CONCUSSION RECOVERY AND SKILLED PERFORMANCE IN WORKING-AGED ADULTS: SEX DIFFERENCES IN THE NEURAL CORRELATES OF PERSISTING SYMPTOMS AFTER CONCUSSION

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Abstract

Cognitive-motor integration (CMI) refers to the ability to follow rules that guide perception and action. Following a concussion, CMI neural networks are often disrupted, impairing complex movement. We previously identified links between white matter integrity and visuomotor performance in working-age adults with persistent post-concussion symptoms (PPCS). We investigated the impact of sex, age, and CMI processes on visuomotor performance in PPCS. Forty-two adults (47.5 ± 9.87 years; 25 females, 17 males) completed a direct hand-to-target task and an indirect CMI task (plane-change and feedback reversal). Symptom severity, dizziness, cortical volumes and thickness, and resting-state functional connectivity (RSFC) were assessed. Females demonstrated slower CMI task performance, reduced cortical volume (left cuneus and superior frontal), thinner cortex (left precuneus), greater RPQ-3 symptom severity, and lower RSFC across multiple brain networks. Regression showed female sex and older age predicted poorer CMI performance. Findings highlight sex- and age-related neural factors underlying post-concussion motor deficits.

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List of Abbreviations

AE = Absolute error

AFNI = Analysis of functional neuroimages

BOLD = Blood oxygen level-dependent

BrDI = Brain Dysfunction Indicator

CI = Confidence interval

CM = Centromedial

CMI = Cognitive-motor integration

DAN = Dorsal attention network

DHI = Dizziness-related inventory

DMN = Default mode network

DR = Directional reversal

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition

fMRI = Functional magnetic resonance imaging

FOV = Field of view

FPCN = Frontoparietal control network

GAD-7 = General Anxiety Disorder-7

GPIP = Group prior individual parcellation

LB = Laterobasal

LIN = Limbic Network

LOC = Loss of consciousness

ME-ICA = Multi-echo independent components analysis

MP-RAGE = Magnetisation-prepared rapid gradient echo

MRI = Magnetic resonance imaging

mTBI = Mild traumatic brain injury

MTf = Full movement time

PC+FR = Plane change + feedback reversal

PHQ-9 = Patient Health Questionnaire-9

PLf = Full path length

PPCS = Persistent post-concussion symptoms

PV = Peak velocity

TBI = Traumatic brain injury

ROI = Region of interest

RPQ = Rivermead post-concussion Symptoms questionnaire

RPQ-3 = Rivermead post-concussion Symptoms questionnaire (early symptoms)

RPQ-13 = Rivermead post-concussion Symptoms questionnaire (late symptoms)

RSFC = Resting state functional connectivity

rsfMRI = Resting state fMRI

RT = Reaction time

SD = Standard deviation

SMN = Sensorimotor control network

TE = Echo time

TR = Repetition time

VE = Variable error

VN = Visual network

Chapter 1: Introduction and Literature Review

1.1. Concussion and Persistent Symptoms After Concussion

Concussion is a prevalent and concerning form of mild traumatic brain injury (mTBI) affecting upwards of 400,000 Canadians annually (Churchill et al., 2021; Choe, 2016; Pelley & Miller, 2023). Concussion can be defined as "a complex pathophysiological process affecting the brain, induced by biomechanical forces" (McCrory et al., 2009). Mechanisms of concussion can include, but are not limited to, direct impact to the head in the case of vehicular accidents, falls, or blows. The head undergoing rapid acceleration and deceleration (i.e., whiplash) can also result in a concussion (Kinney, Richmond, & Mizner, 2024). Concussion can onset a series of physical, somatic, cognitive, and behavioural symptoms and changes. Affected individuals can experience the following self-reported symptomology based on the severity of injury: loss of consciousness (LOC), dizziness, nausea, headaches, fatigue, amnesia, mood swings, concentration difficulties, and much more (Chancellor et al., 2019). It is generally accepted that concussion involves temporary neurological dysfunction; up to 80-90% of cases resolve spontaneously within 14-30 days and present without any detectable brain injury (Chancellor et al., 2019). For the remaining 10-20% of cases, if symptoms persist beyond 30 days post-injury, the diagnosis evolves to Persistent Post-Concussion Syndrome (PPCS) (Leddy et al., 2021). The aforementioned symptoms can last months to years post-injury, causing chronic pain and even disability (Ryan & Warden, 2003). Studies have found, particularly the somatic and cognitive symptoms (i.e., memory deficits or loss of consciousness), situational factors, or general psychological distress as strong predictors of PPCS development (Ryan & Warden, 2003). The latest edition of the DSM-5 classifies PPCS as either a major or mild neurocognitive disorder resulting from TBI. This condition is characterized by neurological symptoms such as LOC, disorientation,

confusion, and amnesia, along with cognitive impairment that persists for more than three months (Tator et al., 2016). Given these stringent criteria, the DSM-5 definition is inadequate for classifying and assessing patients with PPCS since LOC is not required for a diagnosis (Tator et al., 2016).

General literature on LOC within the PPCS realm agrees that LOC does not predict greater symptomology than individuals who only experience a daze. For example, Lenniger et al. (1990) compared 53 individuals who experienced PPCS symptoms for over one-month post-vehicular accident. 31 individuals experienced LOC, and 22 individuals only experienced a daze. The authors found no evidence that the LOC participants' injuries were more debilitating than those who experienced a daze but no LOC (Lenniger et al., 1990). The variability in head injury outcomes underscores the multidimensional mechanisms underlying concussion and PPCS. For instance, some concussion patients can experience amnesia, and their retrospective interview may not be accurate, leading to a premature clinic discharge (Anderson, 1996). Similarly, it can be argued that there are levels to LOC (e.g., responding to select stimuli) and not an "all-or-nothing" phenomenon (Anderson, 1996). Loosely defined terminology and stringent criteria in the DSM-5 often lead to misdiagnosis and inadequate treatment.

There are significant gaps in research regarding concussion mechanisms and their connection to PPCS. With most of the concussion research being centred around the young and athletic demographic, many of the research gaps reside within the working-age population, gender, non-sport-related concussion mechanisms, and longer-term symptoms (King, 2014). Unsurprisingly, middle-to-older-aged adults are more susceptible to longer hospital stays, more severe injuries because of a TBI, and worse cognitive, physical, and functional outcomes (Karr et al., 2020). Although the prevalence of traumatic brain injury (TBI) in the older adult population

has grown, there are few evidence-based recommendations for the therapeutic care of these patients after a TBI of any severity. The scarcity of standards stems, in part, from a lack of research on TBI in older individuals overall, despite a clinical need to comprehend prognosis and rehabilitation requirements across the range of TBI severity (Karr et al., 2020). Five years after a brain injury, Marquez de la Plata et al. (2008) discovered that the older adult population had a much greater rate of disability than any other group. In the ageing brain, regeneration and recovery are much more restricted. A brain injury exacerbates an already declining structure in an aged person, making their future functionality and quality of life even more impaired (Demenik et al., 2016).

1.2 Concussion and Sex-Related Differences

Several studies have highlighted that sex-related differences are a factor in concussion occurrence and onset of PPCS. A common finding in concussion literature is that females tend to have higher rates of concussion, more severe symptoms, and longer recovery time thus, making them more susceptible to PPCS (Berz et al., 2015; Dick, 2009; Hannah et al., 2019; Broshek et al., 2005; Bazarian et al., 2010). For example, Hannah et al (2019) looked at a large, multisport cohort (5216) and found that female athletes are at a greater risk of experiencing more frequent and severe concussions compared to their male counterparts. Similarly, Bazarian et al (2010) found their female participants were more likely to report more severe PPCS symptomology and sought to explain how mTBI impacts estrogen and progesterone and therefore, results in worse outcomes in females compared to males. Female athletes experienced larger decreases in reaction time post-concussion and were 1.7 times more cognitively impaired than their male counterparts post-concussion (Broshek et al, 2005). It is theorized that females have a higher rate of concussions as they have a smaller head size, on average, which requires less force to move

violently enough to cause brain damage, and they are prone to honestly self-report their symptoms leading to diagnosis compared to males (Arnold, 2013; Dick 2009).

1.3 Concussion and Cognitive-Motor Integration (CMI)

With little conscious awareness, healthy individuals can combine thinking and moving and execute a series of direct and indirect interactions (Sergio et al., 2020). However, following a mTBI, it is proposed that rule-based skilled performance decreases due to a lack of communication between damaged brain networks (Sergio et al., 2020; Kaushal et al., 2018). Nearly all our daily activities require the brain to coordinate cognitive function with motor actions using sensory information, memory, and decision-making to control movement. Neural networks in the frontal lobes, cerebellum, and basal ganglia collaborate to govern both cognitive and motor functions (Leisman et al., 2016). This integration enables executive control, intentional movement, and the ability to anticipate and react to actions. The interaction of these brain regions allows adaption to our surrounding environment and facilitates purposeful behaviour (Leisman et al., 2016). Studies have also reported sex-related differences in CMI performance. Sex-specific brain activation patterns suggest cerebral injuries could lead to distinct visuomotor impairments between males and females (Sergio et al., 2020). Observed in different clinical populations, males and females were often found to have different CMI performances. For example, in an at-risk Alzheimer's Disease population, females had greater endpoint error scores and corrective path lengths than males in the CMI task (Rogojin, 2018). Research by Gorbet and Sergio (2007) revealed that women exhibited greater bilateral brain activation patterns than men during CMI tasks however, there were no statistically significant differences in task performance between the sexes. This implies that the CMI neural networks governing task execution may vary between men and women and ultimately extend beyond behavioural

measures. Smeha et al (2022) found that females were more resilient during a 4-week recovery program post-concussion and found they had a stronger recovery in skilled performance, suggesting sex-related differences in the effect of injury on CMI-related brain networks. Together, this highlights the need for personalized neurological evaluations and rehabilitation strategies to effectively address the unique requirements of both men and women with PPCS.

