity age, which may go beyond the early 20's where developmental myelination of most fibre tracts is thought to plateau. However, given the nature of sex-related differences in cognitive performance, and brain network activation patterns in CMI tasks, there is a possibility that previously observed differences in CMI performance in those with a concussion were driven by males. Indeed, in terms of recovery from concussion, there is evidence of sex-related differences in both the rate of recovery and the form of recovery, although these findings are mixed (Bazarian et al., 2010; Ono et al., 2016). In humans it has been proposed that these differences may be related to neck girth (Streifer et al., 2019), hormonal influences (Gallagher et al., 2018), and cerebral blood flow and metabolic differences (Hamer et al., 2020). Additionally, recent work by Dumais et al. (2018) found that males and females have a difference in activation of the default mode network, and the dorsal attention network when exposed to punishment and reward; however, no difference in activation was seen during working memory. Study one noted sex-related differences in visuomotor recovery whereby males with a history of concussion showed differences in performance when compared to controls, but no such differences were seen in females. Both study 2 and the current study (of the same participants) were able to repeat these findings of no visuomotor differences in females. Additionally, rodent studies support these ideas. Intriguingly, a recent study by McCorkle et al. (2019) observed sex-related differences in concussion recovery, whereby male mice experienced longer recovery of visuomotor skills, while female mice experienced longer recovery of emotion-related symptoms (but not visuomotor skills). To this end, further research is needed to determine whether analogous behavioural differences in CMI performance exist in male varsity athletes, and whether they exhibit a correlation between resting state functional network connectivity and CMI performance.

Interestingly, we do see a statistically significant correlation between concussion history and rs-FC in the visual network (-0.447) indicating a decreased rs-FC in the visual network in those with a history of concussion (Fig. 3a), but no correlations in other networks examined. The visual network is not one that has been studied greatly in terms of concussion and rs-FC. However, most of the current focus has fallen on correlations between rs-FC and symptom presentation and severity. It is well known that visual symptoms following concussion are common (McCrory et al., 2017; Capo-Aponte, Beltran, Cole, & Dymayas, 2018; Master, Scheiman, et al., 2016). The results of this study suggest that a history of concussion in female athletes results in reduced functional connectivity in the visual network. However, further research including a measure of symptoms, and including males as a separate group is necessary to further investigate this suggestion.

Of particular interest for this study was the idea that concussion may cause a dysregulation of the hypothalamic-pituitary-gonadal axis, resulting in a disruption of estrogen and progesterone (Duffy et al., 2021). A previous study from our lab found no differences in estrogen and progesterone between the females with concussion history and controls, and no correlation between estrogen or progesterone with concussion history. Therefore, in this study we sought to further investigate whether underlying functional connectivity was sensitive to the effects of estrogen and progesterone, and whether we could make a connection between concussion history and these underlying neural fluctuations. Of the three hormones tested, progesterone appears to be the only one with correlations to rs-FC; specifically in the DAN (-.378) and SVAN (-.344). The dorsal attention network comprises the intraparietal sulcus and frontal eye fields of each hemisphere (Vossel, Geng, and Fink, 2014). The salience ventral attention network comprises the temporoparietal junction and the ventral frontal cortex (Vossel, Geng, and Fink 2014). To our knowledge, no previous work has looked at progesterone influence on these specific networks and related nodes. Interestingly, levels of progesterone were also correlated with both overall visuomotor performance. However, no correlations were seen between overall visuomotor performance and rs-FC in these networks. It would therefore be interesting to conduct a task-based fMRI scan using the same study design to detect whether fluctuation of FC in these networks is associated with our visuomotor task, and whether these fluctuations are modified by concussion history and hormone levels.

As with our previous study, both progesterone and testosterone had correlations with aspects of visuomotor performance. These correlations indicate that higher levels of progesterone are correlated with better overall performance on a visuomotor task, and higher levels of testosterone are correlated with better performance on both the standard and the rule-based version of a visuomotor task. This is in line with previous research indicating the importance of progesterone in cognition (Henderson, 2018; Sofuoglu, Mouratidis, & Mooney, 2011) in different populations. Lastly, we suggest that higher levels of testosterone in our participants at the time of testing may have imparted an advantage on our visuomotor tasks, based on previous findings that females perform better on tasks requiring spatial orientation and visualization during periods of higher testosterone (Kimura, 2002; Hausmann et al., 2000; Pintzka et al 2014). Further research in this area, observing specific phase of menstrual cycle as well as the impact of hormones on performance in males, is necessary.

It is important to note that majority of participants in this study were taking an oral contraceptive (n=21) at the time of testing. The number of participants taking an oral contraceptive did not differ between groups ($p>0.05$), but it is important to take this into account when interpreting the results of this study. Additionally, further research is necessary to investigate whether oral contraceptives have an impact on the variables examined, and whether different types of oral contraceptives result in different impacts.

In conclusion, we suggest that levels of sex hormones at the time of testing may create a difference in performance on important metrics used to track recovery from concussion. This study provides a starting point for many more interesting questions surrounding the sex- and sex-hormone related effects of concussion on skilled performance recovery.

Chapter five: General Discussion

The studies included in this dissertation explored the impact of concussion on behavioural performance and neural connections. By exploring the relationship of concussion history with behavioural outcomes, hormone levels, and functional connectivity, the goal was to report helpful information for the improvement of diagnostic and recovery tracking metrics. It has previously been established that concussion is one of the most complex injuries in sports medicine to diagnose, assess, and manage (McCrory et al., 2017) due to the individualized mechanisms of injury, presentation and resolution of symptoms, and confounding demographic variables.

The results of study one adds to the literature in support of sex-related differences on visuomotor performance and emotionality-related symptoms in those with a history of concussion. This study found that male athletes with a history of concussion performed worse than their control counterparts on a visuomotor task, while no such differences were seen in females. Additionally, this study provides support that a greater number of males with a history of concussion exhibit increased Anxious symptoms when compared with females with a history of concussion, and their control counterparts. However, this study was cross-sectional in nature and therefore, further investigation into the longitudinal progression of these symptoms is required. Additionally, investigation into symptom total and symptom severity is necessary to provide a more detailed picture of symptom expression in males and females. These results provide evidence that emphasis on different aspects of recovery may be necessary for males versus females to ensure the safety of all athletes in return to play decisions. Just as the decision has been made to create different management protocols for younger children versus older youth and adults (Davis et al., 2017), it too may be beneficial to consider differences based on sex. As well, due to the presence of both visuomotor and emotionality symptom expression in males with and without a history of concussion, the results of this study provide support for the need for baseline testing in athletes.

These results indicate an impact of concussion on visuomotor performance and emotionality in many athletes, as has been seen previously; however, due to the cross-sectional nature it is difficult to definitively attribute these differences to concussion alone without considering the potential differences in nature and skill of each participant. Currently, baseline assessments are not considered mandatory in concussion management protocol (McCrory et al., 2017), and debates continue about the use of baseline information versus normative data comparisons (Iverson & Schatz, 2015; Schatz & Robertshaw, 2014; Schmidt et al., 2012; Arnett et al., 2016). However, this research provides evidence that normative data may not encompass important differences between males and females and therefore, may put athletes at the risk of being returned to play before completely recovered.

Study two provides further support for exploring modifications of concussion management protocols based on sex. Building on study one, study two provides evidence that levels of progesterone and testosterone are correlated with overall visuomotor and cognitive-motor integration performance in female athletes, respectively. These results suggest that females may perform differently on visuomotor tasks depending on which stage of their menstrual cycle they are in at the time of testing. Based on this understanding, there is a possibility that the lack of difference in visuomotor performance between females with a history of concussion and females with no history of concussion is as a result of fluctuating hormone levels. The question then becomes, are these hormones providing a protective effect and improving recovery, or are they masking lingering damage in functional network connectivity caused by concussion? Study three sought to explore this question by examining the relationship between hormones and resting-state functional connectivity in athletes with a history of concussion, and controls. Results from this study indicate a relationship between progesterone and rs-FC in the DAN (-.378) and SVAN (-

.344), in which higher levels of progesterone relate to decreased resting-state functional connectivity of these networks regardless of concussion history. However, no relationship between overall visuomotor performance, standard visuomotor performance, and cognitive-motor integration performance was seen within any of the seven networks examined. Given that previous research has looked at brain activity during CMI performance using task-based fMRI in healthy individuals, it would be interesting to explore whether visuomotor performance is associated with activity in the DAN and SVAN during task-based fMRI in concussed individuals, and whether the relationship of progesterone remains. These data would provide further insight into the impact of hormones on visuomotor performance, and whether modifications need to be made to account for time of menstrual cycle in return-to-play metrics. Additionally, in order to determine whether these relationships can be attributed to sex-related differences, study two and three should be repeated with male athletes.

