EXAMINING COGNITIVE-MOTOR INTEGRATION, PERSISTENT SYMPTOMS, AND BRAIN FUNCTION IN INDIVIDUALS WITH CONCUSSION

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Abstract

In everyday life we interact with our environment in an indirect way, where there is a mapping between the viewed goal of our action and the required movement (e.g., using a computer mouse). Such tasks require cognitive-motor integration (CMI), where rules dictate the relationship between perception and action. The underlying CMI control networks that rely on intact frontal, parietal, and subcortical brain region connectivity may be compromised following concussion, resulting in an impaired ability to engage in complex movements. Here we investigate whether such relationships also exist in working-aged adults with persistent post-concussion symptoms (PPCS). **Methods:** Twenty-two individuals (5 males) performed two visuomotor tasks: one requiring direct (standard) interaction with visual targets, and one comprising a plane-change and feedback reversal (non-standard interaction) between viewed target and required hand motion (CMI). PPCS and dizziness were related to brain network function via resting state functional connectivity (RSFC) in six networks and structural integrity via cortical thickness in CMI-related brain regions and white matter tracts via diffusion tensor imaging. **Results:** We observed that lower cortical thickness in the inferior and superior parietal cortices were associated with dizziness and impaired non-standard visuomotor performance, respectively. Furthermore, higher PPCS severity was associated with hyperconnectivity within the visual, sensorimotor control, frontoparietal control, and dorsal attention networks, whilst hyperconnectivity within the salience ventral attention network was associated with higher non-standard visuomotor performance. Lastly, we found that lower white matter tract integrity in several long associative, projection, and commissural tracts were associated with lower visuomotor performance, PPCS severity, and dizziness. **Conclusions:** These findings characterise the impact of PPCS on the structure and function underlying impaired visuomotor performance, and suggest that CMI may be a non-invasive, easily accessible tool for brain network function assessment in those affected by concussion.

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Abbreviations

AD = Axial diffusivity

AE = Absolute error

AFNI = Analysis of functional neuroimages

ANTs = Advanced normalization tool

BOLD = Blood oxygen level-dependent

CC = Corpus callosum

CI = Confidence intervals

CMI = Cognitive-motor integration

CST = Corticospinal tract

DAN = Dorsal attention network

DHI = Dizziness-related inventory

DMN = Default mode network

DR = Directional reversal

DSM-5-TR = Diagnostic and statistical manual of mental disorders

DTI = Diffusion tensor imaging

DWI = Diffusion weighted images

EPI = Echo planar imaging

FA = Fractional anisotropy

fMRI = Functional magnetic resonance imaging

FOV = Field of view

FPCN = Frontoparietal control network

FPCNa = Frontoparietal control network part a

FPCNb = Frontoparietal control network part b

FPCNc = frontoparietal control network part c

FWHM = Full-width half-maximum

GLM = General linear model

GPIP = Group prior individual parcellation

ICs = Independent components

ICD-11 = International Classification of Diseases Version 11

ILF = Inferior longitudinal fasciculus

LOC = Loss of consciousness

MCP = Middle cerebellar peduncle

MD = Mean diffusivity

ME-ICA = Multi-echo independent components analysis

MP-RAGE = Magnetisation-prepared rapid gradient echo

mTBI = Mild traumatic brain injury

MTf = Full movement time

PASTA = Pointwise assessment of streamline tractography attributes

PC+FR = Plane change + feedback reversal

PPCS = Persistent post-concussion symptoms

PL = Path length

PLb = Full path ballistic

PLf = Full path length

PV = Peak velocity

RD = Radial diffusivity

ROI = Region of interest

RPQ = Rivermead post-concussion Symptoms questionnaire

RPQ-13 = Rivermead post-concussion Symptoms questionnaire group 2

RPQ-3 = Rivermead post-concussion Symptoms questionnaire group 1

RSFC = Resting state functional connectivity

rsfMRI = Resting state fMRI

RT = Reaction time

SD = Standard deviation

SLF = Superior longitudinal fasciculus

SLF-1 = Superior longitudinal fasciculus part 1

SLF-2 = Superior longitudinal fasciculus part 2

SMN = Sensorimotor control network

sMRI = Structural MRI

SVAN = Salience ventral attention network

TE = Echo time

TR = Repetition time

TRACULA = TRActs Constrained by UnderLying Anatomy

VE = Variable error

VN = Visual network

Chapter 1: Introduction and Literature Review

1.1. Concussion and Persistent Symptoms After Concussion

Concussion is a form of mild traumatic brain injury (mTBI) that results in a clinical syndrome due to biomechanical forces acting on the brain (Dimou & Lagopoulos, 2014; McCrory et al., 2013). Mechanisms of concussion include but are not limited to falls, sports, vehicular accidents, and inter-personal violence. Concussion usually produces a constellation of symptoms such as headaches, dizziness, sleep disturbance, sensitivity to light and noise, and memory and attention problems (Pardini et al., 2010; Prigatano & Gale, 2011). In most individuals experiencing symptomatic effects of concussion, symptoms usually recover within 7 – 10 days post-injury or gradually over three months (Leddy et al., 2012). However, approximately 10 – 30% of individuals continue to experience cognitive, physical, and somatic symptoms which can persist over an extended period of time (i.e. months, years, or permanently) as persistent post-concussion symptoms (PPCS) (McCrory et al., 2013; Prigatano & Gale, 2011; Toledo et al., 2012). Although there is a deliberation over the definition of PPCS, the diagnosis is defined according to the International Classification of Diseases (ICD-11) as a mild neurocognitive disorder with a subjective experience of a deterioration from a previous level of cognitive functioning, accompanied by objective evidence of impairment in performance on one or more cognitive domains due to TBI (World Health Organisation, 2019). Furthermore, it may be captured to some degree from the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) by the diagnosis of a major or mild neurocognitive disorder due to TBI that is accompanied by a loss of consciousness, posttraumatic amnesia, disorientation and confusion, and/or neurological signs, with the neurocognitive decline persisting beyond the acute post-injury period (~ > three months) (American Psychiatric Association, 2022).

Loss of consciousness (LOC) can occur with concussion and is associated with more severe injury and longer recovery periods. However, it is not necessary for a concussion diagnosis since individuals with mTBI may experience transient confusion and lingering symptoms without LOC (Kelly, 2001). The heterogeneity of head injury outcomes emphasises the multidimensional mechanism underlying PPCS, thereby rendering it vulnerable to misconceptions in the diagnostic procedures because it lacks both a validated diagnostic biomarker and clear clinical guidelines (Choe, 2016; Origenes et al., 2019; Sharp & Jenkins, 2015). Whilst there is advancement in concussion research, there are still many aspects that require further investigation. These include risk factors associated with increased likelihood of PPCS such as previous history of concussion, pre-existing psychological and mood disorders, age, and sex/gender (Fino et al., 2017; Sharp & Jenkins, 2015).

Little is known about the association between different concussion mechanisms and the development of PPCS, but emerging evidence from several studies have indicated that certain populations such as older adults and women are at an increased risk of developing PPCS (Broshek et al., 2005; Brown et al., 2015; King, 2014; Varriano et al., 2018). Falls and vehicular accident-related concussions are a growing concern amongst older adults because it puts them at an increased risk for concussion and possible PPCS (King, 2014; Varriano et al., 2018). This is not surprising because complex tasks like driving require the integration of cognitive, motor, and visual functioning that have been shown to decline with both healthy and pathological ageing (Burke & Barnes, 2006; Stutts et al., 1998). Additionally, the increased risk of fall-related concussion commonly observed in older adults can be attributed to physical frailty (Chittrakul et al., 2020; Rivan et al., 2021). Several studies have reported that frailty is a stable predictor of future falls in older adults (> 60 years), and is associated with cognitive impairment and dementia (Cheng &

Chang, 2017; Fhon et al., 2016; Rivan et al., 2021; Samper-Ternent et al., 2012). Falls are the second highest cause of mortality in older adults and a significant predictor of injuries, loss of independence, and disability (Bloch et al., 2010; World Health Organisation, 2008). Thus, PPCS from fall-related concussions in older adults might be due to a greater number of comorbidities that increase their likelihood of never fully recovering. Conversely, sport-related concussion is the most common mechanism seen in younger groups (Wang et al., 2023). A retrospective study by Tator & Davis (2014) found that over half of their patient sample (50.7%) diagnosed with sport-related PPCS were under the age of 18. Their reported higher than usual prevalence of PPCS amongst adolescents was due to the inclusion of patients from ages 11 years and up, in contrast to other studies focusing on a target population of only professional and/or varsity athletes (Field et al., 2003; Moore et al., 2014).

Sex-related differences also impact the prevalence of concussion and PPCS. Several studies have reported the aforementioned differences on incidence rate of concussion, expressed symptoms, and recovery time (Broshek et al., 2005; Covassin et al., 2003; Farace & Alves, 2000; Varriano et al., 2018). Although the highest rates of concussion are usually observed in male-dominated sports like American football, sports in which both sexes compete equally like soccer have observed that female athletes experience more concussions than male athletes (Kerr et al., 2014). Also, female athletes showed higher rates of acute neurological problems post-concussion such as impaired memory function, slower processing speed and reaction times, increased symptom severity, and longer recovery time compared to male athletes (Broglio et al., 2022; Brook et al., 2016; Broshek et al., 2005; Covassin et al., 2003; Master et al., 2021; Solomito et al., 2019). The longer recovery time in female athletes might also increase their vulnerability to another concussion before full recovery, thus increasing the possibility of PPCS (Bock et al., 2015;

Covassin et al., 2003). Regarding other concussion mechanisms, a study found that more women experienced PPCS after falls and vehicular accident-related concussions than men (Varriano et al., 2018). The greater risk of PPCS in women from vehicular accident-related concussion was an interesting finding given that men are involved in vehicular accidents more often than women (Ramage-Morin, 2008). Possible explanations may be that vehicular accident-related concussions in men are less serious than other injuries, or that women are at an increased risk of developing PPCS from vehicle accident-related concussion, like sport (Varriano et al., 2018). It may also suggest a difference in symptom reporting or other factors like reduced neck strength and girth (Tiernery et al., 2005) that may put women at a greater risk for concussion.

1.2. Neuroimaging and Concussion

Structural, or anatomical, magnetic resonance imaging (sMRI) detects declines in grey matter morphology as an indicator of atrophy resulting from focal and/or global neuronal loss (Symms, 2004). Although there are no visible concussion-related structural changes observable in conventional neuroimaging like computerised tomography and sMRI (Klein et al., 2019), many studies have demonstrated alterations in grey matter morphometry using advanced neuroimaging techniques (Burrowes et al., 2020; Hurtubise et al., 2022; Mavroudis et al., 2022; Niu et al., 2020). A recent meta-analysis and systematic review investigating grey matter changes post-concussion (acute, subacute, and chronic phases) found higher and lower cortico-subcortical volume mainly in the frontal and temporal cortices, in addition to the thalamus and amygdala regions (Mavroudis et al., 2022). These results were further corroborated when using cortical thickness as a measure of grey matter morphometry, with regions including the parietal lobe (Mills et al., 2020; Wang et al., 2015). Since these aforementioned areas are implicated in several cognitive, motor, and sensory processes, these findings suggest that most PPCS may be associated with focal injury in these areas

(Mavroudis et al., 2022). Moreover, emerging studies have suggested that axonal injury may play a key role in the pathophysiology of concussion and PPCS (Warner et al., 2010).

Experiencing biomechanical forces to the brain initiates a neurometabolic cascade from damage to axons, and leads to a state of energy crisis due to increased glucose requirements that are needed to restore ionic balance (Barkhoudarian et al., 2011; Giza & Hovda, 2014). Moreover, cytoskeletal breakdown resulting from phosphorylation, ionic disruption, and altered axonal membrane permeability are by-products of the mechanical shearing and tensile strain associated with concussion (Barkhoudarian et al., 2011; Giza & Hovda, 2014). These pathophysiologic processes may lead to disrupted axonal transport, demyelination, and slowed neurotransmission, resulting in the loss of white matter microstructural integrity (Barkhoudarian et al., 2011; Choe, 2016; Giza & Hovda, 2014). These factors may also initiate multiple neural responses including neuroinflammation and vasogenic and cytotoxic oedemas (Choe, 2016; Michinaga & Koyama, 2015), which may or may not be reversible.

White matter microstructural changes can be detected using diffusion tensor imaging (DTI), which measures water diffusion along white matter tracts (Taylor, 2003). Tissue water diffusion is assessed based on rate of diffusion along three orthogonal axes (*x, y, and z*) using several DTI metrics namely Fractional Anisotropy (FA), Mean Diffusivity (MD), Axial Diffusivity (AD), and Radial Diffusivity. FA ranges from 0 to 1 representing the directionality of water diffusion, where a value of zero corresponds to unrestricted or equally restricted diffusion in all directions, and 1 corresponds to maximal diffusion in one direction (Rabinowitz et al., 2014). MD denotes mean diffusivity across all three orthogonal axes, with higher MD meaning increased rate of diffusion (Madden et al., 2012). AD represents diffusion along or parallel to the primary axis, whilst RD measures diffusion perpendicular to the primary diffusion axis, thereby providing more

information about the integrity of the white matter (Madden et al., 2012). Moreover, it has been proposed that lower FA with higher MD indicates microstructural declines associated with increased tissue water content and macrostructural tissue loss (Sen & Basser, 2005). Whilst lower FA without higher MD suggests microstructural changes without gross tissue loss (Sen & Basser, 2005). Moreover, lower FA with higher RD may denote demyelination, whereas lower FA and AD without higher RD may indicate axonal damage (Concha et al., 2006; Song et al., 2003, 2005; Sun et al., 2006). Regarding concussion-related white matter changes, multiple studies have demonstrated that specific white mater tracts are particularly vulnerable to traumatic damage (Gumus et al., 2021, 2022; Rabinowitz et al., 2014). DTI abnormalities are particularly prevalent in the corpus callosum (CC), internal capsule, superior longitudinal (SLF) and inferior longitudinal (ILF) fasciculi, corticospinal tract (CST), and thalamic radiation, and have been shown to separate participants with PPCS from healthy normal controls (Gumus et al., 2021). For instance, lower FA and higher MD in the SLF, ILF, body of CC, and internal capsule were sensitive to group differences between participants with PPCS and healthy controls and were associated with worse performance on attention and processing speed tasks (Xiong et al., 2014). One study examined longitudinal white matter changes in patients with PPCS over a period of four years and found lower and higher FA in the CC and SLF respectively, which was driven by changes in RD due to demyelination (Farbota et al., 2012). They also observed that the aforementioned FA changes were associated with both slower and faster visuomotor speed, thus emphasising important limitations when interpreting findings from diffusion data, especially on long-association, projection, and commissural tracts.

In addition to microstructural changes, functional connectivity changes have been documented post-concussion. Functional MRI (fMRI) measures brain activity based on the

relationship between neural activity and haemodynamic responses, based on blood oxygen level-dependent (BOLD) contrast (Rosenthal et al., 2018). Factors that determine the level of BOLD response include cerebral blood flow, blood volume, and ratio of oxyhaemoglobin to deoxyhaemoglobin (Rabinowitz et al., 2014). Unlike task-based fMRI where BOLD signal is associated with a participant's performance on a sensorimotor or cognitive task, resting state fMRI (rsfMRI) examines the BOLD signal whilst a participant is at rest, awake, and not engaging in an explicit task (Raichle et al., 2001). Using rsfMRI, spatially distributed neuroanatomical regions that show functionally connected BOLD signal, i.e. significantly correlated changes in BOLD signal over time, have been characterised into various brain networks (Fox et al., 2005). Alterations in resting state functional connectivity (RSFC) have been observed after concussion in a number of networks, including the default mode (DMN), salience ventral attention (SVAN), and the frontoparietal control (FPCN) networks (Gumus et al., 2021; Hayes et al., 2016; Rabinowitz et al., 2014; Rosenthal et al., 2018; Sharp et al., 2014; So et al., 2023). The DMN is essentially involved in internally-directed cognition, such as mentalisation (Spreng et al., 2009), autobiographic memory (Andrews-Hanna, Saxe, et al., 2014), and emotional processing (Andrews-Hanna, Smallwood, et al., 2014). However, during the anticipation of and the responding to tasks that require attention to the external environment, this network is inhibited, allowing the brain to immediately switch to task-positive networks (e.g. SVAN and FPCN) (Dixon et al., 2018; Menon & Uddin, 2010). As such, both higher and lower RSFC have been reported in these networks and such changes are correlated with cognitive and behavioural impairments and or PPCS (Goswami et al., 2016; Gumus et al., 2021; Mayer et al., 2015; Wong et al., 2023). For instance, lower RSFC within several networks including the DMN, FPCN, and SVAN were associated with impaired working memory performance (Kasahara et al., 2011) and greater PPCS (Stevens et al., 2012). Also, Churchill et al. (2021) found that compared to non-concussed athletes, those that were

concussed in same season as neuroimaging acquisition had higher RSFC between the SVAN and DMN that was associated with higher symptom severity and reduced FA in white matter tracts connecting the networks. No significant neuroimaging and clinical results were found in athletes concussed in later seasons. The authors suggested the higher RSFC with lower structural connectivity may reflect a short-term predisposition towards internal stimuli, thus affecting their ability to anticipate blows and self-monitor for symptoms. Another study from the same group observed higher DMN-FPCN RSFC, which may be mediated by higher DMN-SVAN RSFC in addition to elevated FA, MD, AD, and RD in several white matter tracts of participants with mTBI (Wong et al., 2023). The enhanced RSFC was associated with improved performance on neurocognitive testing, whilst the higher diffusivity was related to higher symptom severity. Several studies have suggested that higher RSFC in the presence of abnormal structural integrity may reflect compensatory recruitment of additional neural resources to sustain cognitive processing (Rosenthal et al., 2018; Sharp et al., 2014). So et al. (2023) reported that in patients with moderate-to-severe TBI, there was higher RSFC within the DMN and bilateral FPCN between 6 – 18 months post-injury, which changed trajectory in the opposite direction at 18 months post-injury. Also, Bharath et al. (2015) found initial higher DMN RSFC spread to other brain networks after 3 months, and their patients had neurocognitive test scores and RSFC that were comparable with healthy controls after 6 month post-injury. Conversely, an alternative explanation may suggest that the higher RSFC represents the dyssynchronisation of neurons due to brain injury resulting in a need for hyperconnectivity to achieve the same neural signal (Meier et al., 2017), as hyperconnectivity has been observed in other neurological conditions and may lead to cognitive and behavioural deficits (Schultz et al., 2017).

Together, these structural and functional neuroimaging studies provide strong evidence in support of incorporating MRI as a biomarker that may be sensitive to the immediate and long-term effects of concussion and persistent symptoms on the brain, in addition to potentially being useful for tracking neural recovery.

1.3. Cognitive-motor integration, Concussion, Structural Integrity, and Brain networks

Whilst many of our activities of daily living (work or non-work related) involve simple direct interactions in which the guiding visual information is also the goal of the movement, an increasingly technology-driven world has introduced many situations which require indirect interactions. An example of a direct standard interaction is looking at and then reaching to grab a cup of tea whilst an example of an indirect non-standard interaction is driving a car, where the limb motions are decoupled from the motion of the vehicle being operated. Successful completion of the non-standard interaction requires the integration of cognitive and motor skills. Moreover, cognitive-motor integration (CMI) explains how our brains plan and execute movements when there is a complex relationship between sensory input and motor output, especially in reaching movements when the hand and eyes are decoupled. This is because CMI is essential during these incongruent hand-eye coordination tasks, where rules dictate the association between perception and action (Sergio et al., 2009; Wise et al., 1996). As a result, CMI tasks employ different levels of decoupling, namely implicit sensorimotor recalibration and/or explicit strategic control, depending on the complexity of the task. Implicit sensorimotor recalibration requires the brain to adapt to the changes in spatial location and orientation when the sensory input is misaligned with the motor output (Bock, 2005; Granek & Sergio, 2015; Redding & Wallace, 1996), e.g. moving your computer mouse on the horizontal plane, while looking at the moving cursor on the vertical computer screen. However, explicit strategic control requires the implementation of a task-

dependent rule to align the motor output with the desired outcome (Bock, 2005; Clower & Boussaoud, 2000; Granek & Sergio, 2015; Redding & Wallace, 1996), e.g. moving your computer mouse to the left in order for the cursor to move right. The explicit nature of the strategic control uses external feedback to overcome errors in hand movement (Clower & Boussaoud, 2000).