The sex-related differences in CMI performance are theorized to be due to differences in sex hormones. Males and females have different predominant hormones and play distinct roles in the ageing experience and brain health. Females undergo constantly fluctuating sex hormone levels through all phases of life such as during the menstrual cycle, pregnancy and menopause, while men's hormone levels steadily decline with age (Farage et al., 2012). A study by Engman and colleagues (2016) identified gender-specific patterns in resting-state functional connectivity of the left and right laterobasal (LB) and centromedial (CM) amygdala and investigated the relationship between estrogen and functional brain connectivity. They suggest that estrogen could play a key role in regulating emotional processes through its effects on brain connectivity patterns. This hormonal influence might contribute to the observed differences in women who have a greater susceptibility to negative conditions than men (Engman et al., 2016). Furthermore, testosterone levels increased in women across all age groups following a mTBI, suggesting a worsening of symptoms at subsequent appointments and longer recovery times (Blaya et al., 2022). This rise in testosterone may be due to a disruption in the conversion of testosterone to estradiol, thus potentially leading to a loss of estradiol's protective effects against brain damage after a mTBI (Blaya et al., 2022). Di Battista and colleagues (2019) found distinct neuroendocrine patterns were linked to specific clusters of cognitive, physical, fatigue, and emotional symptoms. Disruptions in the neuroendocrine system post-concussion may play a role

in the severity of symptoms and recovery duration. Several studies have looked into the effect of sex hormones in females, leading to the following paradigm: hormones involved in regulating the menstrual cycle and their levels at the time of head injury seem to impact symptom severity. These findings suggest that concussions are more likely to occur during the phase of the menstrual cycle characterized by low or decreasing estrogen and progesterone levels (Gallagher et al., 2018; Snook et al., 2017; La Fountaine et al., 2019). To relate hormones to CMI performance, Pierias (2021) found that progesterone and testosterone were positively linked to visuomotor and CMI performance. Nonetheless, research on the effects of age, brain injury, and changes in sex hormone levels on CMI brain networks and pathways that our group is interested in is, however, very limited. Additionally, with much of the literature looking at young female athletes and their hormone levels at the time of injury during their menstrual cycle, it is imperative to extend it to other concussion mechanisms and consider the effect of hormones on concussed working-aged males.

1.4 Purpose and Hypotheses – Current Study

This research study examined how sex influences CMI abilities in adults of working age who are experiencing PPCS. This study extended beyond performance inconsistencies between sexes and sought to determine the potential role of sex-specific factors in recovery following brain injury. We sought to find potential variations in the resting state neural networks, assess structural integrity, and explore the relationship between these neural structural and functional properties and behavioural outcomes.

Based on our lab's previous research, we theorized that sex would influence the correlation between neural connectivity and grey matter volume in working-age individuals suffering from PPCS. This hypothesis maintains validity even if behavioural outcomes seem

similar across sexes, potentially due to females presenting more bilateral brain activation patterns. To test this theory, we have devised two key predictions:

1) There will be sex-related disparities expected in resting state network connectivity. Moreover, an interaction is expected between the experimental condition and sex regarding the relationship between CMI performance and resting-state network function. Behaviourally, females with PPCS will demonstrate a stronger correlation in the plane-change reversal task, while males will show a stronger relationship in the same-plane reversal task. (Task details are in the Methods section.)
2) Volumetric differences in the frontal, parietal, or cerebellar regions will correlate weakly with CMI behavioural outcomes in females compared to males. This prediction assumes that females typically display a more bilateral visuomotor representation in their brains.

This study's exploratory analysis utilized a novel approach to gender analysis. Instead of a traditional male-female dichotomy, we represented gender as a continuous spectrum. Our primary goal was to uncover the connections between CMI performance, hormone levels, and various brain measures across this gender continuum. This continuous and fluid variable offered a comprehensive view of gender compared to conventional binary classifications. The objectives of this method were to: 1) provide a greater understanding of how gender-related factors influence our variables of interest; 2) close gaps between existing literature and offer new knowledge and fresh perspectives; and 3) discover patterns or relationships that binary gender categorizations might miss.

Chapter 2: Methods

2.1 Participants

This study included forty-two participants who were working-aged adults between 30 and 65 years of age (47.50± 9.87; 25 females and 17 males). Technically, working-aged adults ranges from age 16 to 65; however, since much of the concussion literature is focused on youth, athletes, and seniors, we have chosen to focus on underrepresented middle-to-older working-aged adults to get more insight into the influence of age on motor control, cognition, and recovery. Specifically, the recruited participants were experiencing PPCS symptoms for at least three months post-concussion. Exclusion criteria included history of stroke, epilepsy/seizures, active vestibular or neurodegenerative disorder(s) with an 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. Additionally, interested participants who were taking any form of birth control, hormone replacement therapy, or had any implants or tattoos that were not MRI-safe were excluded, as these criteria are required for another branch of this broader research study. Participants were obligated to complete an MRI safety screening form to ensure they could be safely scanned and confirm their eligibility before booking their data collection appointment (**Appendix E**). A diagnosis of PPCS was contingent on participants being assessed by a physician for concussion symptoms or the ability to relay the date and mechanism of injury. Participants completed a series of questionnaires to gauge the extent to which their prior concussion(s) have impacted them. Questionnaires include the Dizziness Handicap Inventory (DHI), which quantifies the impact of dizziness on daily activities, a Pretest Intake Questionnaire, which assesses the participant's all-encompassing health history, and the

Rivermead Post-Concussion Symptoms Questionnaire (RPQ) to determine PPCS symptoms present along with their severity. The questionnaires and the nature of their questions can be found in **Appendices B**, **C**, and **D**, respectively.

The Human Participants Review Sub-Committee of York University's Ethics Review Board approved this study's procedure. Written informed consent was provided to each participant for their review and signature before any data was collected (**Appendix A**).

2.2 Measures

2.2.1 Measuring Hormones Through Salivary Collection

Saliva samples (1.5 mL) were collected from each participant. Note, however, that these data were used for a different branch of the larger research project and will not be analyzed for this thesis.

2.2.2 Behavioural Cognitive-Motor Integration (CMI) Assessment Task

Using custom-written software, participants were administered 4 tasks requiring visual information to be translated into motor actions. Participants were directed to move the cursor from a central target to one of four peripheral targets (up, down, left, or right) by sliding the index finger of their dominant hand along the touch screen (either on the touchscreen on the Dell laptop or on a horizontal screen using an external KeytechTM (Tyco Touch, Inc.) touchpad that was positioned perpendicular to the Dell laptop screen depending on the condition). The Dell laptop displayed the targets for each condition of this CMI assessment task. The tasks were divided into 1 standard condition and 3 distinct non-standard conditions where the finger motion and target viewed are spatially coupled and decoupled, respectively (**Figures 1a-d**). The finger movement in the standard mapping exercise directly matched the location of the visual cue (**Figure 1a**). Finger movements in the non-standard conditions took place in relation to the target

position on a different plane (plane change (PC); **Figure 1b**), in the opposite direction (feedback reversal (FR); **Figure 1c**), or both (PC+FR; **Figure 1d**).

All conditions were randomized. From the central target, peripheral targets are placed 55 mm away. Participants completed a practice trial in all four conditions to ensure they understood the task. The task sequence was as follows:

1) A 7.5 mm diameter central yellow target appears on the laptop touchscreen.

2) Participants move a white cursor to the yellow target, turning it green upon contact.

3) A red peripheral target appears after 2000 ms, and the central target disappears, prompting the start of a movement.

4) Participants identify the peripheral target and slide their finger on the laptop touchscreen or touchpad to move the cursor toward one of the four peripheral targets (up, down, left, right).

5) After reaching the peripheral target and holding it for 500 ms, it disappears, marking the trial's end.

6) After another 2000 ms delay, the central yellow target reappears, prompting the participant to return to the centre for the next trial (**Figure 2**).

Participants directly engaged with the objectives on the vertical Dell laptop touchscreen in the standard condition (**Figure 1a**), with the cursor moving beneath their finger. In the PC condition, they moved on a horizontal KeytechTM touchpad (**Figure 1b**), using the vertical laptop screen to see the peripheral target and direct the cursor accordingly. The FR condition (**Figure 1c**) required the user to move the cursor on the laptop touchscreen in the opposite direction to reach the target (i.e., move left to reach the peripheral target on the right). To steer the cursor in the PC+FR condition (**Figure 1d**), participants had to move their finger in the opposite direction and

on a different plane. Participants were directed to complete the CMI task as fast and accurately as possible. Each participant performed 20 trials in each condition, equalling a total of 80 trials across all 4 conditions (see path trajectory examples in **Figure 9**).

2.2.3 Behavioural Data Processing

The analysis of the CMI task focused on key movement data from each trial, including timing, finger position, and errors. Custom software will be used to convert this data into a MATLAB-readable format for further processing. The system flagged trials that do not meet specific criteria: early movement (< 2000 ms), excessively quick (< 150 ms) or delayed (> 8000 ms) reaction times, or extremely delayed movement times (> 10000 ms), which were later manually excluded. Direction reversal errors, defined as initial movements deviating more than 45° from the target path, were analyzed separately. For successful trials, velocity profiles were generated, demonstrating the speed of the finger movement along with the central-to-peripheral target trajectory. This analysis was conducted using specialized software developed for this study (MATLAB, Mathworks, Inc., USA). Movement phases were analyzed using velocity-based criteria: 1) Movement onset identified at 10% of peak velocity; 2) Ballistic phase end identified as initial deceleration to 10% of peak velocity; 3) Total movement end identified as final deceleration to 10% within the target area. For direct movements, ballistic and total movement endpoints may coincide. These automated measurements were visually verified and adjusted if needed. From this data, seven key Movement performance and execution metrics were derived. The analysis focuses on two key aspects of movement: timing and execution. For movement timing, we examined three primary measures. 1) The response initiation speed, Reaction time (RT, in ms), the time interval between stimulus presentation and movement onset; 2) Movement time, the total duration from initiation to completion (MT, in ms); 3) Finally, we recorded the