Future directions

As mentioned previously, the overall goal of this research is to add to the literature regarding the potential sex-specific differences that may impact current concussion metrics. This research provides good evidence that future studies on concussion should not include females and males in a single group for analyses. While the studies in this dissertation provide a good start into the exploration of sex differences and concussion, it is necessary to repeat the work of study two and study three in male athletes to better determine whether the differences can be strongly attributed to sex or perhaps are a result of other demographic characteristics. This understanding is necessary to best ensure the safety of athletes and others recovering from concussive injury.

Additionally, it would be interesting to repeat aspects of this work in a longitudinal study design to determine differences within individuals rather than comparing cross-sectionally.

Limitations

One of the main limitations of these studies are that they are cross-sectional in nature. Therefore, the comparisons being made between concussion history groups and control groups also have the confounding impact of individual differences on top of the potential impact of concussive injury. The nature of the individual may impact expression of symptoms and visuomotor performance ability without presence of concussive injury and therefore, caution should be taken when attributing cross-sectional results to the impact of injury alone.

As well, as is often the case with concussion research, the participants in these studies are a very specific cohort with related characteristics such as age, education level, sport experience, and sex (specifically in study 2 and 3). As mentioned throughout this dissertation, differences have been noted in the impact of concussion on age, sex, and previous number of concussions; in the impact of hormones on balance in perimenopausal and postmenopausal women; in the impact of birth control on symptom severity; and in number of years experience in sport on concussion recovery. Therefore, these results provide insight into a specific population, and caution should be taken if generalizing the results to a population with different characteristics than the ones studied.

Lastly, these studies focused on sex-related differences in brain and behaviour. However, given the proposed impact of gender norms on expression of symptoms and potential impacts of encouraged behaviour resulting in differences in skilled performance, it would ultimately be more useful to characterize the gender-related differences rather than sex. The standard forms that our participants filled out as part of their varsity participation paperwork typically only had a binary sex response, and sex was related to the binary category of team that they were on (e.g. women’s hockey, women’s rugby). We recognize the limitations of these provided categories.

Conclusion

These studies provide evidence that not only is it important to consider the sex-related differences in the impact of concussion and the recovery trajectory, it is also increasingly evident that there is no gold-standard metric with which to compare all concussed athletes. While the goal of research in this area is to improve knowledge surrounding tracking metrics, the additional piece to this is that while standards and benchmarks are important, caution should be taken to rely solely on the normative numbers.

Glossary of Abbreviations

Abbreviation	Term
AE	absolute error
AFNI	Analysis of Functional NeuroImages
ANCOVA	Analysis of Covariance
AVOVA	Analysis of Variance
BOLD	blood-oxygen-level-dependent
CBF	cerebral blood flow
CMI	cognitive-motor integration
CMI-VM	cognitive-motor integration visuomotor
DAN	Dorsal attention network
DMN	Default mode network
DR	direction reversals
GPIP	Group Prior Individual Parcellation
ICA	independent components analysis
LN	Limbic network
mBESS	modified balance error scoring system
MCI	mild cognitive impairment
ME-ICA	multi-echo independen components analysis
MT	movement time
mTBI	mild traumatic brain injury
OA-VM	overall visuomotor
PCS	post-concussive syndrome
PLf	full pathlength
PMd	dorsal premotor cortex
PMv	ventral premotor cortex
PPC	posterior parietal cortex
PV	peak velocity
rs-FC	resting-state functional connectivity
rs-fMRI	resting-state functional magnetic resonance imaging
RSN	resting-state network
RT	reaction time
S-VM	standard visuomotor
SCAT	sport concussion assessment tool
SMN	Somatomotor network
SPL	superior parietal lobule
SVAN	Salience ventral attention network
VE	variable error
VN	Visual network

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Date of Assessment:

What is the SCAT3?[1]

The SCAT3 is a standardized tool for evaluating injured athletes for concussion and can be used in athletes aged from 13 years and older. It supersedes the original SCAT and the SCAT2 published in 2005 and 2009, respectively[2]. For younger persons, ages 12 and under, please use the Child SCAT3. The SCAT3 is designed for use by medical professionals. If you are not qualified, please use the Sport Concussion Recognition Tool[1]. Preseason baseline testing with the SCAT3 can be helpful for interpreting post-injury test scores.

Specific instructions for use of the SCAT3 are provided on page 3. If you are not familiar with the SCAT3, please read through these instructions carefully. This tool may be freely copied in its current form for distribution to individuals, teams, groups and organizations. Any revision or any reproduction in a digital form requires approval by the Concussion in Sport Group.

NOTE: The diagnosis of a concussion is a clinical judgment, ideally made by a medical professional. The SCAT3 should not be used solely to make, or exclude, the diagnosis of concussion in the absence of clinical judgement. An athlete may have a concussion even if their SCAT3 is "normal".

What is a concussion?

A concussion is a disturbance in brain function caused by a direct or indirect force to the head. It results in a variety of non-specific signs and/or symptoms (some examples listed below) and most often does not involve loss of consciousness. Concussion should be suspected in the presence of **any one or more** of the following:

- Symptoms (e.g., headache), or
- Physical signs (e.g., unsteadiness), or
- Impaired brain function (e.g. confusion) or
- Abnormal behaviour (e.g., change in personality).

SIDELINE ASSESSMENT

Indications for Emergency Management

NOTE: A hit to the head can sometimes be associated with a more serious brain injury. Any of the following warrants consideration of activating emergency procedures and urgent transportation to the nearest hospital:

- Glasgow Coma score less than 15
- Deteriorating mental status
- Potential spinal injury
- Progressive, worsening symptoms or new neurologic signs

Potential signs of concussion?

If any of the following signs are observed after a direct or indirect blow to the head, the athlete should stop participation, be evaluated by a medical professional and **should not be permitted to return to sport the same day** if a concussion is suspected.

Any loss of consciousness?	Y	N
"If so, how long?"		
Balance or motor incoordination (stumbles, slow/laboured movements, etc.)?	Y	N
Disorientation or confusion (inability to respond appropriately to questions)?	Y	N
Loss of memory:	Y	N
"If so, how long?"		
"Before or after the injury?"		
Blank or vacant look:	Y	N
Visible facial injury in combination with any of the above:	Y	N

1 Glasgow coma scale (GCS)

Best eye response (E)	
No eye opening	1
Eye opening in response to pain	2
Eye opening to speech	3
Eyes opening spontaneously	4
Best verbal response (V)	
No verbal response	1
Incomprehensible sounds	2
Inappropriate words	3
Confused	4
Oriented	5
Best motor response (M)	
No motor response	1
Extension to pain	2
Abnormal flexion to pain	3
Flexion/Withdrawal to pain	4
Localizes to pain	5
Obeys commands	6
Glasgow Coma score (E + V + M)	of 15

GCS should be recorded for all athletes in case of subsequent deterioration.

2 Maddocks Score[3]

"I am going to ask you a few questions, please listen carefully and give your best effort."

Modified Maddocks questions (1 point for each correct answer)

What venue are we at today?	0	1
Which half is it now?	0	1
Who scored last in this match?	0	1
What team did you play last week/game?	0	1
Did your team win the last game?	0	1
Maddocks score		of 5

Maddocks score is validated for sideline diagnosis of concussion only and is not used for serial testing.

