BEHAVIOURAL EFFECTS OF CONCUSSION HISTORY AND THEIR UNDERLYING NEURAL MECHANISMS IN ELITE AND NON-ELITE ATHLETES

Johanna M. Hurtubise

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York University

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Abstract

Purpose: Rule-based visually guided movements, in which cognitive-motor integration is required, are essential for tasks in our daily lives and in sport performance. The frontoparietal-cerebellar network is essential for adequate performance on these visuomotor tasks. The purpose of these dissertation projects was to investigate the limits of our motor system, in both those with healthy brain states and those with a previous concussion, including those with persistent symptoms or post-concussion syndrome. Furthermore, we sought to better understand the effects of concussion and its association with motor performance by examining structural differences in the brain between those with post-concussion syndrome and healthy individuals. **Methods:** We tested elite athletes with a history of concussion, females with post-concussion syndrome, and healthy control participants on a visually-guided reaching task requiring cognitive-motor integration. Additionally, we examined structural correlates, including white matter integrity, cortical thickness and volume, and cerebellar lobule volume, in those with persistent symptoms compared to healthy controls. **Results:** Overall, the results of the included studies added to the body of literature in understanding visually-guided reaching and the underlying neural correlates for skilled performance. When looking at the effects of concussion, the cerebellum appears vulnerable, which may be due to its anatomical location and reciprocal relationship with the cortex. Finally, the results suggest that there may be neurological compensatory mechanisms following concussive injury, with elite athletes able to better compensate due to their existing neural efficiency. **Conclusion:** The results of these studies add to our understanding of the effects of concussion on the motor system, specifically in rule-based visually-guided reaching. These findings may help to improve current rehabilitation and return to play procedures following concussive injury.

Dedicated to my athletes – who were the reason I went looking for answers

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Glossary of Abbreviations

Abbreviation	Non-Abbreviated Term
AD	axial diffusivity
AE	absolute error; accuracy
AIP	anterior intraparietal area
ANOVA	analysis of variance
BET	brain extraction tool
BPL	ballistic path length
BrDI™	brain dysfunction indicator
CC	corpus callosum
CDC	centers for disease control and prevention
CE	constant error; accuracy
CH	concussion history
CISG	concussion in sport group
CMA	cingulate motor area
cMFG	caudal middle frontal gyrus
CMI	cognitive-motor integration
CR	cue reversal
CST	corticospinal tract
CTE	chronic traumatic encephalopathy
DAI	diffused axonal injury
DLPFC	dorsolateral prefrontal cortex
DR	direction reversal error
DTI	diffusion tensor imaging
EEG	electroencephalography
FA	fractional anisotropy
FAST	FMRIB's automated segmentation tool
FDT	FMRIB's diffusion toolbox
FLIRT	FMRIB's linear image registration tool
fMRI	functional magnetic resonance imaging
FMRIB	functional magnetic resonance imaging of the brain
FNIRT	FMRIB's non-linear image registration tool
FOV	field of view
FPL	full path length
FSL	FMRIB software library
FWHM	full-width/half-max smoothing
GRAPPA	generalized autocalibrating partial parallel acquisition
ICP	inferior cerebellar peduncle
IFOF	inferior fronto-occipital fasciculus
ILF	inferior longitudinal fasciculus
IPL	inferior parietal lobe
IPS	intraparietal sulcus
LIP	lateral intraparietal area
M1	primary motor cortex; precentral region
MCI	mild cognitive impairment
MCP	middle cerebellar peduncle
MD	mean diffusivity

MDP	medial dorsal parietal area
MIP	medial intraparietal area
MP-RAGE	magnetization prepared rapid acquisition gradient echo
MRI	magnetic resonance imaging
MT	ballistic movement time
mTBI	mild traumatic brain injury
NC	no concussion history
NFL	national football league
NHL	national hockey league
PC	plane change
PCS	post-concussion syndrome
PC+CR	plane change with cue reversal
PFC	prefrontal cortex
PMC	premotor cortex
PMd	dorsal premotor cortex
PMv	ventral premotor cortex
PO	parieto-occipital extrastriate cortex
PPC	posterior parietal cortex
PV	peak velocity
RD	radial diffusivity
rMFG	rostral middle frontal gyrus
ROI	region of interest
RT	reaction time
S1	primary somatosensory cortex
SAC	sideline assessment of concussion
SCAT3	sport concussion assessment tool, 3rd edition
SCP	superior cerebellar peduncle
SMA	supplementary motor area
SLF	superior longitudinal fasciculus
SPL	superior parietal lobe
SPM	statistic parametric mapping software
SPSS	statistical package for the social sciences
SS-EPI	single shot echo planar imaging
SUIT	spatially unbiased template
TBI	traumatic brain injury
TBSS	tract-based spatial statistics
TE	echo time
TFCE	threshold-free cluster enhancement
TMT	full movement time
TIV	total intracranial volume
TR	repetition time
V1	primary visual cortex
VE	variable error; precision
VLPFC	ventrolateral prefrontal cortex
%Equal	percent of trials with one smooth movement
%SubMvt	percent of trials with sub-movements
#SubMvt	average number of sub-movements per trial

Chapter One

General Introduction

[1.1] Introduction

Cognitive-motor integration (CMI), which involves thinking and moving at the same time, is essential for daily tasks such as using a computer mouse to move the cursor on the vertical screen[1,2]. Yet, there is still a lack of understanding of the behavioural consequences in CMI tasks when there are deficits in brain function. While concussion, a form of mild traumatic brain injury (mTBI), involves injury to the neural network required for CMI[3], current assessment methods for concussion measure cognitive and motor ability sequentially and not concurrently[4]. Furthermore, the effect of persistent symptoms, or post-concussion syndrome (PCS), on both CMI and the underlying neural network has not been investigated. The objective of the following research projects is to examine the effects of concussion history on CMI by measuring visuomotor tasks in elite level athletes as well as those suffering from PCS. Additionally, the underlying neural networks affected in those with PCS, and their associations to CMI performance are explored.

This chapter begins with an introduction to CMI and visuomotor tasks, with an examination into the neural network required for their accurate execution. It follows with an overview of research looking at the behavioural performance of visuomotor tasks in both healthy and unhealthy brain states. Concussions, including the current protocols and the microstructural consequences, are then discussed. Finally, it concludes with a summary of the research projects included in the following chapters.

[1.2] Cognitive-Motor Integration and Visually Guided Reaching

In everyday reaching tasks we often look towards the target we are reaching for and directly interacting with. This type of visuomotor transformation is considered "standard"

mapping in which the visual stimulus guiding the action is also the target[1,2]. An example of this would be reaching out to grab a cup of coffee or to shake someone's hand. It is known that there is a close relationship between the eye and the hand within the brain allowing for quick and accurate movements, this is referred to as the default reaching network[1,5]. However, reaching movements in which the eye and hand are incongruent are also common in our daily lives. These decoupled movements involve a "non-standard" visuomotor transformation which requires integration of spatial and cognitive rules and therefore must be learned or calibrated[1,2]. These decoupled eye-hand coordination tasks require CMI, where rules dictate the relationship between perception and action[2,6]. Non-standard movements can be decoupled in two ways; there is an arbitrary relationship between the stimulus and the action - such as stepping on the brake pedal when you see a red light, or there is a transformational disassociation between gaze, spatial attention, or limb movements and the target – such as when surgeries are performed laparoscopically[1,2]. These disassociated tasks can be further divided based on the CMI rules they employ; either spatial recalibration or strategic control. Spatial recalibration requires the adaptation of the brain to changes in spatial orientation so that the motor output is not aligned to the sensory input[7–9]. An example would be moving your hand in the horizontal plane, while looking up in the vertical plane, such as with a computer. This adaptation is slower and without conscious awareness and is therefore implicit in nature[7–10]. Recalibration is thought to occur due to this implicitly-based feedback; the inaccuracies in the movement are related to an internal error, such as limb error, where there is a mismatch between the proprioceptive and visual input[10]. On the other hand, strategic control requires a task-dependent rule to be integrated in order to align the motor response with the target or goal[7–10]. An example would be to move the hand in the opposite direction of the visual target. Strategies used may include anticipation or

prediction of results, online-feedback corrections, or performance errors in order to ensure rapid adaptation[7,8]. Consequently, strategic control is explicit in nature as it uses external feedback in order to overcome errors in movement[10]. While a default reach network within the brain exists in order to ensure rapid and accurate standard movements, it is important to understand how this network is altered to allow for the disassociated tasks used in our daily lives.

[1.3] Frontal-Parietal Networks for Sensorimotor Transformation

In order for visually-guided reaching to occur, a visual stimulus input must become a motor output, and thus a sensory to motor - or in this case a visual to motor - transformation must occur. This is thought to involve a transformation between coordinate or reference frames, where an extrinsic frame must be translated to an intrinsic frame[11–13]. Extrinsic frames of references refer to those in external space, whereas intrinsic frames relate to the body, muscle, and joint activations[11,12]. This extrinsic and intrinsic information needs to be combined to create a motor plan of action in order for goal directed reaching movements to occur[12,14]. This is possible due to reciprocal connections within a network that is organized both hierarchically and in parallel in order to generate coordinated movement[12,15]. It has been well established that the frontoparietal network is essential for the visuomotor integration required for reaching[2,14–16]. In a simplified hierarchical approach, the visual information enters through the primary visual cortex (V1) of the occipital lobe and is further processed through the extrastriate cortex. For reaching movements, this requires visual information to pass through the parieto-occipital extrastriate cortex (PO) to the posterior parietal cortex (PPC). This area includes the superior parietal lobule (SPL), the medial dorsal parietal area (MDP), and areas of the intraparietal sulcus (IPS), including anterior, medial, lateral and ventral intraparietal areas (AIP, MIP, LIP, VIP respectively)[13,16]. These areas

are essential for the linking of sensation to action and receive information from both sensory (visual) areas and motor areas in order to create a spatial representation of both limb and stimulus[11,13,16,17]. Information from the PPC must travel to the premotor cortex (PMC), including the medial supplementary motor area (SMA) and cingulate motor area (CMA), and the lateral dorsal (PMd) and ventral (PMv) premotor areas[1,12,15]. These areas are where motor plans are created and sent to the primary motor cortex (M1) for execution[2,11,13,16]. The activity within this frontoparietal network gradually transforms extrinsic visuospatial information into motor commands for reaching. However, visuomotor transformation is much more complex than described as it depends upon local interaction and long-range corticocortical projections that act serially and in parallel, and are often reciprocal in nature[12,13,16]. For example, the PMd, which is essential for arbitrary mapping and incongruent visuomotor transformations[1], not only receives information from the PPC but also receives input from the inferior parietal lobe (IPL) both directly and indirectly through the dorsolateral prefrontal cortex (DLPFC), an area important for decision making[16,18] (see Figure 1.1 and 1.2).

The underlying white matter tracts connecting these areas include the corticospinal tract (CST), the superior longitudinal fasciculus (SLF), the inferior fronto-occipital fasciculus (IFOF), and the corpus callosum (CC)[19–21]. The CST, the largest descending fiber tract from the brain, originates primarily from M1 and the PMC of the frontal lobe with some fibers from the primary sensory area and the parietal cortex[15,21]. These fibers descend through the internal capsule and enter the midbrain via the cerebral peduncle. They then course through the pons and medulla before terminating in the spinal cord grey matter[21]. This tract is essential because it is responsible for movement of the distal extremities and, in particular, for reaching movements of the hand[20] (see Figure 1.3a). Both the SLF and the IFOF are long association fibers connecting cortical

brain areas within the same hemisphere. The SLF connects the temporal, frontal, and parietal regions with its superficial anterior segment running from PMv and M1 to the IPL and is speculated to have a relationship with the verbal working memory network[19]. The IFOF runs from the prefrontal region and merges with the SLF to terminate on parietal (SPL), temporal, and occipital lobes. While its function is still poorly understood, it is thought to be involved in attention and visual processing[19] (see Figure 1.3b). The CC is a large commissural white matter tract connecting the two hemispheres[15] (see Figure 1.1).

A non-standard task, in which a decoupling of vision and action is required, also relies on this frontoparietal network for the transformation from an extrinsic to an intrinsic frame of reference. However, changes in the pattern of brain activity, specifically within the PMd, SPL, IPL (which plays an important role in spatial attention), DLPFC, and the cerebellum have been noted[2,6,9,22–25]. It has been suggested that inhibition of the default reaching network (for direct object interaction) is required when performing non-standard tasks[22,23]. In addition, brain regions which are able to discriminate between the standard and non-standard tasks include the precuneus and cuneus (located within the posterior parietal cortex and neighbouring occipital lobe), and areas of the prefrontal cortex. The former regions are essential for selecting an appropriate response for the given stimulus, while the prefrontal cortex is essential for context-related rules[9,23,26–28] (Figure 1.2).

[1.4] The Cerebellum

Subcortical brain structures, including basal ganglia-cortical loops and cerebellar-cortical loops, also play an important role in both standard and non-standard reaching tasks[2,5,9,29,30]. While often excluded in discussion of visuomotor transformations, their role is nonetheless

important. When considering subcortical structures in visually-guided reaching, Glickenstein (2000)[31] argues that the most crucial structure is the cerebellum due to the large amount of information which must pass through it, with one of the major circuits of the brain running from the cerebral cortex to the cerebellum[2,31]. The cerebellum is responsible for motor coordination (comparing the predicted and actual motor commands for corrected movement), and is also involved in motor learning, and spatial attention[15,28,29]. In addition, the cerebellum plays a role in both cognition and emotion processing[32,33].

The cerebellum is a phylogenetically ancient subcortical structure located in the posterior cranial fossa and is composed of grey matter (the cerebellar cortex), white matter (the arbor vitae) and three pairs of deep nuclei[15,34]. Anatomically, the cerebellum is divided by two major transverse fissures: the primary fissure divides the cerebellum into anterior and posterior lobes, while the posterolateral fissure divides the posterior lobe from the flocculonodular lobe. These lobes can be further subdivided into 10 lobules, with lobules I-V composing the anterior lobe, VI-IX the posterior lobe, and lobule X the flocculonodular lobe[33,34] (see Figure 1.4a,b). The cerebellum is also divided by two longitudinal furrows, creating a central midline (vermis) and two cerebellar hemispheres. By subdividing these hemispheres into intermediate and lateral regions we can functionally divide the cerebellum into 3 regions[15,34]. The vestibulocerebellum (flocculonodular lobe) is responsible for balance, vestibular reflexes, and oculomotor movements, receiving inputs directly from vestibular afferents and projecting to the nearby vestibular nuclei. The spinocerebellum region, including the vermis and intermediate hemisphere of the cerebellar cortex, receives somatosensory information from the proximal and distal limbs respectively. Fibers from these areas project to both the fastigial and interposed deep cerebellar nuclei to influence the medial and lateral descending pathways, including the CST, via M1.

Lesions to these deep nuclei result in disrupted accuracy, hand path, and timing errors in reaching movements[15,34]. Finally, the cerebrocerebellum region is important for motor learning (including the planning and programming of hand movements) and receives afferent information from the association areas of the cerebral cortex. These projections synapse at the dentate nucleus, with efferent information terminating at both M1 and PMC via the ventrolateral thalamus. Lesions to this deep cerebellar nucleus lead to delays in initiating movement and irregularities in movement timing[15,34].

The cerebellum receives information from the limbs both directly and indirectly. The spinocerebellar tracts carry kinesthetic information directly from the limbs and terminate primarily in the anterior lobe (lobules I-V) and lobule VIII, while afferents from the spinal cord also reach the cerebellum indirectly through the inferior olivary complex of the medulla[32,33]. The cerebellum also projects and receives information to and from the cortex. This feed-forward/ feedback system is known as the cerebro-cerebellar loop. The afferent cortico-ponto-cerebellar projections enter the contralateral cerebellar cortex indirectly via the pons, with motor-related cortices preferentially running through the caudal pons to the anterior lobe of the cerebellum, and the cortical association areas terminating in the posterior cerebellar lobe. Efferent fibers of the cerebellum project back to the cortex via the cerebello-thalamic-cortical projections. Output from the deep cerebellar nuclei synapses with either the motor or non-motor thalamic nuclei before running to the motor and association areas of the cortex[32,33].

The afferent and efferent projections of the cerebellum course through the three major white matter pathways, connecting the cerebellum to the dorsal brainstem[34,35]. Input fibers from the cerebral cortex course through the pons and the middle cerebellar peduncle (MCP) to reach the deep cerebellar nuclei. The primary efferent pathway is the superior cerebellar peduncle

(SCP), running from the deep cerebellar nuclei through the pons and thalamus to the cerebral cortex, including prefrontal, premotor, motor, and parietal areas[15,35]. Finally, the inferior cerebellar peduncle (ICP) has both afferent fibers from the spinal cord, as well as efferent fibers from the flocculonodular lobe to the vestibular nuclei[35] (see Figure 1.4c).

Both functionally and anatomically, there is evidence that suggests the cerebellum plays a key role in reaching movements. In particular, cerebellum function is important for coordination, especially during the later stages of movement, when sensory feedback allows for a corrective movement[14,15,31,36]. The cerebellum also plays a critical role in forward models (in predicting motor output), and is essential for motor adaptation, motor learning, and proprioceptive sense during active movement[37–40]. Consequently, it is not surprising that increased cerebellar activity has been noted in non-standard compared to standard visuomotor tasks due to the need for strategic control and sensorimotor recalibration[2,28–30,41].

[1.5] CMI in Healthy Brain States

It is evident that both standard and non-standard reaching movements require a complex collaboration of multiple brain regions. In addition, there are differences in activation within this frontoparietal-cerebellar network during non-standard tasks compared to the default visually-guided reaching movements. It may be unsurprising then that behaviour, or motor performance, differs between the two conditions[1,2,5]. Specifically, when vision and action are dissociated, movements are less accurate and require more time due to the additional planning and incorporation of required cognitive rules. These performance decrements have been attributed to the recalibration and strategic control requirements for these tasks[1,2]. In standard visually-guided movements, the eyes typically move prior to the onset of hand movement, resulting in gaze

stabilization at the target during the subsequent arm movement. In addition, hand-path

trajectories are straight, with bell-shaped and unimodal velocity profiles[2,42]. In comparison, in

non-standard tasks, in which vision and action are spatially incongruent, the reaction time for the

initiation of eye movement is significantly slower. This delay in movement onset reflects the

need for additional planning in non-standard tasks[2,5]. In addition, Gorbet & Sergio (2009)[5] found

that hand-paths demonstrated a 1.5-2 times greater curvature in a dissociated task compared to a

standard task. These kinematic differences are thought to reflect the additional 'noise' in the

system due to the alterations in the frontoparietal network required for adequate performance[5].

[1.5.1] How does Expertise Influence this?

While the above findings on performance of CMI tasks reflect the general population, we

know that the underlying neural mechanisms and performance outcomes may be modified by the

level of motor skill expertise. Expert musicians and athletes demonstrate 'neural efficiency'

during task planning and performance[43,44]. Both EEG and fMRI (electroencephalography and

functional magnetic resonance imaging) studies have demonstrated that novice performers have

more overall brain activity, while skilled performers have both fewer activated brain regions as

well as less activity within these regions. This reduced activity suggests that extensive practice of

motor skills leads to efficient organization of the underlying neural network[43,44]. Previous

research in our laboratory investigated expert video-gamers in the performance of CMI tasks.

They found that while performance on the task was similar between groups, the video-gamers

had decreased activity along the frontoparietal network and cerebellum, with a concomitant

increase in prefrontal regions compared to novice gamers[45,46].

[1.6] CMI in Unhealthy Brain States

While performance on CMI tasks is well understood in healthy individuals, behaviour on

these tasks is less known in those with altered brain function. Understanding the effects of brain

dysfunction of skilled performance is important because many neurological disorders impact

large-scale brain networks and connections, thus leading to impaired daily function. Therefore,

we need to better understand how altered brain function affects our ability to perform these

complex cognitive-motor integration tasks in order to better understand the etiology, progression,

prevention, and rehabilitation for affected individuals. Previous work in Dr. Sergio's laboratory

has looked at how CMI performance in non-standard tasks is affected in those with mild

cognitive impairment (MCI)[47] and Alzheimer's disease[48–51]. In particular, they observed that

both MCI and Alzheimer's patients performed the same as healthy aged-matched and young

controls in the standard conditions, where vision and action are congruent; however, the patient

population had difficulty in decoupled tasks in which CMI was required[47,49,50]. Compared to

controls, Alzheimer's patients had difficulty in non-standard conditions requiring either spatial

recalibration or strategic control, with some unable to complete the task when both were

combined[49–51]. Specifically, they had impaired timing, consistency, and accuracy, reflecting an

insufficient ability in planning motor movements as well as in sustaining an effective motor plan

after initiation[49,50]. 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[47]. Furthermore, Hawkins et al. (2015)[51] observed that the

impaired motor planning and execution is associated with decreased white matter integrity within

the frontoparietal network in asymptomatic women at an increased risk for Alzheimer's disease.

These results support the notion that degenerative disease may affect the functional network

required for CMI tasks. More recently Dr. Sergio's research has also investigated the effects of concussion history on visuomotor transformation task performance in both university aged[52] and young[53] athletes. Both studies found that those with a history of concussion had impaired movement planning and execution relative to healthy age-matched controls when there were two levels of disassociation; that of combined spatial recalibration and strategic control. Specifically, Dalecki et al. (2016)[53] found deficits in ballistic movement time, ballistic path length, and full path length in the non-standard task in children, while Brown et al. (2015)[52] found deficits in only two kinematic variables in university aged athletes, that of movement time and precision. Moreover, both studies were able to discriminate between those with a history of concussion and healthy controls with 70-94% accuracy[52,53].

[1.7] Concussion and Post-Concussion Syndrome

Concussions, a form of mild traumatic brain injury (mTBI), affect an estimated 1.6-3.8 million Americans[54] and 653/100,000 Ontario residents[55] each year. However, these numbers under-represent the true proportion of injury due to the number of unreported concussions[54,56]. A recent poll suggests that one in five Canadians will sustain a sport-related concussion in their lifetime[57]. Moreover, the Centers for Disease Control and Prevention (CDC)[54] recognizes mTBI as a 'silent epidemic'[58], stating that concussions may affect a person's ability to return to their daily life and may result in long-term consequences. While the terms mTBI and concussion are often used interchangeably in the literature, it is important to note that brain injury severity is measured on a continuum, with severe injury on one end of the spectrum, and mild injury on the other. It has been suggested that concussions are considered a subset of mTBIs and are milder than mTBIs on this continuum[56].

A sport-related concussion has been defined by the Concussion in Sport Group (CISG) as a "traumatic brain injury induced by biomechanical forces"[4]. Concussions occur when linear and/or rotational forces are transmitted to the brain[56] through either direct or indirect impulsive mechanisms[4]. 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[4]. In the majority (80-90%) of those who sustain a concussion, the symptoms will resolve within 10-14 days; however, in some, the signs and symptoms persist longer and may result in PCS[4,56].

PCS has been defined as symptoms persisting for longer than 1-3 months following a head related trauma[59–62], and affects 10-15% of those who sustain a concussion[4,56]. Persistent symptoms can cause long-term disability, costing approximately $17 billion dollars each year due to direct expenses and lost income[63].

While no abnormality is seen on standard diagnostic imaging techniques[4], it has been suggested that the symptoms associated with concussion are a result of a functional disturbance. Hence such symptoms may reflect cellular or molecular neuropathological and neurophysiological changes including ionic shifts, metabolic changes, and impaired neurotransmission[4,64]. The acceleration and deceleration forces of concussion trauma initiates a 'neurometabolic' cascade, resulting in a state of energy crisis due to the increased need of glucose in order to restore ion homeostasis and a decreased supply of glucose through decreased cerebral blood flow[64–66]. While it is unknown how long this state of impaired metabolism lasts in humans, it is speculated that it is during this time that the brain is most vulnerable to the effects of another concussion. It has been found that a second injury during this time leads to prolonged symptoms and a longer recovery to normal metabolic levels[67]. Concurrently with the ionic shifts

and metabolic changes, there may also be an alteration in neurotransmission. Specifically, axonal injury occurs due to the mechanical shearing and tensile strain from the inertial forces associated with brain injury, including acceleration, deceleration, and rotational forces[68–72]. This leads to altered axonal membrane permeability and ionic disruption, as well as cytoskeletal breakdown[64,66,70]. This axonal dysfunction can lead to impaired functioning due to slowed conduction, damage to cerebral networks, or deficits in neurotransmission[64], and it is believed that this may be an underlying cause of the persistent symptoms associated with PCS. However, the ability of axons to recover or the time frame to do so is not well understood.

The etiology of post-concussion syndrome and persistent symptoms following concussion is poorly understood. In fact, even the existence of PCS is controversial[73–77] as some professionals believe that the symptoms are only associated with psychological factors, while others consider underlying neuropathological factors to be the cause. The etiology and neurophysiology underlying PCS has not yet been established, but may involve prolonged changes in metabolic functioning, cerebral blood perfusion, or axon and neurotransmitter functioning[64,66,69,78,79]. Recent evidence has emerged that suggests axonal injury may play a key role in the neuropathology underlying PCS[64–66,68,71,80,81]. This diffused axonal injury (DAI), due to the mechanical shearing as described above, is a gradual event with delayed axonal disruption[70], leading to impaired neurotransmission and a decreased speed of processing[64,69]. Conversely, similar symptoms have been reported in those suffering from insidious neck pain or whiplash disorders[79,82–84], chronic pain[85], depression[86], and even in healthy individuals[87]; therefore non-neurological causes of symptoms must also be considered. Currently, the accepted theory is that PCS is due to both psychological and biological aspects[74,88,89], which may be influenced by either pre- or post- injury factors such as a previous brain injury, being female, or

a psychiatric illness[60,74,76,77]. While our understanding of PCS is continually growing, it remains that a large percentage of the population is currently suffering from persistent concussion symptoms, hindering activities of daily living and adding strain to our healthcare system[69,77].

[1.8] Neuroimaging: A Brief Overview of Magnetic Resonance Imaging

Imaging techniques, including that of Magnetic Resonance Imaging (MRI), allow us to better understand the brain's structure and function. By looking at the brain in-vivo, we may be better able to understand the etiology and progression of disease and therefore advance prevention and rehabilitation techniques in order to improve the quality of life for those individuals. Recently, there has been an increase in the number of studies using imaging techniques to better understand the brain's response to concussion.