peak velocity (PV) achieved during each movement, providing insight into the maximum speed participants can generate. Regarding movement execution, four critical parameters were evaluated. 4) Trajectory length (mm) was calculated, the total distance covered for both the entire movement and the initial ballistic phase (full Path Length, PLf, in mm); 5) To assess absolute error (AE), the average distance between movement endpoints and the actual target location was determined in mm^2; 6) We also examined variable error (VE), quantifying the spread of movement endpoints (in mm^2) around their mean position to gauge precision; 7) Lastly, directional control was calculated using the percentage of trials where the initial trajectory deviated significantly ($\pm 45°$) from the ideal path (Direction Reversal, DR). With the large number of outcome metrics derived from data scoring, measures were combined into composite scores to decrease the number of comparisons in the data analysis. Kinematic measures to be combined into composite scores were standardized using z-scores. Z-scores were calculated for the males and females based on the combined male and female control groups' means and SD to allow us to assess how the at-risk individuals compared to all of the healthy controls. The means and standard deviations of RT, MT, PV, AE, VE, and PLf were first calculated for all control participants. A positive value indicates the score was above the control mean, a negative value indicates the score was below the control mean, and a value of 0 indicates the score is identical to the control mean. The z-score for PV was multiplied by -1 to match the other two timing measures, RT and MT (where a lower value indicates better performance). Composite scores were created using simple averaging, which is the most commonly used approach when original variables are continuous (Song et al., 2013). The timing score ($\alpha = .879$) is a composite score of reaction time, full movement time, and peak velocity. The endpoint error score ($\alpha = .772$) is a composite score of absolute error and variable error. These metrics provide

an assessment of participants' motor performance, capturing aspects of speed, accuracy, consistency, and strategic control. By examining both timing and spatial characteristics, we gained insights into the underlying CMI processes involved in task execution. To ensure data quality, outlier trials over two standard deviations from the participant's mean for each metric were excluded before calculating final outcomes. This approach allowed for precise quantification of movement dynamics while accounting for individual differences and potential measurement errors.

2.2.4 Dizziness Handicap Inventory (DHI) Assessment

The Dizziness Handicap Inventory (DHI) is a 25-item questionnaire that requires participants to identify and self-report any difficulties they experience due to dizziness (see **Appendix B**). Three subcategories within the DHI (physical, emotional, and functional) make up the total experienced vestibular dysfunction. Each item is assigned a score based on the three-point ordinal scale (No = 0, Sometimes = 2, and Always = 4). The total score can aid in determining the extent of the impact of dizziness on disability. 16-34 points indicate mild handicap, 36-52 points indicate moderate handicap, and 54+ points indicate severe handicap.

2.2.5 Health Questionnaire

This pretest intake questionnaire collects confidential demographic, health, and lifestyle data. This includes age, date of birth, dominant hand, sex assigned at birth, gender identity, education, ethnicity, employment status, occupation, sports history, previous non-head injuries, health history, medication use, menstrual cycle if applicable, alcohol and substance use frequency, concussion history, concussion mechanisms and symptoms, mental health over the last two weeks using the PHQ-9 (depression) and GAD-7 (anxiety) scales, technology use, family dementia history, and frequency of various activities (e.g., watching TV, exercising,

socializing). The questionnaire, developed by Drs. Magdalena Wojtowicz and Lauren E. Sergio, provided a comprehensive baseline for the study.

2.2.6 Persistent Post-Concussion Syndrome (PPCS) Assessment

The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) was utilized to determine the extent of the participants' persisting concussion symptoms (see **Appendix D**). RPQ is a patient-reported 16-item questionnaire consisting of early and late symptoms. The first 3 items in the questionnaire are known as RPQ-3 and consist of typical early symptoms of a concussion (headaches, dizziness, and nausea). The remaining 13 cognitive and psychological items are known as RPQ-13 and pertain to symptoms that typically occur later when one suffers from PPCS. This includes symptom clusters regarding noise sensitivity, sleep disturbance, fatigue, irritability, depression, frustration, poor memory, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision, and restlessness. The 5-point ordinal scale ranges from 0 (not experienced at all) to 4 (a severe problem) for all items.

2.3 Data Retrieval Using Magnetic Resonance Imaging (MRI)

Participants partook in an MRI scanning session where data were obtained using York University's 3 Tesla Siemens Trio scanner. Each participant underwent multiple scans to collect various types of neuroimaging data. First, a high-resolution structural scan was performed using a T1-weighted magnetization-prepared rapid gradient echo (MP-RAGE) sequence. This captured 192 sagittal slices at 1 mm thickness without gaps, covering a 256 x 256 mm field of view (FOV) with 1 x 1 x 1 mm^3 voxel resolution. The scan parameters included a 2.26 ms echo time (TE), 2300 ms repetition time (TR), and 8° flip angle. Second, resting-state functional MRI (rsfMRI) data were collected using a multi-band acceleration factor of 4 and a multi-echo EPI sequence optimized for BOLD (Blood Oxygen Level-Dependent) contrast over 12 minutes.

Participants were instructed to keep their eyes open and fixate on a white cross set against a black backdrop while keeping their head still. The white cross was projected on the MRI screen, which was visible to participants using a mirror. During these 12 minutes, the functional scan was conducted with the following specifications: 52 axial slices (3 mm thick, no interslice gap), a 240 x 240 mm FOV, an 80 x 80 matrix, yielding a voxel size of 3.0 x 3.0 x 3.0 mm^3, TR = 961 ms, TEs = 12.40, 30.15, and 47.90 ms, and a 50° flip angle. Each TR generated three volumes, corresponding to the three TEs. The time series for each TE was independently converted to NIfTI format, producing one NIfTI file per echo. For each participant, a single resting-state run was collected, consisting of 2274 images (758 per echo time). Note that there was also a diffusion tensor imaging protocol that was collected for the larger research project. These data are beyond the scope of this thesis. In total, the participants were in the scanner for approximately 45 minutes.

2.4 MRI Preprocessing

2.4.1 Structural Volumetric Data

FreeSurfer version 7.4.1 was utilized to process all anatomical scans using a recon-all pipeline with the input being the T1-weighted MR. This software package executed a series of preprocessing steps, including the segmentation of white matter and subcortical structures, skull stripping, and mapping of cortical regions with thickness measurements. The pipeline began with intensity normalization and correction, followed by Talairach transformation. A deformable template model facilitated skull stripping on the transformed, intensity-adjusted image. Voxels were then categorized as gray matter, white matter, or cerebrospinal fluid based on their intensity values. Subcortical regions were segmented, and cortical surfaces—defining the white matter boundary (white surface) and the gray matter-cerebrospinal fluid boundary (pial surface)—were

constructed in each participant's native anatomical space. These surfaces were inflated into a spherical shape and aligned to the FreeSurfer fsaverage template through non-linear, surface-based registration, ensuring precise matching of gyral and sulcal patterns. Cortical parcellation, based on the gyral Desikan-Killiany atlas (Desikan et al., 2006), was mapped onto each participant's brain, with minor adjustments for individual variations (see **Figure 3**). Cortical thickness was determined by measuring the distance between the white and pial surfaces across both hemispheres. All scans underwent visual inspection to identify issues like excessive motion, signal dropout, or other artifacts. To account for variations in head size among individuals and sexes, all regions of interest were adjusted using total intracranial volume as a corrective factor.

2.4.2 rsfMRI for Functional Connectivity

The processing of multi-echo resting-state fMRI data employed a specialized preprocessing pipeline. This process utilized the Multi-Echo Independent Components Analysis (ME-ICA) approach, implemented through the Analysis of Functional NeuroImages (AFNI) software suite. The initial stages involved enhancing data quality by addressing various artifacts and aligning the data temporally and spatially. The process began by removing signal spikes, adjusting for differences in slice acquisition timing, masking, and correcting for participant movement (Kundu et al., 2012; Kundu et al., 2017). The data underwent spatial smoothing and normalization to a standard space. To further improve signal quality, nuisance regression techniques were implemented, and time points with excessive motion were excluded. Following preprocessing, each participant's resting-state data was aligned with their respective anatomical images within the FreeSurfer framework. To parcellate the rsfMRI data into functional networks at the individual level, a method called Group Prior Individual Parcellation (GPIP) was applied. This innovative approach starts with a group-level atlas template but refines it based on each

participant's unique resting-state data, allowing for individual variations in network boundaries as seen in **Figure 4** (Chong et al., 2017). The analysis focuses on seven primary functional connectivity networks, as defined by established neuroimaging literature. These networks include the Frontoparietal Control Network (FPCN), Somatomotor Network (SMN), Salience Ventral Attention Network (SVAN), Visual Network (VN), Limbic Network (LN), Dorsal Attention Network (DAN), and Default Mode Network (DMN) (Glasser et al., 2016; Yeo et al., 2011). This approach enables the examination of brain connectivity patterns with consideration for both group-level organization and individual variability.

2.4.3 Resting State Functional Connectivity (RSFC) Matrix

For each participant, a 200 × 200 functional connectivity matrix was generated using their personalized brain parcellation. Pairwise correlations were calculated between the mean BOLD signal time-series extracted from each parcel. These correlations were transformed into z-scores via Fisher's r-to-z transformation to standardize the distribution, creating the final matrix. Mean Fisher z-transformed resting-state functional connectivity (RSFC) values were then derived for six key resting-state networks: the default mode network (DMN), frontoparietal control network (FPCN), dorsal attention network (DAN), sensorimotor control network (SMN), visual network (VN), limbic network (LN), and salience/ventral attention network (SVAN) (see **Figure 5**). These values served as indicators of within-network connectivity strength. The FPCN was further divided into three subnetworks, – FPCNa, FPCNb, and FPCNc – based on the Schaefer et al. (2018) 17-network parcellation (see **Figure 6**). This subdivision was motivated by research highlighting distinct FPCN cores: FPCNa, which connects more strongly with the DMN, and FPCNb, which aligns closely with the DAN (Beaty et al., 2021; Dixon et al., 2018; Murphy et al., 2020; Yin et al., 2022). The DMN supports introspective processes independent of

sensory input (Konishi et al., 2015), while the DAN is critical for visuospatial attention and visually guided actions, often interacting with the SMN (Ptak, 2012; Ptak et al., 2017; Thomas Yeo et al., 2011). The FPCN subnetworks were defined by aligning the MNI centroid coordinates of the FPCN from the 7-network atlas to those in the 17-network atlas. Notably, FPCNc (encompassing the posterior cingulate and precuneus) lacks frontal regions but was included due to evidence of altered connectivity following concussion (Leech & Sharp, 2014).