Notes: Mechanism of Injury ("tell me what happened"?):

Any athlete with a suspected concussion should be REMOVED FROM PLAY, medically assessed, monitored for deterioration (i.e., should not be left alone) and should not drive a motor vehicle until cleared to do so by a medical professional. No athlete diagnosed with concussion should be returned to sports participation on the day of Injury.

BACKGROUND

Name: ______ Date: ______

Examiner: ______

Sport/team/school: ______ Date/time of injury: ______

Age: ______ Gender: M F

Years of education completed: ______

Dominant hand: right left neither

How many concussions do you think you have had in the past? ______

When was the most recent concussion? ______

How long was your recovery from the most recent concussion? ______

Have you ever been hospitalized or had medical imaging done for a head injury?	Y	N
Have you ever been diagnosed with headaches or migraines?	Y	N
Do you have a learning disability, dyslexia, ADD/ADHD?	Y	N
Have you ever been diagnosed with depression, anxiety or other psychiatric disorder?	Y	N
Has anyone in your family ever been diagnosed with any of these problems?	Y	N
Are you on any medications? If yes, please list:	Y	N

SCAT3 to be done in resting state. Best done 10 or more minutes post excercise.

SYMPTOM EVALUATION

3 How do you feel?

"You should score yourself on the following symptoms, based on how you feel now".

	none	mild		moderate		severe	
Headache	0	1	2	3	4	5	6
"Pressure in head"	0	1	2	3	4	5	6
Neck Pain	0	1	2	3	4	5	6
Nausea or vomiting	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Blurred vision	0	1	2	3	4	5	6
Balance problems	0	1	2	3	4	5	6
Sensitivity to light	0	1	2	3	4	5	6
Sensitivity to noise	0	1	2	3	4	5	6
Feeling slowed down	0	1	2	3	4	5	6
Feeling like "in a fog"	0	1	2	3	4	5	6
"Don't feel right"	0	1	2	3	4	5	6
Difficulty concentrating	0	1	2	3	4	5	6
Difficulty remembering	0	1	2	3	4	5	6
Fatigue or low energy	0	1	2	3	4	5	6
Confusion	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
Trouble falling asleep	0	1	2	3	4	5	6
More emotional	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6
Nervous or Anxious	0	1	2	3	4	5	6

Total number of symptoms (Maximum possible 22) ______

Symptom severity score (Maximum possible 132) ______

Do the symptoms get worse with physical activity? Y N

Do the symptoms get worse with mental activity? Y N

self rated | self rated and clinician monitored

clinician interview | self rated with parent input

Overall rating: If you know the athlete well prior to the injury, how different is the athlete acting compared to his/her usual self?

Please circle one response:

no different | very different | unsure | N/A

Scoring on the SCAT3 should not be used as a stand-alone method to diagnose concussion, measure recovery or make decisions about an athlete's readiness to return to competition after concussion. Since signs and symptoms may evolve over time, it is important to consider repeat evaluation in the acute assessment of concussion.

COGNITIVE & PHYSICAL EVALUATION

4 Cognitive assessment

Standardized Assessment of Concussion (SAC)[4]

Orientation (1 point for each correct answer)

What month is it?	0	1
What is the date today?	0	1
What is the day of the week?	0	1
What year is it?	0	1
What time is it right now? (within 1 hour)	0	1
Orientation score		of 5

Immediate memory

List	Trial 1		Trial 2		Trial 3		Alternative word list		
elbow	0	1	0	1	0	1	candle	baby	finger
apple	0	1	0	1	0	1	paper	monkey	penny
carpet	0	1	0	1	0	1	sugar	perfume	blanket
saddle	0	1	0	1	0	1	sandwich	sunset	lemon
bubble	0	1	0	1	0	1	wagon	iron	insect
Total									

Immediate memory score total ______ of 15

Concentration: Digits Backward

List	Trial 1		Alternative digit list		
4-9-3	0	1	6-2-9	5-2-6	4-1-5
3-8-1-4	0	1	3-2-7-9	1-7-9-5	4-9-6-8
6-2-9-7-1	0	1	1-5-2-8-6	3-8-5-2-7	6-1-8-4-3
7-1-8-4-6-2	0	1	5-3-9-1-4-8	8-3-1-9-6-4	7-2-4-8-5-6
Total of 4					

Concentration: Month in Reverse Order (1 pt. for entire sequence correct)

Dec-Nov-Oct-Sept-Aug-Jul-Jun-May-Apr-Mar-Feb-Jan 0 1

Concentration score ______ of 5

5 Neck Examination:

Range of motion Tenderness Upper and lower limb sensation & strength

Findings:

6 Balance examination

Do one or both of the following tests.

Footwear (shoes, barefoot, braces, tape, etc.) ______

Modified Balance Error Scoring System (BESS) testing[5]

Which foot was tested (i.e. which is the non-dominant foot) Left Right

Testing surface (hard floor, field, etc.) ______

Condition

Double leg stance:	Errors
Single leg stance (non-dominant foot):	Errors
Tandem stance (non-dominant foot at back):	Errors

And/Or

Tandem gait[6,7]

Time (best of 4 trials): ______ seconds

7 Coordination examination

Upper limb coordination

Which arm was tested: Left Right

Coordination score ______ of 1

8 SAC Delayed Recall[4]

Delayed recall score ______ of 5

INSTRUCTIONS

Words in *Italics* throughout the SCAT3 are the instructions given to the athlete by the tester.

Symptom Scale

"You should score yourself on the following symptoms, based on how you feel now".

To be completed by the athlete. In situations where the symptom scale is being completed after exercise, it should still be done in a resting state, at least 10 minutes post exercise.

For total number of symptoms, maximum possible is 22.
For Symptom severity score, add all scores in table, maximum possible is 22 x 6 = 132.

SAC[4]

Immediate Memory

"I am going to test your memory. I will read you a list of words and when I am done, repeat back as many words as you can remember, in any order."

Trials 2 & 3:

"I am going to repeat the same list again. Repeat back as many words as you can remember in any order, even if you said the word before."

Complete all 3 trials regardless of score on trial 1 & 2. Read the words at a rate of one per second. **Score 1 pt. for each correct response.** Total score equals sum across all 3 trials. Do not inform the athlete that delayed recall will be tested.

Concentration

Digits backward

"I am going to read you a string of numbers and when I am done, you repeat them back to me backwards, in reverse order of how I read them to you. For example, if I say 7-1-9, you would say 9-1-7."

If correct, go to next string length. If incorrect, read trial 2. **One point possible for each string length.** Stop after incorrect on both trials. The digits should be read at the rate of one per second.

Months in reverse order

"Now tell me the months of the year in reverse order. Start with the last month and go backward. So you'll say December, November ... Go ahead"

1 pt. for entire sequence correct

Delayed Recall

The delayed recall should be performed after completion of the Balance and Coordination Examination.

"Do you remember that list of words I read a few times earlier? Tell me as many words from the list as you can remember in any order."

Score 1 pt. for each correct response

Balance Examination

Modified Balance Error Scoring System (BESS) testing[5]

This balance testing is based on a modified version of the Balance Error Scoring System (BESS)[5]. A stopwatch or watch with a second hand is required for this testing.

"I am now going to test your balance. Please take your shoes off, roll up your pant legs above ankle (if applicable), and remove any ankle taping (if applicable). This test will consist of three twenty second tests with different stances."

(a) Double leg stance:

"The first stance is standing with your feet together with your hands on your hips and with your eyes closed. You should try to maintain stability in that position for 20 seconds. I will be counting the number of times you move out of this position. I will start timing when you are set and have closed your eyes."

(b) Single leg stance:

"If you were to kick a ball, which foot would you use? [This will be the dominant foot] Now stand on your non-dominant foot. The dominant leg should be held in approximately 30 degrees of hip flexion and 45 degrees of knee flexion. Again, you should try to maintain stability for 20 seconds with your hands on your hips and your eyes closed. I will be counting the number of times you move out of this position. If you stumble out of this position, open your eyes and return to the start position and continue balancing. I will start timing when you are set and have closed your eyes."