[1.8.1] T1-Weighted Structural Imaging

MR-imaging is based on the electromagnetic field of protons in the body, specifically the hydrogen atom since it is the most abundant atom in the body. In very simplistic terms, when a person is placed in an MRI magnet, hydrogen protons will 'line up' along the machine's magnetic direction (M_z) and will all begin to spin (precess) at the same frequency (Larmour Frequency). A radiofrequency pulse is applied which causes the net magnetization of these protons to flip from the longitudinal direction (M_z) to a perpendicular direction (M_{xy}). Once this radiofrequency pulse is removed, the protons will begin to return to their initial position along the longitudinal direction (M_z). Tissues in the body have different water contents (and thus hydrogen content); therefore the speed at which these protons return to their initial state will also differ. Using a receiver coil we can measure the electrical signal of these differences in the

relaxation of hydrogen protons between tissues, thus creating a contrast in signal intensity between grey matter, white matter, and cerebrospinal fluid. A structural MRI scan is often used with patients who received a head injury since it can determine if there is trauma to the brain, such as bleeding. In concussions or mTBIs, there are no visible structural changes using current imaging protocols. Yet, standard imaging protocols, such as those used in hospitals post-injury, do not examine the brain in detail because they are looking only for gross neuropathological changes.

Due to the advances of imaging techniques, recent studies looking at concussion have demonstrated that structural changes may occur, which may help to explain the long-term consequences of concussion including chronic traumatic encephalopathy (CTE) and PCS. Cerebral atrophy is known to occur after TBI and the predominate opinion is that this is due to direct injury to the neuron body and subsequent apoptosis[90,91]. There is now evidence, however, that this atrophy occurs not only with focal injury but also diffuse axonal injury[91]. Therefore it is possible that structural changes may also occur in more mild brain injuries since axonal injury is the suggested underlying etiology.

The majority of studies investigating structural changes in the acute and subacute stages after concussion (days to months post injury) have noted atrophy in cortical regions, including cortical thinning of the frontal and parietal lobes[92–96].

When looking specifically at the cerebellum, studies looking at moderate to severe brain injury have found cerebellar atrophy, even when it is not the location of focal injury[97]. Animal models looking at mild brain injury have also noted this decrease in cerebellar volume[98,99], most significantly within the ventral regions (lobules 7-10)[98]. Yet, the effect of concussion on

cerebellar volume in humans is poorly investigated. To our knowledge, only one study looked specifically at volume changes in those with persistent concussive symptoms. Ross et al. (2012)[90] found that when compared to controls, those with persistent symptoms had greater atrophy over the course of a year in both total brain (parenchyma) volume and cerebellum volume. In addition, these volume changes correlated with poorer vocational outcomes in those with persistent symptoms. This study, however, did not look at the cerebellum lobules and therefore lacks a more thorough understanding of the effect of concussion on this structure.

Overall, it seems that even mild brain injuries may lead to structural changes to the brain, specifically changes in both volume and cortical thickness, and that these structural changes are related to behavioural outcomes. Furthermore, the literature on moderate and severe brain injuries and animal models of mTBI suggest that the cerebellum may also have structural changes; however the effects of persistent symptoms on this structure have not been thoroughly investigated.

[1.8.2] Diffusion Tensor Imaging

Diffusion Tensor Imaging (DTI), an MRI technique, measures the anatomical structure of white mater by measuring the diffusion of water (hydrogen) along these nerve tracts[100,101]. Particles will always flow from regions of high concentration to low concentration (Fick's Law), but is dependent on the microstructural features of the environment, such as the axon membrane found in white matter[100]. In order to measure the diffusion of hydrogen atoms, the diffusion-weighted MR sequence uses an additional magnetic pulse (bipolar gradient) which is applied after the initial excitation radiofrequency pulse. As a reminder, the radiofrequency pulse causes the protons, which are spinning in phase with one another, to flip to the perpendicular plane. In

diffusion imaging, a positive gradient is then applied which causes the protons to spin out of phase with one another. A second negative gradient is applied in order to reverse this, causing the protons to spin together once again. However, as a result of Brownian motion (random motion of particles) some of these spins will remain out of phase with each other. Tissues which allow for greater diffusion have greater spin incoherence of the protons[100]. Thus, this imaging technique does not measure diffusion directly, but infers diffusion through the observation of water displacement over time. The measurement of diffusion, over time and from different directions, makes it possible to construct a tensor or ellipsoid in order to describe this diffusion. Both the volume and shape of the ellipsoid gives us information about water diffusion and thus, about the microstructure of brain tissue[100]. In white matter, water diffuses predominately in one direction, along the long axis of an axon, therefore any changes in this diffusion value indicates a change in white matter integrity[68,100,102]. Using this constructed tensor, a number of DTI metrics can be determined in order to examine changes in white matter microstructure. Fractional Anisotropy (FA) represents the shape of the measured ellipsoid, and is the most commonly reported measurement of diffusion. Specifically, it represents the fraction of the tensor that can be assigned to anisotropic diffusion, ranging from 0 to 1, with 0 being completely isotropic with water diffusing equally in all directions, and 1 depicting complete anisotropic diffusion along a single axis[100–102]. Reduced FA is thought to reflect a loss of white matter integrity due to either axonal membrane or myelin damage[102]. Mean Diffusivity (MD) is a measure of the ellipsoid size, and is calculated as the total mean diffusion along all directions[100–102]. A decreased FA with an increased MD suggests macro-structural tissue loss; whereas a decreased FA without an increased MD indicates microstructural changes without gross tissue loss[51,100]. Both Axial Diffusivity (AD) and Radial Diffusivity (RD) provide information on possible causes behind

these tissue changes. AD, the measure of diffusion along the primary axis, and RD, the measure

of perpendicular diffusion, provide information on axonal and myelin pathology respectively. A

reduction in FA due to the decrease in AD may reflect axon degeneration, while a reduced FA

due to an increase in RD may signify myelin damage[51,100–102].

While DTI is a relatively new imaging technique (and so is not considered a standard or

clinical imaging technique), there have been a large number of studies using it to investigate the

effects of brain injury, including concussion. This is not surprising due to the underlying etiology

of concussion and the hypothesized axonal injury that occurs.

Imaging studies investigating acute and sub-acute concussion have typically

demonstrated increased FA values[103–105]; however, these results remain controversial[106–112].

Those with prolonged recovery and persistent symptoms also demonstrate changes in white

matter integrity; however, unlike during the acute stage, studies have often found decreased FA

during this period. This was noted with a subsequent increase in MD and RD, but no change in

AD[113–116]. Chong and Schwedt (2018)[117] suggest that while FA initially increases due to neuronal

swelling, this will typically recover during the sub-acute stage. Conversely, in those who have

persistent symptoms, this initial increase in FA not only lasts longer, but will then decrease

below normal, indicating remodeling of these tracts. In both acute concussion and those with

persistent symptoms these white matter changes were noted most often in long coursing and

association fiber tracts including the CC[103,108,114], CST[103,108,112,115], the IFOF[112], and both the SLF

and inferior longitudinal fasciculus (ILF)[108,110,112,115,116].

When looking specifically at the cerebellum, evidence of axonal injury has been found in

animal models after experimental brain injury, with the cerebellum being a highly sensitive

area[81]. However, there has been only one study done in humans, in which increased FA was found within the MCP in acute concussion[118]. To our knowledge, no study has investigated structural changes of the cerebellar peduncles in those with persistent symptoms.

While the literature on the effects of concussion on white matter integrity has been variable, it seems that the white matter tracts most often affected underlie the frontoparietal network – a network essential for CMI performance. Specifically, these white matter tracts include the CC, CST, and the longitudinal fasciculus (SLF, ILF, IFOF). Furthermore, this change in white matter integrity seems to be denoted by a decrease in FA, with a subsequent increase in MD and RD, in those suffering from persistent symptoms and PCS.

[1.9] Overview of Dissertation Projects

In summary, we know that rule-based visually guided movements, in which CMI is required, are essential for both tasks in our daily lives and in sport performance[1,2]. It has been well established that the underlying brain network required for skillful CMI performance is the frontoparietal network[2,14,15]. Furthermore, the cerebellum, a key subcortical structure for motor coordination, is also an important area for non-standard visuomotor tasks due to its reciprocal connections to these frontoparietal brain regions[2,15,28,31]. The following dissertation projects utilize a motor psychophysics framework approach combined with MR-imaging in order to better understand the brain mechanisms in multi-domain processing – that of integrated visual, motor, and cognitive functioning. Specifically, by looking at errors in motor behaviour we can understand the limits of the motor control system and thus how the brain functions in both healthy and unhealthy states. Essentially this hypothesis-driven approach uses performance dysfunction in order to investigate brain function in those with mild brain injury.

Previous research in Dr. Sergio's laboratory has demonstrated that CMI performance is affected by both the level of expertise[45,46] as well as insults to the brain including MCI[47], Alzheimer's disease[48–51], and concussion[52,53]. The first study discussed within this dissertation *'The effect of concussion history on cognitive-motor integration in elite hockey players'* is a continuation of the previous research in our laboratory which looked at the effects of concussion history on CMI performance. Specifically, previous studies examined these effects in children[53] and university level[52] athletes and found deficits in both timing and trajectory kinematics in those who had a previous history of concussion (but were asymptomatic based on standard clinical assessments at the time of testing). Current recommended assessments to determine an athlete's readiness to return to sport test motor and cognitive ability separately[4] – even though sport performance often requires their simultaneous involvement. The previous findings in our laboratory demonstrate that these current single domain assessments may not be sensitive enough to determine readiness to return to a contact sport environment and suggest a multidomain assessment, such as CMI performance, may better capture this. The objective of the current study is to add to this body of literature, which demonstrates that those who have a history of concussion have deficits on a more complex visuomotor task - one involving CMI. Furthermore, this project aims to better understand these effects on an expert athlete population, and thus includes National Hockey League (NHL) draft prospects.

The results from this first study, as well as the previous work from the laboratory, led to both the second and third projects of the dissertation. Both projects investigate how concussion affects brain structure, and therefore function. Previous work by Hawkins et al. (2015)[51] found an association between CMI performance and white matter integrity in those at risk for Alzheimer's and dementia. Similarly, the studies included here aim to explore the relationship

between performance on rule-based visually guided movements and brain structure following concussion. Studies have found that concussive injury leads to decreased volume and cortical thinning within the frontal and parietal lobes[92,95,96]. Similarly, studies investigating the effect of concussion using DTI have noted decreased white matter integrity along the underlying white matter tracts of this network[103,108,115]. Therefore, it seems likely that since this frontoparietal network is often affected by concussion, CMI performance will also be affected. The cerebellum is essential for visuomotor performance, but also has a role in cognition, balance, oculomotor function, and vestibular function – areas in which symptoms are often reported following concussion[15,32,59]. Yet, there is a lack of research investigating the effect of concussive injury on this structure. Furthermore, while PCS is believed to be the result of damaged axons and thus decreased neurotransmission along white matter tracts[64,66,78], the effects of persistent symptoms on brain structure (both volumetric and white matter integrity) have not been thoroughly investigated. Thus, the objective of the second project *'White matter integrity and its relationship to cognitive-motor integration in females with and without post-concussion syndrome'* is to examine the effect of PCS on white matter integrity, specifically along the white matter tracts underlying the frontoparietal-cerebellar network. Additionally, the effect of PCS on performance of CMI tasks and its association to white matter integrity will also be investigated. Whereas the purpose of project 3 *'Cortical and cerebellar structural correlates of cognitive-motor integration performance in females with post-concussion syndrome'* is to investigate the effect of PCS on the gray matter structure of this neural network, including the volume and thickness of cortical regions, and the volume of the cerebellum and its lobules. Furthermore, this study aims to associate these findings with performance on a CMI task.

In the final chapter of this dissertation, the results of each study will be discussed collectively within the framework of motor psychophysics. Overall, by investigating errors in performance of CMI tasks we can better understand the limits of our motor system, in both healthy brain states and in those with a prior concussion. Similarly, by examining differences in brain structure between those with PCS and healthy individuals we may better understand both the effects of concussion but also the association between motor performance and brain function.

[1.10] Summary and Knowledge Dissemination

The work in this dissertation expands on previous studies examining CMI performance deficits in children and university-aged athletes with concussion history, and advances our understanding of the underlying neural mechanisms of these declines. The first study included has been published in the journal '*Concussion*', with pilot findings of project 3 published as an abstract in the '*British Journal of Sports Medicine*'. These findings have also been presented at a variety of conferences including the Society for Neuroscience annual meeting, the 5th International Consensus Conference on Concussion in Sport, the CAPnet Satellite Symposium, the University Health Network Brain Injury Conference, the Canadian Athletic Therapists Association National Conference, the National Athletic Trainer's Association Clinical Symposium, as well as invited talks in the community. The findings of this dissertation are informative for practitioners (through the development of an assessment tool), neuroscientists (through progressing our understanding of the underlying neural correlates of behaviour in healthy and unhealthy brain states), and for both practitioners and researchers (through advancing the knowledge of functional limitations and neural correlates of concussion/PCS in order to improve rehabilitation). The purpose of this research is to understand how the brain's

ability to perform rule-based visually guided reaching tasks, a skill important for both daily life

and sport performance, is disrupted by concussion. Finally, the projects described in this

dissertation also improve our understanding of one of our most basic and imperative behaviours

– interacting with the world around us.
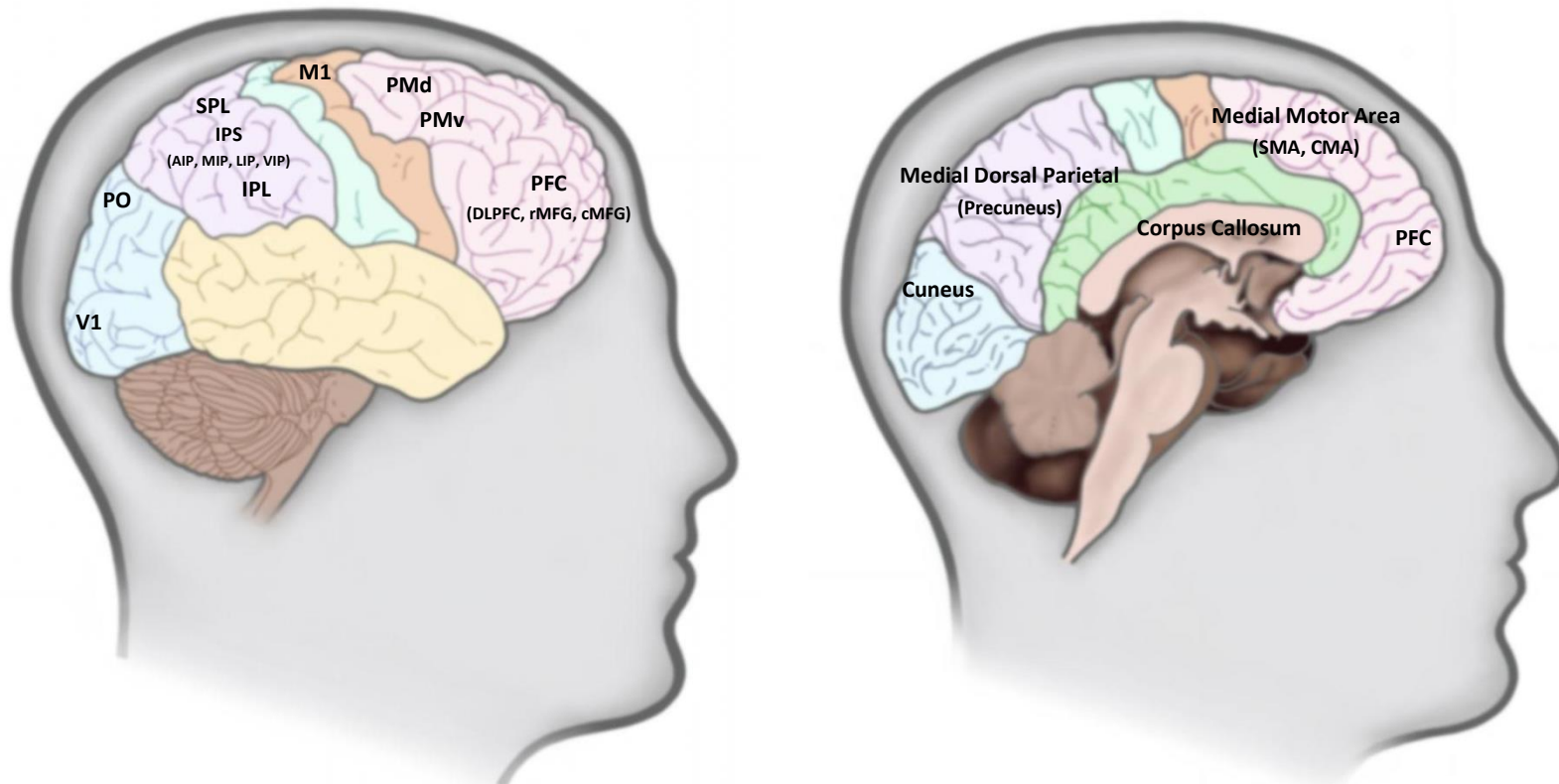
Figure 1.1 A schematic of lateral and medial brain regions

AIP: anterior intraparietal area; CMA: cingulate motor area; cMFG: caudal middle frontal gyrus; DLPFC: dorsolateral prefrontal cortex; IPL: inferior parietal lobe; LIP: lateral intraparietal area; M1: primary motor area, precentral gyrus; MDP: medial dorsal parietal area; MIP: medial intraparietal area; PFC: prefrontal cortex; PMd: dorsal premotor cortex; PMv: ventral premotor cortex; PO: parieto-occipital extrastriate cortex; rMFG: rostral middle frontal gyrus; SPL: superior parietal cortex; V1: primary visual cortex.
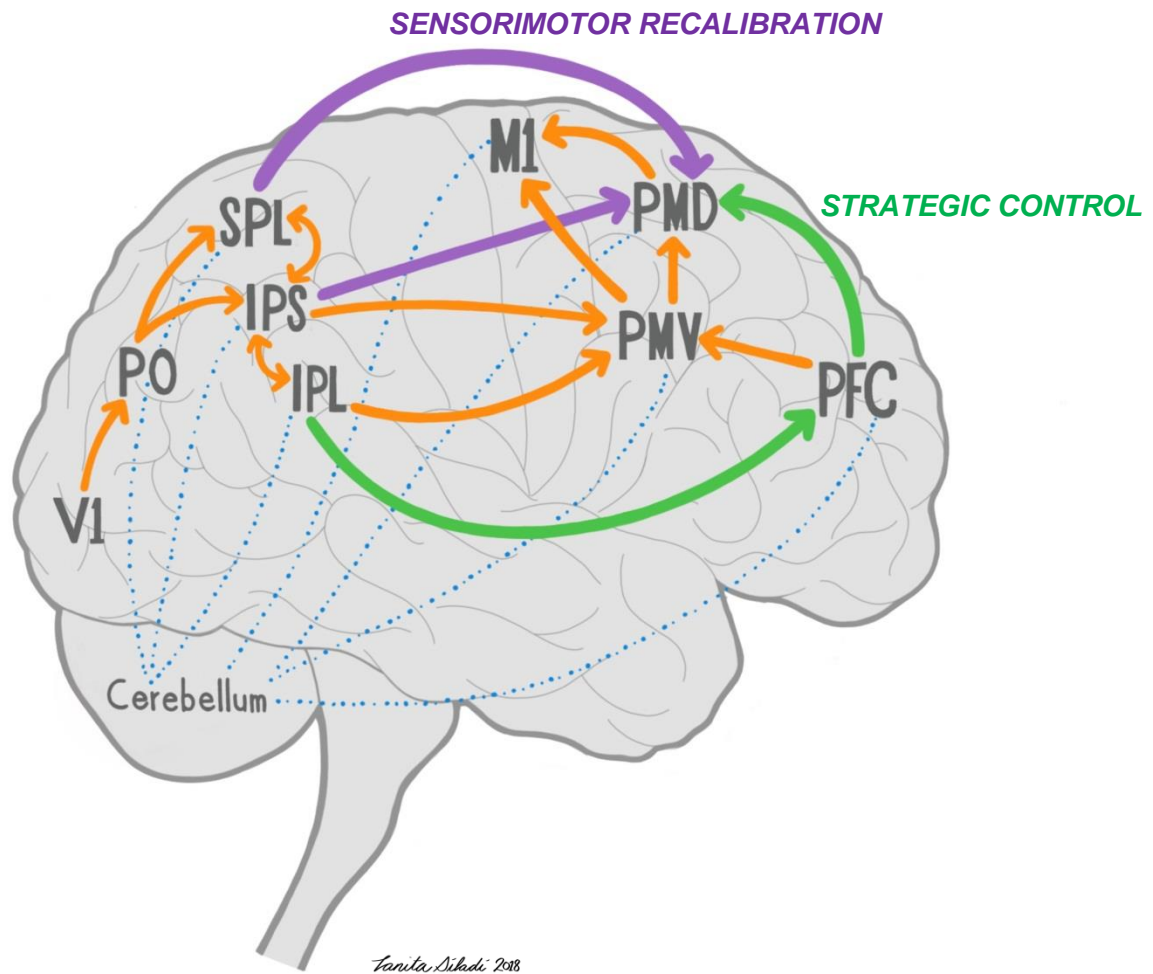
Figure 1.2 Putative cortical and subcortical networks required for cognitive motor integration (CMI)

This includes those regions involved in sensorimotor recalibration (purple), strategic control (green), and between both networks (orange). Dashed blue lines represent subcortical (cerebellar) connections. Note that while the arrows are pointing in one direction, most connections are reciprocal. Figure adapted from Granek & Sergio (2015)[9].

IPL: inferior parietal lobe; IPS: intraparietal sulcus; M1: primary motor cortex; PFC: prefrontal cortex; PMd: dorsal premotor cortex; PMv: ventral premotor cortex; PO: parieto-occipital extrastriate cortex; V1: primary visual cortex.

(A)

Tanita Siladi 2018

(B)

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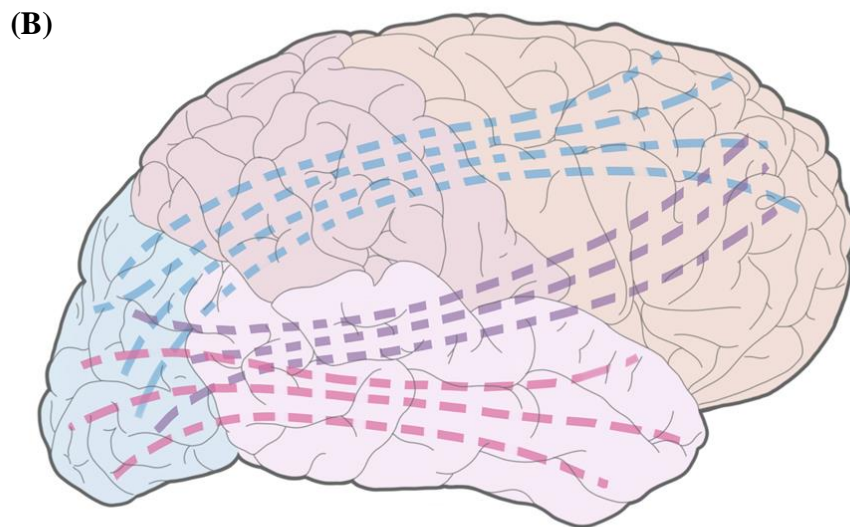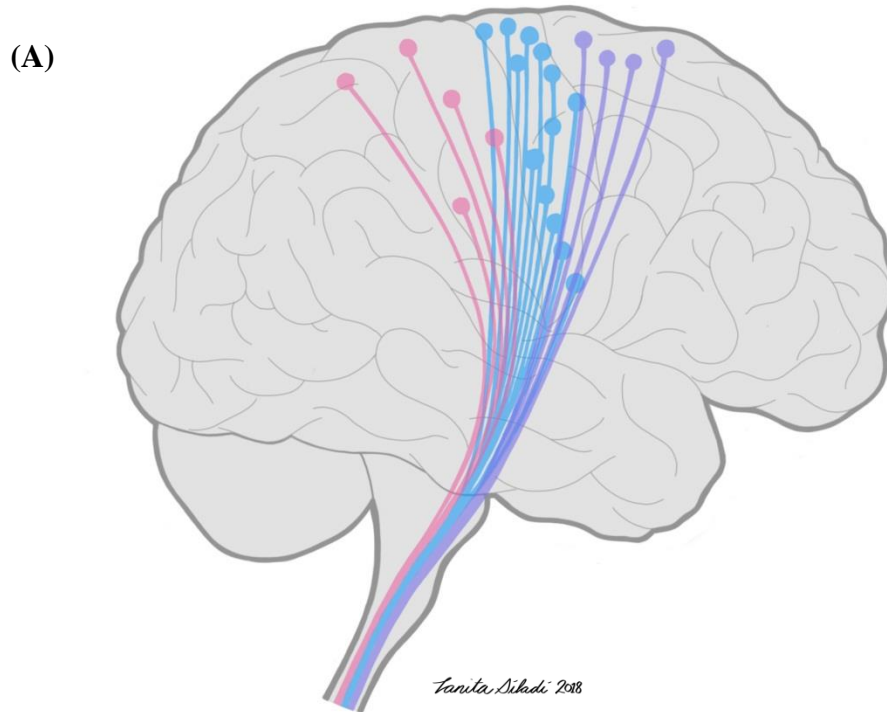
Figure 1.3 Long-coursing white matter tracts

(A) The corticospinal tract; **(B)** The association tracts including the superior longitudinal fasciculus (blue), the inferior longitudinal fasciculus (pink), and the inferior fronto-occipital fasciculus (purple).