The performance of both standard and CMI tasks involves the activation of multiple cortico-subcortical brain networks, especially the frontoparietal-cerebellar and attention networks (Dixon et al., 2018; Ohashi et al., 2018), in addition to recruiting white matter tracts along these networks (Brandes-Aitken et al., 2019). Moreover, there are differences in behavioural and motor performance, in addition to differences in patterns of network activation between both tasks (Gorbet & Sergio, 2009; Sergio et al., 2009; Wise et al., 1996). Unlike the standard task where the eye moves prior to the start of hand motion resulting in straight trajectory of the hand (Neggers & Bekkering, 2000; Sergio et al., 2009), the hand movements during CMI task are less accurate, requiring more time with significantly slower reaction time for the initiation of eye movement (Gorbet & Sergio, 2009; Sergio et al., 2009). Thus, the decreased CMI performance may be a result of the extra neural processes for the required sensorimotor recalibration and strategic control (Gorbet & Sergio, 2009; Sergio et al., 2009; Wise et al., 1996). Recent research has demonstrated alterations in both RSFC of these aforementioned networks and white matter integrity due to ageing, concussion, and neurodegeneration (Hawkins et al., 2015; Hurtubise et al., 2020, 2022; Rogojin et al., 2022, 2023). Although there were no observable differences in CMI performance between females with and without PPCS, Hurtubise et al. (2020, 2022) reported that lower cortical thickness in superior and inferior parietal lobule and reduced FA in the SLF, ILF, and CST tracts were associated with poorer performance on CMI tasks. Several studies have reported sex-related differences in CMI performance and brain networks controlling CMI (Gorbet et al., 2010; Gorbet

& Sergio, 2007; Gorbet & Staines, 2011; Rogojin et al., 2019; Sergio et al., 2020; Smeha et al., 2022). Gorbet & Sergio (2007) and Sergio et al. (2020) observed that CMI task performance in women was associated with greater bilateral pattern activation in the premotor and parietal regions compared to men, whilst men had greater activation compared to women bilaterally in the lateral sulci including the superior temporal gyrus and parietal operculum. Similarly, Pierias (2021) found that male athletes with sport-related concussion history had significantly worse reaction time than female athletes with concussion during a CMI task. Whilst these findings may provide possible insight into the neural correlates of CMI performance in sport-related concussion and sex differences, it is important to extend them to other concussion mechanisms and working-aged adults as indicated by the findings of Smeha et al. (2022), which showed faster recovery in CMI skill in working-aged females compared to males after adjusting for concussion history and age.

Current study - Objective and Hypotheses

Given prior research demonstrating that CMI performance is affected by sport and videogame experience (Gorbet & Sergio, 2018; Granek et al., 2010) in addition to brain injuries resulting from neurodegenerative disease (Hawkins et al., 2015; Rogojin et al., 2019, 2022, 2023) and concussion (Hurtubise et al., 2016; Hurtubise et al., 2020, 2022; Smeha et al., 2022), the main objective of this research project is to characterise the impact of PPCS on the functional and structural neural underpinnings of visuomotor performance in working-aged adults. Examining this demographic is imperative because previous studies have mainly focused on sport-related concussion in children and adolescents, university-aged athletes, and elite athletes. Therefore, the current study provides a novel approach in addressing the aforementioned relationship in working-aged adults with various concussion mechanisms.

Based on our previous findings, we hypothesised that participants with PPCS would demonstrate behavioural deficits on visuomotor tasks, especially in condition involving CMI, and that these deficits would be associated with alterations in RSFC and reduced white and cortical grey matter integrity. Importantly, we hypothesised that these associations would be observed in networks implicated in visuomotor control namely the visual, dorsal and ventral, sensorimotor control, and frontoparietal control networks, as well as several white matter tracts and cortical regions subserving these networks. Lastly, we predicted that alterations in brain functional connectivity and structural integrity would be related to PPCS severity.

Chapter 2: Methods

2.1. Participants

Twenty-two working age participants between the ages of 30 and 65 years were included in the current study (47.23±9.26; 5 males). Whilst we recognise that the term "working age" is between the ages of 16 – 65 years old, we reduced this range given the influence of age on cognition and motor control and focused on the age range for which we have the least available data. This is because our prior work has focused on youth, young adults, and post-retirement seniors (Gorbet & Sergio, 2007, 2016; Hurtubise et al., 2020; Rogojin et al., 2019). In addition to recruiting participants with PPCS (>3 months post-incident), exclusion criteria included uncorrected visual impairments, a history of stroke, epilepsy/seizures, active vestibular or neurodegenerative disorder(s) with the aetiology other than concussion (e.g. Meniere's disease or Parkinson's disease), acute psychiatric disorder(s), diagnosis of dementia or mild cognitive impairment, inability to provide informed consent, and inability to speak and understand English or French. A diagnosis of concussion/PPCS relied either on the accuracy of the participant's physician, referring clinic, or the date and mechanism of injury was recalled. All participants completed a health questionnaire which included mechanism of each concussion, number of previous concussions, and time since last concussion (Appendix A). None of the participants had gross morphological abnormalities upon examination of MR images.

The study protocol was approved by the Human Participants Review Sub-Committee of York University's Ethics Review Board, and all participants provided written informed consent (Appendix B).

2.2. Measures

2.2.1. Persistent Post-Concussion Syndrome (PPCS) Assessment

PPCS was assessed using the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) (Eyres et al., 2005; King et al., 1995; Potter et al., 2006) (Appendix C). RPQ is a 16-item self-report standardised questionnaire that records the presence and severity of PPCS. The 5-point ordinal scale ranges from 0 (not experienced at all) to 4 (a severe problem) with a higher score reflecting greater severity of PPCS. The RPQ is made of 2 groups. The first group consists of the first 3 items (RPQ-3: headaches, dizziness, nausea) and are associated with the early physical symptom clusters of PPCS. The second group comprises of the next 13 items (RPQ-13: noise sensitivity, sleep disturbance, fatigue, irritability, depression, frustration, forgetfulness, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision, restlessness) and are associated with later psychological and cognitive symptom clusters of PPCS although the items from RPQ-3 might also be present.

2.2.2. Dizziness-related Disability Assessment

The impact of dizziness-related disability on quality of life was assessed using the Dizziness Handicap Inventory (DHI). DHI is a 25-item self-reported questionnaire assessing the physical, functional, and emotional components of vestibular dysfunction (Jacobson & Newman, 1990; Mutlu & Serbetcioglu, 2013) (Appendix D). The 3-point ordinal scale ranges from 0 (No) to 4 (Always) where a high score indicates an increased level of self-perceived handicap of vestibular dysfunction. The total score was 100 divided into three domains consisting of physical (24 items), functional (40 items), and emotional (36 items).

2.2.3. Behavioural assessment task

A detailed description of our visuomotor assessment has been previously published (Rogojin et al., 2019). All participants completed two visuomotor transformation tasks that were delivered using custom-written software. These tasks were separated into one standard (direct) condition (target viewed and finger motion are spatially coupled; Figure 1a) and one non-standard (CMI) condition (target viewed and hand motion are spatially decoupled twice; Figures 1b). In all conditions, participants were instructed to slide the index finger of their dominant hand along the touch screen (either on a vertical touchscreen using an ASUS™ touchscreen tablet or on a horizontal touchpad using an external Keytech™ USB-touchpad that was positioned perpendicular to the ASUS tablet depending on the condition) in order to displace the cursor from a central target to one of four peripheral targets (up, down, left, right). The targets for the finger motions were presented on the vertical touchscreen in both conditions. In the standard (direct) mapping task, the spatial locations of the visual target and the required hand movement were the same (Figure 1a), i.e., participants both looked at and moved on the vertical touchscreen, thereby directly interacting with the targets. For the non-standard (CMI) mapping task, the finger movement was made on a different plane and in the opposite direction (plane-change + feedback reversal, (PC+FR); Figure 1b) relative to the spatial target location. Importantly, the PC+FR condition required the participants to look at the vertical touchscreen whilst manipulating a cursor using their finger on the horizontal touchpad requiring implicit sensorimotor recalibration. The feedback was rotated 180°, i.e., in order to move the cursor to the left, the participant must slide their finger right, requiring explicit strategic control and movements of the eyes and hand to be made in opposite directions.

All conditions were randomised. The red peripheral targets were located 55 millimeters (mm) from the central target. The finger motion and trial timings consisted of: 1) a central yellow

target with a diameter of 7.5 mm appearing on the centre of the vertical touchscreen, 2) participants moving a white cursor to the central yellow target and changing its colour to green once the cursor has entered the central target, 3) after a delay period of 2000 milliseconds (ms), a red peripheral target appearing and the central target disappearing, indicating the 'go' signal for initiation of a movement, 4) participants were told to look towards the visual target on the vertical touchscreen and slide their finger along the touchscreen or touchpad to direct the cursor towards the cued peripheral target (up, down, left, or right), 5) once the peripheral target has been reached and the participant has held that position for 500 ms, the peripheral target disappears, signalling the end of the trial, and 6) after a delay of 2000 ms, the central yellow target reappeared, signalling the participant to return to the centre for the next trial (Figure 2).

In all conditions, participants were instructed to move as quickly and accurately as possible. Each participant completed 20 trials per condition, i.e. 5 trials for each peripheral target.

2.2.4. Behavioural data processing

Kinematic measures, including timing, finger position, and error data were recorded for each trial and converted into a MATLAB readable format using a custom written C++ application. Unsuccessful trials (error data) were detected by the data collection software and resulted in trial termination if the finger left the home target too early (<2,000 ms), reaction time (RT) was too short (<150 ms), RT was too long (>8,000 ms), or total movement time was too long (>10,000 ms). Trials in which the first ballistic movement exited the boundaries of the center target in the wrong direction (greater than 45° from a straight line to target) were coded as direction reversal (DR) errors and analysed as separate variables from the correct trials. A custom-written analysis program (Matlab, Mathworks, Inc., USA) was used to analyse the data from the collection program. Velocity profiles were computed for each successful trial and displayed alongside a Cartesian plot

illustrating finger position data and target locations using a custom analysis program. The movement onsets and ballistic movement offsets (the initial movement prior to path corrections) were scored at 10% peak velocity, while total movement offsets were scored as the final 10% peak velocity point once the finger position plateaued within the peripheral target. In situations where the initial movement successfully brought the finger to the peripheral target, the ballistic and total movement offsets were equivalent. These movement profiles for each trial were verified by visual inspection and corrections were performed when necessary. The scored data were processed to compute 7 different movement timing, accuracy, and precision measures described below. Individual trials which exceeded 2 standard deviations (SD) from the participant's mean for any of the outcome measures were eliminated prior to the calculation of outcomes.

The kinematic outcome measures were as follows: 1) Reaction time (RT), the time interval between the central target disappearance and movement onset measured in ms; 2) Full movement time (MTf), the time between movement onset and offset measured in ms; 3) Peak velocity (PV), the maximum velocity obtained during the ballistic movement measured in mm/ms, and used to calculate the 10% threshold used for determining movement onsets and offsets for each trial. 4) Path length (PL), the total distance (resultant of the x and y trajectories) travelled between movement onset and offset, measured in mm, calculated as both the full path length (PLf, start to final offset) as well as the ballistic trajectory (PLb, start to initial movement offset); 5) Absolute error (AE, end-point accuracy), the average distance from the individual movement endpoints ($\sum x/n$, $\sum y/n$) to the actual target location, in mm; 6) Variable error (VE, end-point precision), the distance between the individual movement endpoints ($\sigma 2$) from their mean movement, measured in mm; and 7) The percent direction reversal errors (%DR, only applicable in the PC+FR

condition), the percentage of total trials that constituted a deviation of greater than ±45° from the direct line between the center of the central and peripheral targets.

The procedure for combining some of the kinematic measures into composite scores to decrease the number of comparisons made in the data analysis was previously described (Rogojin et al., 2019). Briefly, all kinematic measures were standardised using z-scores and the composite scores were then created using simple averaging. A "timing score" was created as a composite of RT, MTf, and inversed PV (PV z-score * -1), and a "trajectory score" was a composite of PLf, AE, and VE. The timing and trajectory scores had a good internal consistency, as indicated by Cronbach's alpha values of 0.760 and 0.447, respectively. The timing and trajectory composite scores, RT, PLf, and %DR were then used for statistical analysis.

2.3. Magnetic resonance imaging (MRI) data acquisition

MRI data were acquired using a 3 Tesla (3T) Siemens PrismaFit scanner at York University. Participants received a T1-weighted anatomical scan using a sagittal volumetric magnetisation-prepared rapid gradient echo (MP-RAGE) sequence. The MP-RAGE consisted of the following acquisition parameters: 192 sagittal slices (slice thickness of 1 mm, with no gap), field of view (FOV) of 256 x 256 mm, matrix size of 256 x 256 resulting in a voxel resolution of 1 x 1 x 1 mm^3, echo time (TE) = 2.26 ms, repetition time (TR) = 2300 ms, flip angle = 8^o. For assessing white matter (WM) integrity, whole-brain diffusion-weighted images (DWIs) were acquired with 64 directions using diffusion-weighted spin-echo single-shot echo planar imaging (EPI). The diffusion tensor imaging (DTI) sequence used the following acquisition parameters: 60 axial slices (slice thickness of 2.6 mm, with no gap), FOV of 220 x 220 mm, matrix size of 146 x 146 resulting in a voxel resolution of 1.5 x 1.5 x 2.6 mm^3, TE = 84.0 ms, TR = 2600 ms, *b*-value = 1000 s/mm^2 (including one volume with no diffusion gradient, b = 0 s/mm^2). Additionally, we acquired two

reversed phase-encoded DWIs (60 slices, voxel resolution = 1.5 x 1.5 x 2.6 mm^3, TE = 84.0 ms, TR = 2600 ms, *b*-value = 1000 s/mm^2, *b* = 0 s/mm^2) corresponding to anterior-posterior/blip-up and posterior-anterior/blip-down, respectively. The rsfMRI was acquired with multi-band accelerator factor 4 and multi-echo EPI sequence sensitive to BOLD contrast. Participants were asked to lie in a scanner with their eyes open and fixate on a white cross with a black background for approximately twelve minutes during which the functional sequence with the following parameters was acquired: 52 axial slices (slice thickness of 3 mm, no gap), FOV of 240 x 240 mm, matrix size of 80 x 80 resulting in voxel resolution of 3.0 x 3.0 x 3.0 mm^3, TR = 961 ms, and echo times (TEs) =12.40, 30.15, 47.90 ms, flip angle = 50^o. Each TR resulted in the acquisition of 3 volumes, one for each TE. The time-series for each TE were separately converted to nifti (nii) format resulting in one nii image per echo time. One resting functional run consisting of 2274 images (758 per echo) was acquired for each participant.

2.4. MRI Preprocessing

2.4.1. Structural data

All anatomical scans was processed using FreeSurfer 6.0 (*"recon-all"*) pipeline with T1-weighted MR as input (Fischl, 2012). Briefly, the standard reconstruction steps include intensity correction, Talairach transformation, intensity normalisation, skull stripping, subcortical segmentation, and cortical parcellation. Skull-stripping was performed on the Talairach transformed and intensity corrected and normalised image using a deformable template model. Voxels were then classified as either white matter, grey matter, or cerebrospinal fluid based on intensity values. Next, the segmentation of subcortical structures and generation of the cortical surface, followed by the classification of tissue intensities between the white and grey matters (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. The surfaces were inflated into a sphere and registered to the FreeSurfer template sphere (fsaverage). The non-linear surface-based registration allowed for more accurate alignment of the gyri and sulci landmarks. A cortical parcellation of the template was then mapped back onto the individual participant and adjusted for small variations. The cortical parcellation was founded on the Desikan-Killiany atlas, a gyral-based atlas established using 40 participants (Desikan et al., 2006) (Figure 3). Cortical thickness was calculated as the distance between the grey matter and white matter boundaries (white matter surface) to grey matter and cerebrospinal fluid boundaries (pial surface) on the cortex in each hemisphere. All participants' images were visually inspected for excessive motion, signal drop-out, and/or other artefacts.

2.4.2. DTI data

Diffusion-weighted images were preprocessed in FSL (Andersson et al., 2003; Andersson & Sotiropoulos, 2016; S. M. Smith et al., 2004), MRtrix3 (Tournier et al., 2019), and TRActs Constrained by UnderLying Anatomy (TRACULA) (Maffei et al., 2021; Yendiki, 2011). For each participant, the DWI images were skull stripped using FSL *bet*, corrected for distortion, head motion, and eddy current using FSL *topup* and *eddy tools*. Additionally, they were denoised and bias field corrected using *dwidenoise* and *dwibiascorrect* in MRtrix3. The final corrected DWI was used as an input to TRACULA, a global probabilistic automatic tractography algorithm in FreeSurfer 7.2.0 (Maffei et al., 2021; Yendiki, 2011). TRACULA is capable of reconstructing 42 major white matter tracts, including the fornix which required the segmentation of the thalamic subnuclei (Iglesias et al., 2018). A detailed workflow of the TRACULA algorithm has been described elsewhere (Yendiki, 2011; Yendiki et al., 2016). The processing steps included: 1) cortical and subcortical segmentation of T1-weighted image using FreeSurfer as previously

described above; 2) within-subject registration of DTI to T1-weighted (Greve & Fischl, 2009); 3) between-subject registration in Advanced Normalization tool (ANTs) (Avants et al., 2008) to map each participant onto an FA template constructed from a training dataset in order to ensure that the relative position of the anatomical structures was the same for all participants and to map median streamline from the training data to the participant during initialisation (Maffei et al., 2021); and 4) the applications of tensor fitting for the extraction of tensor-based measures using DTIFIT and ball and stick model using BEDPOSTX (Behrens et al., 2003, 2007). Finally, the probabilistic reconstruction of 42 major white matter tracts. Importantly, step 3 was only used to initialise the reconstruction of the tracts, which was then refined by fitting them to the anatomy of the individual participant.

In this study, we were interested in the following region of interest (ROI) tracts because of their involvement in visuomotor processing and their susceptibility to brain injury (Hurtubise et al., 2020; Mustafi et al., 2022): the CC body (parietal and premotor), CC splenium, middle cerebellar peduncle (MCP), and bilateral CST, ILF, and SLF 1&2 (Figure 4). We visually inspected the above tracts for all participants. Tract reconstructions were considered successful if they traversed the relevant WM regions and reached the cortical regions that were used as inclusion ROIs in the protocols defined to manually label the training set (Maffei et al., 2021). Regarding the tensor-based measures, we extracted the FA and MD values averaged over each entire tract in addition to the FA and MD averaged at consecutive cross-sections of each tract. The latter resulted in an along-tract profile for each tensor measure.

The along-tract profiles for tensor measures were obtained using a pointwise assessment of streamline tractography attributes (PASTA), which is a type of analysis where an along-tract profile of a microstructural measure (e.g., FA) is generated by averaging the values of the measure at

different cross-sections of a tract (Jones et al., 2005). For each of the ROI tract, a 1D along-tract profile of FA and MD were generated by projecting the value of each measure from every point on every automatically reconstructed streamline to its nearest point on a reference streamline (Maffei et al., 2021). The reference streamline was the mean of the training streamlines for each tract in template space, ensuring that all participants' data were sampled at the same number of cross-sections along a given bundle. The length of each 1D profile was the length of the reference streamline i.e., the average length of the manually annotated streamline in template space.

2.4.3. rsfMRI for Functional Connectivity

Multi-echo rsfMRI pre-processing was done using the Multi-Echo Independent Components Analysis (ME-ICA) pipeline in the Analysis of Functional NeuroImages (AFNI) software (Cox, 1996; Kundu et al., 2017). ME-ICA is a method for fMRI analysis and denoising based on the T2* decay of BOLD signals, as measured using multi-echo fMRI. ME-ICA decomposes multi-echo fMRI datasets into independent components (ICs) using FastICA, then categorises ICs as BOLD or noise using their BOLD and non-BOLD weightings (measured as Kappa and Rho values, respectively) (Kundu et al., 2017). Prior to denoising with ME-ICA, the functional data preprocessing steps included discarding the first 5 volumes of each rsfMRI time-series. Images were then skull-stripped and image intensity is normalised (3dSkullStrip). The functional images were de-obliqued (3dWarp). Large signal transients were removed via interpolation ("despiking", 3dDespike) and slice time correction was applied (3dTshift). Motion correction parameters were calculated using the middle echo (TE2 = 30.15 ms, 3dvolreg). The skull-stripped anatomical and functional images were co-registered using the first volume of the middle echo images (3dAllineate). Optimal combination of the 3 echo times was performed prior to initialising ME-ICA denoising. In ME-ICA, BOLD signal was identified as independent

components having linearly TE-dependent percentage signal changes. Non-BOLD noise components were removed from the time-series by ME-ICA using linear regression. The output of this process included a functional time-series that was reconstructed to include only the BOLD signal components of the data. All participants' preprocessed functional images were visually inspected for excessive motion, co-registration errors, and to verify that the functional data were not excessively noisy (a minimum of 10 independent components classified as BOLD signal by ME-ICA).