(c) Tandem stance:

"Now stand heel-to-toe with your non-dominant foot in back. Your weight should be evenly distributed across both feet. Again, you should try to maintain stability for 20 seconds with your hands on your hips and your eyes closed. I will be counting the number of times you move out of this position. If you stumble out of this position, open your eyes and return to the start position and continue balancing. I will start timing when you are set and have closed your eyes."

Balance testing – types of errors

1. Hands lifted off iliac crest
2. Opening eyes
3. Step, stumble, or fall
4. Moving hip into > 30 degrees abduction
5. Lifting forefoot or heel
6. Remaining out of test position > 5 sec

Each of the 20-second trials is scored by counting the errors, or deviations from the proper stance, accumulated by the athlete. The examiner will begin counting errors only after the individual has assumed the proper start position. **The modified BESS is calculated by adding one error point for each error during the three 20-second tests. The maximum total number of errors for any single condition is 10.** If a athlete commits multiple errors simultaneously, only one error is recorded but the athlete should quickly return to the testing position, and counting should resume once subject is set. Subjects that are unable to maintain the testing procedure for a minimum of **five seconds** at the start are assigned the highest possible score, ten, for that testing condition.

OPTION: For further assessment, the same 3 stances can be performed on a surface of medium density foam (e.g., approximately 50 cm x 40 cm x 6 cm).

Tandem Gait[6,7]

Participants are instructed to stand with their feet together behind a starting line (the test is best done with footwear removed). Then, they walk in a forward direction as quickly and as accurately as possible along a 38mm wide (sports tape), 3 meter line with an alternate foot heel-to-toe gait ensuring that they approximate their heel and toe on each step. Once they cross the end of the 3m line, they turn 180 degrees and return to the starting point using the same gait. A total of 4 trials are done and the best time is retained. Athletes should complete the test in 14 seconds. Athletes fail the test if they step off the line, have a separation between their heel and toe, or if they touch or grab the examiner or an object. In this case, the time is not recorded and the trial repeated, if appropriate.

Coordination Examination

Upper limb coordination

Finger-to-nose (FTN) task:

"I am going to test your coordination now. Please sit comfortably on the chair with your eyes open and your arm (either right or left) outstretched (shoulder flexed to 90 degrees and elbow and fingers extended), pointing in front of you. When I give a start signal, I would like you to perform five successive finger to nose repetitions using your index finger to touch the tip of the nose, and then return to the starting position, as quickly and as accurately as possible."

Scoring: 5 correct repetitions in < 4 seconds = 1
Note for testers: Athletes fail the test if they do not touch their nose, do not fully extend their elbow or do not perform five repetitions. Failure should be scored as 0.

References & Footnotes

1. This tool has been developed by a group of international experts at the 4th International Consensus meeting on Concussion in Sport held in Zurich, Switzerland in November 2012. The full details of the conference outcomes and the authors of the tool are published in The BJSM Injury Prevention and Health Protection, 2013, Volume 47, Issue 5. The outcome paper will also be simultaneously co-published in other leading biomedical journals with the copyright held by the Concussion in Sport Group, to allow unrestricted distribution, providing no alterations are made.

2. McCrory P et al., Consensus Statement on Concussion in Sport – the 3rd International Conference on Concussion in Sport held in Zurich, November 2008. British Journal of Sports Medicine 2009; 43: i76–89.

3. Maddocks, DL; Dicker, GD; Saling, MM. The assessment of orientation following concussion in athletes. Clinical Journal of Sport Medicine. 1995; 5(1): 32–3.

4. McCrea M. Standardized mental status testing of acute concussion. Clinical Journal of Sport Medicine. 2001; 11: 176–181.

5. Guskiewicz KM. Assessment of postural stability following sport-related concussion. Current Sports Medicine Reports. 2003; 2: 24–30.

6. Schneiders, A.G., Sullivan, S.J., Gray, A., Hammond-Tooke, G. & McCrory, P. Normative values for 16-37 year old subjects for three clinical measures of motor performance used in the assessment of sports concussions. Journal of Science and Medicine in Sport. 2010; 13(2): 196–201.

7. Schneiders, A.G., Sullivan, S.J., Kvarnstrom. J.K., Olsson, M., Yden. T. & Marshall, S.W. The effect of footwear and sports-surface on dynamic neurological screening in sport-related concussion. Journal of Science and Medicine in Sport. 2010; 13(4): 382–386

ATHLETE INFORMATION

Any athlete suspected of having a concussion should be removed from play, and then seek medical evaluation.

Signs to watch for

Problems could arise over the first 24–48 hours. The athlete should not be left alone and must go to a hospital at once if they:

- Have a headache that gets worse
- Are very drowsy or can't be awakened
- Can't recognize people or places
- Have repeated vomiting
- Behave unusually or seem confused; are very irritable
- Have seizures (arms and legs jerk uncontrollably)
- Have weak or numb arms or legs
- Are unsteady on their feet; have slurred speech

Remember, it is better to be safe.
Consult your doctor after a suspected concussion.

Return to play

Athletes should not be returned to play the same day of injury.
When returning athletes to play, they should be **medically cleared and then follow a stepwise supervised program,** with stages of progression.

For example:

Rehabilitation stage	Functional exercise at each stage of rehabilitation	Objective of each stage
No activity	Physical and cognitive rest	Recovery
Light aerobic exercise	Walking, swimming or stationary cycling keeping intensity, 70 % maximum predicted heart rate. No resistance training	Increase heart rate
Sport-specific exercise	Skating drills in ice hockey, running drills in soccer. No head impact activities	Add movement
Non-contact training drills	Progression to more complex training drills, eg passing drills in football and ice hockey. May start progressive resistance training	Exercise, coordination, and cognitive load
Full contact practice	Following medical clearance participate in normal training activities	Restore confidence and assess functional skills by coaching staff
Return to play	Normal game play	

There should be at least 24 hours (or longer) for each stage and if symptoms recur the athlete should rest until they resolve once again and then resume the program at the previous asymptomatic stage. Resistance training should only be added in the later stages.

If the athlete is symptomatic for more than 10 days, then consultation by a medical practitioner who is expert in the management of concussion, is recommended.

Medical clearance should be given before return to play.

Scoring Summary:

Test Domain	Score		
	Date:	Date:	Date:
Number of Symptoms of 22			
Symptom Severity Score of 132			
Orientation of 5			
Immediate Memory of 15			
Concentration of 5			
Delayed Recall of 5			
SAC Total			
BESS (total errors)			
Tandem Gait (seconds)			
Coordination of 1			

Notes:

CONCUSSION INJURY ADVICE

(To be given to the **person monitoring** the concussed athlete)

This patient has received an injury to the head. A careful medical examination has been carried out and no sign of any serious complications has been found. Recovery time is variable across individuals and the patient will need monitoring for a further period by a responsible adult. Your treating physician will provide guidance as to this timeframe.

If you notice any change in behaviour, vomiting, dizziness, worsening headache, double vision or excessive drowsiness, please contact your doctor or the nearest hospital emergency department immediately.

Other important points:

- Rest (physically and mentally), including training or playing sports until symptoms resolve and you are medically cleared
- No alcohol
- No prescription or non-prescription drugs without medical supervision. Specifically:
  - No sleeping tablets
  - Do not use aspirin, anti-inflammatory medication or sedating pain killers
- Do not drive until medically cleared
- Do not train or play sport until medically cleared

Clinic phone number

Patient's name

Date/time of injury

Date/time of medical review

Treating physician

Contact details or stamp

BJSM Online First, published on April 26, 2017 as 10.1136/bjsports-2017-097506SCAT5
To download a clean version of the SCAT tools please visit the journal online (http://dx.doi.org/10.1136/bjsports-2017-097506SCAT5)

SCAT5©

SPORT CONCUSSION ASSESSMENT TOOL — 5TH EDITION

DEVELOPED BY THE CONCUSSION IN SPORT GROUP
FOR USE BY MEDICAL PROFESSIONALS ONLY

supported by

FIFA

Patient details

Name: ____________________

DOB: ____________________

Address: ____________________

ID number: ____________________

Examiner: ____________________

Date of Injury: ____________________ Time: ____________________

WHAT IS THE SCAT5?