(A)

Anterior Lobe

Posterior Lobe

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(B)

I-IV

V

VI

Vermis IX

X

Crus I

IX

Crus II

VIIIb   VIIIa   VIIb

(C)

Tanita Siladi 2018
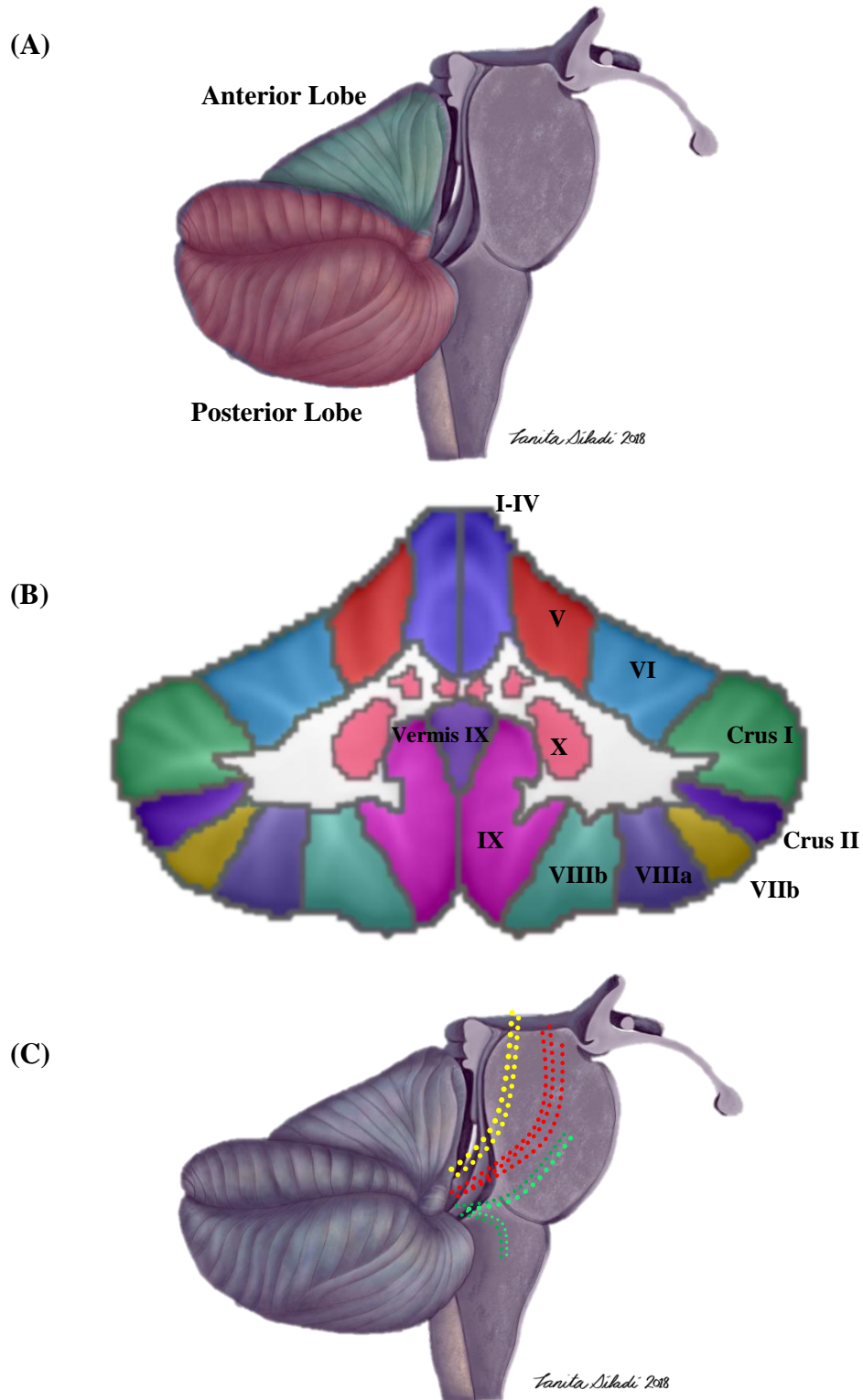
Figure 1.4 The cerebellum

(A) Schematic of the lateral cerebellum subdivided into the anterior (green) and posterior (red) lobes. **(B)** A portrayal of the cerebellar lobules on a coronal view of the cerebellum. **(C)** A representation of the superior cerebellar peduncle (yellow), middle cerebellar peduncle (red), and the inferior cerebellar peduncle (green).

Chapter Two

The effect of concussion history on cognitive-motor integration in elite hockey players

Johanna M. Hurtubise, Diana J. Gorbet, Yehyah Hamandi,
Alison K. Macpherson, & Lauren E. Sergio

Abstract

Aim: To observe the effects of concussion history on cognitive-motor integration in elite-level athletes. **Methods:** The study included 102 National Hockey League (NHL) draft prospects (n = 51 concussion history [CH]; n = 51 no history [NC]). Participants completed two computer-based visuomotor tasks, one involved 'standard' visuomotor mapping and one involved 'nonstandard' mapping in which vision and action were decoupled. **Results:** We observed a significant effect of group on reaction time (CH slower) and accuracy (CH worse), but a group by condition interaction only for reaction time ($p < 0.05$). There were no other deficits found. We discussed these findings in comparison to our previous work with non-elite athletes. **Conclusion:** Previously concussed elite-level athletes may have lingering neurological deficits that are not detected using standard clinical assessments.

Introduction

An estimated 1.6–3.8 million sports-related concussions, or mild-traumatic brain injuries, occur annually in the USA; however, the true incidence rate is likely higher due to the number of unreported concussions[56,58,119]. Elite athletes are not an exception to this phenomenon, and the potential long-term health effects of head injury have recently been brought to light through highly publicized litigations within national hockey and football leagues[120]. The Concussion in Sport Group (CISG) has defined concussion as a pathophysiological injury to the brain caused by biomechanical forces, which leads to clinical alterations but no structural damage[121]. Concussions result in a graded set of clinical symptoms, including physical, cognitive, behavioral and sleep disturbances[56,121]. Furthermore, concussions can lead to cognitive decline and motor deficits[121–123]. Using current clinical neuroimaging protocols, no gross structural damage can be seen after a concussion[121]. However, there are a number of molecular and metabolic events that occur after injury that may lead to changes in brain function[64]. This 'neurometabolic cascade' leads to an alteration in ion homeostasis, an increase in free radicals, a decrease in axonal structural integrity and ultimately, disruption of axonal transportation[64]. The length of time for complete recovery from a concussion-induced altered metabolic state is not yet well understood in humans; however, evidence suggests that during the recovery period the brain may be more vulnerable to the effects of a second, or repeated, concussion[66]. In an animal model study by Prins et al.[67], it was found that repeated concussions during this period of vulnerability lead to increased axonal injury, memory impairment and risk of mortality. In human studies, it was observed that athletes with a history of three or more previous concussions have a threefold higher risk of sustaining another concussion, and have longer recovery periods[124,125]. Importantly, evidence of increased vulnerability to subsequent concussion during

the recovery period indicates that returning an athlete to sport too soon after a concussion may put the athlete at greater risk for further damage, and increase the potential for second impact syndrome and death[56,66,67,121,124]. Therefore, there is a need to better understand the underlying mechanisms and neurological effects of concussion. From a practical standpoint, such an understanding would inform clinicians, charged with making return to play decisions, about the potential for increased vulnerability post-concussion.

Current international protocols recommend that the athletes must be evaluated by a physician and meet baseline measurements of both cognitive and motor assessment tools prior to beginning graded physical activity progressions[119,121]. However, recent studies have shown that commonly used assessment tools, such as neurocognitive testing, and the Sport Concussion Assessment Tool (SCAT3), may not be sensitive enough to determine if the athlete is safe to return to sport[56,58]. These current evaluation tools measure motor and cognitive functions sequentially. In contrast, effective sport performance typically requires their simultaneous involvement – thinking and moving at the same time. To be successful in many sports, a player must apply a wide range of cognitive factors to each of their movements within the game. For example, movements must be made in the context of game-related rules, spatial information regarding the locations of other players and prior knowledge of how to best accomplish a given task. Importantly, this cognition and action is not done sequentially, but rather, concurrently[52,53]. The necessity of this complex cognitive-motor integration (CMI) during game play may help explain why assessment tools that test cognitive and motor functions independently can lack the sensitivity required to detect ongoing concussion-related symptoms.

CMI can be examined in the laboratory by manipulating the mapping of visual information to a required motor response. 'Standard' visuomotor mapping involves directly

interacting with the object, so that the visual stimulus guiding an action is also the target of the action. A common example of this is looking at and then reaching for a coffee cup, or a pass in hockey when looking at one's teammate. In contrast, 'nonstandard' visuomotor mappings decouple vision and movement, must be learned or calibrated, and require integration of spatial or cognitive rules[1]. A common example of a nonstandard visuomotor mapping in daily life is the use of a computer mouse. To successfully use a computer mouse, one must slide the hand forward on a horizontal plane in order to move the cursor upward on a vertical monitor. In hockey, an example would be passing to one's teammate on the left, while looking and attempting to avoid a body check from an opponent on one's right. Previous research has found changes to the movement kinematics of both the eye and hand as a consequence of decoupling vision and movement[5]. Further, the ability to produce decoupled movements is shown to be more vulnerable than the ability to perform standard visuomotor mapping in some forms of clinically altered brain function (Alzheimer's disease, mild cognitive impairment)[47,50].

With respect to concussion, previous research using nonstandard visually guided arm movements revealed differences in performance of collegiate level athletes, adolescents and children with a previous concussion compared with control participants without a history of concussion[52,53]. Significant group differences were found in reaction time (RT), movement time, and precision, in that those with a previous concussion had performance deficits in both motor planning and execution compared with healthy controls, and this was seen more so in the nonstandard task with decoupled vision and action[52]. These studies all looked at non-elite level athletes. While current protocols suggest that concussion management should be the same for both elite and non-elite athletes[121], some literature suggests that the elite population may be an exception to the standard return-to-play protocol[126]. A study on National Football League (NFL)

players, found no significant risk of a subsequent injury when returned to sport on the same day[127], while another study noted that professional athletes performed better in neuropsychological testing post-concussion compared with non-elite athletes[128]. Conversely, it has also been found that retired professional contact-sport athletes with a history of repeated concussion had a fivefold prevalence of being diagnosed with mild cognitive impairment than their peers with no history of concussion[129]. Therefore it is important to understand the effects of concussion in this specialized group, in order to determine effective return-to-play standards. The aim of this study is to better understand how a history of concussion affects CMI in the elite athletic population. We hypothesize that, similar to the collegiate athletes and youth previously studied in our laboratory[52,53], testing with a nonstandard visuomotor mapping that requires CMI will also reveal performance deficits in the young elite-level athlete.

Methods

Participants

Participants were selected from the National Hockey League (NHL) draft combine from the 2012–2014 selection years. All athletes invited to the combine, a total of 322 athletes (mean age 17; all identified male), completed the task. Prior to testing, all athletes underwent medical examination with a team of physicians who reviewed the medical history of every prospect player and recorded the athlete's self-reported history of concussion. A total of 77 athletes reported at least one previous concussion. Athletes who were not medically cleared to participate in sport were excluded from analysis, thus all included participants were medically cleared (including vision), asymptomatic, and currently participating in sport. Data that were missing or unable to be analyzed due to computer malfunction were eliminated from further analysis. Healthy control participants, with no self-reported history of concussion, were randomly

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matched (randperm function; Matlab R2013b, The Mathworks Inc., Natick, MA, USA) to those with a history of concussion from the same collection year (2012, 2013 or 2014). Participants who were greater than two standard deviations from the mean for any dependent variable were deemed an outlier and removed from further analysis for a total of 102 athletes included in this study; 51 had a self-reported history of concussion (mean age 17 years ± 1) and 51 healthy controls (mean age 17 years ± 1). Information on position, number of previous concussions sustained as well as the length of time (in months) since their last concussion was also obtained during the medical examination (see Tables 2.1 & 2.2).

All participants completed an informed consent, administered through NHL central scouting, provided to the athletes prior to the day of testing. Ethics were approved through York University (Toronto, ON, Canada).

Procedure

Participants completed two computer-based visuomotor transformation tasks, one standard and one nonstandard (vision and action decoupled). Participants sat at a desk so they could comfortably reach a dual-touch-screen 15" laptop (ACER Iconia 6120, Acer America, San Jose, CA, USA) allowing for a screen in both the horizontal and vertical planes. In this way the horizontal screen was well within the comfortable reach range of the participant while the vertical screen was at or slightly below the eye level. In both conditions, participants were instructed to slide their index finger of their dominant 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. The central and peripheral targets were viewed on a black background to ensure good contrast. Participants guided a crosshair cursor to the yellow central (or home) target which would change to green when entered. After 4000ms, a red peripheral

target was presented and the central target disappeared, which served as the 'Go' signal for participants to initiate movements. Once the cursor reached and remained in the peripheral target for 500ms, it disappeared, signaling the end of the trial. The next trial began with the presentation of the central target after an interval of 2000ms. Peripheral targets were located 75mm from the center target and target diameters were 20mm. In order to ensure smooth movement of the finger during the task, participants wore a capacitive-touch glove on their preferred hand.

Participants completed the standard and nonstandard conditions in a randomized block design (Figure 2.1). In the standard condition, participants both looked and moved on the vertical screen, and directly interacted with the targets. The nonstandard condition included two levels of decoupling: plane change, in which participants looked at the vertical screen while moving on the horizontal screen, and cue reversal, in which the feedback was rotated 180° (i.e., in order to move the cursor left, you must slide your finger right). Four trials in each of the four directions were completed per condition for a total of 32 trials per participant (4 directions × 4 trials × 2 conditions). Participants were instructed to move as quickly and accurately as possible, and to look at the targets and not their hands (i.e., no central fixation). Eye movements were monitored by the experimenter to ensure participants were looking at the target; however, a vision tracking system was not used in this experiment. The total time to complete the experiment was typically 4–6 min for each participant. This was a novel task for all participants, with no practice trials allowed; therefore no participant had familiarization of the task. The order of conditions was randomized in order to control for potential learning effects.

Data Processing

Custom-written (C++) acquisition software sampled the finger's X-Y screen position at 50 Hz. Custom analysis software (Matlab, Mathworks, Inc.) processed individual movement paths with a fourth-order (dual pass) low-pass Butterworth filter at 10 Hz. Filtered paths were then used to generate a computerized velocity profile of each trial's movement. The movement onsets and ballistic movement offsets (the initial movement prior to path corrections) were scored at 10% peak velocity (PV), while total movement offsets were scored as the final 10% PV point once the finger position plateaued within the peripheral target. Note that in situations where the initial movement successfully brought the finger to the peripheral target, the ballistic and total movement offsets would be equivalent. These profiles were then verified by visual inspection, and corrections were performed when necessary. Trials were deemed errors if the finger/cursor left the center target too early (<4000ms), RT was less than 150ms or more than 8000ms or movement time was more than 10,000ms. Trials in which the first ballistic movement exited the boundaries of the center target in the wrong direction (>45° from a straight line to target) were coded as direction reversal errors (DR), eliminated from further evaluation and were analyzed as separate variable (see below). The scored data were then processed to compute nine different movement timing and execution outcome measures, described in detail below.

Movement timing

The measured kinematic variables for movement timing were as follows: RT; the time interval (milliseconds, ms) between the central target disappearance and movement onset. Movement time; the time between movement onset and offset (ms), calculated as both full movement (TMT, full movement offset) as well as ballistic movement (MT, initial movement

offset). If no corrected movements were made, ballistic movements were equal to full movement trajectories. PV; the maximum velocity obtained during the ballistic movement.

Movement execution

Kinematic variables for movement execution were: Path length; the total distance (resultant of the x and y trajectories) traveled between movement onset and offset (millimeters [mm]), calculated as both the full path length (FPL, full movement offset) as well as the ballistic trajectory (BPL, initial movement offset). Constant error (CE, accuracy); the average distance from the individual ballistic movement end points ($\sum x/n$, $\sum y/n$) to the actual target location (mm). Variable error (VE, precision); was calculated as the distance between the individual ballistic movement end points ($\sigma 2$) from their mean movement (millimeters; mm). DR errors were calculated as a deviation of greater than $\pm 45°$ from the direct line between the center of the central and peripheral targets.

Performance as a level of dissociation

In order to test the hypothesis that performance declines would be significant for the nonstandard (decoupled) task as compared with the standard task, we compared the athletes' performance as a function of their change from their own standard condition behavior. We subtracted the result of the standard condition from the nonstandard condition for each of the given dependent measures.

Data analysis

For eight of the dependent variables described above (RT, MT, TMT, PV, BPL, FPL, CE, VE) main effects of group (concussion history, control) and condition (standard, nonstandard) were analyzed using repeated mixed-model ANOVA. The number of DR, seen only in the nonstandard condition, was analyzed using one-way ANOVA with group (concussion history,

control) as the between-subjects factor. To verify significant results, a pairwise comparison was used to test main effects of group for each condition.

Because condition as a factor was significantly different across all variables, we performed further statistical tests using the level of dissociation (delta) in order to compare participants' performance as a function of their change from the nonstandard condition to the standard condition (see above). One-way ANOVA, comparing group (concussion history, control) across all dependent variables (delta scores; performance) was performed. One-way ANOVA was used to test the effects of the number of previous concussions (1, >2), as well as the length of time since their last concussion (<12 months, 12–24 months, >24 months) on performance. Information as to the number of previous concussions and the length of time since the most recent concussion was not available for all participants, these data were coded as missing and excluded from this analysis. The effect of position (forward, defense, goalie) on performance was analyzed by two-way ANOVA. Correlation of significant variables to both the number of previous concussions and to the length of time since the last concussion was run using point-biserial analysis.

All data were checked for normal distribution (Shapiro–Wilk's test), homogeneity (Levene's test; $p < 0.01$), sphericity (Mauchly's test) and was Greenhouse–Geisser corrected where necessary. Statistical significance levels were set *a priori* to < 0.05. All statistical analyses were performed using SPSS statistical software (SPSS, IBM Corp. released 2013. IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY, USA).

Results

Of the total number of athletes tested, 23.9% reported at least one previous concussion. After outlier removal, 102 athletes were included in this study, 51 with a previous concussion

and 51 matched healthy controls. Of those who reported a previous concussion, 78.4% (n = 40) reported only one prior injury while 19.6% (n = 10) reported two or more (see Table 2.2). The length of time since their last concussion was distributed among less than 12 months (n = 17; 16.7%), between 12 and 24 months (n = 14; 13.7%), or greater than 24 months (n = 16; 14.7%) (see Table 2.2). The majority of the athletes included in the analysis were forward (60.8%, Table 2.1). No significant relationship between the proportion of concussions sustained and player position was found (χ^2 [4] = 7.457; p = 0.114). Examples of typical movement trajectories of one subject with concussion history and one healthy control subject performing in both the standard and nonstandard conditions is shown in Figure 2.2. Descriptive statistics and statistical outcomes of the repeated mixed-model ANOVA for all dependent variables for group (concussion history, control) and condition (standard, nonstandard) are summarized in Table 2.3.

Movement timing

A repeated mixed-model ANOVA revealed a statistically significant main effect of condition (F[1,100] = 441.41; p < 0.001), group (F[1,100] = 6.669; p < 0.02) and group by condition interaction (F[1,100] = 4.630; p < 0.05) for RT. RT was longer in the nonstandard than in the standard condition, was longer for participants with a concussion history than healthy controls and the interaction revealed that this effect was even more pronounced in the nonstandard condition than in the standard for those with a concussion history (see Figure 2.3 & Table 2.3 for values). This finding was confirmed by pairwise analysis; those with a concussion history were significantly slower than healthy controls in the nonstandard (F[1,100] = 7.235; p < 0.01), but did not significantly differ in the standard condition (F[1,100] = 2.069; p > 0.05). For MT, TMT and PV, repeated mixed-model ANOVA revealed statistically significant effects for condition, but not for group or group by condition interaction. MT, TMT and PV were

significantly longer in the nonstandard condition than in the standard condition, independent of group.

Movement execution

Repeated mixed-model ANOVA revealed a statistically significant main effect of condition, but not for group or group by condition interaction for BPL (ballistic path length), FPL (full path length) and VE (variable error, precision) ($p > 0.05$; Table 2.3). BPL was significantly shorter in the nonstandard condition than in the standard condition; while FPL was significantly longer in the nonstandard condition than in the standard condition, independent of group. VE was significantly larger – denoting decreased precision – in the nonstandard condition than in the standard condition, independent of group. CE revealed a statistically significant main effect of condition ($p < 0.001$) and group ($p < 0.05$), but not for group by condition interaction. CE was significantly larger – denoting decreased accuracy – in the nonstandard condition relative to the standard condition, and significantly larger in those with a concussion history compared with no history control participants (Table 2.3).

DR errors were observed only in the nonstandard condition. One-way ANOVA revealed no statistically significant differences in the number of errors between those with a history of concussion and healthy controls ($F[1,100] = 0.517$; $p > 0.05$).

Performance as a level of disassociation

Descriptive statistics and statistical outcomes of the one-way ANOVA for the level of dissociation on all dependent variables in both groups (concussion history, control) are summarized in Table 2.4. One-way ANOVA yielded a statistically significant effect of group for RT only ($F[1,100] = 4.630$; $p < 0.05$); those with a concussion history showing a larger change in performance than healthy controls. All other variables showed no significant differences.

Further analysis on performance as a function of the number of previous concussions revealed no statistically significant differences in performance between those with only one previous concussion or those with two or more. The length of time since previous concussion also showed no significant differences in performance. Additionally, a point-biserial correlation found no relationship between performance and the number of concussions previously sustained and no relationship between performance and the length of time since the most recent concussion ($p >$ 0.05). A two-way ANOVA was conducted to examine the effect of position and concussion history on performance; no statistically significant interactions were found across all variables ($p > 0.05$).

Discussion

This study sought to determine whether young, elite-level athletes with a history of concussion, who were asymptomatic and medically cleared of concussion, exhibited CMI impairments. A computer-based eye–hand coordination task was used to examine several kinematic variables. Performance deficits in arm RT and constant error (accuracy) of arm movement end points were seen in those with a history of concussion compared with healthy age-, sex- and skill-matched control participants. The deficit in RT was exacerbated in the nonstandard task, where there was dissociation between vision and action requiring rule integration to control goal-directed movements. Although this finding supports our hypothesis of decreased performance with an increase in task complexity in elite athletes, these results differ from our previous findings in collegiate level athletes[53]. Specifically, the collegiate level athletes had deficits in multiple variables including both motor planning (RT), and motor execution (movement time, precision)[53]. While the elite athletes also show an impairment of motor planning (RT) and execution (accuracy), this was seen across fewer variables. Furthermore,

while RT was significantly affected by the increase in CMI complexity, ballistic accuracy was impaired independent of condition and therefore these deficits may not be due to a dysfunction within the specific network tested by our task. The performance deficits brought out by testing CMI in this elite sport population were also less severe than those observed in previously concussed select-level youth and adolescent athletes, who displayed an even greater number of impairments in motor planning and execution (movement time, ballistic path length, full path length, accuracy)[52]. Lastly, unlike our previous observations in varsity athletes and select-level youth athletes, the number of previous concussions, the length of time since the most recent concussion or the position played did not influence on any of the variables tested.

Relative to a standard visuomotor mapping, CMI has a greater level of task difficulty due to the simultaneous involvement of cognitive and motor systems, which requires intact reciprocal connections between the frontal (prefrontal, premotor, primary motor), parietal (superior parietal lobule, intraparietal sulcus) and subcortical areas (cerebellum)[6,12,13,17,22]. Task complexity has previously been shown to lead to a decrease in performance, specifically in RT[130], while imaging studies have since shown that the involvement of different brain regions within this frontoparietal network depend on task complexity[9,22,131,132]. Previous research in our laboratory found an increase in activity in both the inferior parietal lobule and cerebellum during a nonstandard CMI task relative to a standard mapping task. Additionally, spatial patterns of activity within the cuneus and medial premotor cortex were able to differentiate between the two tasks[22]. We propose that the significant differences in performance between our standard and nonstandard task (which were observed in both the concussion and healthy control groups of elite athletes) are due to the increased cognitive load, and thus greater activation within the frontoparietal network for the nonstandard task.

While we observed task-related performance deficits across all participants in the

nonstandard task, those with a history of concussion tended to demonstrate even greater

decrements relative to healthy controls. Previous research has looked at the effects of a

concussion on performance in both standard and simultaneous cognitive motor tasks. A study by

Locklin et al.[133] found that athletes with a history of concussion had increased mean response

times compared with control subjects in a standard mapping reaching task. Although they failed

to reach a level of significance, they suggested this may be due to the low difficulty of the task.

Additionally, Hugenholtz et al.[134] noted that those with a concussion performed significantly

slower than controls in choice RT tasks, but not in simple RT tasks; however, the motor aspect of

this task was limited to pressing a button, and therefore complex motor kinematic outcomes

cannot be inferred. Consistent with these results, we found decreased accuracy in the concussed

group across both of our tasks, suggesting that a concussion may impart more general 'noise'

into the motor system. To our knowledge, our task is the only one which includes a cue reversal

as well as a plane change, requiring two levels of vision and motor decoupling, thereby requiring

greater recruitment of brain regions within the frontoparietal network responsible for arbitrary

mapping and attention. Functional imaging studies have also shown a correlation between

frontoparietal network activation and task performance after a concussion[135–138]. Hammeke et

al.[135] conducted a longitudinal study on National Collegiate Athletic Association (NCAA)

football players and found that brain regions associated with attention decreased in activation

during the 'acute' stage of injury, however, increased in activation during the 'subacute' stage,

after overt symptoms had resolved. They theorize that during this 'subacute' period,

neurocognitive functions had improved in order to adequately perform on standardized clinical

concussion tests; however, this improvement likely relied on compensatory cognitive

mechanisms that resulted in the increased brain activity observed in the 'subacute' stage. Further, these findings suggest that performance deficits may appear with an increase in task difficulty that exceeds the capability of the compensatory activity. Similarly, increased brain activity has also been noted within NHL alumni. For example, Esopenko et al.[139] found greater activation of both the prefrontal and posterior parietal regions during a working memory task in those with a history of concussion, despite equivalent behavioral performance when compared with non-concussed participants. Observations of white matter abnormalities reported in retired NHL players[137], adult female athletes[108] and youth athletes[105] could provide an explanation for observations of increased brain activity post-concussion. We postulate that in the present study, where these athletes' brains have ostensibly recovered from mild injury, there may still be deficits in the connections between areas required to successfully integrate thought and action[6,9,22,24,25,50,140]. That is, we suggest that our observed behavioral deficits may be related to underlying changes in the frontoparietal networks necessary for the successful integration of thought and action, and likely these cortical networks' interactions with subcortical brain areas, for example, the cerebellum[9,22,24,25,50,131]. Indeed, we have observed deficits in these brain networks related to impaired performance in this same task in another neurologically compromised group, those at risk for developing dementia[50]. Importantly, on a practical level, our results suggest that athletes with a history of concussion who are slightly slower to react relative to their peers (by ~10%, in the current study) when simultaneous thinking and skilled action is required may be more vulnerable to sustaining a second concussion during this 'subacute' stage. Further, the results presented here and in our previous research suggest that the current return to play assessment – in which thinking and moving are tested separately – does not fully capture the functional disability of a concussion. We postulate that the use of a complex

visuomotor task that requires CMI may be more sensitive to the underlying neurological effects

of a concussion, and thus may be a useful measure to ensure safe return to sport. While the

length of time since their previous concussion was not a significant factor in our study, this may

be due to a low sample size within each "time since concussion" subgroup. Previous research in

our laboratory, looking at asymptomatic children[53], did find a significant recovery time course.