After ME-ICA, the final preprocessed and denoised time-series ("participantID_medn.nii.gz") was used as input data for Group prior individual parcellation (GPIP) analysis. GPIP is an individualised functional parcellation approach that was used here to identify participant-specific functional resting network nodes in the preprocessed data (Chong et al., 2017). Network parcellations refers to the identification of cortical areas that exhibit functionally similar properties (Kim et al., 2010; Raichle et al., 2001; S. M. Smith et al., 2013; Sporns et al., 2005). The most common approach to parcellation relies on a mean functional resting state network parcellation common to a group of participants (i.e., the group average network), which is then projected back onto individual participant data (Thomas Yeo et al., 2011; Wig et al., 2014). These population-average networks have provided important information on the large-scale functional organisation of the brain (Buckner et al., 2013; Wig, 2017). However, population-average networks may obscure participant-specific network organisation and thus lead to inaccuracies at the level of each participant (Chong et al., 2017). Thus, there is a growing focus on person-specific parcellation to define functional parcels independently for each participant. Group prior individual parcellation (GPIP) was implemented to automatically perform parcellation of resting functional data into functional networks at the participant level (Chong et al., 2017). GPIP

is a novel cortical parcellation method that initialises parcellation using an atlas template. This initial parcellation is then refined for each participant using the participant's functional data to allow individual variability across participants in the boundaries of these parcels (Chong et al., 2017). The use of a template atlas for parcellation initialisation results in all participants having corresponding functional regions (aiding group analysis), whilst functional parcel boundaries can vary from participant to participant. GPIP iterates between two steps to continuously update parcel labels until convergence: (1) each participant's parcel boundaries (first obtained from the initialisation to the Schaefer atlas) are refined relative to their resting functional data, and (2) the concentration (inverse covariance/partial correlation) matrices from all individuals are then jointly estimated using a group sparsity constraint (Chong et al., 2017). Specifically, for the results presented in the current study, the preprocessed and denoised resting state functional data were first initialised with the 200-parcel Schaefer atlas (Schaefer et al., 2018), corresponding to the 7 functional networks atlas (Thomas Yeo et al., 2011).

Prior to GPIP initialisation, the denoised functional data were registered to the corresponding T1- weighted FreeSurfer anatomical images for each participant, converted from volumetric to surface space, and resampled to the FreeSurfer cortical surface template (fsaverage5). Spatial smoothing of 6 mm was applied to the anatomically-aligned data in surface space. Visual inspection was used to verify proper co-registration of functional data with the T1-weighted anatomical images. Values from vertices located in the medial wall were resampled into the surface data as they are removed by FreeSurfer but are needed for running GPIP. The functional time-series data were normalised by scaling to a mean value of 0 and a standard deviation of 1. The normalised functional time-series data were then used in subsequent steps for GPIP analysis. GPIP performed its two-step iterative process 20 times for each subject resulting in increasingly refined

functional network parcellations with optimal segmentation with respect to the cortical surface. Each participant's final parcellation was plotted and inspected to verify the quality of the parcellation (an example of a single participant's final parcellation is shown in Figure 5). To further assess the quality of the parcellations, homogeneity was calculated as the mean temporal correlation coefficient between all pairs of vertices within each GPIP parcel, where a large value suggests that the vertices included in a particular parcel have similar time-series (i.e., are homogeneous) and therefore correctly assigned to that parcel. The homogeneity value was calculated for the whole brain as a mean value across all parcels for each GPIP iteration to verify that these values increased with each iteration before plateauing prior to the final iterations, suggesting stable and accurate parcellations. Further, cross-correlation matrices including all GPIP parcels were plotted and visually inspected to verify reasonable patterns of whole-brain connectivity in each participant (see section "Resting state functional connectivity matrix" below for specific details on matrix construction).

2.4.4. Resting state functional connectivity (RSFC) matrix

A functional connectivity matrix was created for each participant based on their individualised parcellation. The mean BOLD signal time-series data was extracted from each parcel and pairwise correlations were computed between each parcel pair. The correlation coefficients were then converted to z-scores using Fisher's r-to-z transformation to normalise the distribution of correlation values, resulting in a 200 × 200 functional connectivity matrix for each participant. Each participant's mean Fisher z-transformed RSFC values were extracted for 6 resting state networks of interest as a measure of overall within-network functional connectivity. The networks of interest were the visual network (VN), sensorimotor control network (SMN), dorsal attention network (DAN), SVAN, FPCN, and DMN (Figure 6). Furthermore, the FPCN was

separated into 3 subnetworks based on the FPCN from the Schaefer et al. (2018) 17-networks parcellation. We chose to divide the FPCN in subnetworks because a growing body of research has identified two functional cores of the FPCN: FPCNa which has stronger connectivity with the DMN and FPCNb which showed stronger connectivity with the DAN (Beaty et al., 2021; Dixon et al., 2018; Murphy et al., 2020; Yin et al., 2022). DAN plays a key role in visuospatial perceptual attention and visually-guided reaching actions (Ptak, 2012; Ptak et al., 2017; Thomas Yeo et al., 2011) and has a close relationship with SMN, whilst DMN is independent of sensory input and involved in introspective processes (Konishi et al., 2015). The division was done by matching the FPCN MNI centroid coordinates from the 7 networks atlas to the corresponding FPCN MNI centroid coordinates from the 17 networks atlas (see Figure 7). Although, the third subnetwork (FPCNc: the posterior cingulate and precuneus) did not contain any frontal components, we included it because there is evidence showing altered functional connectivity post-concussion (Leech & Sharp, 2014).

2.5. Statistical Analysis

With exception of cortical thickness and along-tract DTI analyses, all statistical analyses were conducted using R (v 3.4.1), and scatter and box plots were generated using the ggplot2 package. Data were checked for normality by visual inspection of the distributions and by Shapiro-Wilk's test. One participant was excluded from functional connectivity and cortical thickness analyses because no MRI was acquired (n=21), whilst 2 participants were removed from DTI analyses based on the aforementioned reason and analysis pipeline failure (n=20). Descriptive statistics were used to summarise participants' characteristics. A paired t-test was used to detect any significant differences in timing and trajectory composite scores, RT, PLf, and %DR between standard and PC+FR conditions. Model-based analyses involving RPQ and DHI were adjusted for

age, sex, experience with competitive and/or recreational sports, and days since last concussion whilst we adjusted for age, sex, experience with competitive and/or recreational sports, experience with video games, and days since last concussion for all model-based analyses involving visuomotor performance. The adjusted variables were selected based on previous findings that revealed significant predictors of visuomotor performance and PPCS severity (Hurtubise et al., 2016; Sergio et al., 2020; Smeha et al., 2022). Also, model-based measures were reported as effect estimates and 95% confidence intervals (CI).

2.5.1. Relationship between Cortical thickness, RPQ, DHI, and Visuomotor performance

Whole brain and ROI vertex-wise general linear model (GLM) analyses were conducted using FreeSurfer's built-in *mri_glmfit* tool to investigate the associations between cortical thickness, PPCS severity (RPQ-3 & 13), dizziness-related symptoms (DHI: emotional, physical, functional, and total), and visuomotor performance measures (standard and PC+FR conditions). The ROIs were obtained from the Desikan-Killany atlas (Desikan et al., 2006) based on their involvement in the FPCN for visually-guided reaching (Hurtubise et al., 2022): bilateral superior parietal and inferior parietal cortices, precuneus, precentral, superior frontal, rostral middle frontal, caudal middle frontal, and cuneus (Figure 8). All participants' images were resampled to a common space (fsaverage) and smoothed with a 10-mm full-width half-maximum (FWHM) kernel before GLM analyses. A z-distribution Monte Carlo simulation with 5000 iterations using a cluster-forming threshold of 2 ($p = 0.01$) and cluster-wise $p < 0.05$ were used for multiple comparisons correction (*mri_glmfit-sim*). Bonferroni correction was applied across both hemispheres.

2.5.2. Relationship between RSFC, RPQ, DHI, and Visuomotor performance

Multivariate multiple linear regression models were set up with RSFC as the independent variable and RPQ, DHI, or visuomotor performance measures as dependent variable. The independent variable was the mean within-network functional connectivity of the VN, SMN, DAN, SVAN, FPCN, and DMN as well as the FPCN subnetworks (FPCNa, FPCNb, and FPCNc).

2.5.3. Relationship between DTI measures, RPQ, DHI, and Visuomotor performance

We tested the along-tract FA or MD values for associations with PPCS severity, dizziness-related symptoms, and visuomotor performance measures. We fitted a GLM at each point along each tract using FreeSurfer's *mri_glmfit* tool that was adapted for 1D data. A permutation-based 5000 simulations was used for multiple comparisons correction with both the cluster-forming threshold and cluster-wise set at $p = 0.05$. Bonferroni correction was applied across both hemispheres.

Furthermore, multivariate multiple linear regression analyses were set up with FA or MD values averaged over an entire tract as the independent variable and RPQ, DHI, or visuomotor performance measures as the dependent variable.

All *p*-values obtained from multivariate regression analyses were adjusted for multiple comparisons using the Holm correction method and were considered statistically significant at $p < 0.05$ at the level of each regression analysis.

Chapter 3: Results

3.1. Participant characteristics

Participant's demographic, PPCS, dizziness, and visuomotor characteristics are displayed in Table 1. There was a higher percentage of females (77.27%), and the mean age was 47.23 years old. The median age was 48.5, with a range of 29 — 63 years old. Of the 22 participants, 5 reported

having 1 concussion (22.73%), 3 reported having 2 concussions (13.64%), 8 reported having 3 concussions (36.36%), and 6 reported having 4 or more concussions (27.27%). All participants reported experiencing poor concentration (Table 2). Dizziness, forgetfulness, taking longer to think were the second most reported symptoms (95.45% respectively), whilst double vision was the least reported symptom (50%) (Table 2). During data collection, 8 participants reported full-time employment, 8 reported part-time employment, 1 reported mixed employment (full-time and part-time), 3 reported no employment before and after experiencing concussion, and 2 reported full-time employment prior to concussion and unemployed after concussion. Regarding the mechanisms of concussion, motor vehicle accident had the highest frequency (30.16%), followed by sports (25.39%), and fall and projectile objects (19.05% and 19.05%, respectively). Other mechanisms included fights, bicycle and elevator accidents, and mixed mechanisms (sports and projectile object) which accounted for 6.36% combined.

Behaviourally, there were no significant differences between standard and PC+FR conditions on timing and trajectory composite scores and reaction time (RT) (timing: $t = 0.184$, $p = 0.856$; trajectory: $t = 0.156$, $p = 0.878$; RT: $t = -1.64$, $p = 0.117$). However, the PC+FR condition showed significantly more direction reversal (DR) and longer full path length (PLf) compared to the standard condition as expected (DR: $t = 6.40$, $p < 0.0001$; PLf: $t = 3.10$, $p < 0.01$, Figure 9).

3.2. Relationship between Cortical thickness, RPQ, DHI, and Visuomotor performance

3.2.1. Cortical thickness, RPQ, and DHI

ROI analysis results are summarised in Table 3 and Figure 10. Higher scores on the functional and emotional DHI domains and total DHI were associated with lower cortical thickness in the left inferior parietal gyrus, respectively (functional: cluster-wise $p = 0.048$, CI = [0.043,

0.054]; emotional: cluster-wise $p = 0.036$, CI = [0.031, 0.041]; total: cluster-wise $p = 0.045$, CI = [0.039, 0.050]), such that as thickness decreased, the severity of dizziness-reported symptoms increased. No associations were observed on whole-brain analysis.

Lastly, we observed no relationships between RPQ-3 & 13 and cortical thickness.

3.2.2. Cortical thickness and Visuomotor performance

In the PC+FR condition, ROI analysis showed negative associations between timing score and left superior parietal gyrus thickness (cluster-wise $p = 0.035$, CI = [0.029, 0.039]) and between RT and bilateral superior parietal gyrus (left: cluster-wise $p = 0.011$, CI = [0.008, 0.014]; right: cluster-wise $p = 0.033$, CI = [0.028, 0.037]) (Table 3) (Figure 11). In all regions, a smaller cortical thickness was associated with a higher visuomotor score, implying worse performance. No associations were observed on whole-brain analysis. Further, we found no associations between standard condition visuomotor performance and cortical thickness.

3.3. Relationship between RSFC, RPQ, DHI, and Visuomotor performance

3.3.1. RSFC, RPQ, and DHI

In RPQ-3, higher mean RSFC within the following networks was associated with higher early physical symptoms cluster of PPCS: VN (B = 7.884, unadjusted $p = 0.033$, CI = [0.716, 15.053]), SMN (B = 6.922, unadjusted $p = 0.018$, CI = [1.374, 12.469]), and DAN (B = 9.068, unadjusted $p = 0.039$, CI = [0.545, 17.591]) (Table 4) (Figure 12a-c). In RPQ-13, higher mean RSFC within the following networks was associated with higher later psychological and cognitive symptoms cluster of PPCS: DAN (B = 41.539, unadjusted $p = 0.035$, CI = [3.375,79.702]), FPCN (B = 41.924, unadjusted $p = 0.024$, CI = [6.320, 77.528]), and FPCNb (B = 31.943, unadjusted $p = 0.032$, CI = [3.247, 60.639]) (Table 4) (Figure 13a-c). These results may suggest that higher RSFC

in the aforementioned networks was mainly associated with overall more severe PPCS regardless of stage of injury. Lastly, we did not observe any associations between mean RSFC within-networks and DHI.

3.3.2. RSFC and Visuomotor performance

Shorter PLf in the PC+FR condition, indicating a better performance, was associated with higher mean RSFC within SVAN (B = -108.623, unadjusted p = 0.045, CI = [-214.185, -3.062]) (Table 4) (Figure 14).

3.4. Relationship between DTI, RPQ, DHI, and Visuomotor performance

3.4.1 Along-tract and Entire-tract FA & MD, RPQ, and DHI

Figure 15 shows findings from the statistical analysis of along-tract MD. We found a positive association between RPQ-3 and CC splenium MD (cluster-wise p = 0.019, CI = [0.017, 0.022]) (Table 5) (Figure 15a) and positive associations between DHI functional domain, CC splenium MD, and CC body-premotor MD (CC splenium: cluster-wise p = 0.035, CI = [0.032, 0.039]; CC body-premotor: cluster-wise p = 0.046, CI = [0.043, 0.050]) (Table 5) (Figure 15b-c).

Similarly, results from multivariate multiple regression analysis revealed a positive association between RPQ-3 and the entire right SLF-2 MD (B = 106.750, unadjusted p = 0.002, CI = [44.978, 168.522]) (Table 6) (Figure 16). We found no associations in DHI. In all tracts, higher MD denoted worse PPCS and dizziness-related symptoms.

3.4.2 Along-tract and Entire-tract FA & MD and Visuomotor performance

In the standard condition, the along-tract analysis revealed that the timing score was negatively associated with right ILF FA (cluster-wise p = 0.018, CI = [0.018, 0.021]) (Table 5)

(Figure 17a) and positively associated with left ILF MD (cluster-wise p = 0.009, CI = [0.008, 0.012]) (Table 5) (Figure 17b). Furthermore, the following associations were obtained from the entire-tract analysis: timing score vs right CST MD (B = -98.57, unadjusted p = 0.012, CI = [-171.139, -25.996]) (Table 6) (Figure 18a) and RT vs bilateral SLF-1 MD (left: B = -14389.378, unadjusted p = 0.047, CI = [-28526.332, -252.424]; right: B = -16148.645, unadjusted p = 0.032, CI = [-30663.252, -1634.039]) (Table 5) (Figure 18b-c).

Finally, in the PC+FR condition, we found a negative association between the timing score and right ILF FA on the along-tract analysis (cluster-wise p = 0.023, CI = [0.019, 0.027]) (Table 5) (Figure 17c). Additionally, the entire-tract analysis revealed various significant associations with multiple tracts: right CST FA with trajectory score (B = -52.428, unadjusted p = 0.005, CI = [-85.311, -19.544]), PLf (B = -839.299, unadjusted p = 0.031, CI = [-1585.132, -93.466]), timing score (B = 44.128, unadjusted p = 0.047, CI = [0.656, 87.599]), and RT (B = 10174.886, unadjusted p = 0.004, CI = [4042.646, 16307.126]) (Table 6) (Figure 19a-d); right CST MD with DR (B = 831.019, unadjusted p = 0.035, CI = [70.589, 1591.449]) (Figure 20a); PLF with left ILF MD (B = -735.327, unadjusted p = 0.029, CI = [-1381.525, -89.129]), left SLF-1 MD (B = -802.793, unadjusted p = 0.043, CI = [-1573.682, -31.904]), and bilateral SLF-2 MD (left: B = -1105.439, unadjusted p = 0.021, CI = [-2013.977, -196.902]; right: B = -1565.452, unadjusted p = 0.009, CI = [-2666.056, -464.848]) (Table 6); right SLF-2 MD with RT (B = 13026.401, unadjusted p = 0.033, CI = [1276.233, 24776.569]) (Table 6) (Figure 20b).

No associations were observed either between severity of PPCS or dizziness-related symptoms and our upper limb visuomotor performance.

Chapter 4: Discussion

The main goal of this study was to investigate the functional and structural neural underpinnings of visuomotor performance, and to examine the effects of PPCS and vestibular dysfunction on the observed neuroanatomical correlates. The primary findings in this study were: 1) higher RSFC within the VN, SMN, DAN, and FPCN were associated with worse symptoms/outcomes; 2) lower inferior parietal thickness was related to worse vestibular dysfunction; 3) higher RSFC within SVAN was associated with better visuomotor performance, whilst lower superior parietal thickness was associated with worse visuomotor performance on the task requiring two levels of decoupling (PC+CR), and 4) significant associations between white matter integrity of entire tracts and along specific sections of the long-associative, projective, and commissural tracts with PPCS, vestibular dysfunction, and visuomotor performance. The alteration in white matter integrity was mostly observed on tracts implicated in visuomotor control, particular in association with the challenging CMI task.

Disruption in RSFC in working-aged adults with PPCS has previously been reported (So et al., 2023). We found hyperconnectivity in the VN, SMN, DAN was related to the early symptoms of PPCS (headache, dizziness, and nausea), whilst hyperconnectivity in the DAN, FPCN, and FPCNb was associated with later psychological and cognitive symptoms. Previous studies examining functional connectivity in TBI have reported both hyper- and hypoconnectivity (Han et al., 2016; Konstantinou et al., 2019; So et al., 2023; Stevens et al., 2012; Wong et al., 2023). The mixed results might be attributed to factors including sample size, study design, age, sex ratio imbalance, recovery phase, amongst others. Our findings are in accordance with numerous studies that reported higher RSFC amongst these networks (Champagne et al., 2020; Mayer et al., 2011, 2015; Simos et al., 2023; So et al., 2023). Wong et al. (2023) observed higher RSFC within the

DMN and executive central network/FPCN were associated with improved neurocognitive performance in working-aged females with PPCS. Another study reported higher RSFC in multiple networks including the DAN which was associated with improved behavioural symptoms, FPCN (prefrontal cortex), SMN, and SVAN, whilst lower RSFC was observed in the DMN, VN and FPCN (lateral occipital cortex) (Amir et al., 2021). As previously mentioned, the task-positive network is comprised of the FPCN and DAN; networks that are integral to task-related performance (Dixon et al., 2018). Recent studies have identified two distinct subnetworks of the FPCN (FPCNa and FPCNb) which are functionally connected to the DMN and DAN, respectively (Dixon et al., 2018; Murphy et al., 2020). The connectivity between FPCNb and DAN plays a key role in visuospatial perceptual attention and visually-guided reaching actions, and is required for encoding and maintaining task-relevant information in working memory (Dixon et al., 2018; Ptak, 2012; Ptak et al., 2017). Moreover, they are closely linked with the SMN and VN. Therefore, it is possible then, that the observed hyperconnectivity in the current study may indicate neuro-compensatory adaptive efforts, perhaps in form of functional reorganisation near or distal to the site of injury (Rosenthal et al., 2018).

It has been suggested that most functional recovery happens within the first 3 to 6 months post-injury and that stabilisation of hyperconnectivity may be indicative of PPCS recovery (Bharath et al., 2015). In one study, patients with moderate-to-severe TBI showed increased RSFC within the DMN and bilateral FPCN between 6 – 18 months post-injury, changing trajectory in the opposite direction at 18 months post-injury (So et al., 2023). More supporting evidence of neuro-compensation and functional recovery via ancillary brain networks were reported by Czerniak et al. (2015) that demonstrated higher connectivity between DMN and areas within the SVAN and FPCN which correlated with better performance on measures of inhibition and attention. Bharath

et al. (2015) also showed higher DMN connectivity spreading to other networks, including SVAN, VN, FPCN, and DAN at 3 months post-injury. At 6 months post-injury, these patients had neurocognitive test scores and functional connectivity that were comparable with healthy controls. Taken together, these studies suggest that the higher RSFC could reflect higher metabolic cost during functional reorganisation that may have occurred in our study. Of note, it is important to acknowledge the lack of premorbid RSFC as a limitation to our analysis. This is because our participants may differ extensively on their premorbid RFSC at the group or individual level such that some participants may have lower premorbid RSFC. However, by comparing our results from those obtained from "healthy normal controls" (Bharath et al., 2015; So et al., 2023), our findings suggest that neuro-compensatory efforts may result in within networks' hyperconnectivity as the brain tries to recover from the neuroinflammatory response and PPCS resulting from concussion. Moreover, it is worth a mention that the lack of observable PPCS and normal neurocognitive test scores does not fully guarantee complete neural recovery. For example, multiple studies have reported no notable difference in visuomotor transformation tasks (Hurtubise et al., 2020), visual tracking task (Astafiev et al., 2015), and neurocognitive performance on working memory (Westfall et al., 2015) between participants with PPCS and healthy controls. However, the aforementioned studies noted disruption in functional and/or structural integrity in the form of lower white matter integrity in several tracts (Hurtubise et al., 2020), abnormal BOLD activity along the SLF (Astafiev et al., 2015), and higher connectivity within the FPCN and recruitment of additional brain networks (Westfall et al., 2015) in participants with PPCS. These alterations may reflect the utilisation of extra cognitive resources to compensate for any deficits, resulting in normal-appearing behavioural function. This was supported by the higher RSFC within the SVAN and shorter full path length in the PC+FR condition observed in our study. Thus, it may suggest

that the neural movement control networks may be permanently changed from what is typical following concussion in order to perform pre-injury behaviour to the same level of proficiency.