The SCAT5 is a standardized tool for evaluating concussions designed for use by physicians and licensed healthcare professionals[1]. The SCAT5 cannot be performed correctly in less than 10 minutes.

If you are not a physician or licensed healthcare professional, please use the Concussion Recognition Tool 5 (CRT5). The SCAT5 is to be used for evaluating athletes aged 13 years and older. For children aged 12 years or younger, please use the Child SCAT5.

Preseason SCAT5 baseline testing can be useful for interpreting post-injury test scores, but is not required for that purpose.Detailed instructions for use of the SCAT5 are provided on page 7. Please read through these instructions carefully before testing the athlete. Brief verbal instructions for each test are given in italics. The only equipment required for the tester is a watch or timer.

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Recognise and Remove

A head impact by either a direct blow or indirect transmission of force can be associated with a serious and potentially fatal brain injury. If there are significant concerns, including any of the red flags listed in Box 1, then activation of emergency procedures and urgent transport to the nearest hospital should be arranged.

Key points

- Any athlete with suspected concussion should be REMOVED FROM PLAY, medically assessed and monitored for deterioration. No athlete diagnosed with concussion should be returned to play on the day of injury.
- If an athlete is suspected of having a concussion and medical personnel are not immediately available, the athlete should be referred to a medical facility for urgent assessment.
- Athletes with suspected concussion should not drink alcohol, use recreational drugs and should not drive a motor vehicle until cleared to do so by a medical professional.
- Concussion signs and symptoms evolve over time and it is important to consider repeat evaluation in the assessment of concussion.
- The diagnosis of a concussion is a clinical judgment, made by a medical professional. The SCAT5 should NOT be used by itself to make, or exclude, the diagnosis of concussion. An athlete may have a concussion even if their SCAT5 is "normal".

Remember:

- The basic principles of first aid (danger, response, airway, breathing, circulation) should be followed.
- Do not attempt to move the athlete (other than that required for airway management) unless trained to do so.
- Assessment for a spinal cord injury is a critical part of the initial on-field assessment.
- Do not remove a helmet or any other equipment unless trained to do so safely.

1

IMMEDIATE OR ON-FIELD ASSESSMENT

The following elements should be assessed for all athletes who are suspected of having a concussion prior to proceeding to the neurocognitive assessment and ideally should be done on-field after the first first aid / emergency care priorities are completed.

If any of the "Red Flags" or observable signs are noted after a direct or indirect blow to the head, the athlete should be immediately and safely removed from participation and evaluated by a physician or licensed healthcare professional.

Consideration of transportation to a medical facility should be at the discretion of the physician or licensed healthcare professional.

The GCS is important as a standard measure for all patients and can be done serially if necessary in the event of deterioration in conscious state. The Maddocks questions and cervical spine exam are critical steps of the immediate assessment; however, these do not need to be done serially.

STEP 1: RED FLAGS

RED FLAGS:

- Neck pain or tenderness
- Double vision
- Weakness or tingling/ burning in arms or legs
- Severe or increasing headache
- Seizure or convulsion
- Loss of consciousness
- Deteriorating conscious state
- Vomiting
- Increasingly restless, agitated or combative

STEP 2: OBSERVABLE SIGNS

Witnessed ☐ Observed on Video ☐

Lying motionless on the playing surface	Y	N
Balance / gait difficulties / motor incoordination: stumbling, slow / laboured movements	Y	N
Disorientation or confusion, or an inability to respond appropriately to questions	Y	N
Blank or vacant look	Y	N
Facial injury after head trauma	Y	N

STEP 3: MEMORY ASSESSMENT MADDOCKS QUESTIONS[2]

"I am going to ask you a few questions, please listen carefully and give your best effort. First, tell me what happened?"

Mark Y for correct answer / N for incorrect		
What venue are we at today?	Y	N
Which half is it now?	Y	N
Who scored last in this match?	Y	N
What team did you play last week / game?	Y	N
Did your team win the last game?	Y	N

Note: Appropriate sport-specific questions may be substituted.

Name:
DOB:
Address:
ID number:
Examiner:
Date:

STEP 4: EXAMINATION GLASGOW COMA SCALE (GCS)[3]

Time of assessment			
Date of assessment			
Best eye response (E)			
No eye opening	1	1	1
Eye opening in response to pain	2	2	2
Eye opening to speech	3	3	3
Eyes opening spontaneously	4	4	4
Best verbal response (V)			
No verbal response	1	1	1
Incomprehensible sounds	2	2	2
Inappropriate words	3	3	3
Confused	4	4	4
Oriented	5	5	5
Best motor response (M)			
No motor response	1	1	1
Extension to pain	2	2	2
Abnormal flexion to pain	3	3	3
Flexion / Withdrawal to pain	4	4	4
Localizes to pain	5	5	5
Obeys commands	6	6	6
Glasgow Coma score (E + V + M)			

CERVICAL SPINE ASSESSMENT

Does the athlete report that their neck is pain free at rest?	Y	N
If there is NO neck pain at rest, does the athlete have a full range of ACTIVE pain free movement?	Y	N
Is the limb strength and sensation normal?	Y	N

In a patient who is not lucid or fully conscious, a cervical spine injury should be assumed until proven otherwise.

OFFICE OR OFF-FIELD ASSESSMENT

Please note that the neurocognitive assessment should be done in a distraction-free environment with the athlete in a resting state.

STEP 1: ATHLETE BACKGROUND

Sport / team / school: ____________

Date / time of injury: ____________

Years of education completed: ____________

Age: ____________

Gender: M / F / Other

Dominant hand: left / neither / right

How many diagnosed concussions has the athlete had in the past?: ____________

When was the most recent concussion?: ____________

How long was the recovery (time to being cleared to play) from the most recent concussion?: ____________ (days)

Has the athlete ever been:

Hospitalized for a head injury?	Yes	No
Diagnosed / treated for headache disorder or migraines?	Yes	No
Diagnosed with a learning disability / dyslexia?	Yes	No
Diagnosed with ADD / ADHD?	Yes	No
Diagnosed with depression, anxiety or other psychiatric disorder?	Yes	No

Current medications? If yes, please list:

____

____

____

____

____

____

Name: ____________

DOB: ____________

Address: ____________

ID number: ____________

Examiner: ____________

Date: ____________

2

STEP 2: SYMPTOM EVALUATION

The athlete should be given the symptom form and asked to read this instruction paragraph out loud then complete the symptom scale. For the baseline assessment, the athlete should rate his/her symptoms based on how he/she typically feels and for the post injury assessment the athlete should rate their symptoms at this point in time.

Please Check: ☐ Baseline ☐ Post-Injury

Please hand the form to the athlete

	none	mild		moderate		severe	
Headache	0	1	2	3	4	5	6
"Pressure in head"	0	1	2	3	4	5	6
Neck Pain	0	1	2	3	4	5	6
Nausea or vomiting	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Blurred vision	0	1	2	3	4	5	6
Balance problems	0	1	2	3	4	5	6
Sensitivity to light	0	1	2	3	4	5	6
Sensitivity to noise	0	1	2	3	4	5	6
Feeling slowed down	0	1	2	3	4	5	6
Feeling like "in a fog"	0	1	2	3	4	5	6
"Don't feel right"	0	1	2	3	4	5	6
Difficulty concentrating	0	1	2	3	4	5	6
Difficulty remembering	0	1	2	3	4	5	6
Fatigue or low energy	0	1	2	3	4	5	6
Confusion	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
More emotional	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6
Nervous or Anxious	0	1	2	3	4	5	6
Trouble falling asleep (if applicable)	0	1	2	3	4	5	6

Total number of symptoms:	of 22
Symptom severity score:	of 132
Do your symptoms get worse with physical activity?	Y N
Do your symptoms get worse with mental activity?	Y N
If 100% is feeling perfectly normal, what percent of normal do you feel?	

If not 100%, why?