However, further longitudinal investigation on the change in CMI performance in concussion

and recovery is needed before its use as a measurement to determine if an athlete is safe to return

to play. Importantly, the current task is simple, quick and potentially side-line accessible. Such

characteristics are vital since automated devices have recently become the new 'gold standard' in

concussion assessment since they are simple, portable and reliable[141].

Interestingly, compared with previous findings in varsity-level young adult, non-elite

adolescent, and youth athletes[52,53], the results presented here suggest a reduced effect of

concussion on CMI in elite athletes. This difference in performance between the elite athletic

population and the non-elite athletic populations may be due to a protective effect in the elite

brain, a superior CMI frontoparietal network, or potentially a sampling bias (see below). Some

speculate that elite level athletes may simply be protected from the effects of a concussion, and

thus explains why they are able to compete at the elite level[127,128]. Pellman et al.[128] found that

NFL athletes had no neurocognitive deficits within the first week after sustaining a concussion,

compared with high school athletes who had lingering symptoms. They theorize that this may be

due to a higher tolerance in these professional athletes to the effects of concussion. Alternatively,

we suggest that this may, instead, be due to the lack of testing a more complex task, one which

pushes the movement control system. We propose that elite athletes have a superior

frontoparietal network that allows for greater compensation following concussion (i.e., greater

motor control 'reserve'), and thus fewer performance deficits. Studies have shown that elite performers require less neural activation in order to correctly execute a skill, which may be an effect of motor learning[43,44,142]. Fitts[142] theorized that skilled performers tend to follow patterned processing of skill acquisition, learned through the 'Associative Stages of Learning'. He postulated that novice athletes must rely on more cognitive processes in order to perform a skill, which is attention-demanding and inefficient, whereas experts have a more automatic performance, which is rapid, smooth and effortless. Granek et al.[45], found that expert video gamers displayed a reduction in frontoparietal activity, with increased prefrontal (dorsolateral prefrontal cortex, DLPFC) activity during decoupled (nonstandard) movements compared with non-gamers during a CMI task in which the actual performance was equal between groups. Both EEG and fMRI (functional magnetic resonance imaging) studies have shown that expert, or elite, athletes demonstrate 'neural efficiency' due to more specific neural circuitry and minimal energy consumption[43,44]. Here we suggest that while behavioral deficits may not be as noticeable in the elite athletic population due to these superior networks, the underlying neural effects may still be present. Further research involving both complex CMI tasks and imaging are needed to better understand the neural effect of mild brain injury on this unique population.

When interpreting the results of this study, it is important to acknowledge that our participants were all NHL draft combine invites at the top of their performance level. These athletes likely played on the highest skilled teams as children. Relative to novice level teams, elite level teams often receive a higher level of medical attention, which may have impacted the care these individuals received after sustaining a concussion and ultimately, their recovery[126]. Therefore, it is difficult to disentangle whether our findings of a potentially increased cognitive-motor reserve in elite athletes is an innate characteristic of these individuals or a product of their

environments and training conditions. Additionally, all concussions were self-reported; therefore we cannot be certain that those in our no-history control group had not sustained an unreported concussion. However, as mentioned above, these elite level athletes have likely received higher levels of medical attention throughout their careers and thus likely had better assessment and diagnosis of concussion. Furthermore, we cannot generalize these results to other elite level athletes, since there may be sport-related differences (e.g., in mechanisms of injury), which needs to be further investigated. In addition, while we found no significant effects of position, the number of previous concussions sustained, or the length of time since a participant's most recent concussion, these results should be interpreted with caution due to the low sample size of some of these subgroups within our main concussion group (see Tables 2.1 & 2.2), and potential inaccuracies due to the fact that many concussions likely go unreported. Lastly, while this study did not measure vision or oculomotor control, we acknowledge that it may play an important role in our task, specifically for those suffering an acute concussion. Our participants were asymptomatic and medically cleared by a physician for vision deficits; however, future research should investigate the effects of vision and oculomotor control in CMI tasks, especially in those with an acute concussion. Importantly, for this study we were only able to assess elite male athletes. Given the increasing awareness of the effect of sex (and the completely unstudied effect of gender) on rates of and response to mild head injury[143–145], it will be crucial to repeat this study in elite female athletes in order to adequately address the behavioral effects of concussion history on performance. Future work will utilize imaging in order to investigate the underlying neurological effects of concussion on CMI and its associated networks. Furthermore, a prospective longitudinal study is needed in order to investigate the effects of a concussion on CMI over time. Further research on the specificity, sensitivity, and reliability of this computer-

based CMI task is needed to determine its usefulness as an objective and thorough measurement of an athlete's readiness to return to sport.

Conclusion

Elite level athletes may have lingering neurological deficits after sustaining a concussion, with impairment in movement planning during complex (nonstandard) visuomotor tasks and in overall accuracy of visually guided reaching movements. Our computer-based CMI task, which requires an arbitrary rule association through decoupling vision and action, is able to identify this deficit. This worsening in RT during tasks which require simultaneous CMI (an important aspect of sport) may leave the athlete more vulnerable to subsequent concussions and their potential long-term effects. These results suggest that the current return to play assessments – in which thinking and moving are tested separately – do not fully capture the functional disability of a concussion and therefore future research focusing on their integration (CMI tasks) is needed.

Table 2.1			
Position	Concussion History; n (%)	Healthy Control; n (%)	Total; n (%)
Forward	14 (27.5)	16 (31.4)	30 (29.4)
Defense	33 (64.7)	29 (56.9)	62 (60.8)
Goalie	4 (7.8)	6 (11.8)	10 (9.8)
Total	51	51	102

Table 2.1 Demographic information by group and position

Table 2.2	
	n (%)
Previous number of concussions	
1	40 (78.4)
2+	10 (19.6)
Missing	1 (2.0)
Total	51
Length of time since last concussion	
<12 months	17 (33.3)
12-24 months	14 (27.5)
>24 months	15 (29.4)
Missing	5 (9.8)
Total	51

Table 2.2 Concussion history information

Table 2.3					
Kinematic outcome variables	**Healthy control; mean (SD)**	**Concussion history; mean (SD)**	**Repeated mixed-model ANOVA statistical outcomes**		
			Condition	**Group**	**Group x condition**
Reaction Time (ms)					
Standard	412.69 (48.840)	425.69 (42.224)	$F = 441.410^{**}$	$F = 6.669^{N.S.}$	$F = 4.630^{*}$
Non-Standard	551.26 (73.203)	595.89 (93.176)			
Ballistic Movement Time (ms)					
Standard	264.38 (66.948)	256.85 (65.726)	$F = 84.332^{**}$	$F = 0.362^{N.S.}$	$F = 1.585^{N.S.}$
Non-Standard	411.11 (204.988)	450.20 (232.864)			
Total Movement Time (ms)					
Standard	298.46 (70.447)	299.69 (70.327)	$F = 252.437^{**}$	$F = 1.856^{N.S.}$	$F = 2.818^{N.S.}$
Non-Standard	623.36 (251.648)	701.35 (257.510)			
Ballistic Path Length (mm)					
Standard	67.28 (2.960)	66.05 (3.028)	$F = 10.973^{**}$	$F = 2.778^{N.S.}$	$F = 0.108^{N.S.}$
Non-Standard	65.01 (5.172)	64.19 (5.788)			
Full Path Length (mm)					
Standard	69.85 (2.582)	69.46 (1.987)	$F = 43.488^{**}$	$F = 0.594^{N.S.}$	$F = 1.854^{N.S.}$
Non-Standard	73.18 (4.682)	74.53 (6.950)			
Peak Velocity					
Standard	228.07 (51.853)	221.26 (43.531)	$F = 157.173^{**}$	$F = 1.173^{N.S.}$	$F = 0.409^{N.S.}$
Non-Standard	170.26 (56.853)	157.24 (56.498)			
Constant Error (accuracy) (mm)					
Standard	7.86 (2.099)	8.71 (2.490)	$F = 96.856^{**}$	$F = 6.340^{*}$	$F = 0.460^{N.S.}$
Non-Standard	12.75 (4.630)	14.32 (4.509)			
Variable Error (precision) (mm)					
Standard	5.62 (2.342)	6.24 (3.311)	$F = 8.361^{**}$	$F = 0.070^{N.S.}$	$F = 1.455^{N.S.}$
Non-Standard	7.04 (2.971)	7.43 (3.633)			
			One-way ANOVA statistical outcome		
Direction Reversal Errors (mean number of trials)					
Non-Standard	1.10 (1.237)	0.94 (.947)		$F = 0.517^{N.S.}$	

*p<0.05; **p<0.001
N.S.: Non-significant; SD: standard deviation.

Table 2.3 Descriptive statistics of group, by condition, and statistical outcomes of Repeated Mixed-Model ANOVA

Table 2.4			
Performance score	**Healthy control; mean (SD)**	**Concussion history; mean (SD)**	**ANOVA**
Δ RT	138.58 (68.347)	170.20 (79.652)	F=4.630*
Δ MT	146.74 (172.747)	193.36 (200.263)	F=1.585[N.S.]
Δ TMT	324.90 (229.146)	401.66 (232.680)	F=2.818[N.S.]
Δ BPL	-2.26 (6.326)	-1.85 (6.229)	F=0.108[N.S.]
Δ FPL	3.34 (5.643)	5.08 (7.157)	F=1.854[N.S.]
Δ PV	-57.81 (49.806)	-64.03 (48.335)	F=0.409[N.S.]
Δ CE	4.89 (5.652)	5.61 (5.105)	F=0.460[N.S.]
Δ VE	1.42 (3.881)	1.18 (5.125)	F=0.070[N.S.]
*p<0.05 BPL: Ballistic path length; CE: Constant error (accuracy); FPL: Full path length; MT: Ballistic movement time; N.S.: Non-significant; PV: Peak velocity; RT: Reaction time; SD: Standard deviation; TMT: Total movement time; VE: Variable error (precision)			

Table 2.4 Descriptive statistics of group, by level of dissociation (standard – non-standard) and statistical outcomes of one-way ANOVA
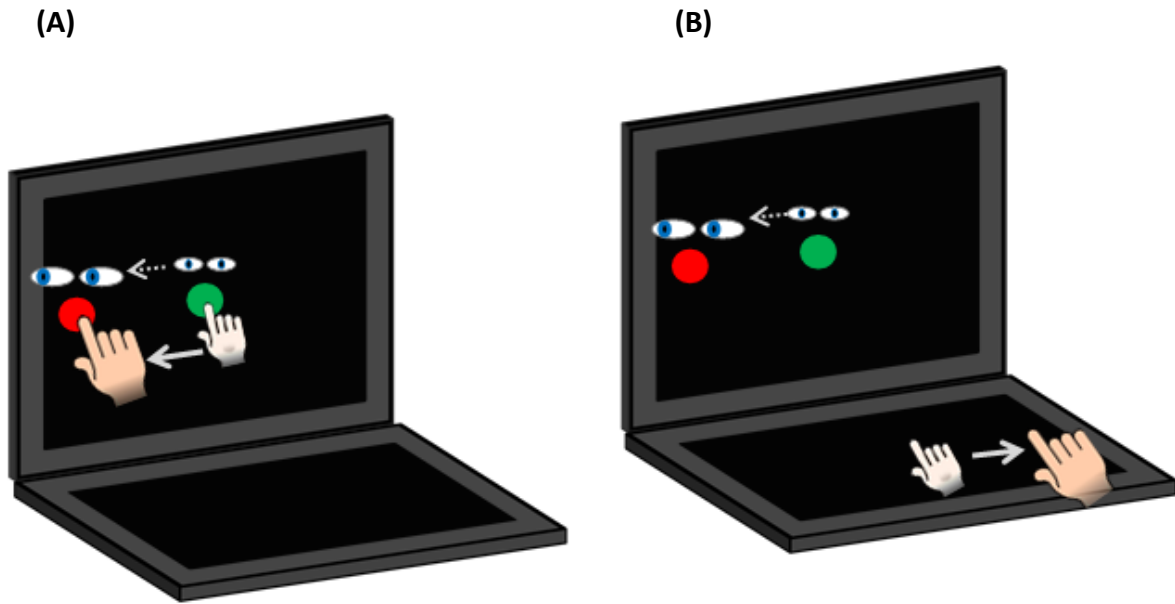
Figure 2.1 Illustration of the computer-based CMI task.
The green circle denotes the central home target in which all movements begin. A red target appears in one of four peripheral directions (90° to top, bottom, left or right of center) after 4000ms which serves as the 'Go' cue. **(A)** The standard condition, in which eye and arm movements are congruent (moved to the same peripheral target). **(B)** The non-standard condition, in which vision and movement are decoupled due to a plane dissociation (eyes look at vertical screen while hand moves along horizontal screen), and visual feedback reversal (cursor movement 180° rotated from hand motion).
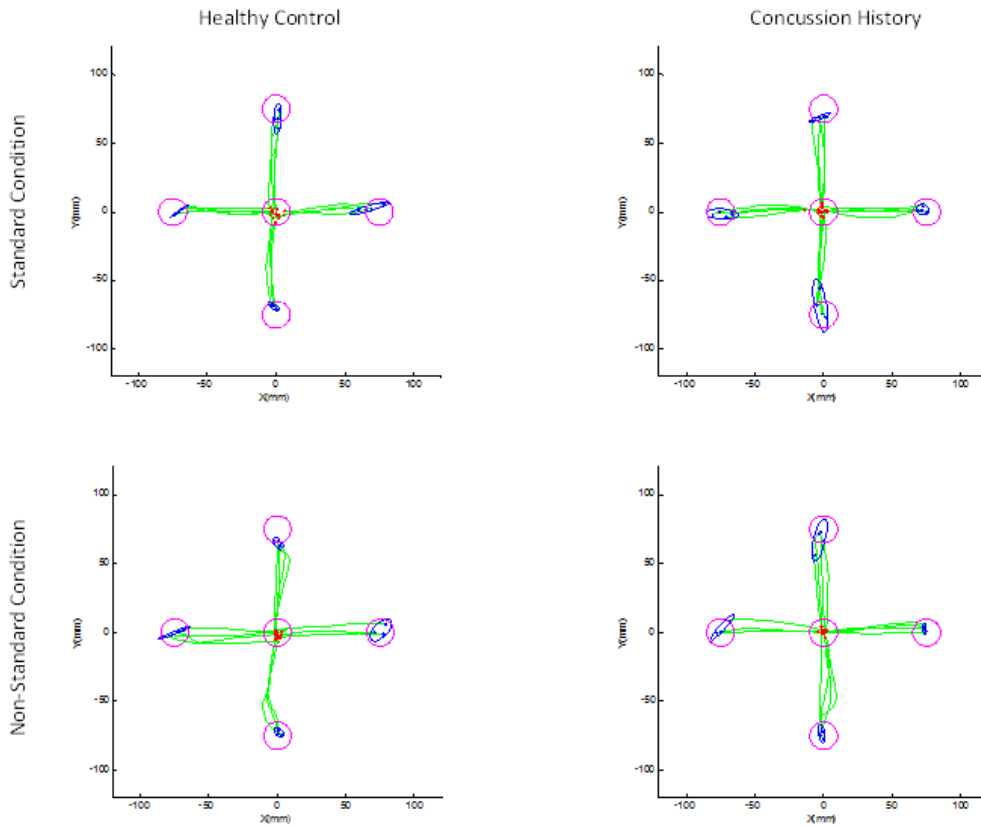
Figure 2.2 Full hand movement trajectories of one healthy control and one concussion history participant in both the standard and non-standard conditions.

Full hand movement trajectories of one healthy control and one concussion history participant in both the standard and non-standard conditions. Red circle and dots represent the center/home target and initial finger position, pink circles represent the 4 peripheral targets, blue dots represent final endpoints of individual movements, green lines represent finger trajectory for individual movements, blue ellipses represent the 95% confidence interval surrounding the final endpoint locations.

(A) Mean reaction time for healthy controls (yellow) and concussion history participants (blue) in both the standard and non-standard condition.
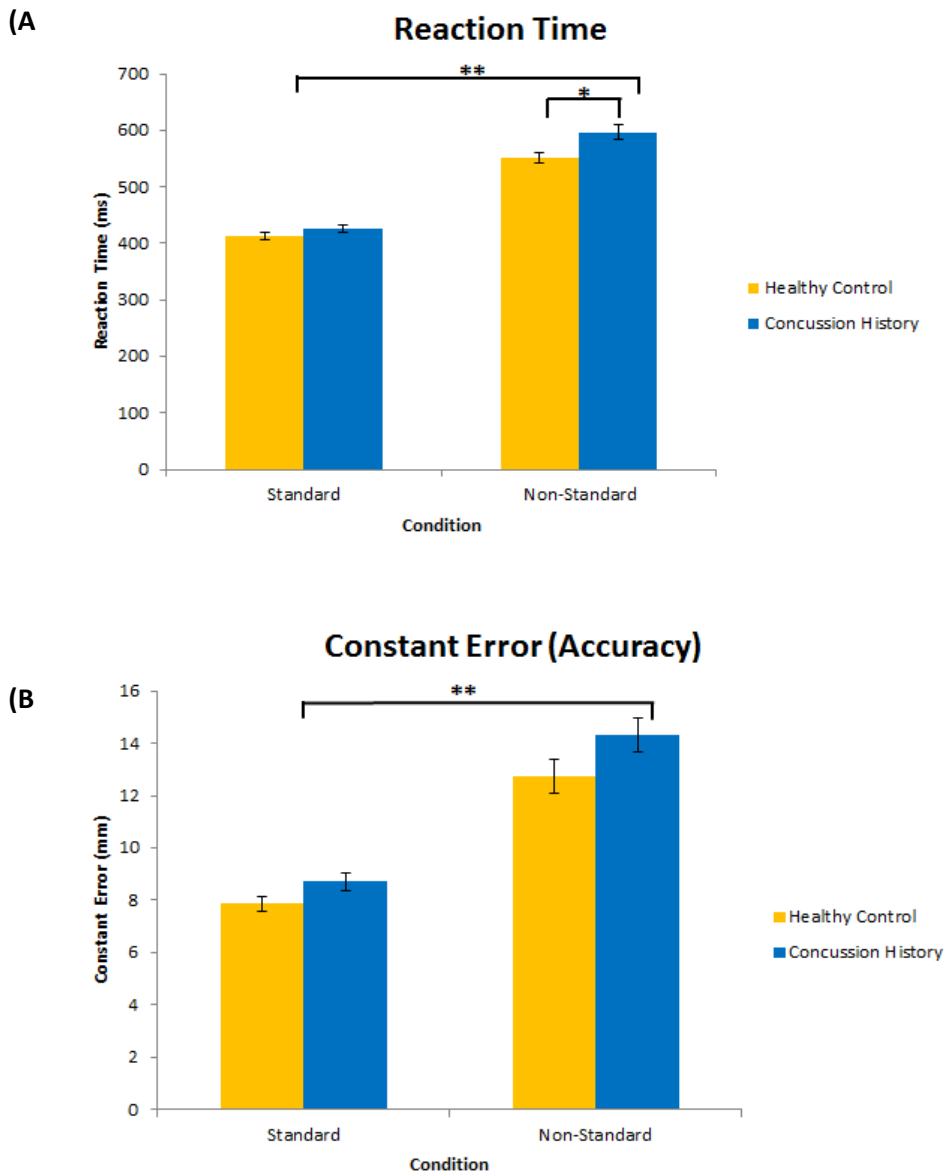
Figure 2.3 Significant kinematic variables.

(A) Mean reaction time for healthy controls (yellow) and concussion history participants (blue) in both the standard and non-standard condition. Repeated mixed-model ANOVA revealed a statistically significant main effect of condition, group, and a group by condition interaction. **(B)** Mean constant error (accuracy) for healthy controls (yellow) and concussion history participants (blue) in both the standard and non-standard condition. Repeated mixed-model ANOVA revealed a statistically significant effect of condition and group, but not a group by condition interaction ($p > 0.05$).
*$p < 0.05$; **$p < 0.001$.
 Error bars represent SEM.

Chapter Three

White matter integrity and its relationship to cognitive-motor integration in females with and without post-concussion syndrome

Johanna M. Hurtubise, Diana J. Gorbet, Loriann Hynes,
Alison K. Macpherson, Lauren E. Sergio

Abstract

Background: Fifteen percent of individuals who sustain a concussion go on to develop post-concussion syndrome (PCS). These persistent symptoms are believed to be due to damage to white matter tracts and impaired neurotransmission. Specifically, declines in white matter integrity following concussion have been found along the long-coursing axons underlying the frontoparietal network. This network is essential for the performance of visuomotor transformation tasks requiring cognitive-motor integration (CMI). We have previously observed deficits in performance on CMI-based tasks in those who have a history of concussion, but were asymptomatic. **Purpose:** The aim of this study was to investigate performance on a CMI task, as well as white matter integrity differences along frontoparietal-cerebellar white matter tracts in those with PCS compared to healthy controls. We hypothesized an association between the behavioural and brain structural measures. **Methods:** Twenty-six female participants (13 with PCS for 6 months or greater and 13 healthy controls) completed four computer-based visuomotor CMI tasks. In addition diffusion tensor images (DTI) were acquired. **Results:** No statistically significant differences were found in CMI performance between groups. Furthermore, there were no statistically significant differences between groups on any DTI metrics. However, when combining groups, there were significant associations between performance on a CMI task and white matter integrity. **Conclusion:** Further investigation into additional causes of symptoms in those with PCS (including psychological and cervicogenic factors) will strengthen our understanding of this diverse group. Nonetheless, this study demonstrates that white matter integrity is related to levels of performance in tasks that require CMI.

Background

Visually-guided reaching movements are often required in our daily lives, including both standard visuomotor and non-standard visuomotor transformation tasks. A standard task, in which we are looking at the target where we are directing our reaching movement, utilizes a default brain network[1,5]. Whereas non-standard movements, in which the gaze and hand are targeting incongruent spatial locations, must be learned or calibrated and therefore require the integration of cognitive rules. As such, non-standard tasks require cognitive-motor integration (CMI)[1,2]. Both types of tasks require the frontoparietal-cerebellar network for accurate movements[14–16], however, reaching tasks which also require the integration of cognition are more difficult, and therefore incorporate a more complex brain network[2,9,18,28]. Deficits in CMI performance have been observed in those with a concussion history[52,53] and dementia risk[50], while performance on a standard visuomotor task did not significantly differ from healthy controls. Furthermore, these movement deficits were associated with decreased white matter integrity in those at risk for dementia[51]. Therefore, non-standard reaching tasks may provide a more thorough assessment of these more complex large-scale brain networks in those with brain injury or impairment, including those with concussion.

Concussions, a form of mild traumatic brain injury (mTBI), affect an estimated 1.6-3.8 million people annually[54,56], with approximately 15% developing persistent symptoms and post-concussion syndrome (PCS)[4,56]. Currently, there is no clear consensus on the definition of PCS, and its differentiation from persistent symptoms; however, all definitions agree on the presence of symptoms following head trauma that persist beyond the typical symptom recovery time of 1-2 weeks[59–62]. Furthermore, Hiploylee et al. (2017)[59] suggest that if an individual does not clinically recover over the first 3 years, they may never fully recover. This affects a person's

ability to return to their daily life, and leads to a high health care cost burden[54,58,69,77]. Therefore, it is essential that we not only improve our understanding of the underlying neural effects of concussion and PCS, but also incorporate more objective measurements into recovery assessment to allow for earlier detection and thus earlier intervention.

PCS is thought to occur due to damage to axons and white matter tracts in the initial injury that does not fully recover, leading to impaired neurotransmission and speed of processing[64,66,69,70]. The MR-imaging technique, diffusion tensor imaging (DTI), allows us to indirectly measure the integrity of these white matter tracts after injury[100]. White matter changes have been most commonly noted along long-coursing and association tracts including the corticospinal tract (CST)[103,107,108,112,115], inferior longitudinal fasciculus (ILF)[108,110], superior longitudinal fasciculus (SLF)[108,110,115,116], inferior frontal occipital fasciculus (IFOF)[107,108,110,112], and the interhemispheric commissure the corpus callosum (CC)[103,108,114,115,146]. These tracts underlie the frontoparietal network, the same network required for CMI[2,14–16]. Thus, CMI performance may also be affected following damage to these tracts. Previous research from our laboratory has demonstrated performance declines in CMI tasks in children and young adults with a history of concussion, but who are asymptomatic[52,53,147]. We have also observed a relationship between white matter integrity and CMI in otherwise asymptomatic older adults at risk for dementia[51]. Many of the tracts showing behaviourally-related integrity deficits were part of the frontoparietal network for rule-based movement control.

Given its crucial role in coordination and feedback-based control of ongoing movements, the cerebellum is putatively essential for CMI-based tasks[22,29,32]. It further plays a role in balance, oculomotor, vestibular, and cognitive functions, and thus may be responsible for, or at least related to, many of the symptoms experienced by those with PCS[15,32]. Yet, the effects of

concussion and PCS on this structure, and its large white matter tracts (the cerebellar peduncles), has received very little attention to date[90].

The objectives of this study are threefold. The first objective is to investigate the behavioural differences in those with PCS compared to healthy controls on tasks which require CMI. Second, we will examine the effect of PCS on white matter integrity, specifically along the tracts underlying the frontoparietal network and the cerebellar peduncles. Third, we will examine the associations between performance on CMI tasks, subjective symptom reporting, and white matter integrity. We hypothesize that individuals with PCS have reduced white matter integrity in tracts that include the frontoparietal-cerebellar network involved in rule-based skilled movement control. From this general hypothesis, we predict that these individuals will display impaired CMI (but unimpaired standard movement control) relative to healthy controls. We further predict that the number and severity of reported symptoms will be associated with CMI task performance, with both being related to white matter integrity declines.