2.5 Statistical Analysis

The purpose of this research project is to explore the sex-based differences and underlying neural processes that impact CMI performance in individuals experiencing PPCS. To fulfil the aforementioned hypotheses, both univariate and multivariate analytical methods were utilized to investigate the neural underpinnings that potentially underlie observed disparities in CMI abilities in individuals with PPCS. The goal was to gain a more nuanced, complete understanding of the complex interplay between sex and neurophysiology in the context of cognitive-motor functioning following a concussion. All statistical analyses were carried out in SPSS. Two participants were excluded from functional connectivity and cortical thickness and volume analyses due to no MRI being acquired, and the MRI protocol had to change to accommodate larger head size (n=40). One participant was excluded from behavioural task analyses as the data was corrupted and could not be translated into valid findings (n=41). Descriptive statistics were used to summarize participants' characteristics (**Table 1**).

To examine sex-based differences, we employed a one-way analysis of variance (ANOVA) approach. This allowed us to investigate any behavioural performance differences between sexes on standard and novel assessment tasks. We also analyzed potential sex differences in demographic factors, symptom scores from the pretest intake questionnaire and

dizziness inventories, as well as the overall severity of PPCS. Parallel analyses were conducted on measures of functional connectivity patterns and cerebellar anatomy, accounting for the influence of age as a covariate.

Multivariate regression analyses were required to explore the complex interrelationships between various factors. For example, we examined how CMI performance relates to sex, age, neuroimaging metrics (functional connectivity patterns and structural physiology) and the overall severity of PPCS. By considering these multifaceted relationships, we gained a more comprehensive understanding of the underlying mechanisms that contribute to disparities in CMI abilities within this understudied research population.

2.5.1 Relationship between RSFC, RPQ, DHI, and Visuomotor Performance

Several hierarchical regressions, a method nestled within the realm of multiple linear regression, were set up on SPSS with RSFC as the independent variable and RPQ, DHI, or visuomotor performance measures as the dependent variable. The blocks in the hierarchical regression were set up as age in the first block, age and sex in the second block, and age, sex, and the aforementioned dependent variable in the third and final block. The independent variable was the mean within-network functional connectivity of the VN, SMN, LN, DAN, SVAN, and DMN, as well as the FPCN subnetworks (FPCNa, FPCNb, and FPCNc).

2.5.2 Relationship between Cortical Thickness/Volume, RPQ, DHI, and Visuomotor Performance

To investigate the relationships between cortical thickness and volume (derived from FreeSurfer's *"recon-all"* pipeline using the Desikan-Killiany atlas) and clinical and performance outcomes, separate hierarchical regression models were constructed for each dependent variable (DV): RPQ 3 and 13 scores, total DHI scores, and visuomotor performance metrics (standard and

non-standard condition timing and movement composite scores). Cortical thickness and volume for regions of interest (ROIs) were tested individually as independent variables (IVs) to avoid multicollinearity. Each model comprised three blocks to control for demographic covariates and assess the unique contribution of the brain measures. Block 1 included age as a covariate to account for age-related variance in brain structure and outcomes. Block 2 added sex to examine its additional explanatory power. Block 3 included age, sex, and either cortical thickness or volume for a given ROI, allowing evaluation of the brain measure's contribution to the DV beyond demographic factors. Models were fitted using ordinary least squares regression, with assumptions of linearity, normality, homoscedasticity, and independence verified via residual diagnostics. The change in the unstandardized beta value was used to assess the significance of each block's contribution, with a significance threshold of $p < 0.05$. Additionally, reverse analyses were conducted, treating RPQ, DHI, and visuomotor performance as IVs and cortical thickness or volume as DVs, using the same hierarchical block structure to explore bidirectional relationships.

2.5.3 Sex Differences in Resting State Functional Connectivity Using Independent Samples t-test

An independent samples t-test was employed using SPSS to assess sex differences in RSFC across various brain networks. The t-test is a statistical method used to determine whether there is a significant difference between the means of two independent groups, male and female participants, on a continuous dependent variable, RSFC measures. This analysis was relevant to confirm potential sex-based variations in RSFC, which could influence brain function and performance outcomes. By examining these differences, the study aimed to provide a comprehensive understanding of sex-specific neural connectivity patterns, enhancing the interpretation of the overall findings.

Chapter 3: Results

3.1 Participant Characteristics

Participants' demographics, PPCS, dizziness, and visuomotor characteristics are displayed in **Table 1**. While the questionnaire used a 7-point gender scale for this study, all the participants in this group self-reported to have a cis-gender identity, which matched their sex assigned at birth. Hence, for the remainder of the document, we will be referring to our groups as male and female. The mean age was 47.50 years old with females making up 59.52% of the participant pool. The median age was 48.5, with a range of 29 – 64 years. Of the 42 participants, 10 reported having 1 concussion (23.81%), 8 reported having 2 concussions (19.05%), 11 reported having 3 concussions (26.19%), and 13 reported having 4 or more concussions (30.95%). Nearly all participants (40 out of 42) reported experiencing poor concentration (**Table 2**). Headaches, forgetfulness, and taking longer to think were the second most reported symptoms (90.48% respectively. Contrarily, double vision was the least reported symptom (42.86%). During data collection, 20 participants reported full-time employment, 10 indicated part-time employment, 5 participants indicated they do not work, 3 participants were retired, 3 participants stated they stopped working full-time post-concussion, and 1 participant indicated mixed full-time and part-time work. Regarding the mechanisms of concussion, sport-related accidents had the highest frequency (36.44%), followed by motor vehicle accidents (25.42%), falls (16.10%), and being struck in the head by an object (15.25%). Other mechanisms of concussion included fights, bike accidents, elevator accidents, and snorkelling accidents, which made up 6.79% of concussion mechanisms combined.

An Analysis of variance (ANOVA) was conducted to investigate sex differences in timing and trajectory composite scores across standard and non-standard tasks. The results revealed a significant effect of sex on the timing composite score in the non-standard task, $F(1, 39) = 5.495$,

$p = 0.024$, partial $\eta^2 = 0.123$. Specifically, females ($M = 0.504$, $SD = 1.423$, $N = 24$) demonstrated higher (slower) timing composite scores than males ($M = -0.712$, $SD = 1.903$, $N = 17$) in the non-standard task, indicating a significant difference (see **Figure 8**). In contrast, no significant sex differences emerged for the timing composite score in the standard task ($p = 0.558$), the trajectory composite score in the standard task ($p = 0.553$), or the trajectory composite score in the non-standard task ($p = 0.732$). These findings suggest that sex influences timing performance specifically in the non-standard task, with females performing slower than males in the non-standard task that requires more CMI.

3.2 Relationship Between Cortical Volume, RPQ, DHI, Age, and Sex

A multiple regression analysis was conducted to examine the effect of age, sex, and RPQ or DHI on adjusted cortical volumes of ROIs of interest. For the left hemisphere cuneus, sex was a significant predictor in the regression model with age and DHI, $\beta = -387.34$, $t(36) = -2.16$, $p = .038$, 95% CI [-751.21, -23.47], and age and RPQ-13, $\beta = -390.47$, $t(36) = -2.16$, $p = .037$, 95% CI [-756.65, -24.30]. It is important to note that sex was trending to near ($p = .055$) in the model with age and RPQ-3 on the left hemisphere cuneus. Similarly, for the left hemisphere superiorfrontal region, sex was a in the model with age and RPQ-13 $\beta = -1278.97$, $t(36) = -2.04$, $p = .049$, 95% CI [-2552.94, -5.01]. Note that, again, sex was trending to near significance ($p = .051$) in the model with age and RPQ-3 on the left superiorfrontal region. The negative beta coefficients indicate that females are associated with lower adjusted cortical volumes in the aforementioned brain regions compared to males (see **Figure 10**). The broader implication of these findings is that sex differences may play a significant role in the structural variations of specific brain regions, such as the left cuneus and left superiorfrontal region, which could influence cognitive, sensory, or emotional processing.

An alternate and reverse analysis was done investigating the effect of age, sex, and cortical volume on DHI or RPQ. The multiple linear regression analysis, which included age, sex, and one of the regions of interest (ROIs) listed in **Table 6** as predictors of RPQ-3 scores, revealed that only sex was significant across various brain regions. Sex emerged as a significant predictor ($p < .05$) for multiple ROIs, including the left and right caudal middle frontal, cuneus, inferior parietal, precentral, precuneus, rostral middle frontal, and superior frontal and parietal regions. The unstandardized beta coefficients ranged from 2.029 to 2.377, with 95% confidence intervals indicating robust effect sizes, and p-values ranging from .007 to .016, underscoring the statistical significance. Notably, the left caudal middle frontal ($\beta = 2.332$, $p = .006$) and right precuneus ($\beta = 2.218$, $p = .009$) exhibited some of the strongest associations. These findings suggest that sex influences post-concussion symptom severity on the RPQ-3, potentially reflecting underlying neuroanatomical or functional differences between males and females, while age and ROI volume did not contribute significantly. The implications of these results are significant, as they highlight the need to consider sex as a critical variable in concussion research and clinical assessments, potentially guiding tailored interventions to address sex-specific recovery patterns.

3.3 Relationship Between Cortical Thickness, RPQ, DHI, Age, and Sex

A multiple regression analysis was conducted to examine the effect of age, sex, and RPQ or DHI on the cortical thickness of CMI-related ROIs. For the left hemisphere precuneus, sex was a significant predictor in the model with age and RPQ-3 $\beta = -.091$, $t(36) = -2.64$, $p = .012$, 95% CI [-.161, -.021], and age and RPQ-13, $\beta = -.074$, $t(36) = -2.25$, $p = .031$, 95% CI [-.141, .003]. It is noteworthy that sex exhibited a trend toward significance ($p = .054$) in its influence on the thickness of the left precuneus within the model incorporating age and DHI. The findings from the multiple regression analysis suggest that sex significantly influences the cortical

thickness of the left hemisphere precuneus, a brain region involved in integrating cognitive and motor functions, such as coordinating movement with spatial awareness or memory (see **Figure 7**). The negative beta coefficients indicate that females tend to have thinner cortical thickness in this region compared to males. This thinning in females could imply a sex-specific vulnerability or difference in CMI-related neural integrity, potentially affecting tasks requiring coordinated cognitive-motor processing, such as balance or fine motor skills, especially in contexts like post-concussion recovery.