The SVAN has functional key nodes anchored in the anterior insular, anterior cingulate, and ventrolateral prefrontal cortices and is integral for several cognitive functions such as, initiating, maintaining, and adjusting of attention (Dosenbach et al., 2006). Moreover, it has been shown to modulate the transition between DMN and FPCN activity, especially in anticipation of a task (Menon & Uddin, 2010). Sridharan et al. (2008) showed that the anterior insula cortex played a critical and causal role in the switch between the DMN and FPCN, demonstrated by the significant deactivation of the former, and the activation of both the latter and the SVAN during a series of an attention-task-based fMRI and rsfMRI analyses. These findings were confirmed by another study that observed greater SVAN-FPCN connectivity than SVAN-DMN during a visuospatial working memory task, which included the visual network (Santangelo & Bordier, 2019). Together, these studies emphasis the role of SVAN, which might also collectively with the FPCN, downregulate the DMN. The DMN was shown to be involved in internally-directed cognition, such as mentalisation (Spreng et al., 2009), autobiographic memory (Andrews-Hanna, Saxe, et al., 2014), and emotional processing (Andrews-Hanna, Smallwood, et al., 2014). Given the role of the SVAN in switching between networks (Menon & Uddin, 2010), and the FPCN's role in externally-directed cognition (Dixon et al., 2018), our observed SVAN hyperconnectivity and shorter full path in the PC+FR condition may reflect a predisposition to recruiting additional cognitive resources when engaging in task(s) with increasing complexity in order to achieve a successful performance. Our results were further corroborated by the lack of significant relationship between the DMN and both visuomotor conditions, thus suggesting greater SVAN-FPCN connectivity and the involvement of SVAN in complex visuospatial attention and

visuomotor task (Benassi et al., 2021; Diwakar et al., 2015; Ohashi et al., 2018; Vossel et al., 2014), particularly in rule-based CMI. Taken together, our RSFC findings suggest that the networks implicated in the integration of sensorimotor and cognitive-motor systems, particularly during the decoupling of visuomotor control, are especially susceptible to concussion.

White and grey matter abnormalities have been implicated in PPCS (Hurtubise et al., 2022; Multani et al., 2016). Although the underlying pathophysiology of concussion and PPCS is not fully understood, multiple studies have suggested that it might be related to diffused axonal and cytoskeletal injury from the biomechanical impact on the skull (Chappell et al., 2006; Cubon et al., 2011; Rabinowitz et al., 2014). Subsequent axonal and cytoskeletal changes disrupt neuronal membrane permeability, resulting in numerous neurochemical and neurometabolic cascades, which puts mounting stress on long associative, projecting, and connecting white matter tracts (Gumus et al., 2021; McCrory et al., 2017; Rabinowitz et al., 2014). These white matter tract alterations have also been associated with post-concussion decreases in cortical volume and thickness due to axonal damage (Ding et al., 2008; Warner et al., 2010). In keeping with these findings, we observed several associations between measures of white and grey matter integrity with PPCS and visuomotor performance. Specifically, lower cortical thickness in the inferior parietal and superior parietal cortices were associated with worse vestibular dysfunction and poor performance on the PC+FR condition, respectively. Our findings are consistent with Zhe et al. (2021) who reported lower cortical thickness in the superior parietal lobule and lower sulci depth in the inferior and superior parietal lobules in patients with vestibular migraine. Similarly, another study from our laboratory demonstrated lower cortical thickness in the inferior and superior parietal lobules were associated with poor performance in various CMI-based tasks in participants with PPCS (Hurtubise et al., 2022). As part of the multisensory vestibular cortical network (Dieterich & Brandt, 2008), the

inferior parietal cortex is involved in vestibular processing and responsible for sustained attention when engaging in ongoing tasks and responding to salient stimuli in space (Singh-Curry & Husain, 2009). Also, the superior parietal cortex is involved in sensorimotor integration and responsible for spatial orientation using proprioceptive cues during reaching movements (Sabes, 2000). Thus, given the contribution of these posterior parietal cortices in sensorimotor transformations between visual inputs and motor outputs and spatial awareness, it is unsurprising that structural changes can result in poor hand-eye coordination and balance, as demonstrated in the current study.

Several white matter tracts were associated with worse PPCS and vestibular dysfunction. Particularly, these white matter abnormalities were observed amongst the most commonly documented tracts differentiating participants with PPCS from healthy controls, and their relationship with sensorimotor integration (SLF, CST, ILF, and CC) (Gumus et al., 2021; Hurtubise et al., 2020). We found that higher MD along the CC splenium and in the whole SLF-2 were associated with worse PPCS, whilst higher MD along the CC splenium and premotor were associated with higher vestibular dysfunction. Our findings reinforce results from previous studies with different sample sizes and cohorts that have reported diffused white-matter damage linked to persistent symptoms after concussion (Gumus et al., 2022; Leh et al., 2017; Multani et al., 2016; Murdaugh et al., 2018; Mustafi et al., 2022; Rabinowitz et al., 2014; Taghdiri et al., 2018). Calzolari et al. (2021) showed lower FA and higher MD in the right ILF was associated with impaired balance in TBI patients with vestibular agnosia, contrary to our vestibular findings. However, another study from the same group demonstrated that vestibular agnosia was associated with higher RSFC between the SLF and the posterior corona radiata tracts (Hadi et al., 2022), supporting our findings. Similarly, Messé et al. (2011, 2012) and Gumus et al. (2022) reported either higher MD or lower FA across the whole brain in patients with severe PPCS with poor

outcome compared to mild PPCS with good outcome. The aforementioned white matter abnormalities were especially observed in the long associated fasciculi (SLF and ILF) and body-splenium junction of the CC which is the thickest part of the CC, thus susceptible to brain injury (Fitsiori et al., 2011; Shiramizu et al., 2008). The SLF is an associative multi-sectional tract functionally connecting the frontoparietal control network and the posterior parietal lobule anatomically, and the integrity of the SLF-2 is related to visuospatial and visuomotor control processes (Janelle et al., 2022; Nakajima et al., 2020), whereas the ILF, CC splenium, and CC-body premotor serve as connections between the temporo-occipital, parieto-occipital, and motor areas, respectively (Maffei et al., 2021; Park et al., 2008). Together, these tracts are critical for various top-down cognitive and vestibular sensorimotor processes that are vulnerable to the shearing and tearing forces due to concussion (Gumus et al., 2021; Narayana, 2017; Ubukata et al., 2016). Of note, given the microstructural changes that could occur within specific sections of the tract, it is imperative to investigate diffusion differences along each tract. This is because analysing the whole tract may ignore the potential rich neuroanatomical variation in diffusion measures along each tract thereby, flattening subtle focal white matter alterations especially in long-association, projection, and commissural tracts. This was supported by Mustafi et al. (2022) who showed that higher MD along the forceps minor, superior and posterior corona radiata, and cingulum tracts was associated with persistent symptoms after sport-related concussion. Similar results were obtained by Veeramuthu et al. (2015) showing that the associations between severe white matter abnormalities and neurocognitive deficits in acute and chronic concussion phases were along the long-association (SLF) and commissural (CC splenium and body) tracts. These findings suggest that the biophysical properties of long and commissural fibre tracts may increase their susceptibility to concussion and PPCS. Possible explanations for the increased vulnerability of these fibres includes the possibility that the myelin sheaths covering the axons in these fibres are stiffer, making

them more vulnerable to damage from concussion (Laksari et al., 2012; D. H. Smith et al., 1999). In addition, their deep and central location (Bayly et al., 2005; Viano et al., 2005), and/or their relative long length and high membrane-to-cytoplasmic ratio (Korn et al., 2005; McKee & Robinson, 2014) might intensify their potential to be damaged by the biomechanical force from concussion. Notwithstanding the heterogeneity in participants and injury mechanisms, our results are consistent with previous works suggesting that investigating the microstructural diffusion changes along white matter tracts (i.e., rather than averaged over an entire tract) may improve the sensitivity of DTI in detecting the effects of concussion and PPCS on white matter structural integrity.

In the present study we observed an overall association between FA, MD, and visuomotor performance across both conditions. Our finding supports prior results from our group and others that implicates healthy white matter integrity for successful CMI task performance (Gorbet & Sergio, 2016; Hawkins et al., 2015; Hurtubise et al., 2020; Rogojin et al., 2023). The whole and along-tract analyses between visuomotor performance scores and DTI measures in several long-coursing and projection tracts (ILF, SLF-1 & 2, and CST; see Tables 5 & 6) showed that alterations in white matter integrity (higher and/or lower FA and MD) were associated with higher movement errors, lower movement accuracy, and slowed psychomotor response. Conflicting results from studies examining concussion-related white matter integrity changes may arise from multiple factors like differences in imaging and methodology protocols, heterogeneity in injury severity and participants, variability in injury mechanism, and injury phase, with some reporting inconsistent changes in FA and MD directions. For instance, some studies have reported lower FA and higher MD during the acute and chronic phases (Kraus et al., 2007; Nakayama, 2006; Niogi et al., 2008; Veeramuthu et al., 2015), whilst others have reported higher FA and lower MD in both phases

(Bazarian et al., 2007; Henry et al., 2011; Veeramuthu et al., 2015; Wilde et al., 2012). Furthermore in concussion, vasogenic oedema is characterised by reduced FA and higher MD because of the release of intravascular proteins into brain parenchyma and the extracellular accumulation of fluid resulting from blood-brain-barrier disruption and may be reversible, whilst cytotoxic oedema is related to higher FA and lower MD due to the abnormal accumulation of intracellular fluid resulting in cell swelling and may be irreversible (Michinaga & Koyama, 2015). These pathogenic oedematous processes coupled with demyelination could explain the visuomotor impairment observed in the current study months or even years post initial injury. Consistent with our results, Hurtubise et al. (2020) found worse performance on the non-standard (PC+FR) condition indicated by lower trajectory composite score was related to lower FA in the ILF, SLF, and CST despite the lack of associations between PPCS, standard visuomotor condition, and white matter MD. Similarly, two studies reported lower FA and higher MD, AD, and RD in ILF, SLF, cingulum, CST, CC, and forceps tracts predicted impaired performance in the PC+FR condition in APOEe4 carriers (Hawkins et al., 2015; Rogojin et al., 2023). As previously mentioned, these white matter tracts pass through the task-positive networks, connecting regions such as the posterior parietal lobule that are involved in visuomotor processing. Furthermore, our CMI condition involved two levels of decoupling that required both implicit sensorimotor recalibration and the explicit strategic control. Such task complexity putatively requires intact large-scale functional and structural network integrity. Hence, disruption of the normal homeostatic neural state and abnormal changes in structural components, combined with the already taxed metabolic capacity required for concussion recovery, may place an energetic strain on the control system resulting in poor motor performance (Bigler, 2013; Hillary & Grafman, 2017).

4.1. Limitations, Future directions, and Strengths

Our study has both limitations and strengths. Firstly, since this was not a longitudinal study, we could not address the causal relationships between RSFC, abnormal white matter integrity, lower cortical thickness, and impaired visuomotor performance in working-aged adults with PPCS. Future studies should investigate the long-term interactive effects of functional and structural integrity on developing PPCS and visuomotor deficits in working-aged adults. Secondly, the absence of informant verified self-reported PPCS and number of concussions may have introduced bias. Thirdly, the lack of a control group meant that we could not compare the performance on visuomotor tasks between participants with PPCS and healthy controls and we could not determine the specific neuroanatomical correlates of PPCS. Since, neuroimaging studies in healthy controls are crucial in identifying the functional and structural neural underpinnings of visuomotor performance, their absence in our study might impact the generalisation of our findings. Moreover, the interpretation and generalisability of our findings is limited by our small sample size. Although we tried to adjust for many covariates including factors such as hormones, pharmacological therapy, socioeconomic status, and years of education, a small sample size may have impacted our results. Therefore, more studies with healthy controls and a larger sample size are required to confirm our results and further investigate the effects of these variables on PPCS, brain function and structure, and visuomotor performance in working-aged adults. Our sample contained proportionately more females, which was consistent and contrary to some TBI studies (Biegon, 2021; Shafi et al., 2020; Smeha et al., 2022; So et al., 2023). As a result, we were unable to explore any sex differences in PPCS and its potential associations with functional and structural integrity and visuomotor performance. Potential sex differences may result from multiple factors including sex hormones, PPCS profiles, length of recovery, neuroanatomy and function, neck muscle

strength, and head/neck ratios (Chaychi et al., 2022; McGlade et al., 2015; Shafi et al., 2020; Tiernery et al., 2005; Varriano et al., 2018). Hence, future studies shall expand on previous research that have observed sex differences in visuomotor performance in working-aged with PPCS (Smeha et al., 2022) by incorporating the aforementioned factors that may explain possible mechanisms underlying sex differences in concussion.

A main strength of our study was the inclusion of working-aged adults with various concussion mechanisms. Prior studies investigating the impact of concussion and PPCS on brain health and quality of life have typically examined elite athletes thereby, excluding participants from the community with various exercise levels and severity of PPCS and concussion. The inclusion of these participants in our study strengthens the generalisability of our findings beyond sport-related concussion and elite athletes. An additional strength was the implementation of along-tract DTI profile analysis to examine the relationships between functional and structural integrity and visuomotor performance in participants with PPCS. This more fine-grained analysis approach is imperative because it provides an opportunity to determine any focal microstructural changes along each white matter tract that may be missed when averaging values over the whole tract.

4.2. Conclusions

Our findings suggest that visuomotor tasks may have the potential for detecting neural changes related to functional and structural integrity in individuals with PPCS. We showed that persistent symptoms after concussion are associated with hyperconnectivity within several functional networks including the visual, frontoparietal control, dorsal attention, and sensorimotor networks. This hyperconnectivity may reflect neuro-compensatory mechanisms of recovery. Specifically, we observed hyperconnectivity within the salience ventral attention network was associated with better performance on a challenging visuomotor task that required cognitive-motor

integration. Additionally, overall visuomotor deficits and more severe persistent symptoms with vestibular dysfunction were associated with lower cortical thickness in the posterior parietal lobule and lower white matter integrity, especially along the long-association, projection, and commissural tracts. Future longitudinal research may benefit from investigating possible mechanisms underlying the neuro-compensatory efforts in brain recovery and how to extend the observed mechanisms, especially in the presence of diminishing structural integrity. These interventions may help in managing persistent symptoms after concussion that can contribute to impaired visuomotor performance, particularly on activities that require complex integration of sensorimotor and cognitive-motor systems.

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Tables

Table 1. Study participants characteristics (n = 22)	
Demographics	
Age	47.23±9.26
Sex, n (%) male	5 (22.73)
Education (yrs)	16.77±1.99
Days since last concussion	1795.13±963.11
Average number of concussion	3.05±1.76
Loss of consciousness, yes (%)*	15.87
Dazed and confused, yes (%)*	92.06
No memory for events immediately after the injury, yes (%)*	28.33
PPCS severity	
RPQ-3	7.18±2.22
RPQ-13	32.68±10.26
Dizziness severity	
DHI-Physical	11.27±4.43
DHI-Functional	20.09±10.26
DHI-Emotional	13.36±7.23
DHI-Total	44.73±20.45
Depression severity	
PHQ-9	12.05±6.59
Visuomotor metrics	
Standard timing composition score	1.46e-15±2.61
Standard trajectory composite score	4.04e-16±1.76
Standard reaction time (ms)	777.50±657.64
Standard full path length (mm)	54.25±1.88
PC + FR timing composition score	-5.75e-16±1.69
PC + FR trajectory composition score	1.71e-16±1.82
PC + FR DR	31.60±22.38
PC + FR reaction time (ms)	476.14±302.88
PC + FR full path length (mm)	74.43±31.02

All data are presented in mean (SD) unless otherwise indicated. DHI = Dizziness Handicap Inventory (DHI); PHQ = Patient Health Questionnaire; PPCS = Persistent Post-Concussion Syndrome; PC + FR = Plane Change + Feedback Reversal; RPQ = Rivermead Post-Concussion Symptoms Questionnaire. * across all number of concussions

Table 2. Frequency of endorsed persistent symptoms after concussion based on rating of 2 and greater* on the Rivermead Post-concussion Symptom Questionnaire (RPQ)		
	n (%)	Mean ± SD
Headaches	19 (86.36)	3.26±0.73
Dizziness	21 (95.45)	2.67±0.86
Nausea and/or Vomiting	14 (63.64)	2.36±0.63
Noise sensitivity, easily upset by loud noise	20 (90.91)	3.45±0.69
Sleep disturbance	18 (81.82)	3.17±0.86
Fatigue, tiring more easily	18 (81.82)	3.56±0.70
Being irritable, easily angered	17 (77.27)	3.18±0.88
Feeling depressed or tearful	12 (54.55)	2.75±0.75
Feeling frustrated or impatient	18 (81.82)	2.73±0.83
Forgetfulness, poor memory	21 (95.45)	3.33±0.73
Poor concentration	22 (100.00)	3.09±0.75
Taking longer to think	21 (95.45)	3.14±0.79
Blurred vision	14 (63.64)	2.93±0.83
Light sensitivity, easily upset by bright light	18 (81.82)	3.00±0.84
Double vision	11 (50.00)	2.55±0.69
Restlessness	12 (54.55)	2.67±0.49
*Rating of 2 = a mild problem		

Table 3. Brain regions showing a significant relationship between cortical thickness, dizziness-related symptoms, and visuomotor performance.

Measures	Regions	MNI Coordinates *x, y, z*	Cluster size (mm^2)	Cluster-wise *p-value*	Confidential Interval
DHI					
Functional	Left inferior parietal gyrus	-30.2, -66.5, 41.0	329.31	0.048	0.043 – 0.054
Emotional	Left inferior parietal gyrus	-32.7, -77.5, 39.9	354.35	0.036	0.031 – 0.041
Total	Left inferior parietal gyrus	-31.0, -66.4, 41.3	337.21	0.045	0.039 – 0.050
PC+FR Condition					
Timing score	Left superior parietal gyrus	-19.6, -79.5, 42.2	347.40	0.035	0.029 – 0.039
Reaction time	Left superior parietal gyrus	-16.6, -86.4, 31.8	400.71	0.011	0.008 – 0.014
Reaction time	Right superior parietal gyrus	9.3, -64.2, 59.6	345.39	0.033	0.028 – 0.037

Note. MNI coordinates reflect location of peak voxel within cluster. DHI, dizziness handicap inventory; MNI, Montreal neurological institute; PC+ FR, plane change and feedback reversal

Table 4. Multivariate linear regression models used to assess the relationship between resting state functional connectivity (RSFC), persistent PCS, and visuomotor performance.