Methods

Participants:

Twenty-six female participants between the ages of 18-60 were included in this study; 13 with PCS and 13 age-matched (± 1 year) healthy controls (average = 30 ± 10.8). PCS was defined according to Tator et al. (2016)[60] as 3 symptoms lasting at least 1 month after concussive brain injury. This study defined concussion according to the 4th International Consensus Conference on Concussion in Sport[121] as a "complex pathophysiological process affecting the brain, induced my biomechanical forces". Specifically, an injury was considered a concussion if there was a known mechanism of injury (either a direct blow or an impulsive force) which resulted in the rapid on-

set of at least one sign or symptom. A self-reported concussion was determined as a concussive

incident in which there was either a diagnosis by a medical physician or in which the date and

mechanism of injury was recalled. All PCS participants had symptoms persisting for 6 months or

longer at the time of the study (average = 36 months ±28.6; range 6-108). Age-matched control

volunteers who self-reported no prior history of concussion were recruited. None of the

participants had a diagnosed neurological disease, sustained their head injury due to a motor

vehicle accident, or were deemed unsafe to undergo MR imaging. All participants were right-

handed, with no injury (other than PCS) that would prevent them from participating in physical

activity or sport. Upon examination of MR images, no gross morphological abnormalities were

observed in any participants who were included in the study. Information about the concussive

injury, including the number of previous concussions and length of time since the concussion,

was collected through a questionnaire.

This study was approved by York University research ethics committee, and all

participants provided informed written consent.

Procedure:

All participants completed the Sport Concussion Assessment Tool, 3rd Edition (SCAT3),

a computerized CMI task (BrDI[TM]) involving 4 visuomotor transformation conditions, and

diffusion-weighted imaging.

Sport Concussion Assessment Tool (SCAT3):

Symptoms were measured through the symptom inventory as part of the SCAT3[121]. The

symptom inventory consists of 22 commonly reported symptoms, which were 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) were reported. The

SCAT3 also incorporates both cognitive (the Sideline Assessment of Concussion) and motor (balance and coordination) components. The Sideline Assessment of Concussion (max score 30) measures cognitive ability over 4 subdomains, including orientation (max 5), immediate memory (max 15), delayed recall (max 5), and concentration (max 5). A higher SAC score indicates higher cognitive ability. Balance is measured through the modified Balance Error Scoring System, incorporating three 20 second tests of different stances on a firm ground. Deviation from the stance is counted as an error, up to a maximum of 10 errors per stance (max 30 total). The final component of the SCAT3, coordination, looks at the ability to perform 5 finger to nose movements accurately within 4 seconds and is scored as yes (1/1) or no (0/1). Each of these different components has shown reliability, sensitivity, and specificity[148].

Visuomotor Task (BrDI^TM^):

Participants completed four computer-based visuomotor transformation tasks that included one standard and three non-standard (vision and action decoupled) conditions. Participants sat at a desk so they could comfortably reach a 10.1" tablet (ASUS Transformer Book) placed on the desk in front of them. The tablet was connected to a 15" external monitor allowing for a screen in both the horizontal and vertical planes. The monitor was placed 70cm from the tablet to ensure a consistent visual angle. All hand movements were made on the tablet, which was placed at a 15° angle tilted upwards toward the participant to allow for comfortable movements.

In all conditions, participants were instructed to slide the index finger of their dominant (right) hand along the touch screen tablet in order to displace a cursor from a central target to one of four peripheral targets (up, down, left, or right relative to center) 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 changed to green when entered. After a 4000ms centre hold time, a red peripheral target was presented and the central target disappeared, which served as the 'Go' signal for the participant to initiate movement. Once the cursor reached and remained in the peripheral target for 500ms, it disappeared, signaling the end of the trial. The next trial began with the presentation of the central target after an inter-trial interval of 2000ms. Peripheral targets on the tablet were located 55mm from the center target, with target diameters of 10mm. In order to ensure smooth movement of the finger during the task, participants wore a capacitive-touch glove on their right hand.

Participants completed four conditions in a randomized block design. In the standard condition participants both looked at and moved on the tablet, thereby directly interacting with the targets. The three non-standard conditions required the decoupling of the eyes and the hand: (i) plane change (PC), in which participants looked at the vertical screen while moving on the horizontal tablet screen, requiring implicit sensorimotor recalibration; (ii) cue reversal (CR), in which the feedback was rotated 180° (i.e. in order to move the cursor left, you must slide your finger right), requiring explicit strategic control and movements of the eyes and hand to be made in opposite directions. Participants both looked at and moved on the horizontally placed tablet; and (iii) plane change + cue reversal (PC+CR), in which both previously mentioned non-standard tasks were combined, thereby requiring 2 levels of decoupling. Four trials in each of the four directions were completed per condition for a total of 64 trials per participant (4 directions x 4 trials x 4 conditions). Eye movements were monitored by the experimenter to ensure participants were looking at the correct target. Participants were provided a practice of 2 trials in each of the 4 directions prior to each condition to ensure familiarity of the task in order to obtain the greatest ability of each participant (see Figure 3.1).

Data Processing:

Custom-written (C++) acquisition software sampled the finger's X-Y screen position at 50Hz. Custom analysis software (Matlab, Mathworks Inc.) was used to process individual movement paths with a fourth-order (dual pass) low-pass Butterworth filter at 10Hz. Filtered paths were 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 (i.e. including path corrections) were scored as the final time point at which movement decreased back down to 10% peak velocity once the finger position was 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 prior to the required center hold time (< 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 number of sub-movements, or corrective movements, was verified by visual inspection. These were defined as a decelerated movement followed by an accelerated movement throughout the movement trajectory. Both the first author researcher and a blinded researcher manually inspected and counted sub-movements, and the final measure was determined as the average between the scorers. The scored data were then processed to compute both movement timing and execution outcome measures. Trials in which one of the variables was greater than 2 standard deviations from the individual's mean score were excluded from further analysis.

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) Total Movement Time (TMT), the time between movement onset and full movement offset (milliseconds); and 3) Peak Velocity (PV), the maximum velocity obtained during the movement (millimeter/millisecond). Kinematic variables for movement execution were: 1) Full Path Length (FPL), 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); 4) The Percentage of Equal Trials (%Equal), determined by the percentage of correct trials in which the initial ballistic movement was equal to that of the full movement, resulting in one smooth movement; 5) Percent Sub-Movements (%SubMvt), the percent of correct trials in which sub-movements were present; 6) Number of Sub-Movements (#SubMvt), calculated as the average number of sub-movements per each correct trial; and 7) Direction Reversal errors (DR), the percent of total trials in which a direction reversal error occurred.

Imaging Acquisition and Parameters:

Whole-brain diffusion weighted images were acquired on a 3 Tesla Siemens Tim Trio scanner at York University using a 32 channel head coil. The diffusion weighted images were acquired using a single-shot echo planar sequence (SS-EPI), including Generalized Autocalibrating Partially Parallel Acquisition (GRAPPA) to increase the signal-to-noise ratio (TR = 9200ms, TE = 86ms, slice thickness = 2.0mm, voxel size = $2.0mm^3$, FOV = $192mm^2$). A

total of 64 encoding directions were obtained with b-value $= 1000s/mm^2$. In addition, one reference volume with no diffusion weighting was collected (b-value $= 0$ s/mm^2).

Behavioural Data Analysis:

All data were checked for normal distribution (Shapiro-Wilk's test) and homogeneity of variance (Levene's test). Since the data violated normality, non-parametric tests were used. This was due to the homogeneity of variance, in that those with PCS demonstrated significantly greater variability compared to healthy controls on a number of behavioural measures. Statistical significance levels were set a-priori to $p < 0.05$. Statistical analyses were performed using SPSS statistical software (SPSS 24, IBM corp).

To test the main effect of group (PCS, healthy control) on SCAT3 scores, a Mann Whitney U test was used on each component, and corrected for multiple comparisons using Holm-Bonferroni. Likewise, for each of the dependent kinematic variables of the CMI visuomotor task described above (RT, TMT, PV, FPL, AE, VE, %Equal, %SubMvt, #SubMvt, DR), the Mann-Whitney U test was used to test the main effect of Group (PCS, healthy control), and corrected for multiple comparison with Holm-Bonferroni.

In order to minimize the number of variables for correlation analyses, composite scores were calculated based on a 'simple averaging' approach[149]. For each of the included variables, a z-score was calculated (using the control participants' mean and standard deviation) and summed in order to create a timing, trajectory, and sub-movement composite score for each condition. The timing score included RT, TMT, and the inversed PV (PV z-score * -1). The trajectory score included FPL, AE, and VE, while the sub-movement score included %SubMvt and #SubMvt. Each composite score was then transformed (using a mean of 50, standard deviation 10) for ease of interpretation, with a higher score indicating worse performance. Each transformed score was

tested for internal validity using Cronbach's Alpha (averaged across conditions). The main effect of group (PCS, healthy control) on the composite scores for each condition was tested using Mann-Whitney U.

Imaging Analysis:

All diffusion weighted images were analyzed using FMRIB Software Library (FSL)[150]. First the effects of head motion and eddy current were corrected using FSL's Diffusion Toolbox (FDT), followed by the removal of non-brain structures using the Brain Extraction Tool (BET)[151]. Calculation and fitting of tensor models, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), were completed and extracted using DTIFIT within the FDT. Voxel-wise statistical analysis of the FA data were carried out using Tract-Based Spatial Statistics (TBSS)[152], part of FSL[153]. Specifically, first each FA image was slightly eroded and end slices zeroed in order to remove outliers. All subjects' FA data were then aligned into a common space (FMRIB58) using the nonlinear image registration tool (FNIRT) and registered to the MNI152 space via affine transformation[154,155]. The FMRIB58 template is in the same space as the MNI152 template and is constructed from average FA images of 58 healthy individuals. The MNI152 template is based on 152 T1-weighted scans transformed (both linearly and non-linearly) to form a symmetric model. Next, the mean FA image was created and thinned to produce a mean FA skeleton which represents the centers of all tracts common to the group. Each subject's aligned FA data was then projected onto the mean skeleton. Each subject was manually inspected to ensure their major white matter tracts lined up with the created mean skeleton. This procedure was then applied to MD, AD, and RD metrics using TBSS for non-FA images. Voxel-wise cross-subject statistics were performed on the resulting data. Specifically, the 'randomise' algorithm was used, which allows for a non-

parametric permutation analysis, to test the main effect of group (PCS, healthy control) in whole brain FA, MD, AD, and RD values[156]. Multiple comparisons were corrected used a threshold-free cluster enhancement (TFCE). This technique is more sensitive and robust than both cluster-based and voxel-based thresholds as one does not arbitrarily pick a threshold, and is thus more effective at preventing increases in false positive or false negative results[157]. Due to a having a relatively small sample size, variance smoothing of 5mm was used to increase power, and 5000 permutations were run for each metric.

A region of interest (ROI) approach was used to extract FA, MD, AD, and RD measures from white matter tracts chosen a-priori, including the CC, both the right and left CST, SLF, ILF, IFOF, and both the right and left cerebellar peduncles (Superior Cerebellar Peduncle, SCP; Middle Cerebellar Peduncle, MCP; Inferior Cerebellar Peduncle, ICP) (see Chapter 1, Figure 1.3). Masks for CST, SLF, ILF, and IFOF were created based on the probabilistic JHU White-Matter Tractography Atlas in FSL[158]. The mask of the CC was created based on the Juelich probabilistic atlas[159], while the cerebellar peduncle masks were created based on the cerebellar white matter probabilistic atlas within the spatially unbiased atlas template (SUIT) [160]. All atlases used for mask creation are aligned with MNI space. Each mask was then set at a threshold of 10% and binarized. The mean FA, MD, AD, and RD were then extracted from these regions for each participant using FSL. Each region, including each DTI metric (FA, MD, AD, RD), was compared between groups (PCS, healthy control) using the non-parametric Mann Whitney U test in SPSS (SPSS 24, IBM corp.), and corrected for multiple comparisons using Holm-Bonferroni.

Correlation Analysis:

For correlation analysis, group data were combined and outliers which were greater than 3 standard deviations from the full sample mean were excluded. Normality (Levene's Test) was

then rechecked based on the total sample. Due to the violation of normality, the non-parametric

Spearman's Rho correlation analysis with 1000 sample bootstrapping was used.

A Spearman's correlation analysis was used to determine the association of both the total number

of symptoms and the symptom severity to each of the composite scores for the four visuomotor

conditions. In addition, the relationship between FA values of each ROI to the behavioural

components (the number of symptoms, the severity of symptoms, and the composite scores of

each condition) was analyzed. In order to minimize the number of correlations run, the FA

metric was chosen as it is the mostly commonly investigated measure of diffusion.

Results

Behavioural

Sport Concussion Assessment Tool:

The Mann-Whitney U test revealed that the number of symptoms reported by those with

PCS (Mdn = 11.0) was significantly higher than that reported by healthy controls (Mdn = 2.0)

(U=13.5, p<0.001, r = 0.72). Similarly, the severity of reported symptoms was significantly

higher in those with PCS (median = 21.0) compared to controls (median = 2.0) (U=16.0, p<.001,

r= 0.64). No other aspects of the SCAT3 were significantly different between groups after

correcting for multiple comparisons.

The most commonly reported symptoms by those with PCS include 'neck pain' (85%),

'fatigue/low energy' (85%), and 'headache' (77%). When looking at symptom severity, those

with PCS reported significantly greater severity of 'headache' (Mdn=1.0) compared to healthy

controls (Mdn=0.0) (U=27.5, p=0.001, r=0.64). Similarly, those with PCS reported significantly

greater severity compared to controls of 'pressure in head' (Mdn=1.0 and 0.0 respectively;

U=32.5, p=0.001, r=0.64), 'neck pain' (Mdn=2.0 and 0.0; U=16.0, p<0.001, r=0.75), and 'sensitivity to light' (Mdn=2.0 and 0.0; U=31.5, p=0.002, r=0.61). No other symptoms were significantly different between groups after correcting for multiple comparisons.

Visuomotor Task Performance (BrDI^{TM}):

For each of the composite scores, internal validity was tested using Cronbach's Alpha. This was then averaged across conditions for an overall measure of validity. The timing composite score consisted of 3 items (RT, TMT, inversed PV; α=.79), the trajectory composite score consisted of 3 items (AE, VE, FPL; α=.54), and the sub-movement composite score consisted of 2 items (%Submvt, #Submvt; α=.77). Group analysis was completed on each variable as well as each composite score for every condition (standard, PC, CR, PC+CR). For full results, refer to Table 3.1.

Timing Variables

Mann-Whitney U tests revealed that RT, TMT, and PV did not significantly differ between PCS and healthy controls in any condition (p>.05). However, while not statistically significant, it may be worth noting that the median values for all of these variables were slower for those with PCS in each condition. Similarly, when looking at the composite timing score, there were no significant differences found between the two groups, however those with PCS had a worse timing performance on all conditions based on the median score.

Trajectory Variables

There were no statistically significant differences between those with PCS and controls on AE, VE, or FPL in any of the conditions (p>.05). When looking at the overall trajectory composite score, those with PCS had a higher median score (and thus worse performance)

compared to healthy controls on the standard condition, but had a lower median score (and better performance) on the remaining conditions, however this was not statistically significant (p>.05).

Sub-movement Variables

The Mann-Whitney U test revealed that %Equal did not differ significantly between groups on any condition (p>.05). When looking at the median scores, both those with PCS and controls demonstrated equal movements, with no sub-movements, in the standard condition. The %SubMvt did not differ significantly between groups on any condition (p>.05); however those with PCS had a higher median percentage compared to controls in all conditions except PC+CR. Likewise, while there was no significant difference between those with PCS and controls on #SubMvt (p>.05), those with PCS had a higher median across all conditions compared to controls. When looking at the overall sub-movement score, those with PCS had a higher median score (and therefore worse performance) compared to healthy controls in all conditions except PC+FR, albeit not significantly different (p>.05).

Error Variables

Direction Reversal errors were only calculated for the conditions which included visual feedback reversal (CR, PC+CR). Those with PCS had a greater median percentage of direction reversals in the CR condition, while controls had a greater median percentage in the PC+CR condition, however neither was statistically significant (p>.05).

Diffusion Tensor Imaging

The voxelwise TBSS analysis demonstrated no significant differences in overall brain FA, MD, AD, or RD between groups (PCS, healthy control). When looking at the specific regions of interest, the Mann-Whitney U test revealed no significant group differences in FA along any white matter tract investigated, including left and right CST, SLF, ILF, IFOF, SCP,

MCP, ICP, and the CC. Similarly, no statistically significant group differences were noted in MD, RD, or AD in any of these regions (p>.05).

Correlation Analysis

Symptoms & Visuomotor Task Performance

All correlations were run based on overall composite scores (timing, trajectory, sub-movement). Spearman's Rho correlation analysis revealed a significant association between the overall trajectory score on the CR condition with both the number (r_s=-.563, p=.005) and severity of symptoms (r_s=-.623, p=.001). Specifically, as the number and severity of symptoms increased the trajectory score decreased (denoting improved performance). No other significant associations between either the number of symptoms or the severity of symptoms and any of the composite scores were found.

Symptoms & Regional White Matter Integrity

The relationship between both the total number of reported symptoms and the severity of symptoms and the FA of all regions of interest was investigated using Spearman's Rho correlation. No significant associations were noted between the FA of any region and the symptom number or severity (p>.05).

Visuomotor Task Performance & Regional White Matter Integrity

Spearman's Rho correlation was run to explore the relationship between composite scores in each condition and FA for each region of interest. No significant associations were found between any of the composite movement scores and FA in any of the regions of interest for the standard, PC, or CR conditions. However, in the PC+CR condition there was a statistically significant association between FA and the trajectory and sub-movement composite scores, but not the timing composite score. Specifically, a significant relationship was found

between the trajectory score and both the right (r_s=-.543, p=.006, see figure 3.2a) and left ILF (r_s=-.481, p=.017), as well as both the right (r_s=-.475, p=.019) and left IFOF (r_s=-.419, p=.041). In each region an increase on the rank of trajectory score (and thus worse performance) was associated with a decrease in FA. When looking at the sub-movement composite score, a significant relationship with FA values was noted in both the right (r_s=-.652, p=.001, see figure 3.2b) and left ILF (r_s=-.585, p=.003), both the right (r_s=-.547, p=.006) and left IFOF (r_s=-.596, p=.002), the left SLF (r_s=-.495, p=.014), and the left CST (r_s=-.423, p=.039). In all regions, an increase in the sub-movement score was associated with a decrease in FA.

Discussion

The results demonstrated that those with PCS had significantly worse symptom scores relative to healthy controls, but no other significant differences on the remaining aspects of the SCAT3. This finding is not surprising as presence of self-reported symptoms is required for the diagnosis of PCS, whereas the remainder of the SCAT3 has demonstrated reliability in only acute concussion[56]. Additionally, there were no statistically significant differences between groups on any of the visuomotor transformation task conditions, including both the standard task and those requiring CMI. Similarly, there were no group differences on any DTI metric, on either the global or regional level. Importantly, however, when groups were combined we found a significant association between white matter integrity along the long-coursing association tracts and performance on the most challenging CMI task, requiring two levels of dissociation (PC+CR).

There were no statistically significant differences between those with PCS and healthy controls on any of the visuomotor transformation tasks. However, when looking at the median

scores we note that those with PCS have worse timing scores and better (or equivalent) trajectory scores across all conditions. This helps to explain our finding that improved trajectory performance was significantly correlated with greater symptom reporting, as those with PCS may have improved movement execution compared to healthy controls. While these findings were not significantly different, it may indicate a speed-accuracy trade-off in those with PCS in that a slower reaching movement is required for accurate performance. In addition, those with PCS have a greater median number of errors and sub-movement scores in the standard, PC, and CR conditions but not in the PC+CR condition. It seems that healthy controls are making a similar number of errors and sub-movement corrections in this condition. This may indicate that the most difficult condition (PC+CR), in which both explicit and implicit rules are required, may not be sensitive to differences between these two groups. This has also been found in previous work from our laboratory[47], in which adults with mild cognitive impairment performed worse than controls in intermediate levels of non-standard mapping; yet, both groups performed poorly in the condition requiring the greatest amount of dissociation. Furthermore, this study found a similar result in that adults with mild cognitive impairment performed worse in timing measures, but not in trajectory measures. The authors hypothesized that this reflected an inability to plan actions, while the ability to execute the movement was not compromised. Therefore, the performance differences are not likely due to deficits at the neuromuscular level, but rather occur at the stage where one must integrate cognition with action[47].

While the median scores found in our study hinted at group differences similar to previous findings in our laboratory, these non-significant findings may also suggest that those with PCS do not demonstrate behavioural differences on rule-based visually guided movements. Recent studies investigating those with persistent symptoms for greater than 3 months have also

noted a lack of difference on behavioural tasks when compared to healthy controls[161,162].

Astafiev et al. (2015)[161] found equivalent performance on a visual tracking task between controls and those with PCS. However, they also noted abnormal activity (blood-oxygen-level-dependent signals) in those with PCS, specifically along the SLF. It was suggested that this might reflect a compensatory mechanism, where prolonged symptoms may result in adequate behavioural performance due to altered neural networks[161].

In addition to a lack of group differences on these visuomotor tasks, there was also a lack of associations with the number or severity of symptoms reported. In fact, as previously mentioned, the only statistically significant finding indicated that a greater number and severity of reported symptoms was associated with improved trajectory performance on the CR condition (in which those with PCS had a better median score). While the presence of reported symptoms is required for a diagnosis of PCS, this may not be the best indicator of neurological deficits following concussion. The definition of PCS has been controversial[73–77], with many studies finding similar symptom reporting in whiplash disorders[79,82], chronic pain[85], depression[86], and even in seemingly healthy individuals[87]. Therefore, it is essential to determine more objective measures in order to better understand persistent symptoms and the neurological effects of concussion which may lead to them.

While the underlying etiology of persistent symptoms following concussion is still unknown, it is believed to be caused by the axonal damage that occurs in the initial injury[69–71]. This mechanical shearing of axons leads to altered axonal membrane permeability and cytoskeletal breakdown which results in slowed conduction and deficits in neurotransmission[64,66]. This has been demonstrated in studies using DTI, in which a reduction in white matter integrity, measured by a decrease in FA, has been found[114,115,117]. Yet, in this study

we found no whole brain differences on any DTI metric (FA, MD, AD, RD) between those with

PCS and healthy controls. Equally, there were no group differences found on any extracted

region of interest, including the long-coursing and association tracts we examined (CST, SLF,

ILF, IFOF, CC), and the cerebellar peduncles (SCP, MCP, ICP). Comparable findings were

reported by Maruta et al. (2016)[162] who also found a lack of significant group differences on any

of the global DTI metrics between those suffering from persistent symptoms following

concussion and healthy sex- and age-matched controls. When looking at regional differences in

FA, they also demonstrated no statistically significant group differences. The lack of group

differences found in our study, as well as in the investigation by Maruta et al. (2016)[162], could

indicate that those with PCS do not have deficits in white matter integrity, and thus axonal

damage is not the underlying etiology of persistent symptoms. Alternatively, these results may

indicate that while DTI is currently the best method to detect white matter structural

abnormalities[102], it may not be sensitive enough to the subtle white matter pathologies of

persistent symptoms. In addition, it is important to remember that there may be a myriad of

reasons for symptoms to persist following concussion, including both psychological and

cervicogenic causes. Since this was not measured in the current study, we are unable to

determine if the symptoms reported were neurological in nature. There may also be a difference,

for the particular group that we tested, in 'motor skill reserve' based on sport experience, which

may play a role in mitigating behavioural changes following neural injury (Chapter 2).

   While there were no group differences on white matter integrity, we did observe an

association between FA and visuomotor task performance. This relationship strengthens the

previous findings from our laboratory that performance on our CMI task requires healthy white

matter integrity[9,22,23]. Moreover, while no significant correlations were found between FA and

performance in the standard (default) condition, the PC condition (which requires intrinsic sensorimotor recalibration), or the CR condition (which requires extrinsic, rule based strategic control), there were significant associations found in the PC+CR condition (in which both intrinsic and extrinsic recalibration is required). Both the trajectory composite score performance and the sub-movement composite performance were significantly correlated with FA along several long-coursing tracts, including the ILF, IFOF, SLF, and CST. In all cases, a worse performance score was associated with decreased white matter integrity. These results provide further evidence that by decoupling our vision and action in two ways, requiring both implicit and explicit rule integrations, there is an increase in task complexity that relies upon large-scale brain network integrity for successful performance.

This study adds to the small body of literature investigating the effects of PCS on both behaviour and the underlying white matter integrity. To our knowledge, it is the first study to investigate the effects of PCS on cerebellar peduncle integrity, and the first study to look specifically at performance on visuomotor tasks requiring CMI in this population. Future research with a larger sample size is required. Additionally, investigation into the underlying cause of symptom reporting, including cervicogenic and psychological reasons, is needed in order to better understand the variability seen within this population. Moreover, longitudinal studies, in which neurological and behavioural changes can be tracked over time, are required in order to better understand their progression after injury, and therefore may help to determine ideal intervention strategies. Lastly, this study looked specifically at females due to the known neurological differences in both concussion response and skilled movement control between the sexes[163–167]. Consequently, a study investigating males is needed, as well as research into sex, gender, and movement control following brain injury more generally.

In the end, there were no statistically significant differences between those with PCS and healthy controls on the behavioural measures of CMI, nor on either the global or regional measure of white matter integrity. Irrespective, this study highlights the effectiveness of our CMI task in measuring the integrity of long-coursing white matter tracts. We speculate that with a larger sample size, and one that is more uniform in the cause of symptom reporting, we may be able to detect group differences in both white matter integrity as well as task performance. Lastly, these results demonstrate the need for further studies on this diverse population in hope of better understanding the underlying neurological effects and behavioural changes of persistent symptoms in order to improve the definition and thus diagnosis of PCS.

Table 3.1

Kinematic variables	Group	standard	plane-change (PC)	cue-reversal (CR)	plane-change + cue-reversal (PC+CR)
			Condition		
Timing Composite	Control	44.04	48.78	38.86	47.60
	PCS	66.54	61.65	60.46	65.70
RT (ms)	Control	355.00	351.00	513.00	494.00
	PCS	365.00	385.00	530.00	567.00
TMT (ms)	Control	331.00	538.00	477.00	763.00
	PCS	436.00	608.00	640.00	909.00
PV (mm/ms)	Control	130.89	102.19	103.81	73.42
	PCS	104.50	86.74	83.32	63.92
Trajectory Composite	Control	48.40	49.69	45.04	44.26
	PCS	52.39	40.99	43.62	33.00
AE (mm)	Control	2.50	3.58	3.25	4.87
	PCS	2.40	3.04	3.27	3.97
VE (mm)	Control	2.32	2.78	3.12	4.37
	PCS	2.42	3.10	2.63	3.74
FPL (mm)	Control	39.40	39.38	39.55	40.61
	PCS	39.92	39.10	39.73	40.82
Sub-Movement Composite	Control	49.28	44.34	49.79	53.22
	PCS	67.26	47.36	65.12	46.56
%SubMvt (%)	Control	6.25	50.00	36.84	73.33
	PCS	12.50	53.33	53.33	62.50
#SubMvt (#)	Control	0.06	0.56	0.41	1.00
	PCS	0.13	0.57	0.57	1.06
%Equal (%)	Control	100.00	71.43	78.95	66.67
	PCS	100.00	78.57	78.57	69.23
DR (%)	Control	0.00	0.00	7.14	8.33
	PCS	0.00	0.00	7.69	5.56

AE: absolute error; DR: direction reversal errors; FPL: full path length; PV: peak velocity; RT: reaction time; TMT: total movement time; VE: variable error; %Equal: percent of trials with no corrective movements; %SubMvt: percent of trials with sub-movements; #SubMvt: mean number of sub-movements per trial. No significant differences between groups were found (p>.05).