3.4 Relationship Between Cortical Volume, Age, Sex, and BrDI Performance

As highlighted in **Table 3**, multiple linear regression analyses revealed significant associations between age, sex, and CMI timing performance, as measured by the timing composite score for the PC+FR condition, in regression models including regions of interest (ROIs) in working-age adults with persistent post-concussion symptoms (PPCS) (df = 35). In the left hemisphere, age significantly predicted poorer CMI performance in models including caudal middle frontal (β = .071, 95% CI [.018, .124], p = .010), cuneus (β = .077, 95% CI [.027, .127], p = .003), inferior parietal (β = .073, 95% CI [.021, .125], p = .007), precuneus (β = .074, 95% CI [.022, .126], p = .006), rostral middle frontal (β = .086, 95% CI [.030, .142], p = .004), and superior parietal (β = .069, 95% CI [.017, .122], p = .011) regions. Sex also emerged as a significant predictor in these regions, with females showing greater impairment (LH caudal middle frontal: β = 1.068, 95% CI [.028, 2.109], p = .044; cuneus: β = 1.462, 95% CI [.411, 2.513], p = .008; inferior parietal: β = 1.087, 95% CI [.059, 2.114], p = .039; precuneus: β = 1.176, 95% CI [.131, 2.220], p = .029; rostral middle frontal: β = 1.232, 95% CI [.193, 2.272], p = .021; superior parietal: β = 1.081, 95% CI [.053, 2.110], p = .040). Similar patterns were observed in the right hemisphere (RH), with age significantly associated with reduced CMI

performance in the regression models with caudal middle frontal (β = .077, 95% CI [.025, .129], p = .005), cuneus (β = .077, 95% CI [.024, .131], p = .006), inferior parietal (β = .071, 95% CI [.019, .123], p = .009), precuneus (β = .072, 95% CI [.017, .127], p = .012), rostral middle frontal (β = .078, 95% CI [.025, .132], p = .005), and superior parietal (β = .070, 95% CI [.018, .123], p = .010) regions. Sex was also a significant predictor in the right hemisphere, with females again showing greater impairment (caudal middle frontal: β = 1.196, 95% CI [.158, 2.234], p = .025; cuneus: β = 1.180, 95% CI [.129, 2.231], p = .029; inferior parietal: β = 1.064, 95% CI [.024, 2.104], p = .045; precuneus: β = 1.081, 95% CI [.049, 2.114], p = .041; rostral middle frontal: β = 1.188, 95% CI [.139, 2.236], p = .028; superior parietal: β = 1.076, 95% CI [.046, 2.105], p = .041). These findings indicate that both older age and female sex are associated with poorer CMI timing performance in regression models containing bilateral frontal, parietal, and cuneus regions in individuals with PPCS.

3.5 Relationship Between Resting State networks, Age, Sex, and BrDI Performance

A hierarchical multiple regression was conducted to predict the BrDI PC+FR condition timing composite score, a measure of timing performance. In the first step, age was entered as a predictor, followed by sex (1 = female, 0 = male) in the second step, and the resting state functional connectivity of the 7 resting state networks, the three subnetworks of the Frontoparietal Control Network (FPCN a,b, and c), Somatomotor Network (SMN), Salience Ventral Attention Network (SVAN), Visual Network (VN), Limbic Network (LN), Dorsal Attention Network (DAN), and Default Mode Network (DMN) in the third step. Each step included a constant term, with predictors added sequentially to assess their contributions to explaining variance in BrDI PC+FR condition's timing performance. Age and sex were significant for FPCN a, b, and c, SMN, VN, LN, and DAN. The statistical results are outlined in

Table 4. The results revealed that both age and sex were significant predictors across various models that involved the 7 resting state networks. For the visual network model, age (β = .066, t = 2.434, p = .020, 95% CI [.011, .121]) and sex (β = 1.138, t = 2.209, p = .034, 95% CI [.092, 2.183]) were significant. In the somatomotor network model, age (β = .071, t = 2.725, p = .010, 95% CI [.018, .123]) and sex (β = 1.153, t = 2.085, p = .046, 95% CI [.024, 2.282]) were significant. For the limbic network model, age (β = .073, t = 2.807, p = .008, 95% CI [.020, .125]) and sex (β = 1.118, t = 2.139, p = .039, 95% CI [.057, 2.179]) showed significance. In the default mode network model, age (β = .071, t = 2.748, p = .009, 95% CI [.020, .123]) and sex (β = 1.132, t = 2.099, p = .043, 95% CI [.037, 2.228]) were significant. For the FPCN A model, age (β = .072, t = 2.737, p = .010, 95% CI [.019, .125]) and sex (β = 1.077, t = 2.060, p = .047, 95% CI [.016, 2.138]) were significant. In the FPCN B model, age (β = .069, t = 2.695, p = .011, 95% CI [.017, .121]) and sex (β = 1.243, t = 2.285, p = .028, 95% CI [.139, 2.347]) were significant. Finally, for the FPCN C model, age (β = .074, t = 2.869, p = .007, 95% CI [.022, .126]) and sex (β = 1.094, t = 2.164, p = .037, 95% CI [.068, 2.121]) were significant. These findings indicate that both age and sex consistently influence CMI timing performance in the PC+FR condition across models that involve different resting state networks. There were no notable effects of resting state network, age, or sex on any of the trajectory or timing composite scores for the direct standard condition, or the trajectory composite score for the PC+FR condition.

3.6 Sex Differences in Resting State Functional Connectivity

Although the RSFC Networks in the aforementioned regression models were not significant predictors of BrDI performance, we sought to confirm any sex differences in RSFC in this population of individuals affected by persisting concussion symptoms. The t-test results for sex differences in resting state functional connectivity across various brain networks revealed

several significant findings (**Table 5**). The somatomotor network demonstrated the strongest difference, with a t-value of 2.747, a p-value of .009, and a Cohen's d of .886, suggesting a large effect size. Other networks showing notable differences included the salience network (t = 2.364, p = .027, Cohen's d = .744), default mode network (t = 2.280, p = .028, Cohen's d = .736), and frontoparietal control network B (t = 2.533, p = .016, Cohen's d = .818). These results highlight the somatomotor network, salience ventral attention network, default mode network, and frontoparietal control subnetwork B as exhibiting the most pronounced sex differences in RSFC (see **Figure 11**).

Chapter 4: Discussion

The main goal of this study was to investigate the functional and structural neural underpinnings of visuomotor performance and examine how the effects of PPCS differed by sex. Using MRI, fMRI, and our BrDI task assessing CMI, vestibular dysfunction on the observed neuroanatomical correlates between male and female participants were assessed. The primary findings in this study were: 1) females exhibited significantly higher timing composite scores (slower/worse performance) in the non-standard CMI task (PC+FR condition) compared to males; 2) sex significantly predicted lower cortical volumes in females for the left cuneus and left superiorfrontal region; 3) females reported greater RPQ-3 symptom severity; 4) females had significantly thinner cortical thickness in the left precuneus; 5) both older age and female sex are associated with poorer CMI timing performance in regression models containing bilateral frontal, parietal, and cuneus region volume in individuals with PPCS; 6) age and sex significantly predicted slower CMI timing performance in older adults and females across models involving visual, somatomotor, limbic, default mode, and frontoparietal control networks although RSFC networks themselves were not significant predictors; and 7) significant sex differences in RSFC

were observed, with females showing altered connectivity in the somatomotor, salience ventral attention, default mode, and frontoparietal control subnetwork B networks.

The findings of this study highlight significant sex differences in cognitive-motor integration (CMI) performance among individuals with persistent post-concussion symptoms (PPCS), with females demonstrating higher timing composite scores in the non-standard CMI task (PC+FR condition) compared to males. This disparity suggests that females may face greater challenges in tasks requiring complex coordination of cognitive and motor processes following concussion, potentially due to sex-specific neuroanatomical or functional vulnerabilities, as the PC+FR condition requires the most spatial and feedback adjustment. Covassin, Schatz & Swanik (2012) found that concussed female collegiate athletes performed worse on their visual memory task in comparison to their male counterparts. However, the authors did not find any sex differences in reaction time, motor processing speed, or verbal memory. Much of the concussion literature predominantly focuses on young athletes or older adults; this study uniquely examines middle-aged working adults (mean age 47.50 years), a less-studied demographic in PPCS research. Young athletes, often studied due to their high concussion incidence, typically exhibit enhanced CMI due to extensive training that strengthens neural connectivity in sensory and motor regions, leading to superior proprioception and reaction speed (Yarrow et al., 2009). Similarly, a study done on young athletes (8-16 years old) showed that the asymptotic concussed group performed slower than the age-matched control group in the non-standard task but returned to the same level as the control group on average 18 months later (Sergio et al., 2020). Similarly, 17-year-old asymptomatic NHL draft prospects with a history of concussion had slightly slower reaction time on the non-standard CMI task, which can be detrimental at the elite level. However, they seem to have neurological “reserve” in which their

experience in complex tasks compensates for behavioural performance (Sergio et al., 2020). Enhanced skilled performance developed through extensive training may provide a protective effect against performance decline after brain injury by fostering more efficient and robust neural networks essential for managing complex skills. On the other hand, older adults with mTBI experience higher morbidity and mortality, are more likely to be functionally dependent, have worse functional and cognitive outcomes, and have slower recovery timelines in comparison to younger individuals (Peters & Gardiner, 2018). Older adults often show CMI declines linked to age-related cortical thinning and reduced neurotransmitter efficiency, such as dopamine, impacting processing speed, executive function, and motor coordination, especially when it comes to a novel task (Bäckman et al., 2006). The observed age-related decline in CMI performance aligns with evidence suggesting that ageing reduces neuroplasticity and increases susceptibility to persistent symptoms, potentially due to cumulative neural stress or disrupted recovery mechanisms (Giza & Hovda, 2014; Prins et al., 2013). This study's focus on middle-aged adults bridges these populations, revealing that CMI impairments in PPCS are influenced by both age and sex, with older age predicting poorer performance and females performing slower in the PC+FR condition of the CMI task in comparison to males. The diverse concussion mechanisms in this cohort (e.g., 36.44% sport-related, 25.42% motor vehicle accidents) further enhance the generalizability of these findings compared to athlete-centric studies, offering novel insights into how age and sex modulate recovery in a real-world, working-age population. Additionally, significant sex differences found in resting state functional connectivity, particularly in the somatomotor network, suggest altered neural communication in motor-related networks among females, potentially contributing to female-specific CMI impairment that was also discovered in the condition of the CMI task. Previous lab work looking

at females with PPCS and age-matched female controls found no significant differences in CMI performance, highlighting the unique contribution of this study in identifying sex-specific deficits in a middle-aged cohort (Hurtubise et al., 2020).