Outcome	Independent variables	Unstandardised B	S.E.	*t-value*	Unadjusted *p-value*	Adjusted *p-value*
RPQ-3	Intercept	-2.559	3.917	-0.653	0.523	-
	VN	7.884	3.363	2.344	**0.033**	0.166
	Sex:Female	2.354	1.835	1.283	0.219	0.876
	Age	0.002	0.069	0.032	0.975	1.000
	Days since last concussion	-0.0001	5.321e-4	-0.192	0.851	1.000
	Sport experience	0.647	0.602	1.075	0.299	0.898
	Intercept	-2.363	3.557	-0.664	0.517	-
	SMN	6.922	2.603	2.660	**0.018**	0.089
	Sex:Female	2.248	1.667	1.348	0.198	0.790
	Age	0.034	0.060	0.565	0.581	1.000
	Days since last concussion	-0.0003	5.165e-4	-0.657	0.521	1.000
	Sport experience	0.392	0.517	0.758	0.460	1.000
	Intercept	-2.187	3.885	-0.563	0.582	-
	DAN	9.068	3.999	2.268	**0.039**	0.193
	Sex:Female	2.279	1.850	1.232	0.237	0.948
	Age	0.001	0.070	0.015	0.988	0.993
	Days since last concussion	-0.0004	5.447e-4	-0.697	0.496	0.993
	Sport experience	0.762	0.644	1.183	0.255	0.948
RPQ-13	Intercept	-9.083	17.396	-0.522	0.609	-
	DAN	41.539	17.905	2.320	**0.035**	0.174
	Sex:Female	13.356	8.286	1.612	0.128	0.511
	Age	-0.059	0.315	-0.188	0.854	0.854
	Days since last concussion	-0.003	0.002	-1.078	0.298	0.596
	Sport experience	3.944	2.883	1.368	0.192	0.575

	Intercept	-17.582	19.057	-0.923	0.371	-
	FPCN	41.924	16.704	2.510	**0.024**	0.120
	Sex:Female	16.223	8.711	1.862	0.082	0.329
	Age	0.165	0.269	0.613	0.549	1.000
	Days since last concussion	-0.0005	0.002	-0.204	0.841	1.000
	Sport experience	4.718	2.959	1.594	0.132	0.395
	Intercept	-12.222	18.111	-0.675	0.510	-
	FPCNb	31.943	13.463	2.373	**0.032**	0.157
	Sex:Female	13.706	8.273	1.657	0.118	0.473
	Age	0.238	0.267	0.891	0.387	0.774
	Days since last concussion	-0.001	0.002	-0.717	0.484	0.774
	Sport experience	3.672	2.775	1.323	0.206	0.617
PC+FR (PLf)	Intercept	147.944	68.943	2.146	0.051	-
	SVAN	-108.623	48.863	-2.223	**0.045**	0.178
	Sex:Female	-75.352	24.981	-3.016	0.009	0.059
	Age	2.145	0.891	2.406	0.032	0.157
	Days since last concussion	-0.008	0.007	-1.107	0.288	0.865
	Sport experience	-8.956	8.474	-1.057	0.309	0.865
	Video game experience	-2.177	4.284	-0.508	0.619	0.865

Unadjusted and adjusted p-values reported. Values were adjusted for multiple comparisons using Holm correction method and considered significant at $p < 0.05$. PC+FR, plane change and feedback reversal; PLf, full path length; RPQ, rivermead post-concussion symptoms questionnaire; FPCN, frontoparietal control network; FPCNb, frontoparietal control network subnetwork b; SVAN, salience ventral attention network; VN, visual network; SMN, sensorimotor control network; DAN, dorsal attention network; S.E, standard errors.

Table 5. White matter tracts showing a significant relationship between along-tract measures, persistent PCS, dizziness-related symptoms, and visuomotor performance.

Measures	Regions	Voxel Coordinates *x, y, z*	Cluster size (mm^3)	Cluster-wise *p-value*	Confidential Interval (CI)
RPQ					
RPQ-3	CC splenium MD	72.00, 0.00, 0.00	40.5	0.019	0.017 – 0.022
DHI					
Functional	CC splenium MD	72.00, 0.00, 0.00	33.8	0.035	0.032 – 0.039
	CC splenium MD	6.00, 0.00, 0.00	33.8	0.035	0.032 – 0.039
	CC body-premotor MD	46.00, 0.00, 0.00	47.2	0.046	0.043 – 0.050
Standard Condition					
Timing score	right ILF FA	57.00, 0.00, 0.00	54.0	0.018	0.014 – 0.021
	left ILF MD	74.00, 0.00, 0.00	74.2	0.009	0.008 – 0.012
PC+FR Condition					
Timing score	right ILF FA	6.00, 0.00, 0.00	50.6	0.023	0.019 – 0.027

Note. voxel coordinates reflect location of peak voxel within cluster. DHI, dizziness handicap inventory; PC+ FR, plane change and feedback reversal; RPQ, rivermead post-concussion symptoms questionnaire; CC, corpus callosum; MD, mean diffusivity; ILF, inferior longitudinal fasciculus; FA, fractional anisotropy.

Table 6. Multivariate linear regression models used to assess the relationship between entire white matter tracts measures, persistent PCS, and visuomotor performance.

Outcome	Independent variables	Unstandardised B	S.E.	t-value	Unadjusted p-value	Adjusted p-value
RPQ-3						
	Intercept	-80.403	22.436	-3.584	0.003	-
	Right SLF-2 MD	106.750	28.801	3.706	**0.002**	**0.009**
	Sex:Female	-0.831	1.046	-0.794	0.441	0.959
	Age	0.213	0.055	3.900	0.002	0.008
	Days since last concussion	-0.001	0.001	-1.031	0.319	0.959
	Sport experience	0.099	0.389	0.253	0.804	0.959
Standard Condition						
Timing score	Intercept	63.327	24.901	2.543	0.030	-
	right CST MD	-98.568	33.308	-2.959	**0.012**	0.059
	Sex:Female	-1.817	0.892	-2.037	0.064	0.193
	Age	0.241	0.047	5.081	$p < 0.001$	0.002
	Days since last concussion	-0.001	0.0004	-2.032	0.064	0.193
	Sport experience	-0.200	0.386	-0.519	0.613	0.613
	Video game experience	0.642	0.225	2.850	0.015	0.059
RT	Intercept	9700.227	5069.963	1.913	0.079	-
	Left SLF-1 MD	-14389.378	6488.375	-2.218	**0.047**	0.154
	Sex:Female	-743.888	304.884	-2.445	0.031	0.154
	Age	55.072	16.284	3.382	0.005	0.033
	Days since last concussion	-0.227	0.137	-1.651	0.125	0.249
	Sport experience	-20.555	130.009	-0.158	0.877	0.877
	Video game experience	184.348	78.109	2.360	0.036	0.154
	Intercept	10961.562	5159.528	2.125	0.055	-
	right SLF-1 MD	-16148.645	6661.704	-2.424	**0.032**	0.114
	Sex:Female	-818.289	293.573	-2.787	0.016	0.082
	Age	55.101	15.794	3.489	0.004	0.027

	Days since last concussion	-0.169	0.129	-1.311	0.214	0.428
	Sport experience	-59.668	124.525	-0.479	0.640	0.640
	Video game experience	189.836	76.276	2.489	0.028	0.114
PC+FR Condition						
Trajectory score	Intercept	26.813	7.822	3.428	0.005	-
	right CST FA	-52.428	15.092	-3.474	**0.005**	**0.028**
	Sex:Female	0.233	0.708	0.329	0.748	1.000
	Age	-0.008	0.037	-0.214	0.834	1.000
	Days since last concussion	0.0001	0.0003	0.388	0.705	1.000
	Sport experience	0.341	0.301	1.133	0.279	
	Video game experience	-0.469	0.181	-2.599	0.023	0.116
PLf	Intercept	443.560	177.409	2.500	0.027	-
	right CST FA	-839.299	342.312	-2.452	**0.031**	0.183
	Sex:Female	-37.211	16.056	-2.318	0.039	0.195
	Age	1.877	0.847	2.216	0.047	0.195
	Days since last concussion	-0.002	0.007	-0.285	0.780	1.000
	Sport experience	0.590	6.823	0.086	0.933	1.000
	Video game experience	1.341	4.094	0.328	0.749	1.000
	Intercept	610.778	241.584	2.528	0.027	-
	left ILF MD	-735.327	296.583	-2.479	**0.029**	0.174
	Sex:Female	-27.262	16.419	-1.660	0.123	0.614
	Age	1.389	0.852	1.629	0.129	0.614
	Days since last concussion	-0.004	0.007	-0.604	0.557	1.000
	Sport experience	6.617	7.048	0.939	0.366	1.000
	Video game experience	0.739	4.054	0.183	0.858	1.000
	Intercept	640.476	278.466	2.317	0.039	-
	left SLF-1 MD	-802.793	353.812	-2.269	**0.043**	0.255
	Sex:Female	-31.588	16.593	-1.904	0.081	0.406
	Age	1.282	0.888	1.444	0.174	0.697

	Days since last concussion	-0.007	0.007	-0.910	0.381	1.000
	Sport experience	4.728	7.089	0.667	0.517	1.000
	Video game experience	2.093	4.259	0.491	0.632	1.000
	Intercept	858.497	321.618	2.694	0.019	-
	left SLF-2 MD	-1105.439	416.987	-2.651	**0.021**	0.127
	Sex:Female	-28.746	15.888	-1.809	0.096	0.478
	Age	1.444	0.829	1.742	0.107	0.478
	Days since last concussion	-0.007	0.007	-1.013	0.331	0.873
	Sport experience	7.710	6.982	1.104	0.291	0.873
	Video game experience	4.023	4.229	0.951	0.360	0.873
	Intercept	1175.812	374.669	3.138	0.009	-
	right SLF-2 MD	-1565.452	505.139	-3.099	**0.009**	0.055
	Sex:Female	-32.663	14.709	-2.221	0.046	0.232
	Age	1.336	0.782	1.709	0.113	0.453
	Days since last concussion	0.004	0.007	0.579	0.573	0.789
	Sport experience	5.587	6.329	0.883	0.395	0.789
	Video game experience	6.186	4.207	1.470	0.167	0.502
Timing score	Intercept	-26.084	10.341	-2.522	0.027	-
	right CST FA	44.128	19.952	2.212	**0.047**	0.283
	Sex:Female	0.486	0.936	0.519	0.613	1.000
	Age	0.095	0.049	1.916	0.079	0.397
	Days since last concussion	-0.001	0.0004	-1.781	0.100	0.401
	Sport experience	0.074	0.398	-0.186	0.856	1.000
	Video game experience	0.084	0.239	0.350	0.732	1.000
RT	Intercept	-4577.085	1458.654	-3.138	0.009	-
	right CST FA	10174.886	2814.487	3.615	**0.004**	**0.021**
	Sex:Female	348.622	132.016	2.641	0.022	0.108
	Age	-6.429	6.965	-0.923	0.374	0.969

	Days since last concussion	-0.026	0.058	-0.454	0.658	0.969
	Sport experience	57.832	56.102	1.031	0.323	0.969
	Video game experience	-64.088	33.666	-1.904	0.081	0.325
	Intercept	-9062.405	4000.007	-2.266	0.043	-
	right SLF-2 MD	13026.401	5392.922	2.415	**0.033**	0.196
	Sex:Female	307.959	157.041	1.961	0.074	0.294
	Age	-1.364	8.347	-0.163	0.873	1.000
	Days since last concussion	-0.074	0.072	-1.024	0.326	0.978
	Sport experience	11.523	67.579	0.171	0.867	1.000
	Video game experience	-99.348	44.918	-2.212	0.047	0.236
% DR	Intercept	-674.259	260.916	-2.584	0.024	-
	right CST MD	831.019	349.011	2.381	**0.035**	0.139
	Sex:Female	-17.943	9.348	-1.919	0.079	0.237
	Age	2.712	0.497	5.456	$p < 0.001$	$p < 0.001$
	Days since last concussion	-0.013	0.004	-3.197	0.008	0.038
	Sport experience	6.320	4.042	1.564	0.144	0.289
	Video game experience	1.219	2.361	0.516	0.615	0.615

Unadjusted and adjusted p-values reported. Values were adjusted for multiple comparisons using Holm correction method and considered significant at $p < 0.05$. PC+FR, plane change and feedback reversal; PLf, full path length; RPQ, rivermead post-concussion symptoms questionnaire; S.E, standard errors; RT, reaction time; DR, direction reversal; MD, mean diffusivity; ILF, inferior longitudinal fasciculus; FA, fractional anisotropy; CST, corticospinal tract; SLF-1&-2, superior longitudinal fasciculus 1 & 2.

Figures

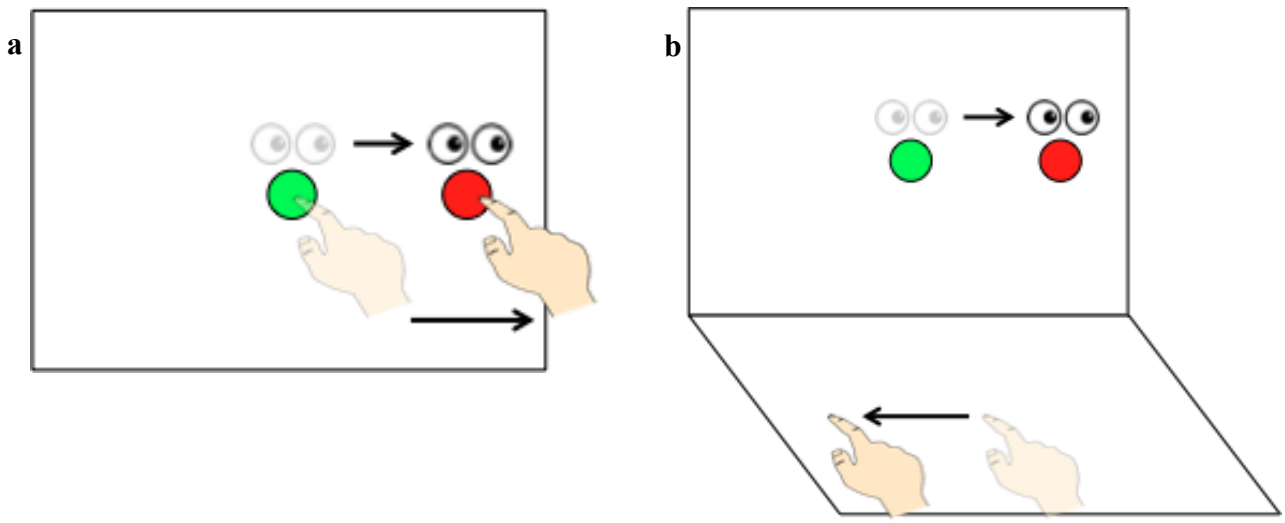

Figure 1. Schematic drawing of the visuomotor transformation tasks. Lighter eye and hand symbols denote the starting position for each trial (green central target). Darker eye and hand symbols denote the instructed eye and hand movements for each task. Red circles denote the peripheral (reach) target, presented randomly in one of four locations (left, up, right, or down relative to the central target). The direct interaction/standard condition requires standard mapping, where participants slide their finger on a touch screen to move a cursor from a central target to one of four peripheral targets **(Figure 1a).** The non-standard condition is a cognitive-motor integration (CMI) condition, where targets are either spatially dissociated from the plane of hand motion (plane-change) and have a 180° feedback reversal (plane-change + feedback reversal (PC+FR)) **(Figure 1b).**

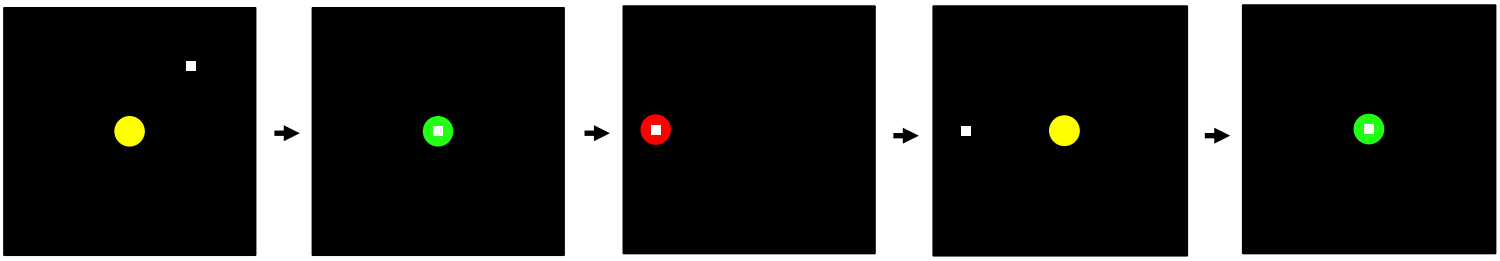

Figure 2. Sequence of events during one trial of the visuomotor task. The central (home) target is where all trials begin. Once the participant moves the cursor (white square) into the central target, the target changes from yellow to green to signify a movement preparation period. After 2000 milliseconds (ms), a red peripheral target appears in one of four directions (up, down, left or right of the centre) and serves as the 'go' signal. Once the peripheral target is acquired and held for 500 ms it disappears, signalling the end of the trial. After an inter-trial interval of 2000 ms, the central yellow target reappears and the participant moves back to the central target to start the next trial.

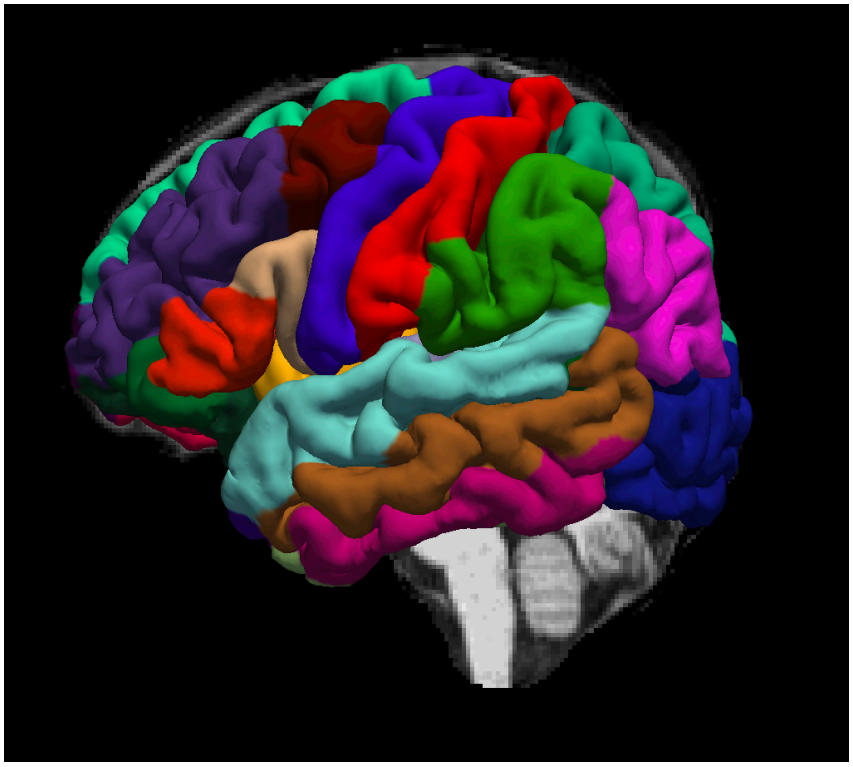

Figure 3. 3D depiction of Desikan-Killiany atlas obtained from FreeSurfer parcellation of cortical regions.

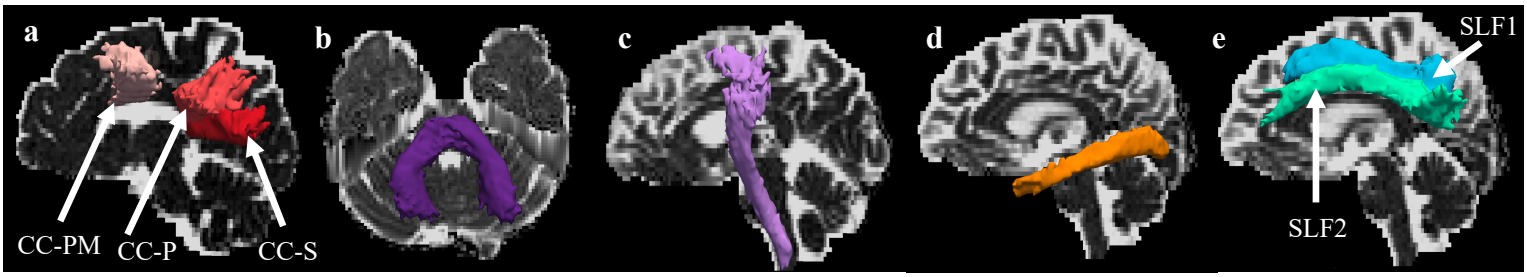

Figure 4. White matter tracts of interest obtained from Tracula Constrained by UnderLying Anatomy (TRACULA), shown in **a)** CC—PM, corpus callosum–premotor; CC—P, corpus callosum—parietal; CC-S, corpus callosum—splenium; **b)** MCP, middle cerebellar peduncle; **c)** CST, corticospinal tract; **d)** ILF, inferior longitudinal fasciculus; **e)** SLF, superior longitudinal fasciculus 1, superior longitudinal fasciculus 2.