Table 3.1 Median scores between groups (PCS, healthy control) on kinematic variables of each visuomotor task condition
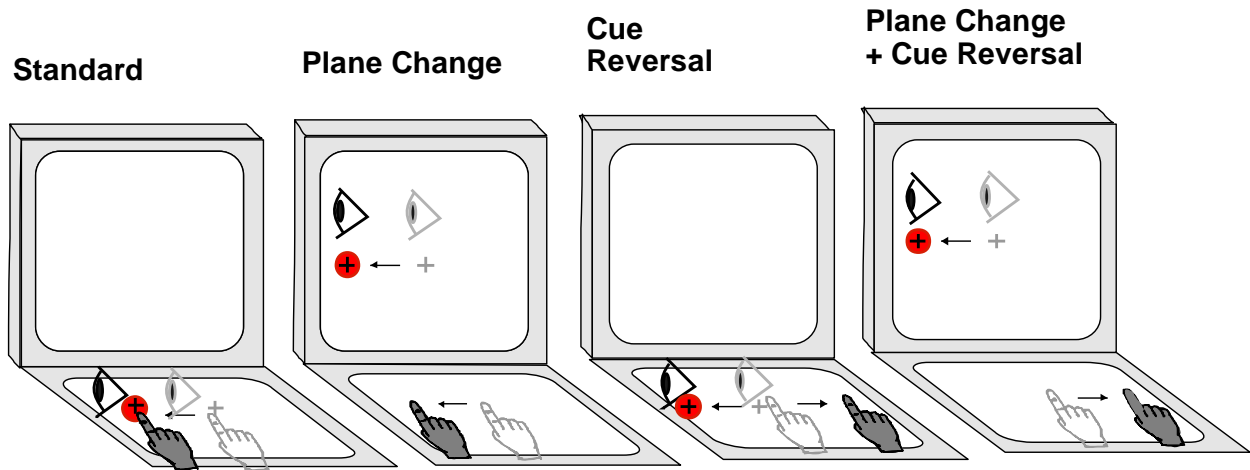
Figure 3.1 Schematic drawing of the four experimental conditions.

Visual stimuli were presented on either the vertical or horizontal monitor, while movement direction was either towards the target or 180° reversed. Light grey cursor, eye, and hand symbols denote the starting position for each trial (home target). Dark 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, down). The dark crosshair denotes the cursor feedback provided during each condition.
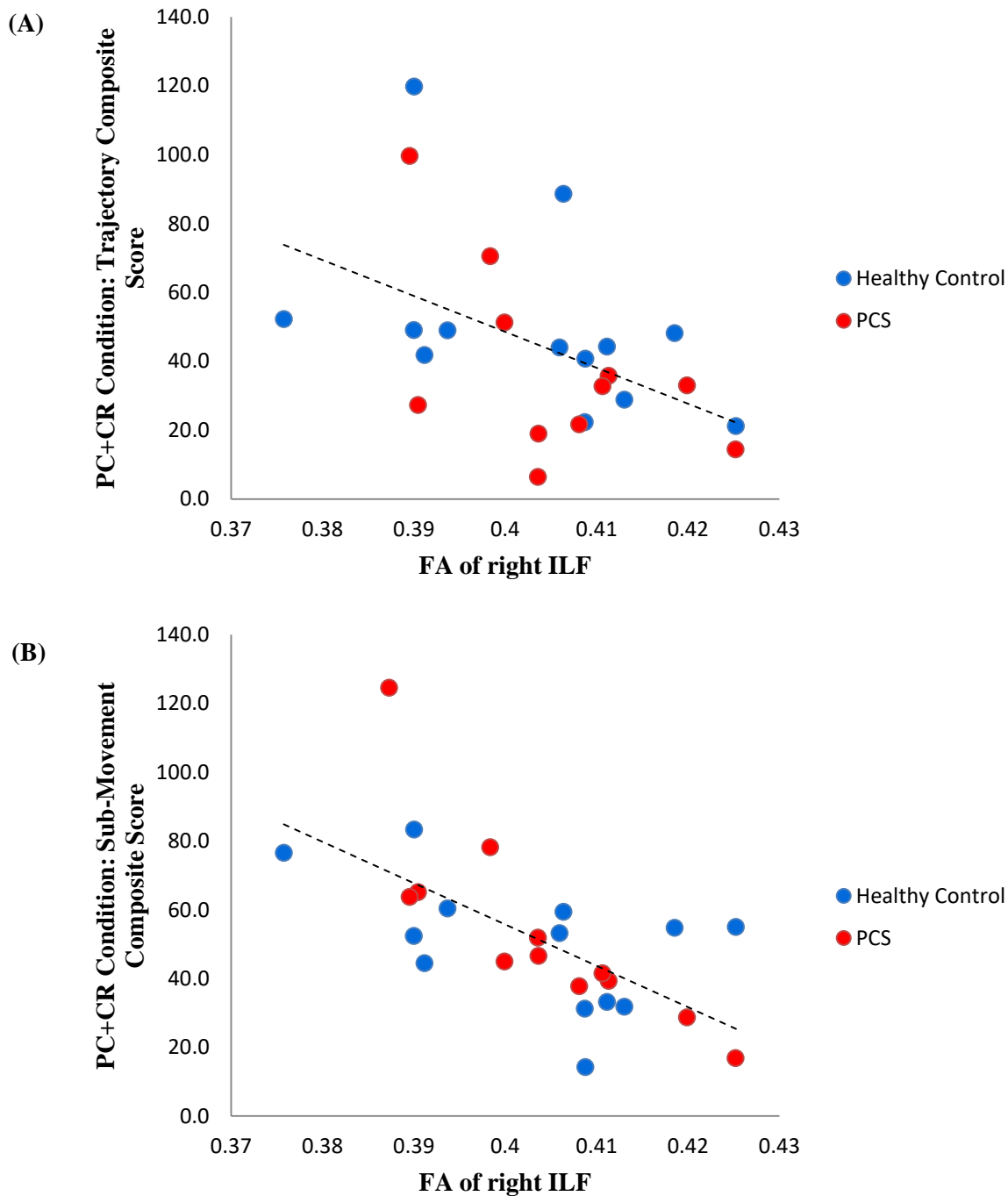
Figure 3.2 Graphical representation of the relationship between the FA of the right ILF and performance on the PC+CR task

The composite scores reflect an overall score, with a higher score indicating worse performance. Significant associations were found with **(A)** the trajectory composite score (r_s=-.543, p=.006) and **(B)** the sub-movement composite score (r_s=-.652, p=.001). Red circles denote individual participants with PCS, while blue denotes healthy control participants.

FA: fractional anisotropy; ILF: inferior longitudinal fasciculus; PC+FR: plane-change with cue reversal.

Chapter Four

Cortical and cerebellar structural correlates of cognitive-motor integration performance in females with post-concussion syndrome

Johanna M. Hurtubise, Diana J. Gorbet, Loriann Hynes,
Alison K. Macpherson, Lauren E. Sergio

Abstract

Background: Fifteen percent of individuals who sustain a concussion develop post-concussion syndrome (PCS), however the underlying etiology of these persistent symptoms is poorly understood. Recent literature has demonstrated atrophy and thinning of the cortex following concussive injury, specifically in frontal and parietal regions; however this has not been examined in those suffering from PCS. Furthermore, atrophy of the cerebellum and its lobules has been found in moderate to severe brain injury and murine models, but has not been fully investigated in humans with mild brain injury. The frontoparietal-cerebellar network is essential for performance of visuomotor transformation tasks requiring cognitive-motor integration (CMI). Previous work from our laboratory has demonstrated behavioural deficits in tasks requiring CMI in those who have a history of concussion, but were asymptomatic. **Purpose:** The purpose of this study was to investigate cortical and subcortical structural differences between those with PCS and healthy controls. In addition, we examined if these structural differences were associated with performance on a CMI task. **Methods:** Twenty-six female participants (13 with PCS for 6 months or greater and 13 healthy controls) completed four computer-based visuomotor CMI tasks. In addition T1-weighted structural MR-images were acquired, and analyzed for cortical thickness and volume, and cerebellar lobule volume. **Results:** No statistically significant differences were found in CMI performance between groups. However, those with PCS demonstrated a significantly thicker and larger precuneus, and significantly smaller cerebellar lobules (VIIIa, VIIIb, X) compared to healthy controls. While no statistically significant differences were found in CMI performance between groups, when looking at the groups combined, volumes of both the cerebellar lobules and cortical regions (within the frontal and parietal lobes) were associated with performance on the visuomotor tasks requiring CMI.

Conclusion: The lack of behavioural differences combined with the structural differences (i.e. larger precuneus) may reflect a compensatory mechanism for those with PCS. Further investigation into the interaction between psychological and injury factors following concussion will strengthen our understanding of these structural differences. Nonetheless, this study highlights the effectiveness of our CMI task in measuring the structural integrity of the frontoparietal-cerebellar network, and is among the first to demonstrate structural correlates of PCS.

Background

Concussions, a form of mild traumatic brain injury, affects an estimated 1.6-3.8 million Americans each year[54]. Of these, 10-15% will develop post-concussion syndrome (PCS)[4,56], in which symptoms persist beyond the typical recovery period[59–62]. These persistent symptoms can lead to long-term disability, costing approximately $17 billion dollars each year in direct expenses and lost income[63]. Therefore, it is important to better understand the underlying effects of PCS in order to improve recovery. The etiology of persistent symptoms is poorly understood. However, it is believed that PCS has both psychological and biological aspects[73,74,88]. Biologically, it has been suggested that axonal damage, sustained in the initial injury, leads to impaired neurotransmission and speed of processing[64,69]. Cerebral atrophy is known to occur after traumatic brain injury involving diffuse axonal injury (DAI)[91]. Therefore, since axonal injury is also the suggested etiology of concussion and PCS, structural changes may also occur after mild brain injuries or concussions. Studies investigating both acute and subacute concussive injuries have found cortical thinning in those who sustained a concussion compared to healthy controls[92,93]. Specifically, this was found within the frontal lobe (dorsolateral prefrontal cortex, DLPFC; precentral region, M1) and parietal lobe (inferior parietal lobe, IPL). Similarly,

longitudinal studies, over the course of a year following mild traumatic brain injury (mTBI), have also demonstrated cortical thinning and cortical volume loss in the frontal and parietal lobes[94,96]. For example, a study by Zhou et al. (2013)[96] demonstrated a decrease in the volume of the right precuneus in those who had sustained a head injury, but not in healthy controls. While these studies establish that frontoparietal regions are sensitive to structural changes after concussion, this was investigated in those with acute and subacute concussion, or those who have recovered from the initial injury. To our knowledge, there is an absence of literature investigating potential anatomical changes in those suffering from persistent symptoms and PCS.

Likewise, there is a lack of research examining volume differences in subcortical regions, especially the cerebellum, a structure crucial to many aspects of daily living. Studies on moderate to severe brain injury have found cerebellar atrophy, even when it was not the location of focal injury[97]. In the same way, animal models on mTBI have also noted this decrease in cerebellar volume following injury[98,99]. Yet, the effect of concussion on cerebellar volume is poorly investigated in humans. One study noted no volume differences in any subcortical regions, including cerebellar lobules; however this study only included males who sustained their concussion within the past three months[93]. A study by Ross et al. (2012)[90] looked specifically at those with persistent concussive symptoms and found that, when compared to controls, those with PCS had greater atrophy over the course of a year in overall cerebellum volume. In addition, this correlated with poorer vocational outcomes in those with persistent symptoms. This study, however, did not look at the individual cerebellar lobules, leaving open questions around the effect of concussion on this structure.

Based on these human and animal model findings, it appears that the regions of the frontal and parietal lobe, as well as the cerebellum, are the most commonly affected following

concussion. Therefore, it is reasonable to assume that behavioural tasks requiring these regions for performance would also be affected by the injury. As such, behavioural performance might demonstrate an indirect measure of the structural integrity of the underlying brain network. This frontoparietal-cerebellar network is essential for the visuomotor transformation required for reaching[14–16], such as in cognitive-motor integration (CMI) tasks, in which a rule is used to align the required motor output and the guiding visual information[1,2]. Previous studies from our laboratory have demonstrated deficits in CMI performance in those with a history of sport-related concussion including children and adolescents[53], university-aged athletes[52], and elite athletes[147]. Here we seek to extend these findings to individuals with PCS, given the neurophysiological and behavioural findings in those with concussion history. The primary objective of this study was to investigate cortical volume and thickness differences as well as cerebellar volume differences in females suffering from PCS compared to healthy controls. Secondly, we aim to examine if these structural differences are associated with performance on a CMI task. We hypothesize that those with PCS will demonstrate behavioural deficits on a CMI task and exhibit structural deterioration in frontal, parietal, and cerebellar regions compared to healthy controls.

Methods

Participants:

The same participants from Chapter three were included in this study. To reiterate, 13 pairs of female participants, for a total of 26, were included. Thirteen participants had PCS as defined by Tator et al. (2016)[60] as 3 or more symptoms persisting for greater than 1 month after concussive head injury. PCS participants were included if their symptoms had persisted for 6

months or longer at the time of data collection (mean = 36 months). Thirteen age-matched

controls (±1 year) were recruited with no self-reported history of concussion. A self-reported

concussion was determined as a concussive incident (as defined by the 4th International

Consensus on Concussion in Sport[121]) in which there was either a diagnosis by a medical

physician or in which the date and mechanism of injury was recalled. None of the participants

had been diagnosed with a neurological disease, sustained their head injury due to a motor

vehicle accident, or were deemed unsafe to undergo MR imaging. All participants were right-

handed, with no injury (other than PCS) that would prevent them from participating in physical

activity or sport. Upon examination of MR images, it was confirmed that none of the participants

included in the study had any gross morphological abnormalities. Information about the

concussive injury, including the number of previous concussions and length of time since the

concussion, was collected through a questionnaire.

This study was approved by York University research ethics committee, and all

participants provided informed written consent.

Procedure:

All participants completed the Sport Concussion Assessment Tool 3rd Edition (SCAT3), a

computerized CMI task (BrDI^{TM}) involving 4 visuomotor transformation conditions, and

structural T1-weighted MR imaging.

Sport Concussion Assessment Tool 3(SCAT3):

The full description of the SCAT3 can be found in Chapter 3. Briefly, the SCAT3[121]

incorporates a symptom inventory, a cognitive component, and a motor component. The

symptom inventory consists of 22 commonly reported symptoms which were self-rated on a 7-

point Likert scale from 0 (no issue) to 6 (severe). Both the number of symptoms and the sum of

all reported symptoms (the symptom severity score) were calculated, with a higher score reflecting worse symptom reporting. The cognitive aspect (the Sideline Assessment of Concussion) measures cognitive ability over 4 subdomains for a maximum score of 30; a higher score indicates higher cognitive ability. Lastly, the motor component is comprised of both a balance measure (the modified Balance Error Score System), where a higher score designates worse balance, and a coordination measure, which is scored as an ability to complete the task or not.

Visuomotor Task (BrDI^{TM}):

The visuomotor assessment is described in detail in Chapter 3. Briefly, participants completed four visuomotor transformation task conditions presented on a 10.1" ASUS Transformer Book tablet connected to a 15" external monitor to allow for a screen in both the horizontal and vertical planes. All reaching movements were made on the tablet, and in each condition the participant was instructed to slide their index finger of their right (dominant) hand along the touch screen tablet in order to displace a cursor from a central target to one of four peripheral targets as quickly and as accurately as possible. The four conditions were as follows: (i) the standard condition, in which CMI was not required as participants looked at and moved on the tablet; (ii) plane-change (PC), in which participants looked at the vertical monitor screen while moving on the horizontal tablet screen; (iii) cue reversal (CR), in which participants looked and moved on the tablet but the cursor feedback was rotated 180°; and (iv) plane change with cue reversal (PC+CR), in which the prior two conditions were combined, thus requiring two levels of visual-motor decoupling.

Custom analysis software (Matlab, Mathworks Inc.) was used to process individual movement paths in order to generate a velocity profile for each movement. Each movement was

individually inspected and scored in order to compute movement timing and execution outcome measures. In order to minimize the number of variables for correlation analyses, a composite score was calculated using a 'simple averaging' approach[149]. The timing composite score included: reaction time (RT), total movement time (TMT), and peak velocity (PV). The trajectory composite score included: full path length (FPL), absolute error (AE), and variable error (VE). Finally the sub-movement composite score included: the percent of trials with sub-movements (%SubMvt), and the average number of sub-movements per trial (#SubMvt). For ease of interpretation, each composite score was transformed (based on a mean of 50 and a standard deviation of 10), with a higher score indicating worse performance.

Behavioural Data Analysis:

Behavioural data analysis was previously described in Chapter 3. Briefly, all data were checked for normal distribution (Shapiro-Wilk's test) and homogeneity of variance (Levene's test). Since the behavioural data were skewed, non-parametric tests were used. Statistical significance levels were set a-priori to $p < 0.05$. Statistical analyses were performed using SPSS statistical software (SPSS 24, IBM Corp).

The Mann-Whitney U test was run to test the main effect of group (PCS, healthy control) on SCAT3 scores. Furthermore, the Mann-Whitney U test was used to analyze composite scores between groups (PCS, healthy control) for each condition.

Imaging Acquisition and Parameters:

MRI data were acquired using a 3 Tesla Siemens Tim Trio scanner at York University using a 32 channel head coil. High resolution whole-brain T1-weighted images were obtained using 3D magnetization prepared rapid acquisition gradient echo (MP-RAGE; TR = 2300ms, TE

= 2.62ms, slice thickness = 1.0mm, voxel size = $1.0mm^3$, FOV = $256mm^2$, flip angle = 9°). A total of 192 sagittal slices were obtained, with no gap.

Imaging Analysis:

Cortical reconstruction and volumetric segmentation was performed using FreeSurfer imaging analysis software suite (Version 6.0, www.surfer.nmr.mgh.harvard.edu)[168]. Briefly, the preprocessing steps included motion correction, intensity normalization, and transformation to Talairach space[169,170]. Skull-stripping and removal of non-brain tissue was then performed on the intensity normalized image using a deformable template model[171]. This was then visually inspected and manually edited if required. Voxels were then classified as either white matter or other based on intensity values. This was, again, visually inspected and manually edited if required. This process was then followed by segmentation of subcortical structures and tessellation of the cortical surface (consisting of a triangular mesh) so that the position of the triangle vertex followed the intensity gradient between the white and gray matter (referred to as white surface) and between the gray matter and cerebral spinal fluid (referred to as pial surface). All surfaces were constructed in the individual anatomical space[170,172]. Again, the images were visually inspected and manually edited if required. These surfaces were inflated into a sphere and registered to the FreeSurfer template sphere (fsaverage, based on 40 participants). This non-linear surface-based registration allowed for more accurate alignment of the gyri and sulci landmarks[173,174]. A cortical parcellation of the template was then mapped back onto the individual subject and adjusted for small variations. The cortical parcellation was founded on the Desikan-Killiany atlas, a gyral-based atlas established using 40 participants[175] (see Figure 4.1). The distance between the white and pial surfaces was used to determine the thickness at each cortical location[172]. The procedures for the calculation of cortical thickness have been validated

against histological analysis and manual measurement[176,177]. The gray matter volume was computed as the area of a vertex times the thickness, where area is defined as the average area of the triangles in which that vertex is a member[178]. The morphometric procedures of FreeSurfer have demonstrated good test-retest reliability across scanner manufacturers and field strengths[179].

Total intracranial volume (TIV) was calculated using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL, v5.0)[150], which has been found to be a robust measure of total brain volume[180,181]. Brain tissue volume, normalized for head size, was estimated with SIENAX, part of FSL[153,182]. First, the non-brain tissue is removed from the image using the brain extraction tool (BET)[151], and is registered to a standard space (MNI152) using FMRIB's Linear Image Registration Tool (FLIRT)[183]. Segmentation is completed using FMRIB's Automated Segmentation Tool (FAST)[184]. The non-normalized (i.e. in subject space) total intracranial volume is calculated as total gray matter, white matter, and cerebrospinal fluid.

The cerebellum (including brainstem) was extracted using the Spatially Unbiased Atlas Template (SUIT) toolbox within the Statistical Parametric Mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm/, installed in MATLAB version 2014, Natick, Massachusetts, The MathWorks, Inc), and left in subject space[185] (see Figure 4.2). Total cerebellum volume (including total white matter and grey matter) was calculated using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL, v5.0)[150]. A ratio of cerebellum volume to brain size was then calculated as a proportion of the TIV (to account for differences in brain sizes between participants). The cerebellum was further parcellated into 28 lobules using SUIT-cerebellum within SPM12[186](see Chapter 1, Figure 1.4c). The volume of each lobule was then corrected for TIV using a proportion method.

Statistical analysis of imaging:

Global cortical thickness was compared between groups using Freesurfer (version 6.0). First the data were assembled (resampling each participant's image into a common space) and smoothed at a full-width/half-max (FWHM) of 10mm. A z-distribution Monte Carlo simulation with 5,000 permutations was then applied to correct for multiple comparisons using a cluster-forming threshold of $p<0.01$[187,188].

In addition, the volume and thickness of cortical regions of interest were examined. These regions were determined a-priori and known to be involved in the frontoparietal network for visually-guided reaching[2,9,189]. Regions in the parietal lobe included the right and left superior parietal lobe (SPL), inferior parietal lobe (IPL), and precuneus. In the frontal lobe, regions of interest included the right and left precentral, superior frontal, rostral middle frontal (rMFG), and caudal middle frontal (cMFG) regions. Lastly, the cuneus, which is a region within the occipital lobe, was also investigated. Both the thickness and volume were extracted from each subject using the Desikan-Killiany cortical parcellation atlas[175] (see Figure 4.3). The cortical parcellation of the FreeSurfer template was mapped back onto the individual subject and adjusted for small variations. The values of each individual subject's thickness and volume of the aforementioned regions were then extracted, with structural volumes were corrected for TIV using a proportion method. Statistical analysis was then conducted using IBM SPSS Statistics (version 24). Data were checked for normality (Shapiro-Wilk's) and homogeneity of variance (Levene's). Non-parametric tests (Mann-Whitney U) were used to compare regional thickness and volume between groups (PCS, healthy control) due to violations of normality.

Total cerebellum volume and cerebellar lobule volumes (calculated as a proportion of total TIV) were analyzed using IBM SPSS statistics (version 24). Data were checked for normal

distribution (Shapiro Wilks') and homogeneity of variance (Levene's). Due to the violations of normality, non-parametric tests (Mann-Whitney U) were used to compare the total cerebellum volume as well as cerebellar lobule volumes between groups (PCS, healthy controls).

Correlation Analysis:

Correlation analyses were run on collapsed group data. Data points which were greater than 3 standard deviations from the total group mean were considered outliers and removed from further analysis. Due to violations of normality, non-parametric correlation analyses (Spearman's Rho) with bootstrapping (1000 samples) were used to investigate the associations between cortical thickness and cortical volume of each region of interest and both the number and severity of symptoms reported. Similarly, Spearman's correlation analysis was run to explore the relationship between cortical thickness and volume to the composite performance scores (timing, trajectory, sub-movement) of each visuomotor task. The association between total cerebellum volume to both the number and severity of symptoms, as well as to each composite performance score was analyzed using Spearman's Rho non-parametric correlation analysis. Likewise, a Spearman's correlation was run to investigate the relationship between the volumes of cerebellar lobules (in which a statistically significant group difference was found) and the number and severity of symptoms reported, as well as each composite performance score. Lastly, the relationship between the volumes of each cortical region of interest and the volumes of cerebellar lobules in which there were significant group differences was analyzed using Spearman's correlation analysis using IBM SPSS Statistics (version 24).

Results

Behavioural

      The results of the Mann-Whitney U test in which groups (PCS, healthy controls) were compared on each component of the SCAT3, as well as on the performance composite scores for each condition of the visuomotor task are described in Chapter 3. Briefly, those with PCS demonstrated a significantly greater number (Mdn=11.0, U=13.5, p<.001, r=0.72) and severity (Mdn=21.0, U=16.0, p<.001, r=0.64) of reported symptoms compared to healthy controls (Mdn=2.0, Mdn=2.0 respectively).

      Furthermore, there were no statistically significant differences between groups on any of the composite performance scores (timing, trajectory, sub-movement) in any of the conditions of the visuomotor task. When looking at median scores, it was noted that for the composite timing score those with PCS had a higher score (and therefore worse performance) on each condition. Similarly, for the sub-movement composite score those with PCS performed worse on each condition, except in the PC+CR condition, while for the trajectory composite score, those with PCS had a lower median score (and thus better performance) on the conditions requiring CMI (Full results can be found in Chapter 3, Table 3.1).

Structural Imaging

Cortical Thickness & Volume

      There were no statistically significant differences between groups in whole brain cortical thickness. When looking at the thickness of cortical regions of interest, the Mann-Whitney U test revealed a statistically significant difference between PCS and healthy controls in the cortical thickness of both the left (U=39.0, p=.02, r=0.46) and right precuneus (U=46.0, p=.048, r=0.39). In both hemispheres, those with PCS demonstrated a significantly greater median thickness (left,

Mdn=2.59mm; right Mdn=2.63mm) than controls (left, Mdn=2.48mm; right Mdn=2.52mm). No other statistically significant differences between groups were noted (Table 4.1).

The Mann-Whitney U test was used to test the difference in cortical volume between groups (PCS, healthy control). A statistically significant difference between groups was found in the left precuneus (U=39.0, p=.02, r=.46). Specifically, those with PCS had a significantly larger volume (Mdn=0.0089mm^3) than healthy controls (Mdn=0.0083mm^3). No other regions demonstrated a statistically significant difference between groups (Table 4.2).