The RSFC findings, coupled with lower cortical volumes in females (e.g., left cuneus) and thinner cortical thickness in the left precuneus, suggest that females may experience more pronounced disruptions in neural networks critical for motor execution and sensory integration post-concussion. Similarly, Wang et al. (2018) found that male TBI patients presented with increased functional connectivity within motor, ventral stream, executive function and cerebellum networks compared with female patients; these identified resting state networks have been previously associated with somatosensory and motor functions, executive control, and self-related processing. These sex-specific RSFC differences may underlie the observed CMI performance disparities in this study, where males' faster timing scores in non-standard tasks could be linked to stronger connectivity in motor-related networks, such as the somatomotor network (Konstantinou et al., 2019). Higher RSFC in males may reflect compensatory neural mechanisms that enhance efficiency in motor-cognitive integration, potentially conferring an advantage in CMI tasks by facilitating more robust communication between sensory and motor regions (Wang et al., 2018). For example, increased connectivity in the somatomotor network in males may support better coordination and timing, critical for the complex demands of the non-standard CMI task, as evidenced by their superior performance in the PC+FR condition. However, this hyper-connectivity could also indicate maladaptive reorganization, where increased neural activity may lead to inefficient resource allocation or heightened metabolic demand, potentially risking neural fatigue or delayed recovery over time (Hillary et al., 2015; Konstantinou et al., 2019). In contrast, females reduced RSFC in the somatomotor, salience ($p =$

0.027), default mode ($p = 0.028$), and frontoparietal control B networks ($p = 0.016$) may reflect disrupted neural communication, contributing to slower CMI performance and greater symptom severity. These disruptions, combined with structural deficits like lower cortical volumes and thinner precuneus, may exacerbate challenges in integrating visuospatial and motor processes, particularly in tasks requiring novel cognitive-motor coordination (Konstantinou et al., 2019; Wang et al., 2018; Hillary et al., 2015). The nature of increased functional connectivity is likely dependent on several factors such as age, pre-injury cognitive function, or availability of neural resources (Amir, 2021). Establishing a direct connection between our findings and a specific pathophysiology remains challenging; however, future longitudinal studies, integrated with advanced neuroimaging methods, could better clarify the neurological and metabolic impacts of mTBI and their influence on functional connectivity.

The findings of this study demonstrate that older age and female sex significantly predict poorer Cognitive-Motor Integration (CMI) timing performance across bilateral frontal, parietal, and cuneus regions in working-age adults with persistent post-concussion symptoms (PPCS), underscoring unique vulnerabilities in this understudied demographic. Females exhibited more pronounced impairments, possibly driven by hormonal influences such as estrogen and progesterone, which modulate inflammation and symptom sensitivity, contributing to prolonged visuomotor deficits (Roof & Hall, 2000; Bazarian et al., 2010; Wunderle et al., 2014). These sex differences corroborate prior findings of distinct recovery trajectories in females (Smeha et al., 2022; Shafi et al., 2020; Wunderle et al., 2014) and highlight the need to investigate hormonal dynamics, such as menstrual cycle phase or menopausal status, which may exacerbate symptoms like dizziness or cognitive fog during the luteal phase (Stein, 2015; Ripley et al., 2008). Ripley and colleagues (2008) found that females often experience missed menstrual periods or complete

amenorrhea following TBI, indicating potential post-injury deficiencies in sex hormone levels. The involvement of a distributed visuomotor network, including cerebellar-linked regions tied to the BrDI task and DHI, suggests that white matter disruptions may underpin these deficits, warranting future studies using DTI to map structural connectivity in these areas (Mori & Zhang, 2006; Shenton et al., 2012). By focusing on working-age adults with diverse concussion mechanisms, this study extends beyond the sports-centric focus of prior research, offering generalizable insights for community-based populations affected by occupational or accidental injuries (Langlois et al., 2006). These results emphasize the need for age- and sex-specific clinical assessments and targeted visuomotor rehabilitation to enhance functional outcomes, particularly for non-athlete populations with PPCS (Langlois et al., 2006).

Furthermore, the significant associations between age, sex, and CMI timing performance in working-age adults with PPCS align with and extend existing literature on traumatic brain injury. Older age consistently predicted poorer CMI performance, supporting evidence that ageing reduces neuroplasticity and exacerbates neural vulnerabilities, potentially disrupting large-scale network dynamics critical for visuomotor integration (Giza & Hovda, 2014; Andrews-Hanna et al., 2007; Tremblay et al., 2014). Females exhibited greater impairments across 4 resting state networks, likely influenced by hormonal factors such as estrogen and progesterone, which modulate neuroinflammation and symptom sensitivity, as noted in studies linking menstrual cycle phase to worse TBI outcomes (Roof & Hall, 2000; Bazarian et al., 2010; Wunderle et al., 2014; Shafi et al., 2020). A study by Syan et al. (2017) demonstrated that progesterone levels in healthy women modulated RSFC in the salience network, with higher levels associated with stronger connectivity. This study's finding of reduced RSFC in the salience network in females compared to men may partly result from post-TBI progesterone deficiencies, considering the age

group also includes post-menopausal women. Such reduced connectivity may underlie the observed impairment in sensory-motor integration, contributing to the female-specific CMI deficits observed in this cohort. The involvement of diverse resting state networks, including the visual and somatomotor networks for sensory-motor processing, the DMN for cognitive integration, and the FPCN for executive control, emphasizes the distributed neural impact of PPCS, consistent with prior findings of network-specific disruptions in TBI (Slobounov et al., 2011; Zhou et al., 2012).

The findings of this study highlight several critical insights into traumatic brain injury and concussion outcomes in working-age adults, a demographic that remains understudied compared to the extensive research focused on youth and sports-related injuries. While the literature on concussions in younger populations often emphasizes resilience and relatively rapid recovery, our results align with emerging evidence that age interacts with concussion history to increase vulnerability and reduce recovery capacity. Specifically, our lab has consistently observed that older working-age adults exhibit greater susceptibility to persisting symptoms, with significant deficits in CMI performance now evident in females. This finding highlights a potential sex-specific divergence in recovery trajectories, which may be influenced by a combination of ageing and biological factors unique to women.

4.1 Strengths, Limitations, and Future Directions

A key strength of this study is its focus on working-age adults with diverse concussion mechanisms, capturing a wide range of injury contexts beyond the sports-related concussions typically studied in elite athletes. Unlike prior research, which often centres on professional or collegiate athletes with consistent fitness levels and concussion profiles, our inclusion of community-based participants with varied exercise habits, concussion severities, and PPCS

significantly enhances the generalizability of our findings. This approach ensures relevance to a broader population affected by concussions through occupational hazards, motor vehicle accidents, or other non-sport-related incidents, addressing a critical gap in the literature. Additionally, our study's comprehensive assessment of visuomotor performance and its correlation with neuroimaging metrics, such as resting-state functional connectivity (RSFC) and white matter integrity, provides a robust framework for understanding the complex interplay between brain function, structure, and behavioural outcomes in PPCS. By integrating these multimodal measures, our research offers a nuanced perspective on the neurological impacts of concussion in working-age adults, paving the way for more targeted clinical interventions.

This study is constrained by some methodological limitations that warrant consideration for future research. The cross-sectional design prevents us from establishing causal links between resting-state functional connectivity (RSFC), compromised white matter integrity, reduced cortical thickness, and visuomotor deficits in working-age adults with persistent post-concussion symptoms (PPCS). Longitudinal studies are needed to clarify the dynamics and interactions of these structural and functional brain changes in the development and persistence of PPCS and associated visuomotor impairments. Additionally, reliance on self-reported PPCS and concussion histories without professional medical verification may introduce reporting biases, potentially affecting the reliability of symptom data. A critical limitation is the absence of a healthy control group, which significantly restricts our ability to contextualize visuomotor performance deficits or identify neuroanatomical correlates specific to PPCS. Including healthy controls is essential for establishing baseline benchmarks for visuomotor tasks and discerning whether observed neural alterations, such as disrupted RSFC or white matter abnormalities, are unique to PPCS or reflective of broader variability in healthy populations. Without controls, it is

challenging to attribute impairments solely to PPCS, as age-related or other non-concussive factors could contribute. Furthermore, control groups enable more precise mapping of functional and structural neural underpinnings, enhancing the validity and specificity of findings related to visuomotor performance and brain integrity. The sample size further limits the generalizability of our results, despite efforts to adjust for covariates such as education, pharmacological interventions, and socioeconomic status. A key limitation of this study is the underrepresentation of male participants, which limits our ability to conduct direct, robust comparisons across sexes. Efforts are currently underway to recruit additional male participants to balance the dataset and enable more comprehensive analyses of sex differences in TBI outcomes. This limitation highlights the challenge of achieving equitable sample representation, particularly in a field where recruitment can be influenced by social, occupational, and health-seeking behavioural differences between sexes. Future studies with larger samples and healthy control groups are crucial to validate these findings, improve statistical power, and provide a clearer understanding of the neural mechanisms driving PPCS and visuomotor deficits in working-age adults.