____

____

____

Please hand form back to examiner

3

STEP 3: COGNITIVE SCREENING

Standardised Assessment of Concussion (SAC)[4]

ORIENTATION

What month is it?	0	1
What is the date today?	0	1
What is the day of the week?	0	1
What year is it?	0	1
What time is it right now? (within 1 hour)	0	1
Orientation score		of 5

IMMEDIATE MEMORY

The Immediate Memory component can be completed using the traditional 5-word per trial list or optionally using 10-words per trial to minimise any ceiling effect. All 3 trials must be administered irrespective of the number correct on the first trial. Administer at the rate of one word per second.

Please choose EITHER the 5 or 10 word list groups and circle the specific word list chosen for this test.

I am going to test your memory. I will read you a list of words and when I am done, repeat back as many words as you can remember, in any order. For Trials 2 & 3: I am going to repeat the same list again. Repeat back as many words as you can remember in any order, even if you said the word before.

List	Alternate 5 word lists					Score (of 5)		
						Trial 1	Trial 2	Trial 3
A	Finger	Penny	Blanket	Lemon	Insect			
B	Candle	Paper	Sugar	Sandwich	Wagon			
C	Baby	Monkey	Perfume	Sunset	Iron			
D	Elbow	Apple	Carpet	Saddle	Bubble			
E	Jacket	Arrow	Pepper	Cotton	Movie			
F	Dollar	Honey	Mirror	Saddle	Anchor			
				Immediate Memory Score				of 15
				Time that last trial was completed				

List	Alternate 10 word lists					Score (of 10)		
						Trial 1	Trial 2	Trial 3
G	Finger	Penny	Blanket	Lemon	Insect			
	Candle	Paper	Sugar	Sandwich	Wagon			
H	Baby	Monkey	Perfume	Sunset	Iron			
	Elbow	Apple	Carpet	Saddle	Bubble			
I	Jacket	Arrow	Pepper	Cotton	Movie			
	Dollar	Honey	Mirror	Saddle	Anchor			
				Immediate Memory Score				of 30
				Time that last trial was completed				

Name: ________________

DOB: ________________

Address: ________________

ID number: ________________

Examiner: ________________

Date: ________________

CONCENTRATION

DIGITS BACKWARDS

Please circle the Digit list chosen (A, B, C, D, E, F). Administer at the rate of one digit per second reading DOWN the selected column.

I am going to read a string of numbers and when I am done, you repeat them back to me in reverse order of how I read them to you. For example, if I say 7-1-9, you would say 9-1-7.

Concentration Number Lists (circle one)					
List A	List B	List C			
4-9-3	5-2-6	1-4-2	Y	N	0
6-2-9	4-1-5	6-5-8	Y	N	1
3-8-1-4	1-7-9-5	6-8-3-1	Y	N	0
3-2-7-9	4-9-6-8	3-4-8-1	Y	N	1
6-2-9-7-1	4-8-5-2-7	4-9-1-5-3	Y	N	0
1-5-2-8-6	6-1-8-4-3	6-8-2-5-1	Y	N	1
7-1-8-4-6-2	8-3-1-9-6-4	3-7-6-5-1-9	Y	N	0
5-3-9-1-4-8	7-2-4-8-5-6	9-2-6-5-1-4	Y	N	1
List D	List E	List F			
7-8-2	3-8-2	2-7-1	Y	N	0
9-2-6	5-1-8	4-7-9	Y	N	1
4-1-8-3	2-7-9-3	1-6-8-3	Y	N	0
9-7-2-3	2-1-6-9	3-9-2-4	Y	N	1
1-7-9-2-6	4-1-8-6-9	2-4-7-5-8	Y	N	0
4-1-7-5-2	9-4-1-7-5	8-3-9-6-4	Y	N	1
2-6-4-8-1-7	6-9-7-3-8-2	5-8-6-2-4-9	Y	N	0
8-4-1-9-3-5	4-2-7-9-3-8	3-1-7-8-2-6	Y	N	1
		Digits Score:			of 4

MONTHS IN REVERSE ORDER

Now tell me the months of the year in reverse order. Start with the last month and go backward. So you'll say December, November. Go ahead.

Dec - Nov - Oct - Sept - Aug - Jul - Jun - May - Apr - Mar - Feb - Jan	0 1
Months Score	of 1
Concentration Total Score (Digits + Months)	of 5

4

STEP 4: NEUROLOGICAL SCREEN

See the instruction sheet (page 7) for details of test administration and scoring of the tests.

Can the patient read aloud (e.g. symptom check-list) and follow instructions without difficulty?	Y	N
Does the patient have a full range of pain-free PASSIVE cervical spine movement?	Y	N
Without moving their head or neck, can the patient look side-to-side and up-and-down without double vision?	Y	N
Can the patient perform the finger nose coordination test normally?	Y	N
Can the patient perform tandem gait normally?	Y	N

BALANCE EXAMINATION

Modified Balance Error Scoring System (mBESS) testing[5]

Which foot was tested (i.e. which is the non-dominant foot) ☐ Left ☐ Right

Testing surface (hard floor, field, etc.) __________

Footwear (shoes, barefoot, braces, tape, etc.) __________

Condition	Errors
Double leg stance	of 10
Single leg stance (non-dominant foot)	of 10
Tandem stance (non-dominant foot at the back)	of 10
Total Errors	of 30

Name: __________

DOB: __________

Address: __________

ID number: __________

Examiner: __________

Date: __________

5

STEP 5: DELAYED RECALL:

The delayed recall should be performed after 5 minutes have elapsed since the end of the Immediate Recall section. Score 1 pt. for each correct response.

Do you remember that list of words I read a few times earlier? Tell me as many words from the list as you can remember in any order.

Time Started __________

Please record each word correctly recalled. Total score equals number of words recalled.

____

____

____

Total number of words recalled accurately: of 5 or of 10

6

STEP 6: DECISION

Domain	Date & time of assessment:		
Symptom number (of 22)			
Symptom severity score (of 132)			
Orientation (of 5)			
Immediate memory	of 15 of 30	of 15 of 30	of 15 of 30
Concentration (of 5)			
Neuro exam	Normal Abnormal	Normal Abnormal	Normal Abnormal
Balance errors (of 30)			
Delayed Recall	of 5 of 10	of 5 of 10	of 5 of 10

Date and time of injury: __________

If the athlete is known to you prior to their injury, are they different from their usual self?
☐ **Yes** ☐ **No** ☐ **Unsure** ☐ **Not Applicable**
(If different, describe why in the clinical notes section)

Concussion Diagnosed?
☐ **Yes** ☐ **No** ☐ **Unsure** ☐ **Not Applicable**

If re-testing, has the athlete improved?
☐ **Yes** ☐ **No** ☐ **Unsure** ☐ **Not Applicable**

I am a physician or licensed healthcare professional and I have personally administered or supervised the administration of this SCAT5.

Signature: __________

Name: __________

Title: __________

Registration number (if applicable): __________

Date: __________

SCORING ON THE SCAT5 SHOULD NOT BE USED AS A STAND-ALONE METHOD TO DIAGNOSE CONCUSSION, MEASURE RECOVERY OR MAKE DECISIONS ABOUT AN ATHLETE'S READINESS TO RETURN TO COMPETITION AFTER CONCUSSION.

CLINICAL NOTES:

Name:
DOB:
Address:
ID number:
Examiner:
Date:

CONCUSSION INJURY ADVICE

(To be given to the person monitoring the concussed athlete)

This patient has received an injury to the head. A careful medical examination has been carried out and no sign of any serious complications has been found. Recovery time is variable across individuals and the patient will need monitoring for a further period by a responsible adult. Your treating physician will provide guidance as to this timeframe.

If you notice any change in behaviour, vomiting, worsening headache, double vision or excessive drowsiness, please telephone your doctor or the nearest hospital emergency department immediately.

Other important points:

Initial rest: Limit physical activity to routine daily activities (avoid exercise, training, sports) and limit activities such as school, work, and screen time to a level that does not worsen symptoms.