Cerebellum Parcellation

The Mann-Whitney U test revealed no statistically significant differences in the proportion of total cerebellum volume between those with PCS (Mdn=0.216mm^3) and healthy controls (Mdn=0.221mm^3; U=52.0, p=.096).

When looking at the 28 lobules, the Mann-Whitney U test found that those with PCS had a significantly smaller volume of left VIIIa (Mdn=0.0052mm^3) compared to healthy controls (Mdn=0.0057mm^3; U=6.0, p=.048, r=0.39). In addition, there was a statistically significant difference in volume percentage of the left VIIIb (U=44.0, p=.038, r=0.41), with those with PCS having a smaller volume (Mdn=0.0043mm^3) compared to controls (Mdn=0.0047mm^3). Similarly, compared to controls, those with PCS had a statistically smaller volume of both the right (U=41.0, p=.026, r=0.44; Mdn=0.00081mm^3, Mdn=0.00076mm^3 respectively) and left lobule X (U=43.0, p=.033, r=0.42; Mdn=0.00034mm^3, Mdn=0.00031mm^3 respectively). See Table 4.3 for full results.

Correlation Analysis

Cortical Regions of Interest & Symptoms

Spearman's Rho correlation analysis revealed no significant associations between either the number or severity of symptoms reported and cortical thickness of any region (p>.05).

When looking at cortical volume, Spearman's correlation demonstrated a statistically significant relationship between the volume of the left precuneus and the number of symptoms reported (r_s=.412, p=.037), in that as the volume increased the number of reported symptoms also increased. There was no significant association between this region and the total severity of symptoms reported. Similarly, no other cortical regions demonstrated a significant correlation with either the number or severity of symptoms (p>.05).

Cortical Regions of Interest & Visuomotor Task Performance

When looking at cortical thickness, Spearman's correlation revealed no statistically significant relationship to any composite scores in either the standard condition or the PC condition. In the CR condition, there was a statistically significant association between the sub-movement score and the thickness of the left IPL (r_s=-.465, p=.026), such that as thickness increased the composite score decreased (denoting improved performance). Lastly, in the PC+CR condition, significant associations were found between cortical thickness and timing, trajectory, and sub-movement scores. Specifically, the timing score was correlated with the thickness of the right IPL (r_s=-.424, p=.039), and similarly, the sub-movement score was also correlated with the right IPL (r_s=-.515, p=.010). Finally, the trajectory score was correlated with the thickness of the left precuneus (r_s=-.547, p=.006). In all regions an increase in thickness was associated with a decrease in composite score, and thus improved performance.

Spearman's correlation was also run in order to determine the association between the visuomotor composite scores and the volume of each of the cortical regions of interest. The correlation analysis demonstrated no statistically significant associations between any regional volume and composite scores of the standard condition. In the PC condition, significant associations were found between the sub-movement composite score and volume of the left (r_s=-.433, p=.031) and right SPL (r_s=-.423, p=.035), and the left (r_s=-.433, p=.031) and right (r_s=-.423, p=.035) superior frontal region. In each region it was found that as volume increased the sub-movement score decreased, which denotes improved performance. In the CR condition, Spearman's correlation demonstrated only one significant association; the trajectory score was correlated with the right rMFG (r_s=-.426, p=.043). Once again, as volume increased the trajectory score decreased. Finally, in the PC+CR condition, significant correlations were found between the composite trajectory score and the volume of the right IPL (r_s=-.492, p=.015), the left rMFG (r_s=-.429, p=.037), and both the left (r_s=-.405, p=.049) and right precuneus (r_s=-.629, p=.001; Figure 4.4). Similarly, the sub-movement composite score was also associated with the volume of the right precuneus (r_s=-.528, p=.008). In each case, an increase in volume was associated with a decrease in the composite score (and thus improved performance).

Cerebellum Lobules & Symptoms

Spearman's correlation analysis revealed no statistically significant associations between the total cerebellum volume and either the number or severity of reported symptoms (p>.05). When looking at the lobules which differed significantly between groups (left VIIIa, left VIIIb, left X, right X), it was noted that the volume of the left VIIIa lobule was significantly correlated with both the number (r_s=-.425, p=.030) and severity of symptoms (r_s=-.393, p=.047). In both

cases, the increase in the number or severity of symptoms was associated with a decrease in volume. No other statistically significant associations were found.

Cerebellum Lobules & Visuomotor Task Performance

Spearman's correlation analysis demonstrated no statistically significant associations between the total cerebellum volume and any of the performance composite scores (timing, trajectory, sub-movement) from any of the conditions of the visuomotor transformation task.

In the same way, no statistically significant correlations were noted between the cerebellar lobules and the composite scores in the standard condition. In the PC condition, Spearman's correlation analysis revealed a statistically significant relationship between the timing composite score and volume of the left VIIIa lobule (r_s=-.404, p=.045), in that as volume increased the timing score decreased (denoting improved performance). Likewise, in the CR condition, there was a significant correlation between the timing composite score and the left lobule VIIIa (r_s=-.423, p=.044, Figure 4.5), where again as volume increased the timing score decreased. In this condition there was also a significant relationship between the composite trajectory score and the volume of the left lobules X (r_s=.438, p=.037). However, in this case as volume increased the trajectory score also increased (signifying worse performance). Finally, in the PC+CR condition, there were no statistically significant associations found.

Cerebellum Lobules & Cortical Regions of Interest

Spearman's correlation analysis was run on the total cerebellum volume and the volume of each of the cortical regions of interest. No statistically significant associations were found (p>.05).

To investigate the relationship between the volume of the cerebellum lobules (left VIIIa, left VIIIb, left X, right X) and the volume of each of the cortical regions of interest, a

Spearman's Rho correlation analysis was used. A statistically significant association was revealed between the volume of the left lobule VIIIa and the left precuneus (r_s=-.458, p=.018, Figure 4.6). Likewise, the volume of the left lobule VIIIb was significantly correlated with the volume of both the left (r_s=-.455, p=.020) and right precuneus (r_s=-.405, p=.040). In each case as the volume of cerebellar lobule (VIIIa, VIIIb) decreased, the volume of the precuneus increased. No other regions were found to be significantly associated.

Discussion

The results demonstrate that those with PCS have significantly thicker and larger grey matter volume of the precuneus when compared to healthy age-matched controls. In addition, those with PCS have a significantly smaller volume in cerebellar lobules including the left VIIIa, left VIIIb, left X, and right X. The volume of both the precuneus and the left lobule VIIIa are also both significantly associated with the number of self-reported symptoms. Furthermore, there was a significant relationship between the volume of the left lobule VIII (VIIIa and VIIIb) and the precuneus, where a smaller cerebellar lobule was associated with a larger precuneus volume. When looking at performance on the visuomotor tasks, there were no significant differences between groups. However, there was a significant correlation between the volume of the left lobule VIIIa and performance on tasks requiring CMI. Finally, performance on CMI tasks were also associated with both the volume and thickness of cortical regions of interest including both frontal (rMFG, superior frontal) and parietal regions (IPL, SPL, precuneus), across both groups.

Cortical Regions of Interest

No cortical regions demonstrated cortical thinning or decreased volume in those with PCS compared to controls. In contrast, those with PCS had a both a thicker and larger volume of

the precuneus, a region located in the medial parietal cortex. These results do not support our initial hypothesis, in which we speculated there would be a decrease in gray matter structure. However, previous research, in which cortical atrophy was noted, was conducted on acute, sub-acute, or asymptomatic individuals, and thus may not reflect the underlying neuropathology of those with persistent symptoms. A few studies have also found evidence of increased cortical volume or thickness following head related injury[190,191]. Albaugh et al. (2015)[191] investigated adolescent male hockey players with and without a history of concussion, and found that those with no concussive history demonstrated typical age-related cortical thinning, while those who had previously sustained a concussion had no thinning. Comparably, Wang et al. (2015)[190] looked at motor vehicle collision survivors who had sustained an mTBI compared to those who had not and found an initial increase in cortical thickness in both the left rMFG and right precuneus. While the thickness of the rMFG decreased over the 3 months following injury, the thickness of the precuneus did not. Furthermore, the precuneus thickness was positively correlated with the number of days of reduced daily activity, as well as the number of post-traumatic stress symptoms. It is possible then, that the increased thickness we found in our study is related to psychological distress or mental health, which is a large factor of post-concussion syndrome.

When looking at the literature of structural changes due to mental health the results are conflicting. Some studies have noted reductions in gray matter volume in those with depression[192], while others have found a positive association between cortical thickness and the severity of depressive symptoms reported[193]. Brül et al. (2014)[194] found a significantly greater cortical thickness in the right frontal and parietal lobes, including the DLPFC, SPL, IPL, and precuneus, in those with social anxiety disorder compared to healthy controls. The authors

suggest this could reflect potential compensatory effects and deregulated networks. Because we did not assess for mental health factors or psychological distress, we cannot draw conclusions on whether the results of our study reflect differences in thickness due to the concussive injury itself or the psychological consequences associated with the injury. Yet, as suggested by Brül et al. (2014)[194], the cortical thickness seen in our results may reflect a compensatory mechanism, which could be due to both the psychological effects and the physiological effects arising from the concussion itself.

Research has suggested that compensatory mechanisms also occur after brain injury. In a study on moderate-to-severe brain injury, an association was found between increased cortical thickness within the frontal, parietal, and temporal regions and slower reaction time on a working memory task[195]. In addition, fMRI results from this study found decreased activation within the frontal regions with greater activation in the posterior parietal regions compared to orthopedic injury controls, suggesting a greater reliance on posterior regions for task performance. Greater activity within brain regions outside of the core task regions has also been found following concussion[139,196–199]. For instance, Chen et al. (2004)[198] looked at male athletes with persistent symptoms following concussion compared to healthy controls on a verbal memory task. They found that while the two groups did not differ on behavioural performance, those with persistent symptoms had differing brain activation during the task. Specifically, those with concussion had significantly decreased activation in the DLPFC, with a subsequent increase of activation in posterior frontal and parietal regions. This would suggest compensation by the brain in order to have normal behavioural performance.

In our study, we also found a lack of behavioural differences between groups, therefore, the increase in thickness and volume of the precuneus may reflect compensation by the brain for

adequate behavioural performance, resulting in structural changes within this region. Further research that is longitudinal in nature is needed in order to test this theory.

Cerebellum Parcellation

In addition to structural differences in the cortex, volume differences between those with PCS and healthy controls were also found within the cerebellum. Those with PCS had a significantly smaller volume of the left VIIIa, left VIIIb, left X, and right X lobules. Ross et al. (2012)[90] had previously looked at subcortical structural changes in those with persistent symptoms following concussion, and found that over a course of a year these individuals had significantly greater atrophy of the cerebellum compared to controls. In our results, while we did not see a global difference of cerebellum volume compared to controls, we did find significantly smaller lobules, which were not investigated by this previous study.

Lobule X, also referred to as the flocculonodular lobe, is the vestibular area of the cerebellum[15,34,37]. This lobule receives inputs directly from the vestibular nerve (cranial nerve 8) and indirectly from the vestibular nuclei, and sends output directly to the vestibular nuclei. The medial aspect of the flocculonodular lobe is involved in controlling axial musculature, while the lateral component is involved in eye pursuit and the vestibulo-ocular reflex (VOR). This reflex allows for the compensatory counter-rotation of the eyes during head movement[15,34,37], and has been found to be abnormal following concussion[200,201]. Additionally, an abnormal VOR reflex has been associated with a significantly longer recovery following injury[201]. However, VOR function was not measured in this study and thus, conclusions on this possible relationship cannot be drawn at this point.

Lobules VIIIa and VIIIb are located in the inferior posterior cerebellum and are considered part of the cortico-cerebellar motor loop[202]. It has been suggested that there are two

motor representations of the body in the cerebellum, the first located in the anterior lobe, and the second in lobule VIII[32,33,203]. Imaging studies have found that lobule VIII is functionally connected to sensory and motor cortical areas, including the primary motor cortex (M1), primary somatosensory cortex (S1), and the premotor cortex (PMC)[32,204]. In addition, activation of both VIIIa and VIIIb has been found during basic sensorimotor tasks and, in particular, hand-reaching tasks[32,202]. Anatomically, the posterior lobe of the cerebellum receives fibers from the cortical association areas, including prefrontal (PFC) and posterior parietal cortex (PPC)[33]. Specifically, it is the lateral cerebellar hemisphere which is reciprocally and indirectly connected to the cortex, with inputs mostly from the parietal lobe, and outputs terminating in PMC and M1[34]. The majority of these cerebro-cerebellar pathways are contralateral; however, 10-30% of these projections are ipsilateral. As such, the right cerebellar hemisphere is associated with language, while the left is associated with visuospatial performance[33,202]. This may explain our findings, in which only the left, and not the right, lobules VIIIa and VIIIb demonstrated differences between groups.

Lastly, Meabon et al. (2016)[98] investigated the effects of mild blast injuries on the cerebellum in murine models and found that the ventral areas of the cerebellum were most vulnerable to injury resulting in significantly greater Purkinje cell loss in these regions. Specifically, these vulnerable ventral regions included lobules VII through to X. Therefore, the results from this study, in which lobules VIII and X demonstrated decreased volume in those with PCS compared to controls, supports these findings.

Cerebellum Lobules & Visuomotor Task Performance

In addition to group differences, it was found that the VIIIa lobule in the left cerebellar hemisphere was significantly correlated to the number and severity of symptoms reported, as

well as timing scores in visuomotor tasks requiring CMI. This finding is unsurprising considering the literature. As previously mentioned, this lobule is considered a part of the cortico-cerebellar motor loop and is activated with sensorimotor tasks, including reaching tasks[32,202]. In addition, it is known that the left hemisphere is associated with visuospatial tasks, which is an important component of our visually guided reaching tasks[33,202]. Further, the cerebellum plays a large role in movement timing[205], with the medial region of the cerebellar hemispheres associated with the implementation of a timed response and the lateral cerebellar hemisphere involved with the operations of the timing process[206]. Lesions to the cerebellar hemispheres result in deficits in motor planning, delays in movement onset, and irregularities in timing[34]. The results of our study add to these findings, with the volume of lobule VIIIa related to timing performance on visuomotor reaching tasks.

Cortical Regions of Interest & Visuomotor Task Performance

Moreover, the thickness and volume of cortical regions was also significantly correlated with performance on CMI based tasks. An improved execution of movement, demonstrated through improved performance on both the trajectory and sub-movement composite scores, was associated with an increased volume or thickness of cortical regions. These findings reflect the general relationship between cortical regions required to perform non-standard visuomotor tasks and behavioural execution on these tasks. Specifically, the PC task was significantly associated with the SPL and the superior frontal region, the CR task was associated with the IPL and right rMFG, while the PC+CR task was associated with the IPL, rMFG, and precuneus.

The association between performance on the PC visuomotor condition and the thickness of the SPL and superior frontal regions is supported by the literature. The PC condition requires implicit sensorimotor recalibration due to the dissociation between the plane of vision and the

plane of action[8,10]. Both the SPL and the superior frontal regions are integral in non-standard

reaching actions which require this spatial recalibration[1,16]. During reaching movements, the SPL

is responsible for the proprioceptive guidance of movement, or knowing where the arm is located

in space[15,16]. This is demonstrated in patients with optic ataxia (lesion of the SPL) as they are

unable to reach towards objects efficiently. When performing non-standard visuomotor tasks

requiring sensorimotor recalibration, Granek et al. (2012,2013)[207,208] found that those with SPL

damage required increased reliance on visual guidance due to the decrease in proprioceptive

feedback. Further, on a comparable task paradigm to ours, Hawkins et al. (2013)[6] found a change

in neural discharge within the SPL in the PC condition, but not the CR condition, highlighting

the importance of this structure in non-standard mapping, specifically when sensorimotor

recalibration is required. Our results also found that performance on the PC condition was

associated with the superior frontal region, which includes the dorsal pre-motor (PMd) and

medial motor areas (supplementary motor area, SMA; cingulate motor area, CMA). Medial

motor areas are responsible for internally guided behaviour, as well as planning and

remembering motor sequences, while the PMd is an important link between the non-spatial

aspects of sensory cues and the motor response[1,15]. The PMd has been shown to play an

important role in the selection of an action based on arbitrary (or non-standard) visuomotor

mapping. Interestingly, one of the largest inputs to the PMd is the SPL, and thus this region plays

a role in tasks requiring implicit non-standard mapping[16].

In comparison, performance on the CR task was associated with the IPL and the rMFG.

While this also requires non-standard mapping, in contrast to the implicit rules required for

performance on the PC task, the CR condition requires an explicit rule for successful

performance[8,10]. That is, one must use strategic control in order to dissociate vision from action.

The prefrontal cortex is essential for this strategic control and goal-directed behaviour as these regions use rules in order to interpret the sensory inputs and associate them with the appropriate motor action[15,26]. This "top-down" processing is especially important when multiple responses are possible as it establishes the mappings required to perform the task and guides the appropriate response. The prefrontal cortex does this through the implementation of attentional templates, rules and goals[26]. In particular, the rMFG, which includes both the DLPFC and the ventrolateral pre-frontal cortex (VLPFC), is important for the strategic control required in our task. These regions have reciprocal connections with visual and motor regions including the cerebellum, PMC, and IPL[26]. Unlike the SPL, which is essential for spatial guidance using proprioceptive cues, the IPL is responsible for spatial attention, or devoting attentional resources to a specific region in space[209,210]. A lesion of the IPL leads to hemispatial neglect and deficits in the ability to direct attention to portions of extrapersonal space[209]. The IPL is not only anatomically connected to prefrontal regions, but also to the cerebellum and PMC[15,211]. Previous work in our laboratory has also demonstrated that these regions are important for non-standard mapping requiring strategic control[22,45]. Increased activation of both the IPL and the rMFG regions was noted in a comparable feedback reversal task. It is not surprising then that we observed relationships between structural measures in these regions and performance on the CMI task requiring explicit rule-based control.

Finally, performance on the PC+CR task was associated with the volume and thickness of the IPL, rMFG, and precuneus. The PC+CR task requires two levels of decoupling, both the implicit sensorimotor recalibration and the explicit strategic control. Therefore, as previously mentioned, the relationship between this task and both the IPL and rMFG is in agreement with current literature[26,209] and the previous findings from our laboratory[22,45]. The precuneus, which is

located in the medial parietal cortex, is reciprocally connected with both the lateral parietal regions (SPL, IPL) and frontal regions (DLPFC, PMC, medial motor areas)[212]. While the exact role of the precuneus is still relatively unknown, it is believed to be a crucial aspect of the neural network specialized for visually guided movement[212]. In particular, the precuneus is activated during shifting of attention, as opposed to sustained attention in the IPL. Furthermore, it plays a role in creating an internal representation of movement, such as with visual rotation[212]. The role of the precuneus in visuomotor transformation tasks has previously been demonstrated in our laboratory. In a recent study, Gorbet et al. (2018)[23] found that activation of this region was able to discriminate between tasks requiring CMI and standard reaching tasks. Thus we suggest that the structural changes seen in the precuneus in the present study may underlie the successful performance of our complex visuomotor task in the face of our observed cerebellar atrophy, which in the healthy brain is crucial for this type of skill, in those with PCS.

Cerebellum Lobules & Cortical Regions of Interest

Interestingly, our results found a statistically significant correlation between the volume of the precuneus and the volume of the cerebellar lobule VIII (both VIIIa and VIIIb). Specifically, a decreased volume of these cerebellar lobules was associated with an increased volume of the precuneus. As stated earlier, both regions play an important role in visuomotor transformation tasks[202,212], and are connected anatomically as the cerebellum has strong reciprocal connections to the parietal lobe[33,34]. Moreover, Churchill et al. (2017)[213] found that the precuneus and posterior cerebellum were abnormally functionally connected in those with a history of concussion. Specifically, they found that both regions (cerebellum and precuneus) were able to distinguish those who had a more severe history of concussion, including those who had a history of multiple concussions and a longer recovery from the most recent injury.

Furthermore, those who had a more severe concussive history demonstrated hypoconnectivity between the precuneus and the cerebellum, with both regions showing hyperconnectivity with associated prefrontal and motor regions. The authors speculate that this change in functional connectivity reflects a compensatory mechanism for adequate behavioural performance[213]. While this study looked only at those who were asymptomatic, this conceivably explains our results in which structural changes between these two regions are related.

Limitations& Future Studies

Our study is one of the first studies to investigate structural differences in those with PCS compared to healthy controls, specifically within the lobules of the cerebellum; however, it is not without limitations. First, as this study is cross-sectional in design, a causal link between the injury and structural changes cannot be made. However, a number of previous longitudinal studies have found structural changes due to concussion, and thus it seems likely to be the underlying cause of the structural differences found in our study. Due to the controversial findings of structural changes due to psychological factors, it would be important to repeat this study investigating this aspect in order to understand how mental health affects both structure and performance on the behavioural task. Lastly, repeating this study with a greater sample size and with men would make the results more generalizable. Future studies should incorporate functional MRI in order to better understand if behavioural compensation is resulting in structural changes.

Conclusion

In summary, we found that those with PCS had a significantly larger volume and thickness of the precuneus. In addition, within the cerebellum, those with PCS had a significantly smaller volume of lobules left VIIIa, left VIIIb, and both the left and right lobule X.

Furthermore, the volume of lobule VIII was correlated with precuneus volume, and both were correlated with symptom reporting. While there were no behavioural differences between groups on the CMI visuomotor transformation tasks, performance on these tasks was correlated with multiple cortical and cerebellar regions, highlighting the importance of the frontoparietal-cerebellar network for task performance. Finally, the lack of behavioural differences combined with the structural differences in those with PCS may reflect a compensatory mechanism. These findings align with, and thus strengthen, previous literature which found a neurological compensation following injury[196–198,213].

	Cortical Regions	Median Thickness (mm)		Mann-Whitney U
		Healthy Control	**PCS**	
Parietal Lobe	left IPL	2.55	2.57	63.0 N.S.
	right IPL	2.64	2.66	62.0 N.S.
	left SPL	2.32	2.37	54.0 N.S.
	right SPL	2.29	2.37	49.5 N.S.
	left precuneus	2.48	2.59	39.0*
	right precuneus	2.52	2.63	46.0*
Frontal Lobe	left precentral	2.78	2.78	84.0 N.S.
	right precentral	2.71	2.72	81.5 N.S.
	left superior frontal	2.32	2.37	54.0 N.S.
	right superior frontal	2.29	2.37	49.5 N.S.
	left rMFG	2.91	2.99	66.0 N.S.
	right rMFG	2.86	2.86	74.0 N.S.
	left cMFG	1.89	1.96	66.5 N.S.
	right cMFG	1.96	1.99	60.5 N.S.
Occipital Lobe	left cuneus	1.89	1.96	66.5 N.S.
	right cuneus	1.96	1.99	60.5 N.S.

Table 4.1

cMFG: caudal middle frontal gyrus; IPL: inferior parietal lobe; N.S.: non-significant; PCS: post-concussion syndrome; rMFG: rostral middle frontal gyrus; SPL: superior parietal lobe
*p<0.05

Table 4.1 Median thickness of cortical regions of interest between groups

Table 4.2

	Cortical Regions	Median Volume (mm³)		Mann-Whitney U
		Healthy Control	PCS	
Parietal Lobe	left IPL	0.0109	0.0107	76.0 [N.S.]
	right IPL	0.0128	0.0136	69.0 [N.S.]
	left SPL	0.0115	0.0119	75.0 [N.S.]
	right SPL	0.0118	0.0117	72.0 [N.S.]
	left precuneus	0.0083	0.0089	39.0*
	right precuneus	0.0088	0.0093	50.0 [N.S.]
Frontal Lobe	left precentral	0.0122	0.0131	64.0 [N.S.]
	right precentral	0.0117	0.0117	82.0 [N.S.]
	left superior frontal	0.0115	0.0119	75.0 [N.S.]
	right superior frontal	0.0118	0.0117	72.0 [N.S.]
	left rMFG	0.0204	0.0217	52.0 [N.S.]
	right rMFG	0.0186	0.0199	60.0 [N.S.]
	left cMFG	0.0028	0.0026	68.0 [N.S.]
	right cMFG	0.0027	0.0029	74.0 [N.S.]
Occipital Lobe	left cuneus	0.0028	0.0026	68.0 [N.S.]
	right cuneus	0.0027	0.0029	74.0 [N.S.]