To build on these findings, future research should prioritize advanced neuroimaging techniques, such as Diffusion Tensor Imaging (DTI), to examine sex differences in white matter tract integrity, including in the cerebellum. Our lab's BrDI task, which targets cerebellar function, aligns closely with the DHI questionnaire, suggesting a promising avenue for linking structural changes to functional and symptomatic outcomes. Investigating white matter alterations, particularly the cerebellum, could clarify the mechanisms underlying persistent symptoms, particularly dizziness and motor coordination deficits, which are prevalent in this population.

Hormonal influences represent another critical area for exploration. Sex hormones, such as estrogen, progesterone, and testosterone, likely modulate brain repair, inflammation, and symptom severity post-concussion. In females, the hormonal timing of the menstrual cycle may influence recovery windows, with slower recovery potentially occurring during the luteal phase, when progesterone peaks and subsequently drops, possibly exacerbating symptoms like headaches and dizziness. Additionally, pre-menopausal women, with higher baseline hormone levels, may exhibit faster initial recovery compared to post-menopausal women, whose lower hormone levels could hinder repair processes. In males, testosterone may influence pain tolerance and symptom reporting, potentially leading to underreporting of symptom severity. Conversely, estrogen in females may heighten sensitivity to common post-concussion symptoms, such as headaches or cognitive fog, contributing to perceived sex differences in recovery duration or severity. These hormonal dynamics warrant further investigation to understand their role in TBI outcomes and to inform the development of tailored interventions.

4.2 Conclusions

In summary, this study highlights the unique vulnerabilities of working-age adults to mTBI and concussion, with age and sex emerging as critical factors in recovery capacity and symptom persistence. The significant CMI deficits and alterations in RSFC in some networks observed in females demonstrate the need for sex-specific clinical guidelines, as one-size-fits-all approaches may overlook sex-specific vulnerabilities, as seen in the results. Understanding these disparities is particularly vital for working-age adults, where diverse concussion mechanisms (e.g., occupational or accidental) amplify the relevance of tailored interventions (Langlois et al., 2006). By revealing sex differences, research can inform personalized rehabilitation strategies, improve individual recovery, and address gaps in the predominantly sports-and-youth-focused

TBI literature. Future studies leveraging DTI and hormonal analyses hold promise for unravelling the structural and biological underpinnings of these outcomes, paving the way for targeted interventions to improve recovery in this understudied population.

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Tables

Table 1. Study Participants' Descriptive Statistics (n = 42)	
Demographics	
Age	47.5±9.87
Sex n (%) male and female, respectively	17 (40.48%) and 25 (59.52%)
Education (yrs)	17.40±2.01
Days since last concussion	1795.13±963.11
Average number of concussions	3.07±1.92
Loss of consciousness, yes (%)*	23.81%
Dazed and confused, yes (%)*	59.52%
No memory for events immediately after the injury, yes (%)*	35.71%
PPCS Severity	
RPQ-3	6.88±2.51
RPQ-13	31.10±11.81
Dizziness Severity	
DHI-Physical	9.79±5.03
DHI-Emotional	12.81±8.39
DHI-Functional	17.52±10.92
DHI-Total	40.12±22.77
Depression Severity	
PHQ-9	14.19±11.81
Visuomotor Metrics	
Standard timing composite score	0.08±2.51
Standard trajectory composite score	-0.02±2.01
Standard reaction time (ms)	623.83±499.46
Standard full path length (mm)	54.16±1.69
PC + FR timing composite score	-1.93e-15±1.73
PC + FR trajectory composite score	7.26e-16±1.71
PC + FR reaction tim (ms)	530.83±240.90
PC + FR full path length (mm)	66.61±23.75
PC + FR DR	23.02±21.55

Table 2. Prevalence of Persistent Post-Concussion Symptoms Rated 2 or Higher on the Rivermead Post-Concussion Symptom Questionnaire (RPQ)			
RPQ Subdivisions	***Symptom***	***n (%)***	***Mean ± SD***
RPQ-3 (Early Symptoms)	Headache	38 (90.48%)	3.11±0.72
	Dizziness	37 (88.10%)	2.70±0.80
	Nausea and/or Vomiting	23 (54.76%)	2.52±0.77
RPQ-13 (Later Symptoms)	Noise sensitivity, easily upset by loud noise	37 (88.10%)	3.30±0.73
	Sleep disturbance	34 (80.95%)	3.18±0.82
	Fatigue, tiring more easily	33 (78.57%)	3.33±0.80
	Being irritable, easily angered	32 (76.19%)	3.06±0.86
	Feeling depressed or fearful	24 (57.14%)	2.88±0.78
	Feeling frustrated or impatient	31 (73.81%)	2.81±0.86
	Forgetfulness, poor memory	38 (90.48%)	3.21±0.77
	Poor concentration	40 (95.24%)	2.95±0.80
	Taking longer to think	38 (90.48%)	3.05±0.76
	Blurred vision	24 (57.14%)	3.00±0.82
	Light sensitivity, easily upset by bright light	36 (85.71%)	2.97±0.80
	Double vision	18 (42.86%)	2.83±0.76
	Restlessness	23 (54.76%)	2.78±0.72

Table 3: Multiple Linear Regression Results for the Effect of Age, Sex, and ROI Volume on CMI Timing Performance

DV: Timing Composite Score for the PC+FR Condition							
	ROI Volume Model	**Significant IVs**	**df = 35** t	**Unstandardized** β	**95% CI**		**p-value**
					Lower Bound	**Upper Bound**	
	LH Caudal Middle Frontal	Age	2.706	.071	.018	.124	.010
		Sex	2.085	1.068	.028	2.109	.044
	LH Cuneus	Age	3.143	.077	.027	.127	.003
		Sex	2.824	1.462	.411	2.513	.008
	LH Inferior Parietal	Age	2.840	.073	.021	.125	.007
		Sex	2.147	1.087	.059	2.114	.039
	LH Precuneus	Age	2.895	.074	.022	.126	.006
		Sex	2.284	1.176	.131	2.220	.029
	LH Rostral Middle Frontal	Age	3.114	.086	.030	.142	.004
		Sex	2.408	1.232	.193	2.272	.021
	LH Superior Parietal	Age	2.675	.069	.017	.122	.011
		Sex	2.134	1.081	.053	2.110	.040
	RH Caudal Middle Frontal	Age	2.986	.077	.025	.129	.005
		Sex	2.340	1.196	.158	2.234	.025
	RH Cuneus	Age	2.932	.077	.024	.131	.006
		Sex	2.279	1.180	.129	2.231	.029
	RH Inferior Parietal	Age	2.761	.071	.019	.123	.009
		Sex	2.077	1.064	.024	2.104	.045
	RH Precuneus	Age	2.649	.072	.017	.127	.012
		Sex	2.126	1.081	.049	2.114	.041
	RH Rostral Middle Frontal	Age	2.960	.078	.025	.132	.005
		Sex	2.300	1.188	.139	2.236	.028
	RH Superior Parietal	Age	2.708	.070	.018	.123	.010
		Sex	2.120	1.076	.046	2.105	.041

Table 4: Multiple Linear Regression Results for the Effect of Age, Sex, and Resting State Networks on CMI Timing Performance

DV: Timing Composite Score for the PC+FR Condition	Resting State Network Model	Significant IVs	df = 35 t	Unstandardized β	95% CI		p-value
					Lower Bound	Upper Bound	
	Visual Network	Age	2.434	.066	.011	.121	.020
		Sex	2.209	1.138	.092	2.183	.034
	Somatomotor Network	Age	2.725	.071	.018	.123	.010
		Sex	2.085	1.153	.024	2.282	.046
	Limbic Network	Age	2.807	.073	.020	.125	.008
		Sex	2.139	1.118	.057	2.179	.039
	Default Mode Network	Age	2.748	.071	.020	.123	.009
		Sex	2.099	1.132	.037	2.228	.043
	FPCN A	Age	2.737	.072	.019	.125	.010
		Sex	2.060	1.077	.016	2.138	.047
	FPCN B	Age	2.695	.069	.017	.121	.011
		Sex	2.285	1.243	.139	2.347	.028
	FPCN C	Age	2.869	.074	.022	.126	.007
		Sex	2.164	1.094	.068	2.121	.037

Table 5: *t*-test Results for Sex Differences in Resting State Functional Connectivity

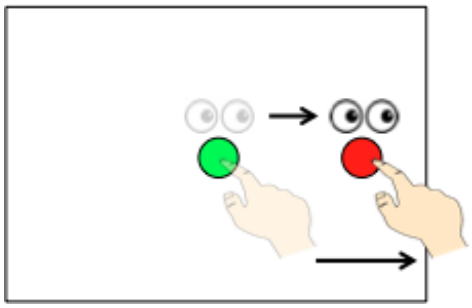
Resting State	Levene's Sig **Equal variance assumed*	df = 38 *t*	p-value (2-sided)	95% CI Lower Bound	95% CI Upper Bound	Cohen's D
Visual Network	.619*	.862	.394	-.0718011145	.17837710718	.278
Somatomotor Network	.843*	2.747	**.009**	.05047966818	.33345837840	.886
Dorsal Attention Network	.735*	1.594	.119	-.0247406694	.20777807268	.514
Salience Ventral Attention Network	.623*	2.304	**.027**	.01644713253	.25434082665	.744
Limbic Network	.253*	1.834	.074	-.0092617458	.18807236495	.592
Default Mode Network	.455*	2.280	**.028**	.01360012901	.22894421757	.736
FPCN A	.836*	1.382	.175	-.0380111982	.20152471512	.446
FPCN B	.649*	2.533	**.016**	.02741153381	.24541006121	.818
FPCN C	.500*	-.265	.793	-.1658731548	.12749706330	-.085

Table 6: Multiple Linear Regression Results for the Effect of Age, Sex, and ROI Volume on RPQ-3