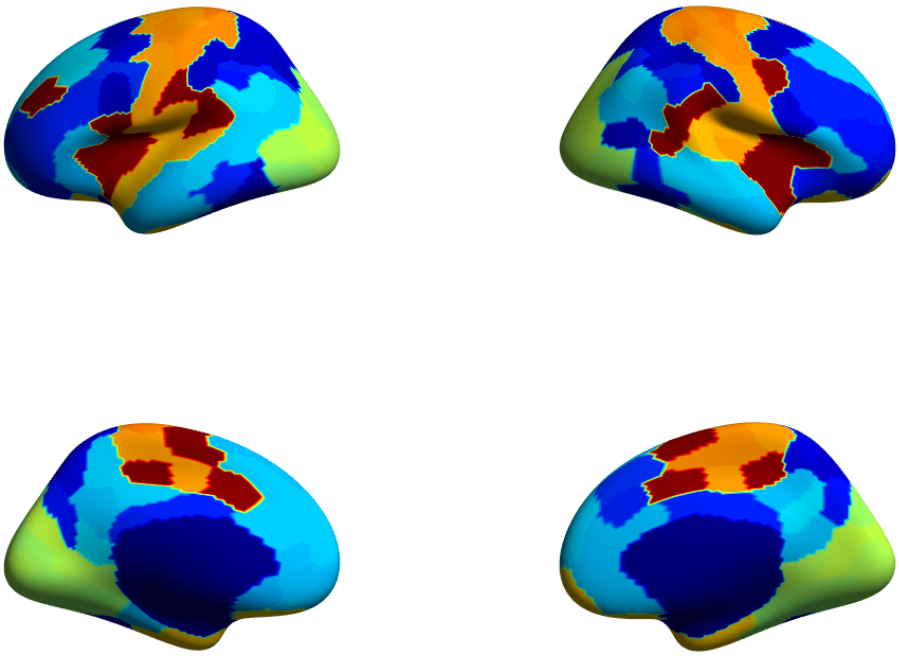

Figure 5. Example parcellation from a single subject initialised with the 200-parcel 7-network Schaefer atlas (Schaefer et al. 2018) with refined parcel borders that functionally correspond to the subject's resting state data as a result of the GPIP process.

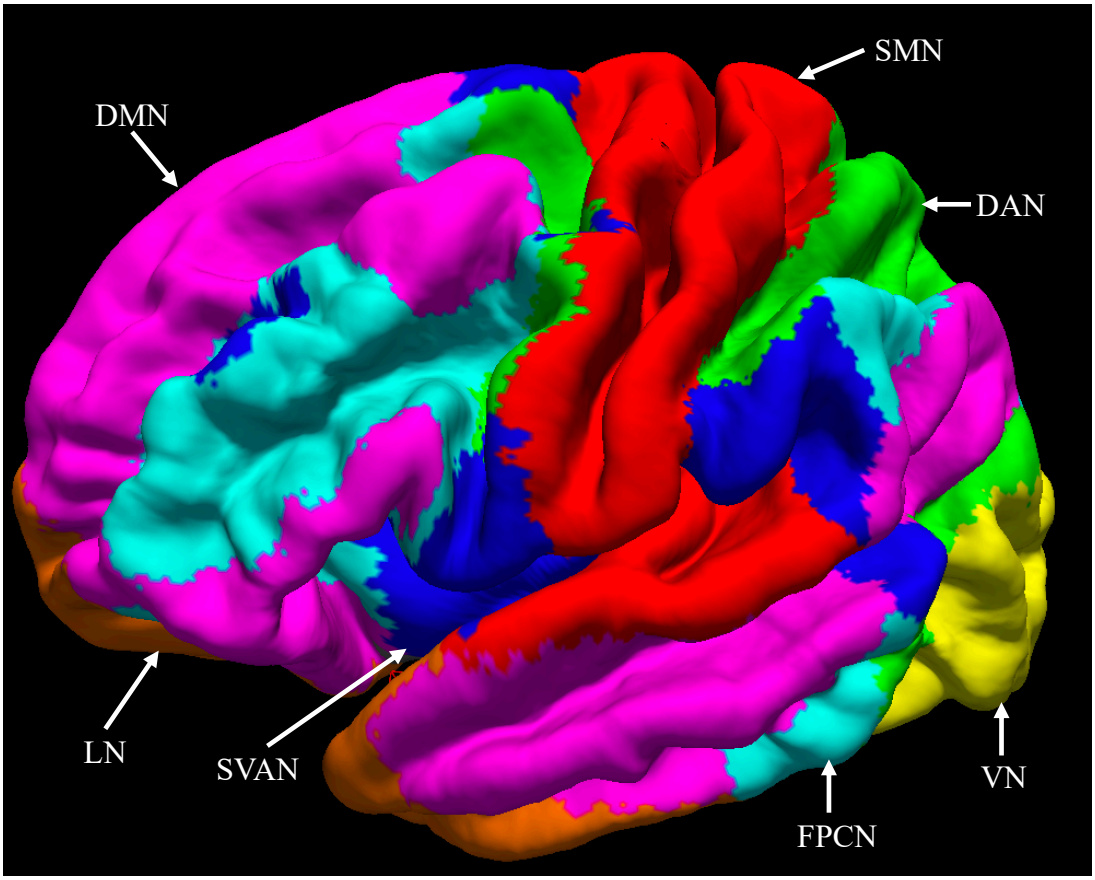

Figure 6. Resting functional connectivity networks. DAN, dorsal attention network; DMN, default mode network; FPCN, frontoparietal network; LN, limbic network; SMN, sensorimotor control network; SVAN, salience ventral attention network; VN, visual network. The limbic network was excluded from analyses.

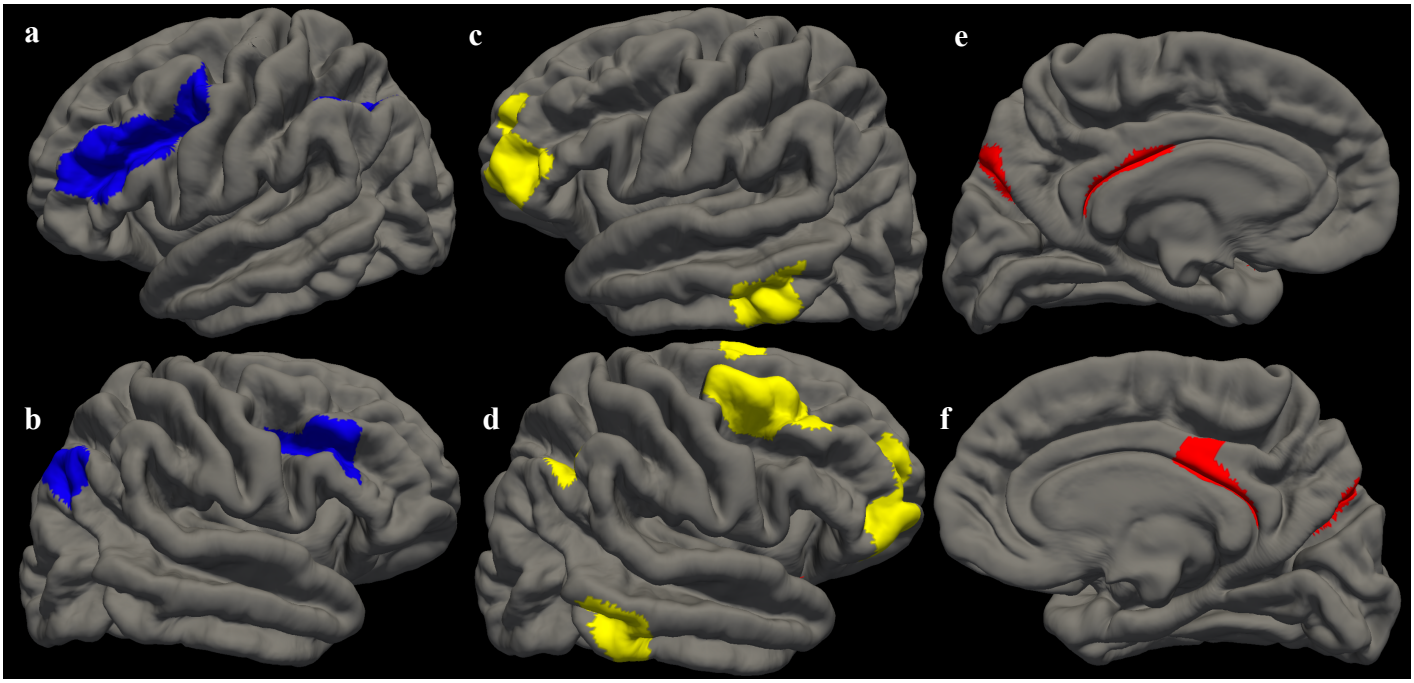

Figure 7. The 3 subnetworks of the frontoparietal control network (FPCN), **a)** left FPCNa; **b)** right FPCNa; **c)** left FPCNb; **d)** right FPCNb; **e)** left FPCNc; **f)** right FPCNc.

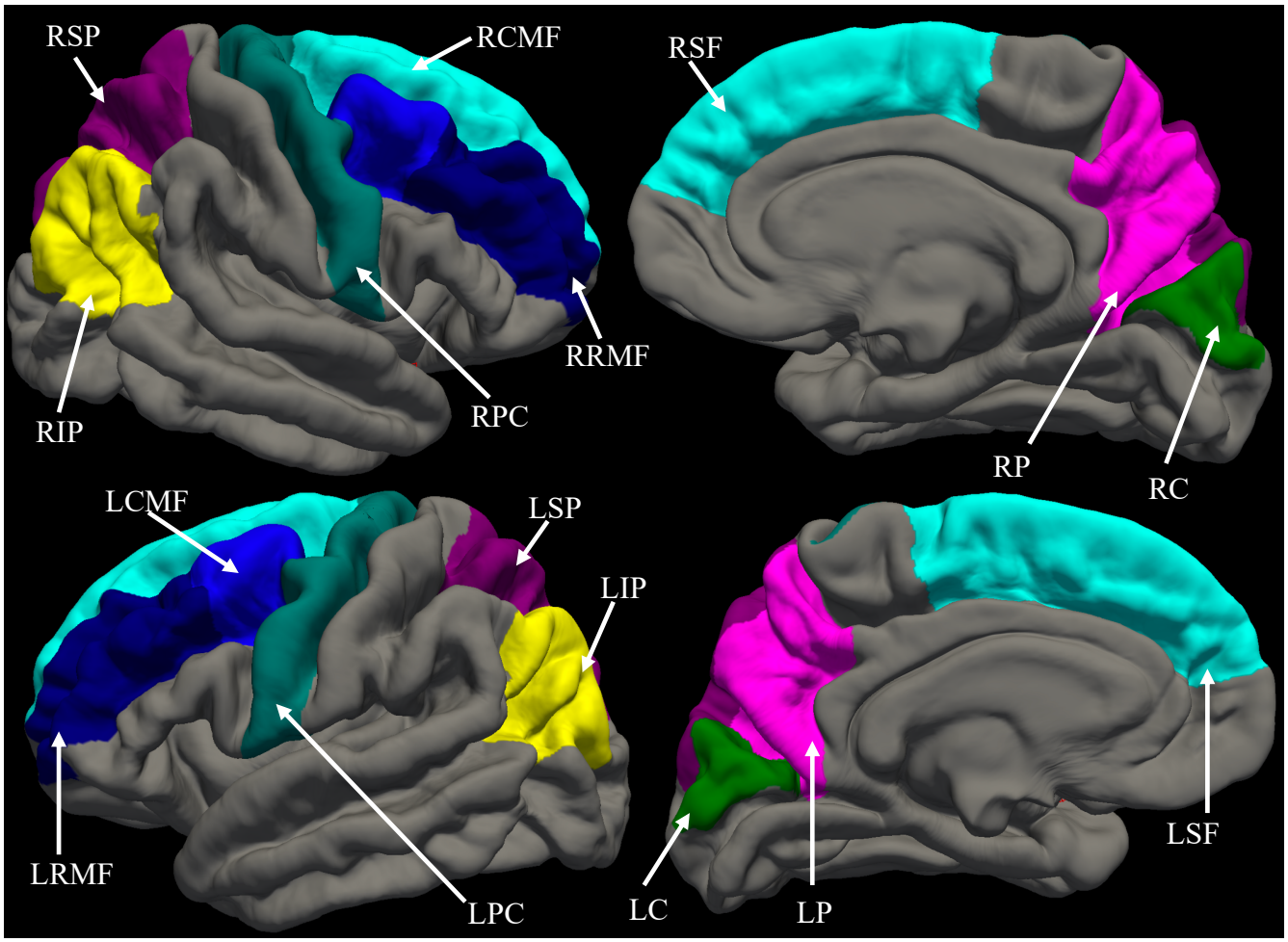

Figure 8. Cortical regions of interest. **Top panel:** RSP, right superior parietal; RIP, right inferior parietal; RPC, right precentral; RRMF, right rostral middle frontal; RCMF, right caudal middle frontal; RSF, right superior frontal; RP, right precuneus; RC, right cuneus. **Bottom panel:** LSP, left superior parietal; LIP, left inferior parietal; LPC, left precentral; LRMF, left rostral middle frontal; LCMF, left caudal middle frontal; LSF, left superior frontal; LP, left precuneus; LC, left cuneus.

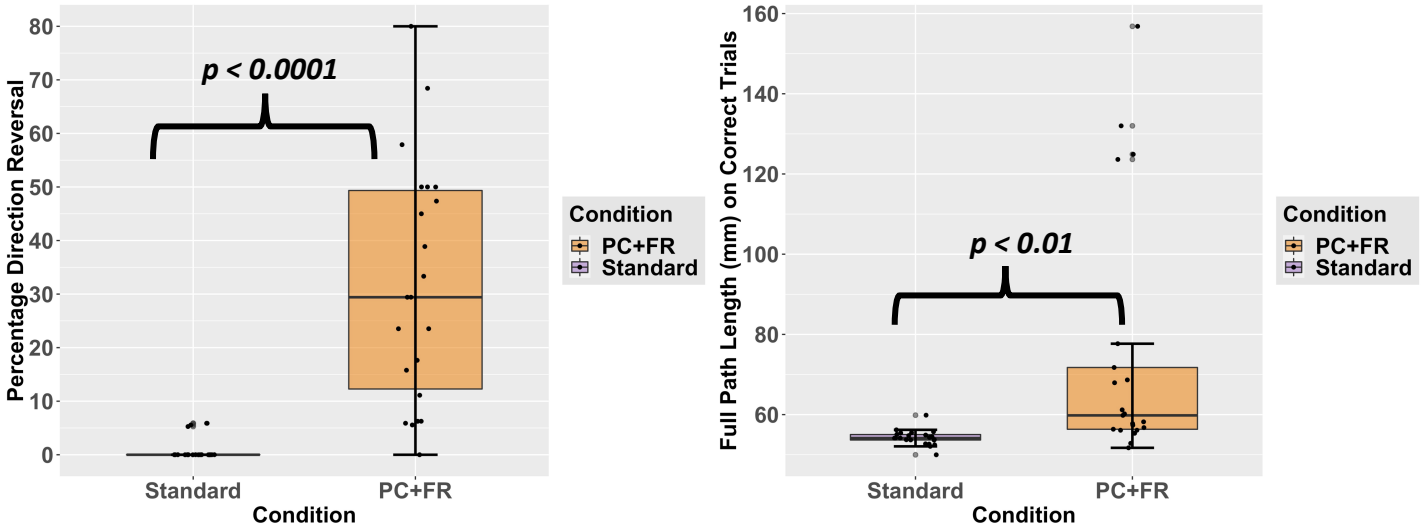

Figure 9. Results from paired t-test between standard and PC+FR conditions on **a)** percentage direction reversal and; **b)** full path length. PC+FR, plane change and feedback reversal.

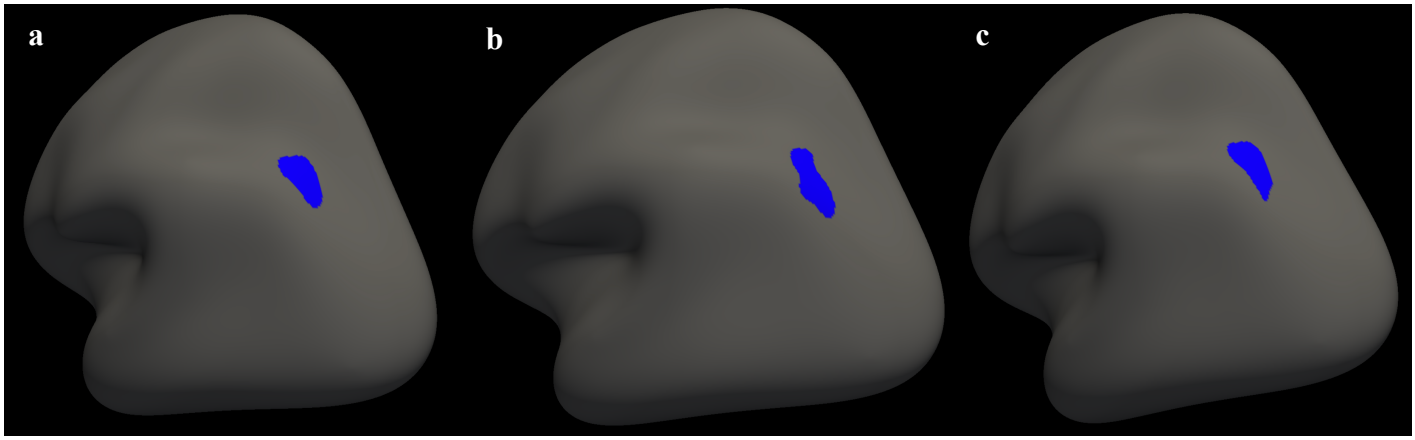

Figure 10. Significant cluster from region of interest analysis overlaid on a left inflated surface. The blue colour depicts a negative association between left inferior parietal gyrus thickness with **a)** DHI functional domain; **b)** DHI emotional domain; **c)** DHI total score. DHI, dizziness handicap inventory.

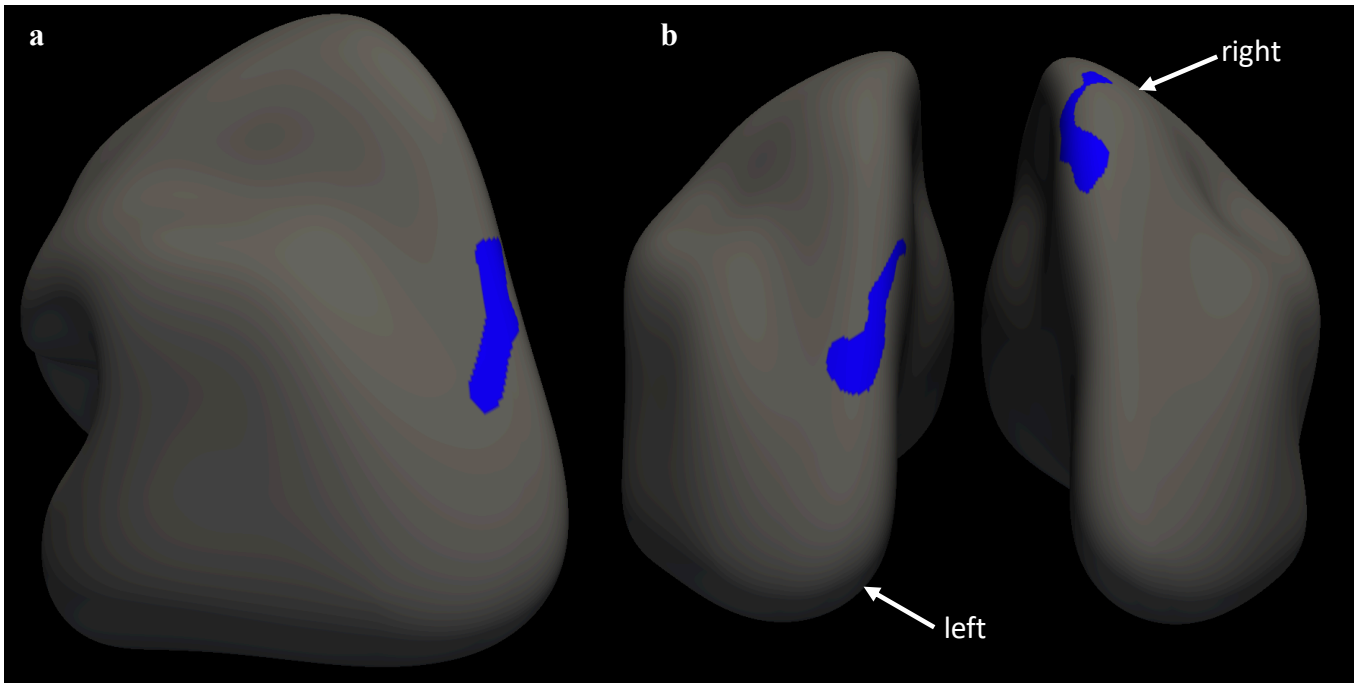

Figure 11. Significant cluster from region of interest analysis overlaid on a left and right inflated surfaces. The blue colour depicts **a)** negative association between cortical thickness cluster in left superior parietal gyrus and timing composite score in PC+FR condition; **b)** negative association between cortical thickness clusters in bilateral superior parietal gyri thickness and reaction time in PC+FR condition. PC+FR, plane change and feedback reversal

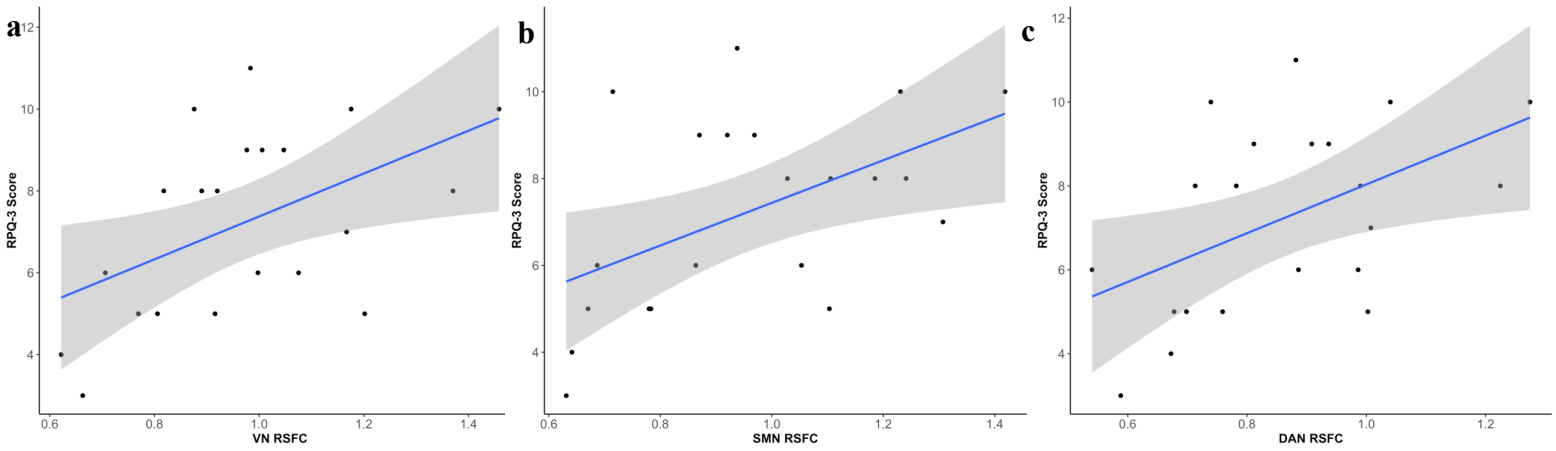

Figure 12. Relationship between mean intra-networks RSFC and RPQ-3 score. Higher score in early persistent PCS cluster was associated with higher RSFC in **a)** VN; **b)** SMN; **c)** DAN. DAN, dorsal attention network; SMN, sensorimotor control network; RSFC, resting state functional connectivity; RPQ-3, rivermead post-concussion symptoms questionnaire cluster 1; VN, visual network.