Volume calculated as a proportion of total intracranial volume
cMFG: caudal middle frontal gyrus; IPL: inferior parietal lobe; N.S.: non-significant; PCS: post-concussion syndrome; rMFG: rostral middle frontal gyrus; SPL: superior parietal lobe
*$p<0.05$

Table 4.2 Median volume of cortical regions of interest between groups

Table 4.3			
	Median Volume (mm^3)		
Cerebellar Lobule	**Healthy Control**	**PCS**	**Mann-Whitney U**
Total Cerebellum	0.22130	0.21640	52.0 [N.S.]
Left IV	0.00384	0.00367	50.0 [N.S.]
Right IV	0.00433	0.00401	54.0 [N.S.]
Left V	0.00485	0.00487	71.0 [N.S.]
Right V	0.00487	0.00470	63.0 [N.S.]
Left VI	0.01010	0.01031	79.0 [N.S.]
Vermis VI	0.00247	0.00249	75.0 [N.S.]
Right VI	0.00965	0.00996	81.0 [N.S.]
Left Crus I	0.01414	0.01518	57.0 [N.S.]
Vermis Crus I	0.00003	0.00003	70.0 [N.S.]
Right Crus I	0.01553	0.01595	75.0 [N.S.]
Left Crus II	0.01069	0.01036	67.0 [N.S.]
Vermis Crus II	0.00059	0.00055	69.0 [N.S.]
Right Crus II	0.01075	0.01092	82.0 [N.S.]
Left VIIb	0.00521	0.00493	54.0 [N.S.]
Vermis VIIb	0.00023	0.00023	80.0 [N.S.]
Right VIIb	0.00575	0.00543	71.0 [N.S.]
Left VIIIa	0.00566	0.00519	46.0 [N.S.]
Vermis VIIIa	0.00128	0.00129	80.0 [N.S.]
Right VIIIa	0.00536	0.00505	53.0 [N.S.]
Left VIIIb	0.00472	0.00426	44.0*
Vermis VIIIb	0.00065	0.00065	84.0 [N.S.]
Right VIIIb	0.00468	0.00433	50.0 [N.S.]
Left IX	0.00365	0.00358	83.0 [N.S.]
Vermis IX	0.00083	0.00081	70.0 [N.S.]
Right IX	0.00393	0.00392	73.0 [N.S.]
Left X	0.00080	0.00075	43.0*
Vermis X	0.00033	0.00031	73.0 [N.S.]
Right X	0.00081	0.00076	41.0*
Volume calculated as a proportion of total intracranial volume. N.S.: non-significant; PCS: post-concussion syndrome *p<0.05			

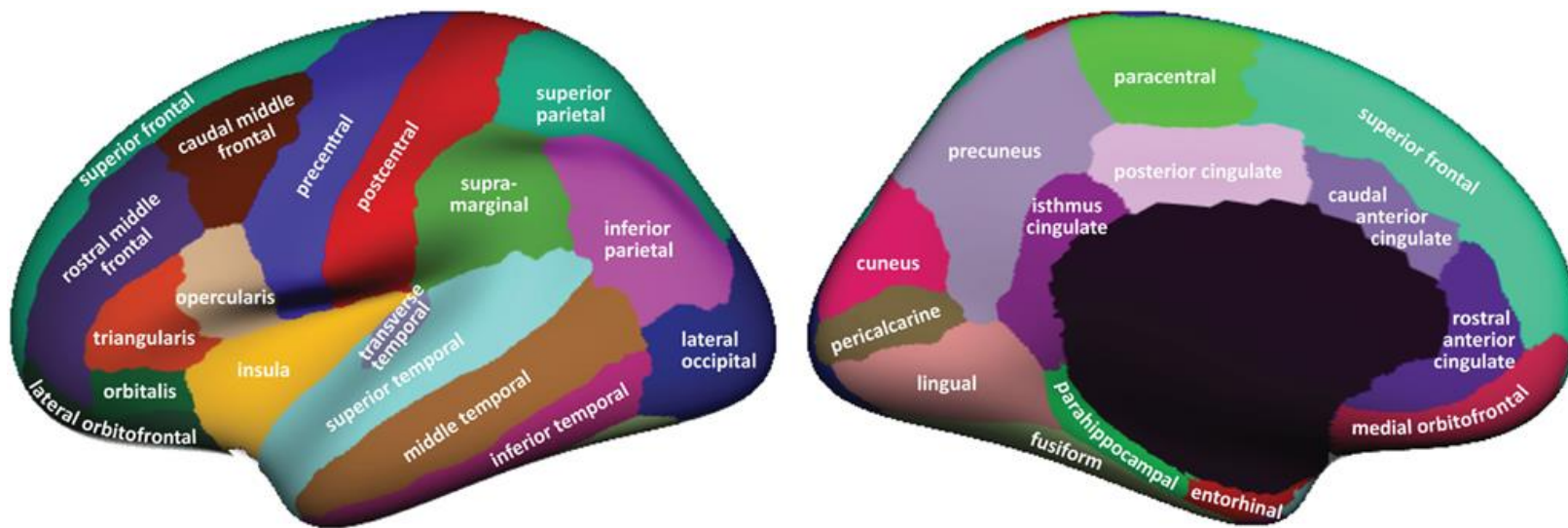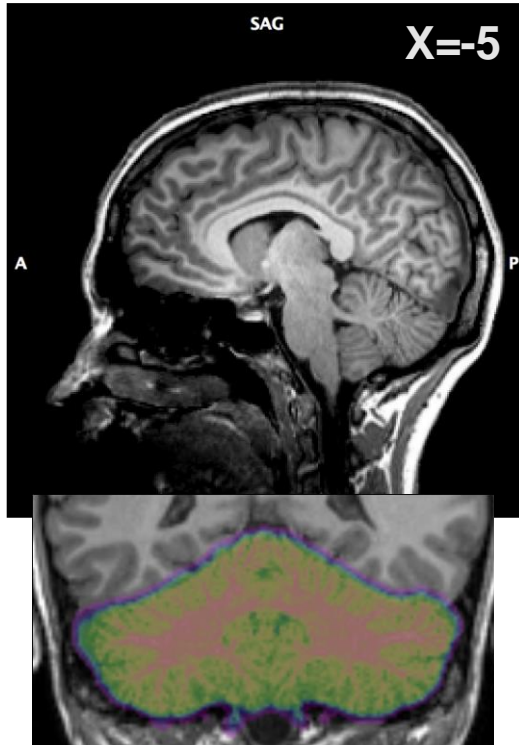**Table 4.3 Median volume of the cerebellum and its lobules in those with PCS and healthy controls**

Figure 4.1 Representation of the Desikan-Killiany cortical parcellations

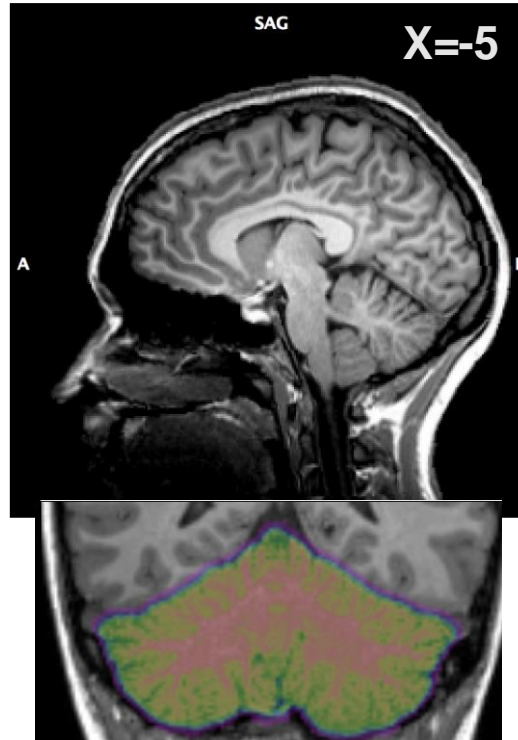Figure reproduced from Klein & Tourville (2012)[214].

Figure 4.2 T1 MR-images of age-matched (22 and 21 years) participants, including cerebellum segmentation.
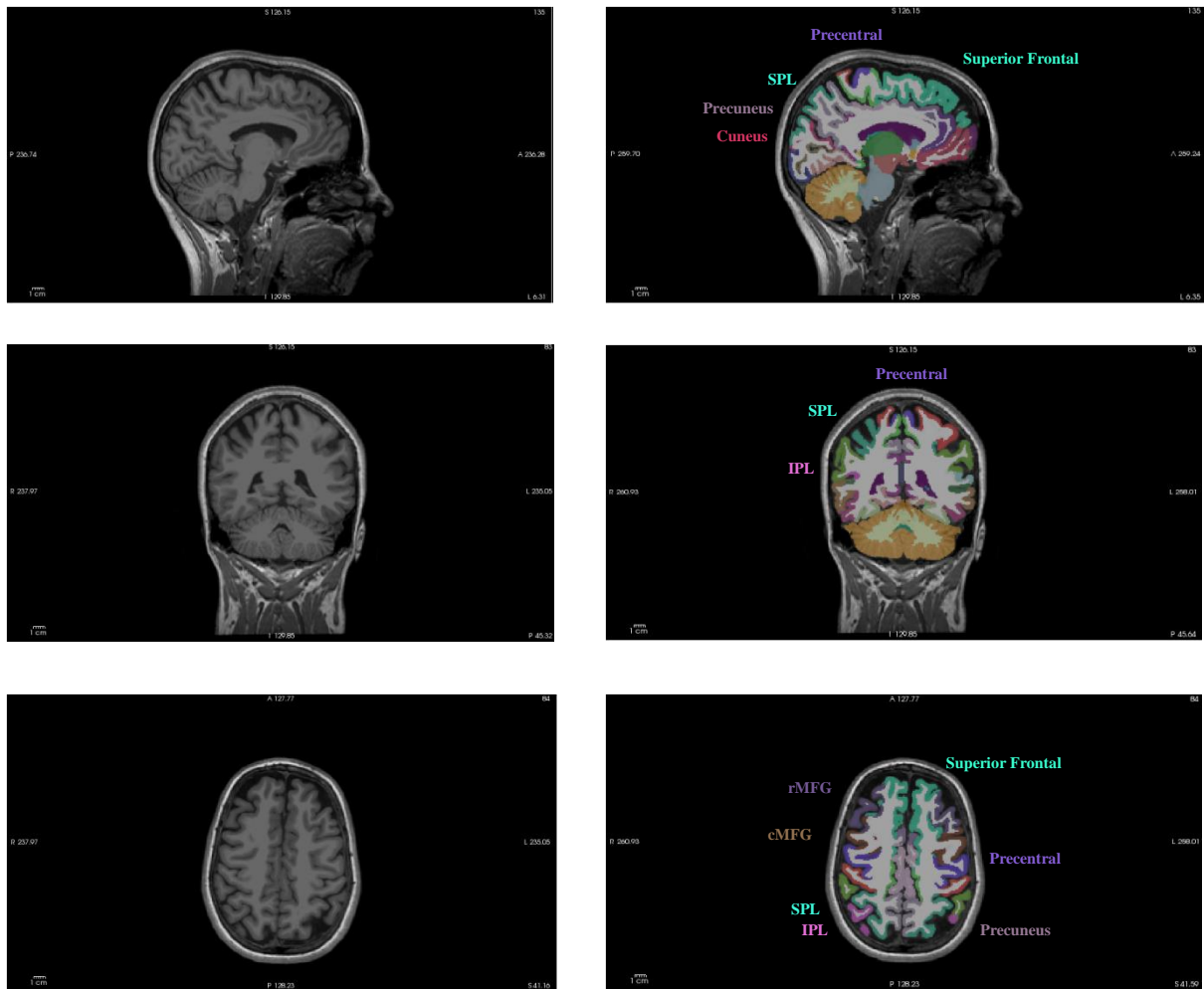
Figure 4.3 Structural MR-image of healthy control participant and a representation of their cortical parcellations

One healthy control participant's (age 24years) T1-weighted raw MR-image in the sagittal, coronal, and transverse planes and their mapped Desikan-Killiany cortical parcellations.
cMFG: caudal middle frontal gyrus; IPL: inferior parietal lobe; rMFG: rostral middle frontal gyrus; SPL: superior frontal lobe

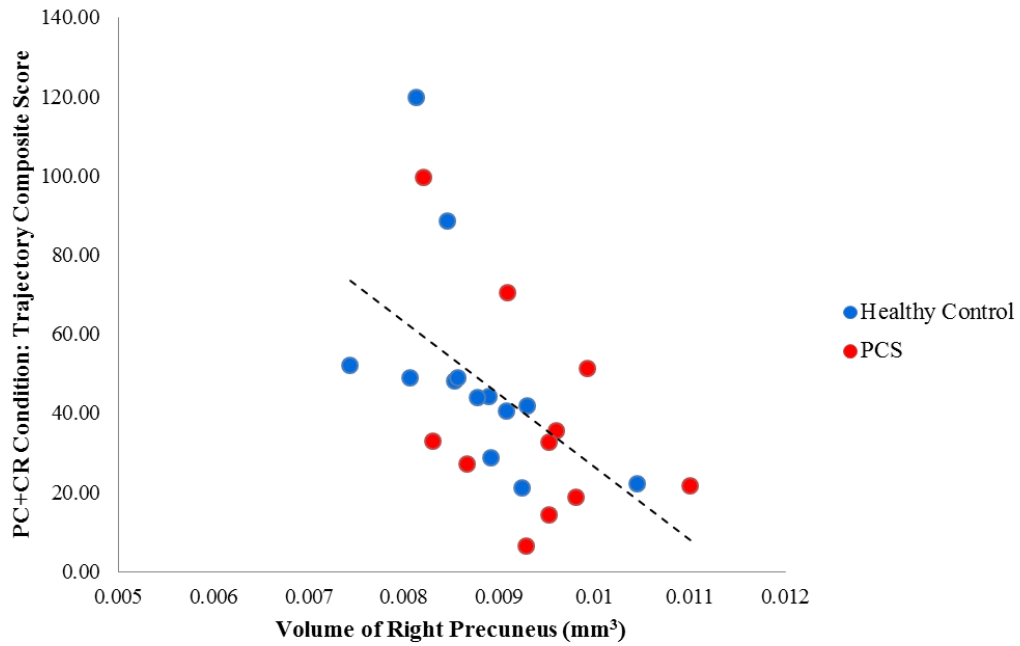**Figure 4.4 Relationship between the volume of the right precuneus and trajectory performance on the plane change + cue reversal condition**
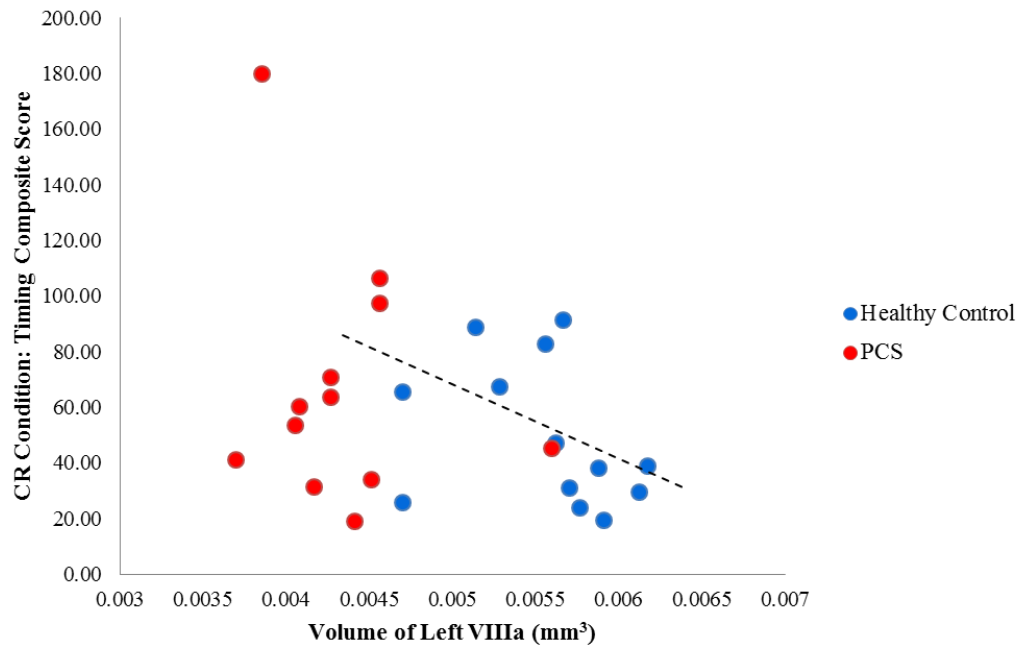

Figure 4.5 Relationship between the volume of the left VIIIa lobule and timing performance on the cue reversal condition
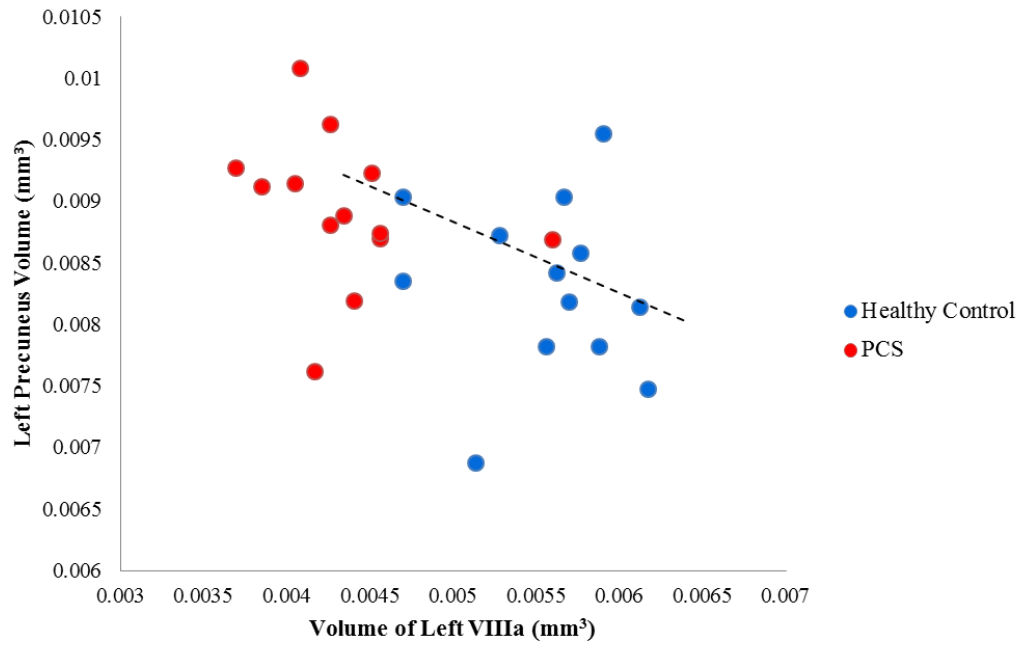
116

Figure 4.6 Relationship between the volume of the left VIIIa lobule and the volume of the left precuneus

Chapter Five

General Discussion

This dissertation used a motor psychophysics framework approach in order to better understand brain mechanisms in multi-domain processing – that of CMI. By looking at performance deficits, in association with structural changes, we are better able to understand brain function, in both healthy and unhealthy brain states. Rule-based visually guided movements, in which CMI is required, is essential for both our daily lives and sport performance[1,2]. Furthermore, it has been established that the underlying brain network required for skillful CMI performance is the frontoparietal-cerebellar network[2,12–15,22,31]. Previous work from our laboratory has demonstrated that CMI performance is affected by both the level of expertise[45,46] as well as insults to the brain including MCI[47], Alzheimer's disease[48–50], and concussion[52,53]. Specifically, deficits in CMI performance were found in both children and university level athletes who had a history of concussion, but deemed clinically recovered. In addition, Hawkins et al. (2015) found an association between CMI performance and white matter integrity in those at risk for Alzheimer's and dementia. The purpose of this dissertation project was to investigate the limits of our motor system, in both the healthy brain states and those with a previous concussion. Furthermore, we aimed to better understand the effects of concussion and its association with motor performance by examining structural differences in the brain between those with a prior concussion and healthy individuals.

In our first study, Chapter two, we investigated the effects of concussion history on performance of CMI tasks in the elite athletic population. The results demonstrated that those with a previous history of concussion had deficits in accuracy across both the standard and non-standard mapping condition, and a decrease in reaction time in the non-standard task compared to healthy controls. Importantly, these athletes were asymptomatic and medically cleared to return to sport based on the current international concussion protocols[121]. The current

recommended assessment to determine an athlete's readiness to return to sport examines

motor and cognitive skill sequentially, even though sport performance requires their

simultaneous involvement. The findings from this study, as well as the previous work in

our laboratory[52,53], would suggest that these single domain assessments may not be

sensitive enough to determine readiness to return to sport and that a multi-domain

assessment, such as CMI performance, may better capture this. Interestingly, the findings

from this study on elite athletes differed from that of children[53] and university-aged

athletes[52]. In these previous studies multiple timing and execution kinematic variables

contrasted significantly between those with a prior concussion and healthy controls;

however we found that fewer variables differed significantly between groups in the elite

population. We postulate that elite athletes exhibit neural efficiency when performing

visuomotor transformation tasks. Improved neural circuitry has been demonstrated

previously in both elite athletes[44] and elite performers[45], and so we suggest that elite

athletes have a superior frontoparietal network, thus allowing for greater compensation

and fewer performance deficits following concussion. Furthermore, we propose that

while behavioural deficits may not be as noticeable in the elite athletic population, the

underlying neural effects of concussion may still be present. Specifically, these neural

deficits may be in the connections between areas required to successfully integrate

thought and action – the frontoparietal-cerebellar network.

The results of this first study led us to both the second and third studies (Chapters

3 and 4), in which we used MR-imaging in order to investigate the underlying neural

effects of concussion along this frontoparietal-cerebellar network. Previous research had

found that concussive injury led to decreased volume and cortical thickness within the

frontal and parietal cortex[92,93]. Similarly, decreased white matter integrity along these tracts was also noted[103,108,115]. Thus it seemed likely that performance on a ruled-based visuomotor transformation task (which requires this network) would also be affected. However the majority of these studies looked at acute, subacute, or those with a history of concussion, and therefore lacked an understanding on the effects of those with persistent symptoms or PCS. This led to the objective of the second project, Chapter 3, which was to investigate performance on CMI visuomotor tasks between those with PCS and healthy age-matched controls. Additionally, we examined the effect of PCS on white matter integrity, specifically along the tracts underlying the frontoparietal-cerebellar network. Likewise, the purpose of the third study included in this dissertation (Chapter 4) was to investigate the effect of PCS on gray matter structure of this neural network and its association to CMI performance. Specifically, we examined the volume and thickness of cortical frontoparietal regions, and the volume of the cerebellum and its lobules.

Overall, the results of both studies add to the body of literature in understanding visually-guided reaching and the different brain regions and structures required for adequate performance. The associations found between performance on CMI tasks and regional volume, thickness, and white matter integrity is in agreement with, and adds to, the previous research from our laboratory. In particular, these results strengthen our understanding of neural mechanisms behind different forms of CMI, that of sensorimotor recalibration and strategic control.

The results of the third study revealed that those with PCS have a significantly smaller volume of cerebellar lobules compared to healthy controls. Specifically, these lobules (VIIIa, VIIIb, X) are located in the ventral cerebellum. A previous study by Meabon et al. (2016)[98] found that this region of the cerebellum is more vulnerable to the effects of concussive injury. In addition, there were no group differences between PCS and healthy participants on measures of

white matter integrity on any of the white matter tracts investigated in the second study. This was in disagreement with the literature, in which a decrease in white matter integrity has been noted following injury[114,115,117], and the current theory of axonal damage being the underlying etiology of persistent symptoms[64,66,78]. We postulate that, based on these findings, the cerebellum is more susceptible to the effects of concussive injury. It has previously been argued that the anatomical location and structure of the cerebellum may leave it more vulnerable to the effects of injury[98]. During a concussive injury, the acceleration and deceleration forces cause the brain to shift within the skull, however, the brain remains tethered to the base of the skull, creating the coup-contrecoup mechanism of injury. This causes the midbrain and cerebellum, which are located just posterior to this tethered region, to experience the shortening and shearing effects known to be associated with concussive injury[69,215]. In addition, the cerebellum contains approximately 80% of all the brain's neurons, with reciprocal connections throughout the cortex[32,34]. These findings suggest that the cerebellum may be highly susceptible to the effects of concussion, however further research is needed in order to better understand the role this subcortical structure plays.

When looking at performance on a CMI task, those with PCS did not demonstrate any significant differences when compared to age-matched controls. Combined with the structural changes noted in both the cerebellum and cortex, we suggest that this may be due to compensation within the brain. We postulate that the brain adapts in order to have adequate performance. This has also been noted within the literature, where additional brain regions were required for task performance[139,196–198]. For example, Chen et al. (2004)[198] found those with persistent symptoms had decreased activation in the frontal lobe, but a subsequent increase in

regions activated in the parietal lobe during a working memory task, even though no behavioural differences existed.

Taken together, the results of all of the studies suggest that a compensatory mechanism following concussion exists. Elite level athletes are better able to compensate following injury due to their existing neural efficiency. Therefore performance deficits and symptoms may not be as evident in these individuals, and more complex tasks may be required in order to determine readiness to return to sport. In those suffering from PCS, the brain may adapt over time in order to allow for adequate task performance. These adaptations lead to structural changes, which may be related to the signs and symptoms experienced by these individuals. In addition, psychological factors may play a role in these structural differences seen in this population, however further research is needed in order to better understand the interaction between these two causes.

Future Directions

Future studies should take level of experience, or years playing the sport, into consideration when investigating the effects of concussion on behavioural performance. Currently the assessments used in order to determine if an athlete is ready to return to sport is the same for everyone – from children to the elite athlete. These should be improved to reflect different levels of task complexity depending on the level of play of the athlete. Furthermore, additional research is required on understanding the effects of concussion on multi-domain processing, especially incorporating motor control, as this is required in sport. Improved assessment techniques and diagnostics are also needed for PCS and persistent symptoms. Currently, a diagnosis is based on self-reported symptoms; however, a more objective measure is needed. Additional research looking at the behavioural consequences of PCS is required in order to determine an appropriate

tool. Future work taking both cervicogenic and psychological factors into consideration is needed in order to better understand the relationship between injury, neurological changes, and persistent symptoms. By gaining a better understanding of the behavioural consequences and underlying neurological pathology of persistent symptoms following concussion, we will be better equipped to determine appropriate treatment plans. Lastly, further studies looking specifically at the effects of concussion on the cerebellum are necessary. Due to the cerebellum's involvement in many domains (motor, cognition, affective, vestibular) and its reciprocal connections with the cortex, it is likely that this structure is affected in concussion, and may be one of the underlying causes of persistent symptoms. The research within this dissertation is one of the first studies to investigate the cerebellum in detail with those suffering from PCS; subsequently, future research replicating this finding is essential.

Limitations

A limitation of all three projects is that they are cross-sectional in nature. In order to understand the neurological changes that occur post-injury and to determine a causal link between concussion and performance on CMI tasks, a prospective or longitudinal study is required. Similarly, all studies used a self-report of previous concussion, and so a reporting bias may be present. However, the number of diagnosed concussions has only recently been on the rise due to the increased understanding about this injury. Therefore, using only diagnosed concussion may not represent the true number of sustained concussions. It is possible, however, that our healthy control participants opted to not report a previous injury, especially in the elite athlete population. Nonetheless we believe that since these athletes have likely been provided a higher level of medical care throughout their careers, they reflect the population who, in all probability, has pursued medical care for their injuries. In addition to the difficulty in defining

and determining a true history of concussion, the definition of PCS and persistent symptoms is also both controversial and subjective in nature. Furthermore, symptoms of PCS may be due to confounding factors, such as psychological and cervicogenic elements. Since we did not measure these factors in our study, we cannot rule these out as potential influences on our findings. Future work is needed in order to better understand how these factors interact to result in neurological changes, behavioural deficits, and the persisting symptoms. Even so, the studies included here are some of the first to look at behavioural and neurological effects of this population group (PCS), and so the result of these studies will aid in delineating future research projects. In order to understand these confounding factors, a larger sample size is required. This will help in comprehending the variability that is noted within the concussion and PCS group. Finally, all studies looked at only one sex. Due to the known sex differences in brain structure and function[163,165,167,216], these studies need to be repeated in the opposite sex.

Conclusion

In conclusion, the results are informative for both researchers and clinicians as it adds to our understanding of the effect of concussion on the motor system, specifically in rule-based visually guided reaching. Such information will help to improve current rehabilitation and return to play procedures. Finally, the projects included here improve our understanding of one of our most basic and essential behaviours – interacting with the world around us.

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