1) Avoid alcohol

2) Avoid prescription or non-prescription drugs without medical supervision. Specifically:

a) Avoid sleeping tablets

b) Do not use aspirin, anti-inflammatory medication or stronger pain medications such as narcotics

3) Do not drive until cleared by a healthcare professional.

4) Return to play/sport requires clearance by a healthcare professional.

Clinic phone number:

Patient's name:

Date / time of injury:

Date / time of medical review:

Healthcare Provider:

Contact details or stamp

INSTRUCTIONS

Words in *Italics* throughout the SCAT5 are the instructions given to the athlete by the clinician

Symptom Scale

The time frame for symptoms should be based on the type of test being administered. At baseline it is advantageous to assess how an athlete "typically" feels whereas during the acute/post-acute stage it is best to ask how the athlete feels at the time of testing.

The symptom scale should be completed by the athlete, not by the examiner. In situations where the symptom scale is being completed after exercise, it should be done in a resting state, generally by approximating his/her resting heart rate.

For total number of symptoms, maximum possible is 22 except immediately post injury, if sleep item is omitted, which then creates a maximum of 21.

For Symptom severity score, add all scores in table, maximum possible is 22 x 6 = 132, except immediately post injury if sleep item is omitted, which then creates a maximum of 21x6=126.

Immediate Memory

The Immediate Memory component can be completed using the traditional 5-word per trial list or, optionally, using 10-words per trial. The literature suggests that the Immediate Memory has a notable ceiling effect when a 5-word list is used. In settings where this ceiling is prominent, the examiner may wish to make the task more difficult by incorporating two 5-word groups for a total of 10 words per trial. In this case, the maximum score per trial is 10 with a total trial maximum of 30.

Choose one of the word lists (either 5 or 10). Then perform 3 trials of immediate memory using this list.

Complete all 3 trials regardless of score on previous trials.

"I am going to test your memory. I will read you a list of words and when I am done, repeat back as many words as you can remember, in any order." The words must be read at a rate of one word per second.

Trials 2 & 3 MUST be completed regardless of score on trial 1 & 2.

Trials 2 & 3:

"I am going to repeat the same list again. Repeat back as many words as you can remember in any order, even if you said the word before."

Score 1 pt. for each correct response. Total score equals sum across all 3 trials. Do NOT inform the athlete that delayed recall will be tested.

Concentration

Digits backward

Choose one column of digits from lists A, B, C, D, E or F and administer those digits as follows:

Say: *"I am going to read a string of numbers and when I am done, you repeat them back to me in reverse order of how I read them to you. For example, if I say 7-1-9, you would say 9-1-7."*

Begin with first 3 digit string.

If correct, circle "Y" for correct and go to next string length. If incorrect, circle "N" for the first string length and read trial 2 in the same string length. One point possible for each string length. Stop after incorrect on both trials (2 N's) in a string length. The digits should be read at the rate of one per second.

Months in reverse order

"Now tell me the months of the year in reverse order. Start with the last month and go backward. So you'll say December, November ... Go ahead"

1 pt. for entire sequence correct

Delayed Recall

The delayed recall should be performed after 5 minutes have elapsed since the end of the Immediate Recall section.

"Do you remember that list of words I read a few times earlier? Tell me as many words from the list as you can remember in any order."

Score 1 pt. for each correct response

Modified Balance Error Scoring System (mBESS)[5] testing

This balance testing is based on a modified version of the Balance Error Scoring System (BESS)[5]. A timing device is required for this testing.

Each of 20-second trial/stance is scored by counting the number of errors. The examiner will begin counting errors only after the athlete has assumed the proper start position. The modified BESS is calculated by adding one error point for each error during the three 20-second tests. The maximum number of errors for any single condition is 10. If the athlete commits multiple errors simultaneously, only one error is recorded but the athlete should quickly return to the testing position, and counting should resume once the athlete is set. Athletes that are unable to maintain the testing procedure for a minimum of five seconds at the start are assigned the highest possible score, ten, for that testing condition.

OPTION: For further assessment, the same 3 stances can be performed on a surface of medium density foam (e.g., approximately 50cm x 40cm x 6cm).

Balance testing – types of errors

1. Hands lifted off iliac crest	3. Step, stumble, or fall	5. Lifting forefoot or heel
2. Opening eyes	4. Moving hip into > 30 degrees abduction	6. Remaining out of test position > 5 sec

"I am now going to test your balance. Please take your shoes off (if applicable), roll up your pant legs above ankle (if applicable), and remove any ankle taping (if applicable). This test will consist of three twenty second tests with different stances."

(a) Double leg stance:

"The first stance is standing with your feet together with your hands on your hips and with your eyes closed. You should try to maintain stability in that position for 20 seconds. I will be counting the number of times you move out of this position. I will start timing when you are set and have closed your eyes."

(b) Single leg stance:

"If you were to kick a ball, which foot would you use? [This will be the dominant foot] *Now stand on your non-dominant foot. The dominant leg should be held in approximately 30 degrees of hip flexion and 45 degrees of knee flexion. Again, you should try to maintain stability for 20 seconds with your hands on your hips and your eyes closed. I will be counting the number of times you move out of this position. If you stumble out of this position, open your eyes and return to the start position and continue balancing. I will start timing when you are set and have closed your eyes."*

(c) Tandem stance:

"Now stand heel-to-toe with your non-dominant foot in back. Your weight should be evenly distributed across both feet. Again, you should try to maintain stability for 20 seconds with your hands on your hips and your eyes closed. I will be counting the number of times you move out of this position. If you stumble out of this position, open your eyes and return to the start position and continue balancing. I will start timing when you are set and have closed your eyes."

Tandem Gait

Participants are instructed to stand with their feet together behind a starting line (the test is best done with footwear removed). Then, they walk in a forward direction as quickly and as accurately as possible along a 38mm wide (sports tape), 3 metre line with an alternate foot heel-to-toe gait ensuring that they approximate their heel and toe on each step. Once they cross the end of the 3m line, they turn 180 degrees and return to the starting point using the same gait. Athletes fail the test if they step off the line, have a separation between their heel and toe, or if they touch or grab the examiner or an object.

Finger to Nose

"I am going to test your coordination now. Please sit comfortably on the chair with your eyes open and your arm (either right or left) outstretched (shoulder flexed to 90 degrees and elbow and fingers extended), pointing in front of you. When I give a start signal, I would like you to perform five successive finger to nose repetitions using your index finger to touch the tip of the nose, and then return to the starting position, as quickly and as accurately as possible."

References

1. McCrory et al. Consensus Statement On Concussion In Sport – The 5th International Conference On Concussion In Sport Held In Berlin, October 2016. British Journal of Sports Medicine 2017 (available at www.bjsm.bmj.com)
2. Maddocks, DL; Dicker, GD; Saling, MM. The assessment of orientation following concussion in athletes. Clinical Journal of Sport Medicine 1995; 5: 32-33
3. Jennett, B., Bond, M. Assessment of outcome after severe brain damage: a practical scale. Lancet 1975; i: 480-484
4. McCrea M. Standardized mental status testing of acute concussion. Clinical Journal of Sport Medicine. 2001; 11: 176-181
5. Guskiewicz KM. Assessment of postural stability following sport-related concussion. Current Sports Medicine Reports. 2003; 2: 24-30

CONCUSSION INFORMATION

Any athlete suspected of having a concussion should be removed from play and seek medical evaluation.

Signs to watch for

Problems could arise over the first 24-48 hours. The athlete should not be left alone and must go to a hospital at once if they experience:

- Worsening headache
- Drowsiness or inability to be awakened
- Inability to recognize people or places
- Repeated vomiting
- Unusual behaviour or confusion or irritable
- Seizures (arms and legs jerk uncontrollably)
- Weakness or numbness in arms or legs
- Unsteadiness on their feet.
- Slurred speech

Consult your physician or licensed healthcare professional after a suspected concussion. Remember, it is better to be safe.

Rest & Rehabilitation

After a concussion, the athlete should have physical rest and relative cognitive rest for a few days to allow their symptoms to improve. In most cases, after no more than a few days of rest, the athlete should gradually increase their daily activity level as long as their symptoms do not worsen. Once the athlete is able to complete their usual daily activities without concussion-related symptoms, the second step of the return to play/sport progression can be started. The athlete should not return to play/sport until their concussion-related symptoms have resolved and the athlete has successfully returned to full school/learning activities.