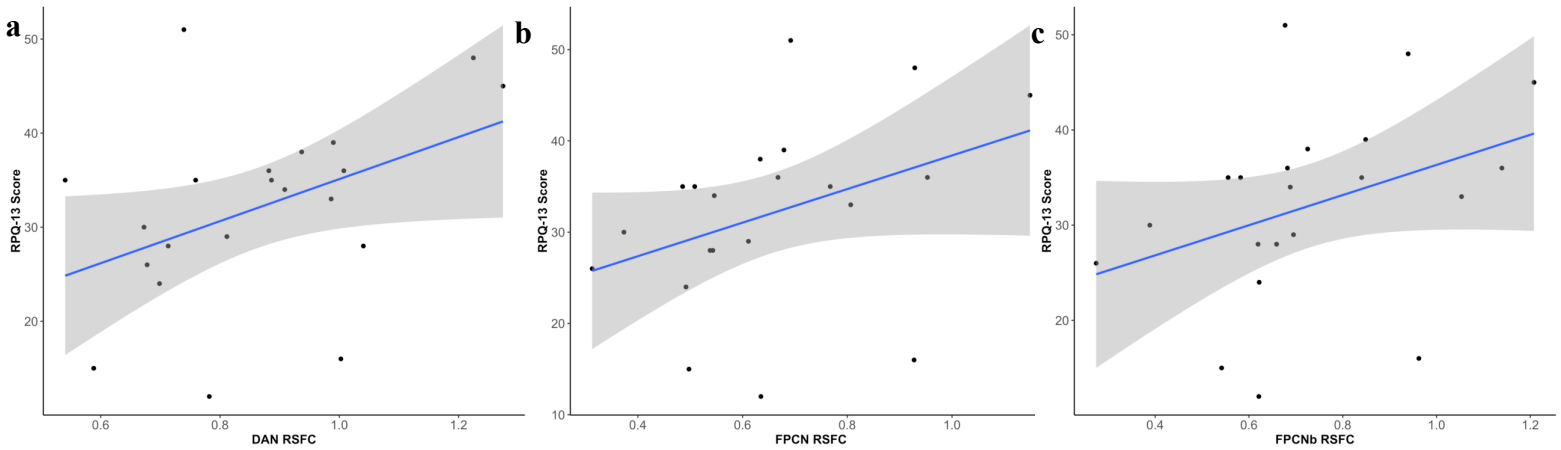

Figure 13. Relationship between mean intra-networks RSFC and RPQ-13 score. Higher score in later psychological and cognitive persistent PCS cluster was associated with higher RSFC in **a)** DAN; **b)** FPCN; **c)** FPCNb. DAN, dorsal attention network; FPCN, frontoparietal control network; FPCNb, frontoparietal control network-subnetwork b; RSFC, resting state functional connectivity; RPQ-13, rivermead post-concussion symptoms questionnaire cluster 2.

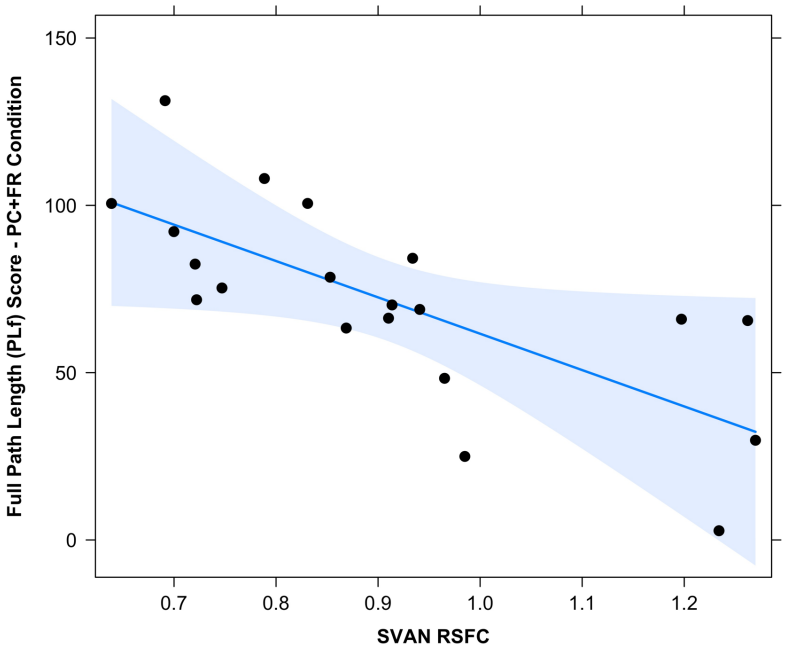

Figure 14. Relationship between mean intra-SVAN RSFC and full path length in PC+FR condition. PC+FR, plane change and feedback reversal; RSFC, resting state functional connectivity; SVAN, salient ventral attention network.

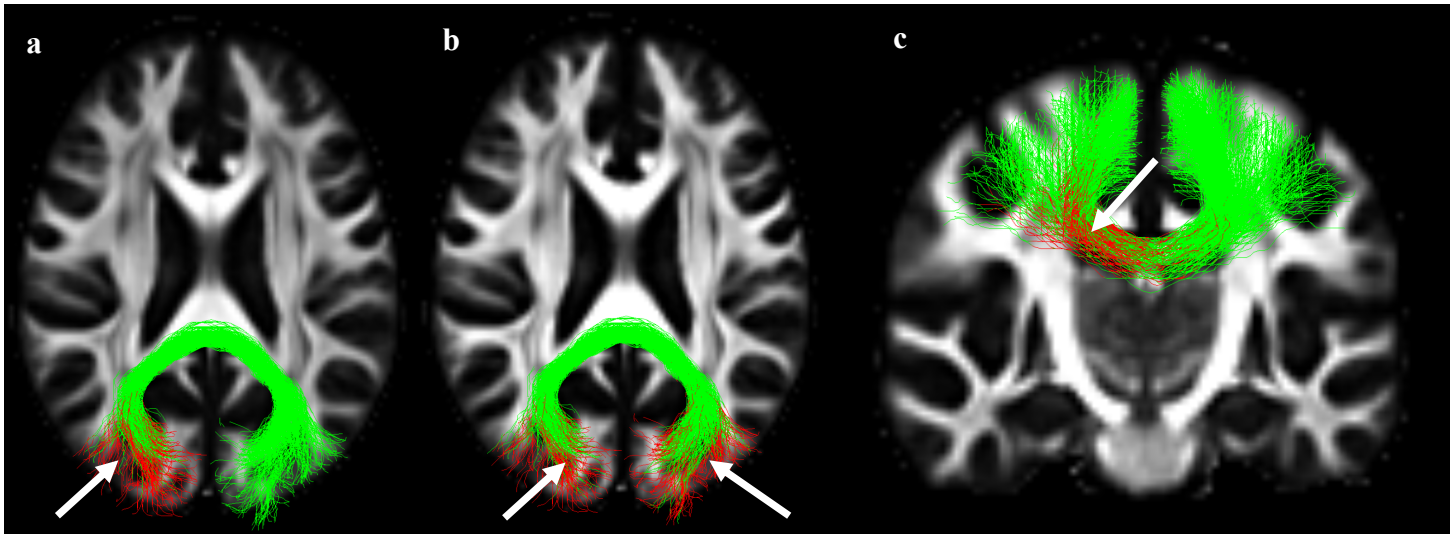

Figure 15. Significant positive associations from along-tract MD analysis with RPQ and DHI scores. White arrows indicate affected areas along each white matter tract. **a)** RPQ-3 and CC splenium; **b)** DHI functional domain and CC splenium; **c)** DHI functional and CC body-premotor. CC, corpus callosum; DHI, dizziness handicap inventory; RPQ, rivermead post-concussion symptoms questionnaire.

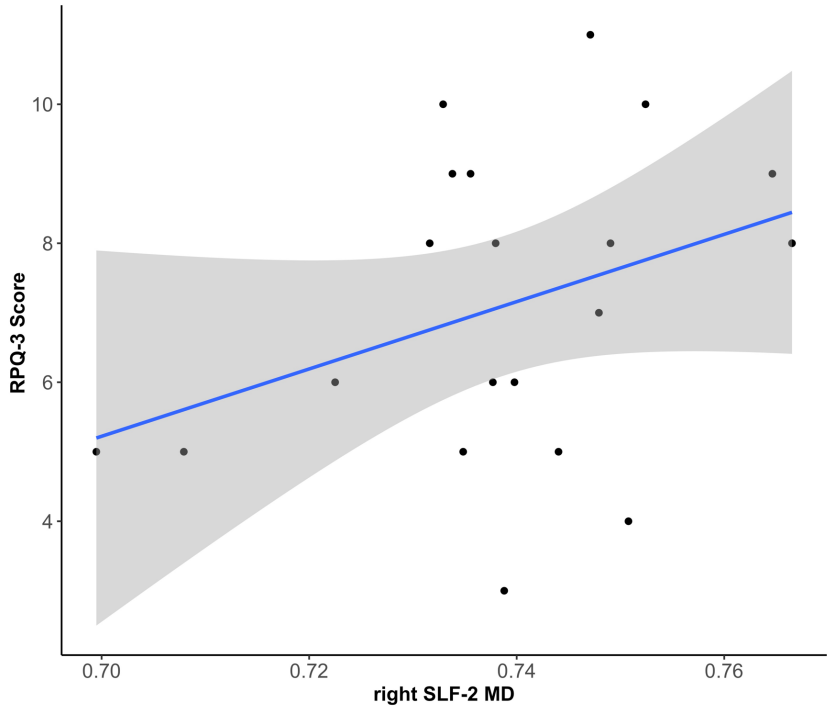

Figure 16. Higher MD in the entire right SLF-2 was associated with higher score in early persistent PCS cluster. MD, mean diffusivity; SLF-2, superior longitudinal fasciculus 2; RPQ-3, rivermead post-concussion symptoms questionnaire cluster 1.

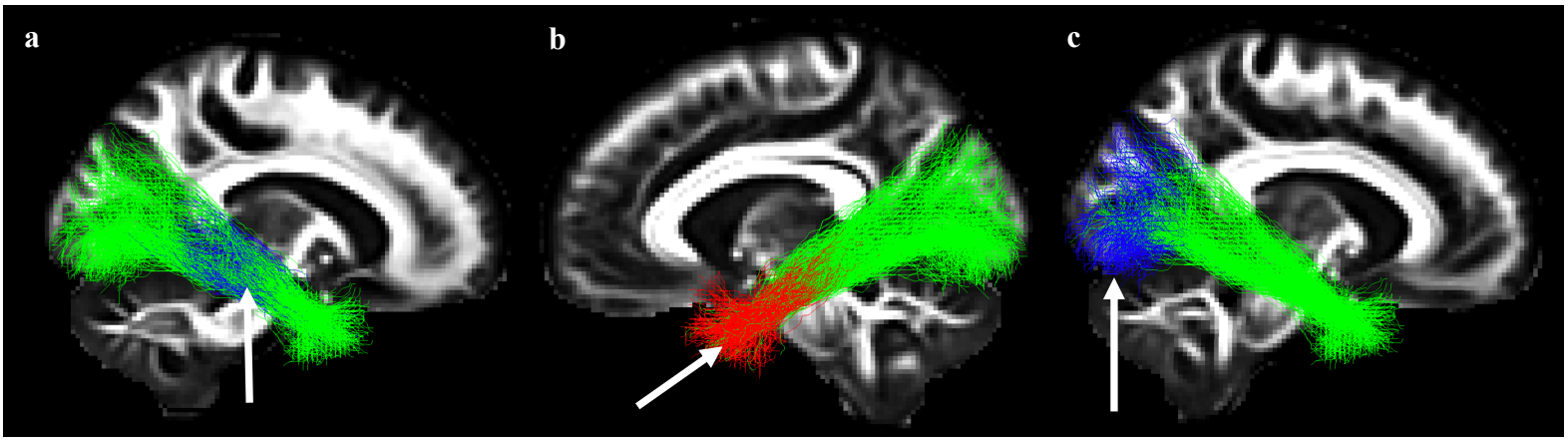

Figure 17. Significant associations from along-tract FA and MD analyses with visuomotor performance. White arrows indicate affected areas along each white matter tract. **a)** negative association between standard condition and right ILF FA; **b)** positive association between standard condition and left ILF MD; **c)** negative association between PC+FR condition and right ILF FA. FA, fractional anisotropy; ILF, inferior longitudinal fasciculus; MD, mean diffusivity; PC+FR, plane change and feedback reversal.

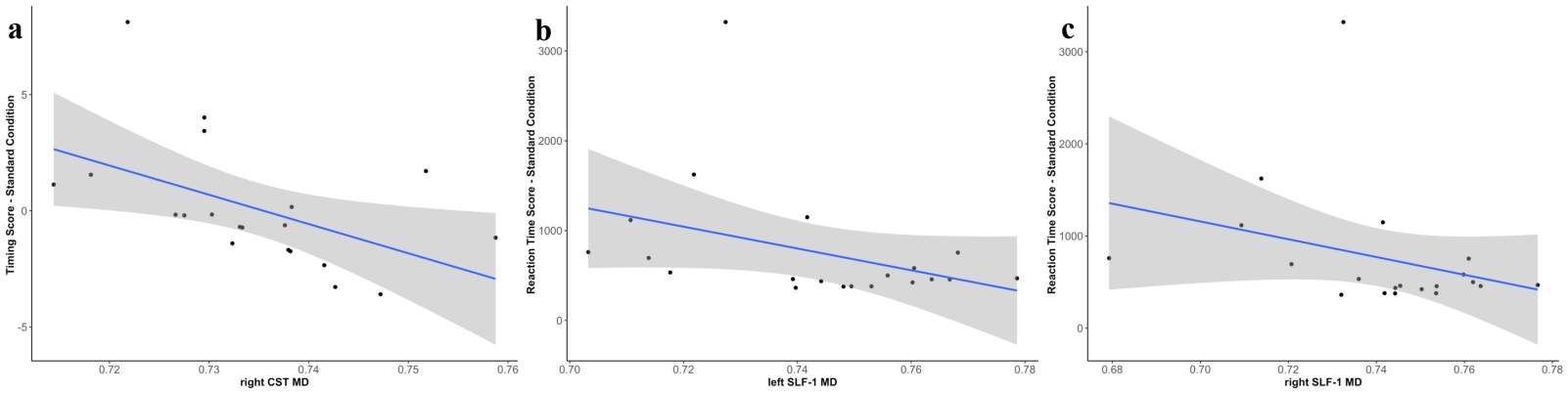

Figure 18. Relationship between MD in the entire-tract and standard condition. **a)** right CST and timing score; **b)** left SLF-1 and reaction time score; **c)** right SLF-1 and reaction time score. CST, corticospinal tract; MD, mean diffusivity; SLF-1, superior longitudinal fasciculus 1.

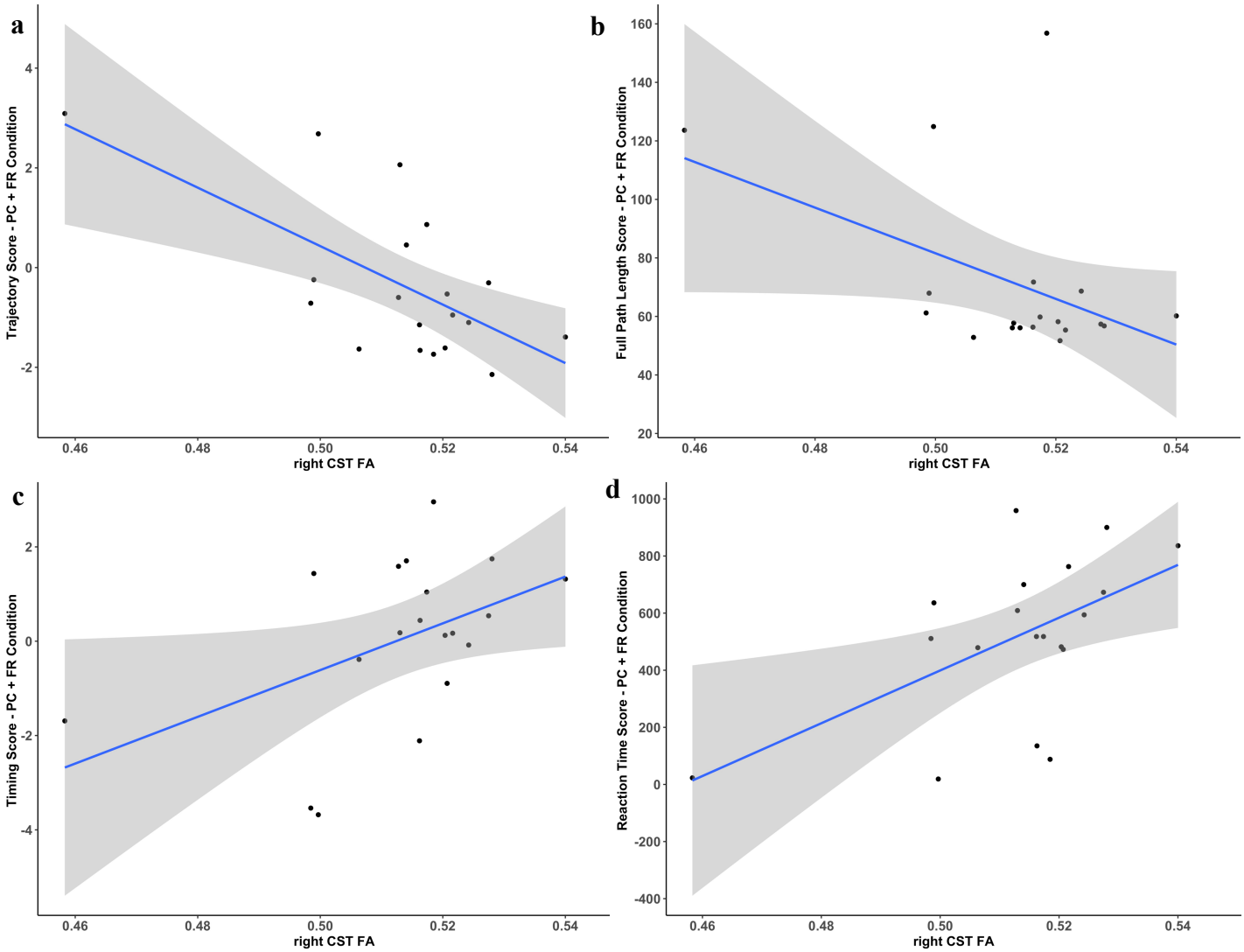

Figure 19. Relationship between FA in the entire-tract and PC+FR condition. **a)** right CST and trajectory score; **b)** right CST and full path length score; **c)** right CST and timing score; **d)** right CST and reaction time score. CST, corticospinal tract; FA, fractional anisotropy PC+FR, plane change and feedback reversal.

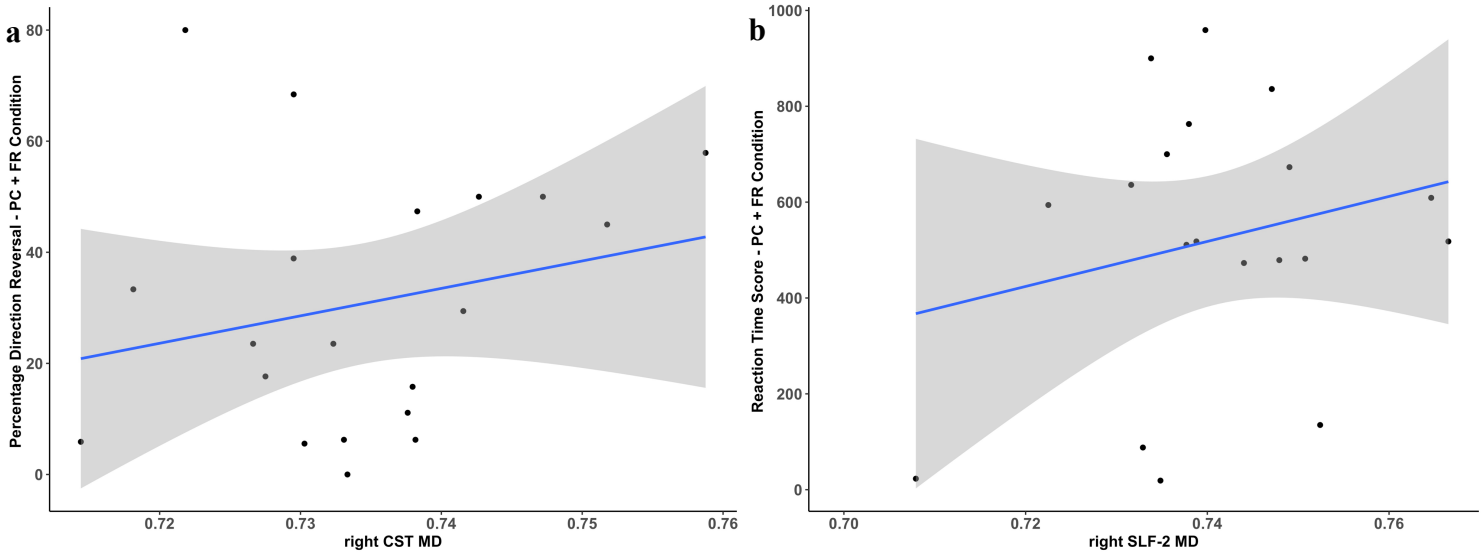

Figure 20. Relationship between MD in the entire-tract and PC+FR condition. **a)** right CST and percentage directional reversal; **b)** right SLF-2 and reaction time score. CST, corticospinal tract; MD, mean diffusivity; PC+FR, plane change and feedback reversal; SLF-2, superior longitudinal fasciculus 2.

APPENDICES

A: Health Questionnaire

PLEASE CIRCLE, FILL IN, OR HIGHLIGHT RESPONSES AS APPROPRIATE

ID: _____ Age: _____ DOB: _____ Today's Date: _____

Dominant Hand: LEFT or RIGHT or BOTH

Sex assigned at birth: Male Female Prefer not to say

To which gender identity do you most identify?

- O Cis-gender (non-trans) woman
- O Trans woman
- O Cis-gender (non-trans) man
- O Trans man
- O Non-binary
- O Not listed _____
- O Prefer not to say

Highest Level of Education: _____ Work Full Time / Part Time / Neither:_____

Ethnicity: _____ Occupation: _____

What sports (recreational or competitive, or none) do you play/have played:

_____

_____

_____

When did you start playing your first organized sport? _____

Do you currently have a non-head related injury? YES or NO

a) Has it kept you from play/work for longer than 48 hours? YES or NO

b) Has it kept you from play/work for longer than 3 weeks? YES or NO

Health History

Please place an 'x' in the appropriate column:

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

Medications

Are you currently taking medication(s): No Yes

If yes, please list all medications:

Menstrual Cycle

Post- menopausal is defined as having no period for the past 12 months. Peri-menopausal is defined as the period around the onset of menopause that is often marked by various physical signs.

Are you: Pre-menopausal or Peri-menopausal or Post- menopausal or Not Applicable (circle one; If you are pre-menopausal, please answer the following questions)

The menstrual cycle is counted from the first day of one period to the first day of the next.

Are you on birth control (e.g., the pill; IUD, patch, etc.)? No Yes

On average, do you have a regular period (i.e., approximately every month)? No □Yes □

On average, approximately how long is your menstrual cycle (see definition above)? ___

When did your last period start (date)? _____How many days did it last? _____

Current Alcohol/Substance Use

Please circle the correct answer for you.

How often do you have a drink containing alcohol?

Never Monthly or less 2-4 times a month 2-3 times per week 4+ times per week

How many drinks containing alcohol do you have on a typical day when you are drinking?

1 or 2 3 or 4 5 or 6 7 or 9 10 or more

How often do you have six or more drinks on one occasion?

Never Less than monthly Monthly 2-3 times per week 4+ times per week

How often do you smoke marijuana?

Never Monthly or less 2-4 times a month 2-3 times per week 4+ times per week

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

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

Using the above definition, how many concussions do you think you have sustained during your whole life? _____ Date of your most recent concussion (as specific as you can recall)? _____

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

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

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

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

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

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

	Circle your answer for each question as it relates to the concussions you listed above									
	Injury #1		Injury #2		Injury #3		Injury #4		Injury #5	
Did someone see you lose consciousness?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Were you dazed and confused?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Did you have no memory for events immediately after the injury?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes

Did you go to the hospital?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Were you medically diagnosed with a concussion or brain injury?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Did you miss any school or work because of this injury?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Did you have symptoms for more than 24 hours?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Did you have symptoms for more than one week?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Did you have symptoms for more than one month?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes

Over the last 2 weeks, how often have you been bothered by any of the following problems? (PHQ-9)

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

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

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

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

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

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

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

1. Do you have a computer (YES or NO) or a tablet (YES or NO) at home?

   How often do you use your computer? (all the time / often / sometimes / rarely / never)

   How often do you use your tablet? (all the time / often / sometimes / rarely / never)

2. Do you do puzzles? YES or NO (all the time / often / sometimes / rarely / never)

3. Do you play video games? YES or NO (all the time / often / sometimes / rarely / never)

   a) What type of games do you typically play? ACTION (time pressure) or NON-ACTION

   b) How would you rate your skill compared to your peers? (Low / Intermediate / High)

4. To your knowledge, does anyone in your family have any form of dementia? YES or NO

   a) What is their relationship to you (e.g., mother/father/brother/sister, maternal aunt/uncle/grandmother/grandfather/cousin, paternal aunt/uncle/grandmother/grandfather/cousin). List all if more than one relative.

THE FOLLOWING IS A LIST OF ACTIVITIES THAT PEOPLE MAY PARTICIPATE IN. PLEASE INDICATE THE FREQUENCY (IN DAYS PER WEEK) THAT YOU TYPICALLY PARTICIPATE IN THESE ACTIVITES FOR EACH ITEM CHOOSE FROM ONE OF THE FOLLOWING ALTERNATIVES:

	NEVER	RARELY (1 DAY /WEEK)	SOMETIMES (2 DAYS /WEEK)	FAIRLY OFTEN (3-4 DAYS /WEEK)	VERY OFTEN (5-7 DAYS /WEEK)
	0	1	2	3	4
1. WATCHING TV OR MOVIES	0	1	2	3	4
2. READING	0	1	2	3	4
3. SOCIALIZING (E.G. PLAYING CARDS, TALKING TO FRIENDS, ETC.)	0	1	2	3	4
4. PLAYING REC SPORTS	0	1	2	3	4
5. PLAYING COMPETITIVE SPORTS	0	1	2	3	4
6. PLAYING VIDEO/ COMPUTER GAMES	0	1	2	3	4
7. WALKING (AT LEAST 25 MINUTES)	0	1	2	3	4
8. LISTENING TO MUSIC	0	1	2	3	4
9. EXERCISING AT A GYM	0	1	2	3	4
10. DOING NON-LABOUR WORK (PAID OR VOLUNTEER)	0	1	2	3	4
11. DOING LABOUR WORK (E.G. LANDSCAPING SHOVELING, PAINTING, ETC. PAID OR VOLUNTEER)	0	1	2	3	4
12. RUNNING/JOGGING	0	1	2	3	4

13. PUZZLES, ARTS & CRAFTS (E.G. KNITTING, CROSSWORDS, ETC.)	0	1	2	3	4

Please return this form to the experimenter (if you are filling this out in the lab), or email the electronic version to lsergio@yorku.ca. Thank you for being in the study!

References:

1. PHQ-9 is adapted from PRIME MD TODAY, developed by Dr. Robert L. Spitzer, Janet B. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer inc. Copyright © 1999 Pfizer Inc. All rights reserved. PRIME MD TODAY is a trademark of Pfizer Inc

2. Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

B: Informed Consent

INFORMED CONSENT

School of Kinesiology and Health Science,

York University, Toronto, ON Canada

Study Title: The influence of sex-related differences in cognitive-motor integration on brain injury recovery in working-aged adults

Principal Investigator: Dr. Lauren E. Sergio (Professor)

This study will look at the brain using MRI (magnetic resonance imaging) to examine if post-concussion coordination dysfunction is associated with altered brain activity/connectivity. The research team is headed by Dr. Lauren Sergio in the School of Kinesiology and Health Science, Faculty of Health, York University.

What you will be asked to do in the research: Your participation involves some questionnaires, an MRI scan, a few coordination tasks, and a saliva sample:

1) Questionnaires (10-15 minutes): Forms include a general medical history, perceived impact of dizziness on daily life, a short checklist of your current concussion symptoms, and an MRI safety screening. You will be asked to fill out the MRI safety screening form ahead of time to be sure it is safe to put them in the MRI. This is the standardized form used by the Neuroimaging Facility at York University. If a safety exclusion is noted in the form, the participant will be informed that we cannot safely scan them, and the form will be destroyed. If initial assessment shows that it is safe to scan the participant using MRI, this form will also be reviewed by the MRI technologist on the day of the scan and will be kept in a locked cabinet in the MRI facility with their records after the session is finished.

2) Magnetic Resonance Imaging (MRI, 30 – 45 minutes): Your participation will involve measuring the anatomy and activity of your brain using MRI. MRI scanners image your brain using radio waves and very strong magnetic fields. You will then be asked to remove any metallic objects (for example, wallets, watches, earrings, or piercings) and possibly to change clothing into a gown that we will provide (if deemed necessary because of large zippers etc.). You will be required to lay completely still on the patient bed that will slide into the MRI scanner. You will be able to communicate with us via a built-in intercom. You will be holding an emergency bulb that you can squeeze at any time to let us know you want to come out of the MRI scanner. You will be given breaks between tasks if you wish.

3) Eye-hand-balance coordination tests: (10 – 15 minutes) You will stand inside an augmented reality space in a laboratory wearing clear, lightweight goggles, and you will be asked to walk around a large circle while reaching to virtual objects along the path. In the second task, you will sit at a desk and move your finger along the screen of a tablet computer to reach targets

that will show up on the screen.

4) Saliva sample: (5 minutes) You will be asked to provide a small saliva sample (a few ml) by spitting into a plastic tube. The purpose of this is so that we can characterize the effect of different hormone levels on brain and behaviour.

This is Not a Clinical Evaluation: The images of your brain collected in this study are not intended to reveal any disease state, in part because this MRI protocol is not designed for clinical diagnosis. Thus, your brain images will not be routinely examined by a clinical radiologist. The personnel at the Neuroimaging Laboratory are not qualified to medically evaluate your images. However, if in the course of collecting images of your brain we have any concerns, we may show your scans to a clinical radiologist, who may suggest that you obtain further diagnostic tests.

At the investigator's discretion, you may view your brain images and receive digital copies of them. However, you should be aware that brain structures within the normal population are highly variable, and that it is difficult to draw any conclusions from your images; you should be aware of the potential distress or discomfort that may occur by viewing your own images. Do not rely on this research MRI to detect or screen for brain abnormalities.

Risks and Discomforts: We do not foresee any risks or discomfort from your participation in the research unless you have one of the conditions listed below - please read thoroughly.

MRI -
Metal: The MRI scanner produces a constant strong magnetic field, which may cause any metal implants, clips and/or fragments within your body to shift position. The magnetic field may also cause any implanted medical devices to malfunction. Thus, if you have any implanted metal, clips, fragments, or devices, it may be hazardous to your health to participate in this study. Please provide us with as much information as you can, for example if you had surgery in the past, so that we may decide whether it is safe for you to be a subject. Metallic objects brought into the MRI environment can become hazardous projectiles. Metal items such as jewelry, body piercings, and hair clips must all be removed prior to the study.

Pregnancy: Exposure to MRI scanning might be harmful to a pregnant female or an unborn child. Although there are no established guidelines at this time about MR and pregnancy, you should be informed that there is a possibility of a yet undiscovered pregnancy related risk. If you know or suspect you may be pregnant or if you do not want to expose yourself to this risk, we recommend that you do not participate in this study.

Inner ear damage: MRI scanning produces loud noises that can cause damage to the inner ear if appropriate sound protection is not used. Earplugs will be provided to protect your ears.

Claustrophobia: When you are inside the MRI scanner, the MRI scanner surrounds your body and your head will also be positioned inside a close-fitting scanning coil. If you feel anxious in confined spaces, you may not want to participate. If you decide to participate and begin to feel claustrophobic later, you will be able to tell us via the intercom and we will discontinue the study immediately.

Burns: In rare cases, contact with the MRI transmitting and receiving coil, conductive materials such as wires, metallic fibers in clothing, other metallic objects, or skin-to-skin contact that forms conductive loops may result in excessive heating and burns during the experiment. The operators of the MRI scanner will take steps, such as using foam pads when necessary, to minimize this risk. Tattoos with metallic inks can also potentially cause burns. Any heating or burning sensations during a scan in progress should be reported to the operators immediately and we will discontinue the scan.

Besides the risks listed above, there are no other known risks from the magnetic field or radio waves at this time. Although functional MRI scanning has been used for more than 20 years, long-term effects are unknown. If new findings about the risks of the MRI technique become available within a year of your participation, we will let you know about them.

As well, you may become fatigued during the experiment. We will be monitoring you continuously and asking you to report your comfort level throughout the experiment. You will be given breaks or can stop entirely as needed.

Voluntary Participation: Your participation in the study is completely voluntary and you may choose to stop participating at any time. If you do not volunteer for the study, this decision will not influence any treatment that you may be receiving, the nature of the ongoing relationship you may have with the researchers or study staff, or the nature of your relationship with York University now or in the future.

Withdrawal from the Study: You can stop participating in the study at any time, for any reason. If you decide to stop participating, all associated data collected will be immediately destroyed wherever possible. Your decision to stop participating, or to refuse to answer questions, will not affect your relationship with the researchers, York University, or any other group associated with this project. You will be provided with a parking pass for the York Imaging facility should you require it. If you withdraw from the study you will still be able to use the parking pass and receive your compensation.

Confidentiality: All information obtained during the research will be held in confidence to the fullest extent possible by law. In no case will your personal information be shared with any other individuals or groups without your expressed written consent. Your brain images and associated data will be stored on secured computer servers and will be archived indefinitely. The experimental data acquired in this study may, in an anonymized form that cannot be connected to you, be used for teaching purposes, be presented at meetings, published, shared with other scientific researchers, or used in future studies. Your name or other identifying information will not be used in any publication, presentation, or teaching materials without your specific permission. The consent forms and code sheets that contain identifying information are kept locked in a secure location.

Questions about the research: If you have questions about the research in general or about your role in the study, please feel free to contact Dr. Sergio either by telephone at (416) 736-2100, extension 33641 or by e-mail (lsergio@yorku.ca). This research has received ethics review and

approval by the Human Participants Review Sub-committee, York University's Ethics Review Board and conforms to the standards of the Canadian Tri-Council Research Ethics guidelines. If you have any questions about this process or about your rights as a participant in the study, please contact the Sr. Manager & Policy Advisor for the Office of Research Ethics, 5th Floor, York Research Tower, York University (telephone 416-736-5914 or e-mail ore@yorku.ca).

Legal Rights and Signatures:

I, _____(fill in your name here) consent to participate in the study ”The influence of sex-related differences in cognitive-motor integration on brain injury recovery in working-aged adults” conducted by Dr. Lauren E. Sergio. I understand the nature of this project and wish to participate. I am not waiving any of my legal rights by signing this form. My signature below indicates my consent.

Signature Date

Participant

C: Rivermead Post-Concussion Symptoms Questionnaire – RPQ*

After a head injury or accident some people experience symptoms which can cause worry or nuisance. We would like to know if you now suffer from any of the symptoms given below. As many of these symptoms occur normally, we would like you to compare yourself now with before the accident. For each one, please circle the number closest to your answer.

0 = Not experienced a tall

1 = No more of a problem

2 = A mild problem

3 = A moderate problem

4 = A severe problem

Compared with before the accident, do you now (i.e., over the last 24 hours) suffer from:

Headaches.....	0	1	2	3	4
Feelings of Dizziness.....	0	1	2	3	4
Nausea and/or Vomiting.....	0	1	2	3	4
Noise Sensitivity, easily upset by loud noise	0	1	2	3	4
Sleep Disturbance.....	0	1	2	3	4
Fatigue, tiring more easily	0	1	2	3	4
Being Irritable, easily angered	0	1	2	3	4
Feeling Depressed or Tearful	0	1	2	3	4
Feeling Frustrated or Impatient	0	1	2	3	4
Forgetfulness, poor memory	0	1	2	3	4
Poor Concentration	0	1	2	3	4
Taking Longer to Think	0	1	2	3	4
Blurred Vision	0	1	2	3	4
Light Sensitivity, Easily upset by bright light.....	0	1	2	3	4
Double Vision	0	1	2	3	4
Restlessness	0	1	2	3	4

Are you experiencing any other difficulties?

1.	0	1	2	3	4
2.	0	1	2	3	4

*King, N., Crawford, S., Wenden, F., Moss, N., and Wade, D. (1995) J. Neurology 242: 587-592

Dizziness Handicap Inventory

Instructions: The purpose of this scale is to identify difficulties that you may be experiencing because of your dizziness. Please check “always”, or “no” or “sometimes” to each question. Answer each question only as it pertains to your dizziness problem.

	Questions	Always	Sometimes	No
1	Does looking up increase your problem?	☐	☐	☐
2	Because of your problem, do you feel frustrated?	☐	☐	☐
3	Because of your problem, do you restrict your travel for business or pleasure?	☐	☐	☐
4	Does walking down the aisle of a supermarket increase your problem?	☐	☐	☐
5	Because of your problem, do you have difficulty getting into or out of bed?	☐	☐	☐
6	Does your problem significantly restrict your participation in social activities, such as going out to dinner, going to movies, dancing or to parties?	☐	☐	☐
7	Because of your problem, do you have difficulty reading?	☐	☐	☐
8	Does performing more ambitious activities like sports, dancing, and household chores, such as sweeping or putting dishes away; increase your problem?	☐	☐	☐
9	Because of your problem, are you afraid to leave your home without having someone accompany you?	☐	☐	☐
10	Because of your problem, have you been embarrassed in front of others?	☐	☐	☐
11	Do quick movements of your head increase your problem?	☐	☐	☐
	Because of your problem, do you avoid heights?			
	Does turning over in bed increase your problem?			

14	Because of your problem, is it difficult for you to do strenuous housework or yard work?	☐	☐	☐
15	Because of your problem, are you afraid people may think that you are intoxicated?	☐	☐	☐
16	Because of your problem, is it difficult for you to go for a walk by yourself?	☐	☐	☐
17	Does walking down a sidewalk increase your problem?	☐	☐	☐
18	Because of your problem, is it difficult for you to concentrate?	☐	☐	☐
19	Because of your problem, is it difficult for you to walk around your house in the dark?	☐	☐	☐
20	Because of your problem, are you afraid to stay home alone?	☐	☐	☐
21	Because of your problem, do you feel handicapped?	☐	☐	☐
22	Has your problem placed stress on your relationship with members of your family or friends?	☐	☐	☐
23	Because of your problem, are you depressed?	☐	☐	☐
24	Does your problem interfere with your job or household responsibilities?	☐	☐	☐
25	Does bending over increase your problem?	☐	☐	☐

DHI Scoring Instructions

The patient is asked to answer each question as it pertains to dizziness or unsteadiness problems, specifically considering their condition during the last month. Questions are designed to incorporate functional (F), physical (P), and emotional (E) impacts on disability.

To each item, the following scores can be assigned: No=0 Sometimes=2 Always=4 Scores: Scores greater than 10 points should be referred to balance specialists for further evaluation.

16-34 Points (mild handicap)

36-52 Points (moderate handicap)

54+ Points (severe handicap)