When returning to play/sport, the athlete should follow a stepwise, **medically managed exercise progression, with increasing amounts of exercise.** For example:

Graduated Return to Sport Strategy

Exercise step	Functional exercise at each step	Goal of each step
1. Symptom-limited activity	Daily activities that do not provoke symptoms.	Gradual reintroduction of work/school activities.
2. Light aerobic exercise	Walking or stationary cycling at slow to medium pace. No resistance training.	Increase heart rate.
3. Sport-specific exercise	Running or skating drills. No head impact activities.	Add movement.
4. Non-contact training drills	Harder training drills, e.g., passing drills. May start progressive resistance training.	Exercise, coordination, and increased thinking.
5. Full contact practice	Following medical clearance, participate in normal training activities.	Restore confidence and assess functional skills by coaching staff.
6. Return to play/sport	Normal game play.	

In this example, it would be typical to have 24 hours (or longer) for each step of the progression. If any symptoms worsen while exercising, the athlete should go back to the previous step. Resistance training should be added only in the later stages (Stage 3 or 4 at the earliest).

Written clearance should be provided by a healthcare professional before return to play/sport as directed by local laws and regulations.

Graduated Return to School Strategy

Concussion may affect the ability to learn at school. The athlete may need to miss a few days of school after a concussion. When going back to school, some athletes may need to go back gradually and may need to have some changes made to their schedule so that concussion symptoms do not get worse. If a particular activity makes symptoms worse, then the athlete should stop that activity and rest until symptoms get better. To make sure that the athlete can get back to school without problems, it is important that the healthcare provider, parents, caregivers and teachers talk to each other so that everyone knows what the plan is for the athlete to go back to school.

Note: If mental activity does not cause any symptoms, the athlete may be able to skip step 2 and return to school part-time before doing school activities at home first.

Mental Activity	Activity at each step	Goal of each step
1. Daily activities that do not give the athlete symptoms	Typical activities that the athlete does during the day as long as they do not increase symptoms (e.g. reading, texting, screen time). Start with 5-15 minutes at a time and gradually build up.	Gradual return to typical activities.
2. School activities	Homework, reading or other cognitive activities outside of the classroom.	Increase tolerance to cognitive work.
3. Return to school part-time	Gradual introduction of school-work. May need to start with a partial school day or with increased breaks during the day.	Increase academic activities.
4. Return to school full-time	Gradually progress school activities until a full day can be tolerated.	Return to full academic activities and catch up on missed work.

If the athlete continues to have symptoms with mental activity, some other accomodations that can help with return to school may include:

- Starting school later, only going for half days, or going only to certain classes
- More time to finish assignments/tests
- Quiet room to finish assignments/tests
- Not going to noisy areas like the cafeteria, assembly halls, sporting events, music class, shop class, etc.
- Taking lots of breaks during class, homework, tests
- No more than one exam/day
- Shorter assignments
- Repetition/memory cues
- Use of a student helper/tutor
- Reassurance from teachers that the child will be supported while getting better

The athlete should not go back to sports until they are back to school/learning, without symptoms getting significantly worse and no longer needing any changes to their schedule.

Appendix B

Health Questionnaire v.2 Developed by: Magdalena Wojtowicz, PhD

ID: ____________ Age: _______ DOB: _____________ Ethnicity: ____________________

Dominant Hand: LEFT or RIGHT or BOTH Highest Level of Education: _________________

Sport History
Current Sport(s):____

Sport(s) played in the past (recreational or competitive):_____________________________________
____

When did you start playing your first organized sport: ____

Health History
Please place an 'x' in the appropriate column:

	No	Yes	If yes, approximate age at diagnosis OR treatment?
Diagnosed with Attention Deficit Hyperactivity Disorder	☐	☐	
Diagnosed with a Learning Disorder	☐	☐	
Received special education (e.g., additional reading/writing/math support)	☐	☐	
Received mental health treatment (e.g., anxiety, depression, etc.)	☐	☐	
Diagnosed with Migraine or a Chronic Headache Condition	☐	☐	
Do you have a family history of migraine?	☐	☐	If yes, please list family members:

Medications
Are you currently taking medication(s): No ☐ Yes ☐
If yes, please list all medications: ____

Menstrual Cycle
The menstrual cycle is counted from the **first day** of one period to the **first day** of the next.
Are you on birth control (e.g., the pill; IUD, patch, etc.)? No ☐ Yes ☐
On average, do you have a regular period (i.e., approximately every month)? No ☐ Yes ☐
On average, approximately how long is your menstrual cycle (see definition above)? ______
When did your last period start (date)? _________
How many days did it last? ____________

Current Alcohol/Substance Use
Please circle the correct answer for you.

How often do you have a drink containing alcohol?
Never | Monthly or less | 2-4 times a month | 2-3 times per week | 4+ times per week

How many drinks containing alcohol do you have on a typical day when you are drinking?
1 or 2 | 3 or 4 | 5 or 6 | 7 or 9 | 10 or more

How often do you have six or more drinks on one occasion?
Never | Less than monthly | Monthly | 2-3 times per week | 4+ times per week

How often do you smoke marijuana?
Never | Monthly or less | 2-4 times a month | 2-3 times per week | 4+ times per week

Please turn over to next page.

Page 1 of 4

For this section, we define a concussion as a blow to the head or whiplash that caused ANY ONE OR MORE of the following:

- Witnessed Loss of Consciousness (being "knocked out", and someone saw it),
- Loss of Memory for Events Immediately Before and/or After the Injury, or
- Feeling Dazed and Confused for at Least 30 Seconds.

Using the above definition, how many concussions do you think you have sustained during your whole life? ___

How long ago was your most recent concussion? _________

Please provide details for your concussions (if you have had more than 5, try to think of your 5 worst injuries).

Injury #1: Approximate Age: _____
How Did it Happen (circle event): Sports, Fall, Struck in Head by Object, Fight, Motor vehicle Accident, Bicycle Accident, Other: ______________________

Injury #2: Approximate Age: _____
How Did it Happen (circle event): Sports, Fall, Struck in Head by Object, Fight, Motor vehicle Accident, Bicycle Accident, Other: ______________________

Injury #3: Approximate Age: _____
How Did it Happen (circle event): Sports, Fall, Struck in Head by Object, Fight, Motor vehicle Accident, Bicycle Accident, Other: ______________________

Injury #4: Approximate Age: _____
How Did it Happen (circle event): Sports, Fall, Struck in Head by Object, Fight, Motor vehicle Accident, Bicycle Accident, Other: ______________________

Injury #5: Approximate Age: _____
How Did it Happen (circle event): Sports, Fall, Struck in Head by Object, Fight, Motor vehicle Accident, Bicycle Accident, Other: ______________________

	Circle your answer for each question as it relates to the concussions you listed above									
	Injury #1		Injury #2		Injury #3		Injury #4		Injury #5	
Did someone see you lose consciousness?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Were you dazed and confused?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Did you have no memory for events immediately after the injury?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Did you go to the hospital?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Were you medically diagnosed with a concussion or brain injury?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Did you miss any school or work because of this injury?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Did you have symptoms for more than 24 hours?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Did you have symptoms for more than one week?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Did you have symptoms for more than one month?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes

Please turn over to next page.

Over the ***last 2 weeks***, how often have you been bothered by any of the following problems?

PHQ-9[1]	Not at all	Several Days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things such as reading a newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or hurting yourself in some way	0	1	2	3

If you checked off any problem on this questionnaire so far, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Please turn over to next page.

[1] PHQ-9 is adapted from PRIME MD TODAY, developed by Dr. Robert L. Spitzer, Janet B. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer inc.

Over the **last 2 weeks**, how often have you been bothered by the following problems?

	Not at all	**Several days**	**More than half the days**	**Nearly every day**
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

If you circled any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
☐	☐	☐	☐

Please return this packet to the research assistant!