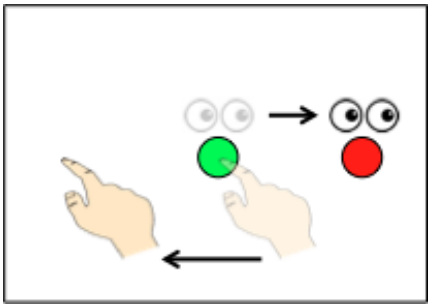
DV: Rivermead Post-Concussion Symptom Questionnaire - 3 (RPQ-3)	ROI Volume Model	Significant IVs	df = 36 t	Unstandardized β	95% CI		p-value
					Lower Bound	Upper Bound	
	LH Caudal Middle Frontal	Sex	2.949	2.332	.728	3.936	.006
	LH Cuneus	Sex	2.852	2.377	.686	4.067	.007
	LH Inferior Parietal	Sex	2.855	2.249	.651	3.848	.007
	LH Precentral	Sex	2.621	2.171	.491	3.852	.013
	LH Precuneus	Sex	2.848	2.326	.670	3.981	.007
	LH Rostral Middle Frontal	Sex	2.611	2.138	.477	3.799	.013
	LH Superior Frontal	Sex	2.838	2.373	.677	4.069	.007
	LH Superior Parietal	Sex	2.778	2.221	.599	3.842	.009
	RH Caudal Middle Frontal	Sex	2.836	2.313	.659	3.966	.007
	RH Cuneus	Sex	2.521	2.029	.397	3.662	.016
	RH Inferior Parietal	Sex	2.711	2.185	.550	3.819	.010
	RH Precentral	Sex	2.632	2.143	.492	3.795	.012
	RH Precuneus	Sex	2.773	2.218	.596	3.841	.009
	RH Rostral Middle Frontal	Sex	2.698	2.216	.550	3.881	.011
	RH Superior Frontal	Sex	2.597	2.185	.479	3.891	.014
	RH Superior Parietal	Sex	2.773	2.218	.596	3.839	.009

Figures

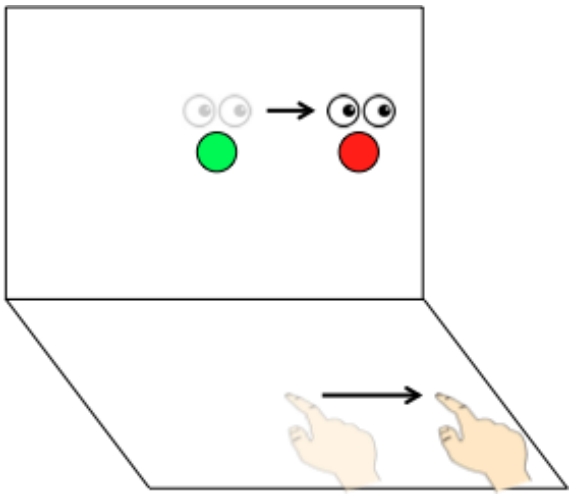
a. Direct (standard)



c. Feedback reversal (non-standard)



b. Plane-change (non-standard)



d. Plane-change + Feedback reversal (non-standard)

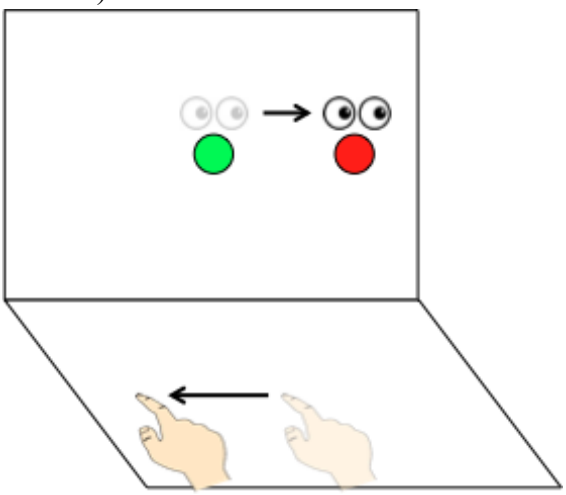


Figure 1. Diagram of the BrDI™ visuomotor task. Lighter eye and hand symbols denote the starting position for each trial (green central target). Darker eye and hand symbols denote the instructed eye and hand movements for each task. Red circles represent the peripheral (reach) target, presented randomly in one of four locations (left, up, right, or down relative to the central target). **a)** Direct condition. Eye and finger movement are coupled when moving from the central target to the peripheral target. The other three non-standard tasks introduce cognitive-motor integration challenges. **b)** Spatial dissociation between hand movement and target planes (plane change). **c)** Reversed visual feedback with 180° rotation. **d)** Combined spatial dissociation and feedback reversal (plane change + feedback reversal (PF+FR)). These non-standard conditions test participants' ability to adapt their motor responses to altered visual-spatial relationships, increasing cognitive demand compared to the direct interaction task.

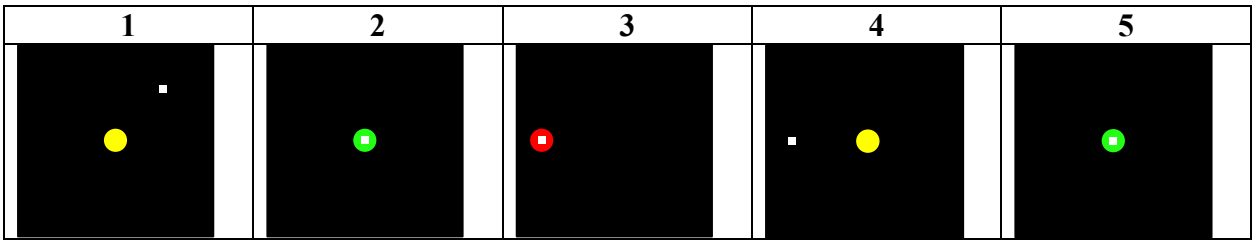


Figure 2. Chronological stages of a single visuomotor trial. Each trial follows a specific sequence. 1) Initiation: The participant moves the white cursor to the central home target. **2)** Preparation: The central target turns green, signalling a 2000 ms wait period. **3)** Execution: A red peripheral target appears randomly in one of four directions (up, down, left, or right), cueing movement. **4)** Completion: The trial ends when the peripheral target is held for 500 ms. **5)** Reset: After a 2000 ms interval, the yellow central target reappears, prompting a return for the next trial. This cycle repeats, with the peripheral target's location varying each time. The colour changes and timing serve to standardize preparation and response periods across all trials.

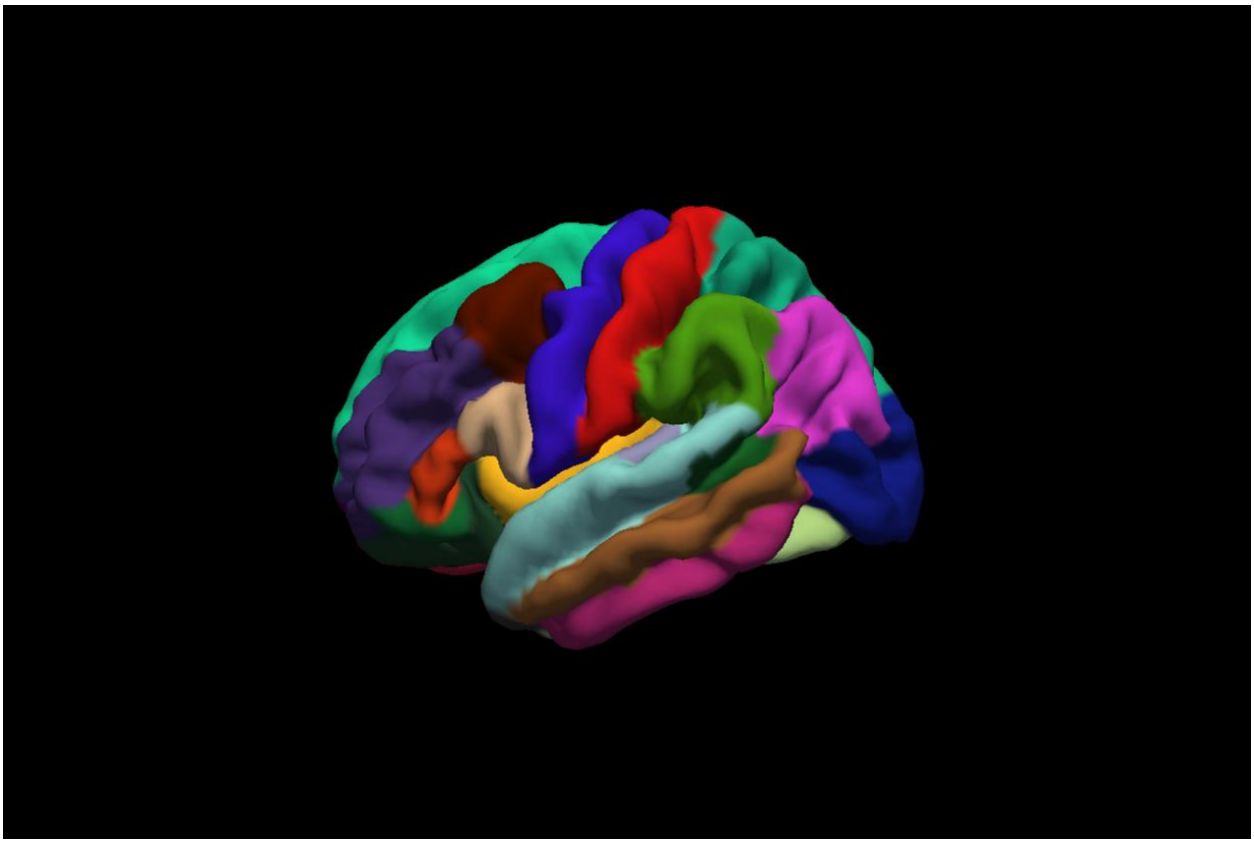


Figure 3. 3D depiction of Desikan-Killiany atlas obtained from the FreeSurfer parcellation of cortical regions. This visualization highlights the segmentation of the human brain's cortical surface into distinct anatomical regions, with each colour representing a unique area as defined by the atlas.

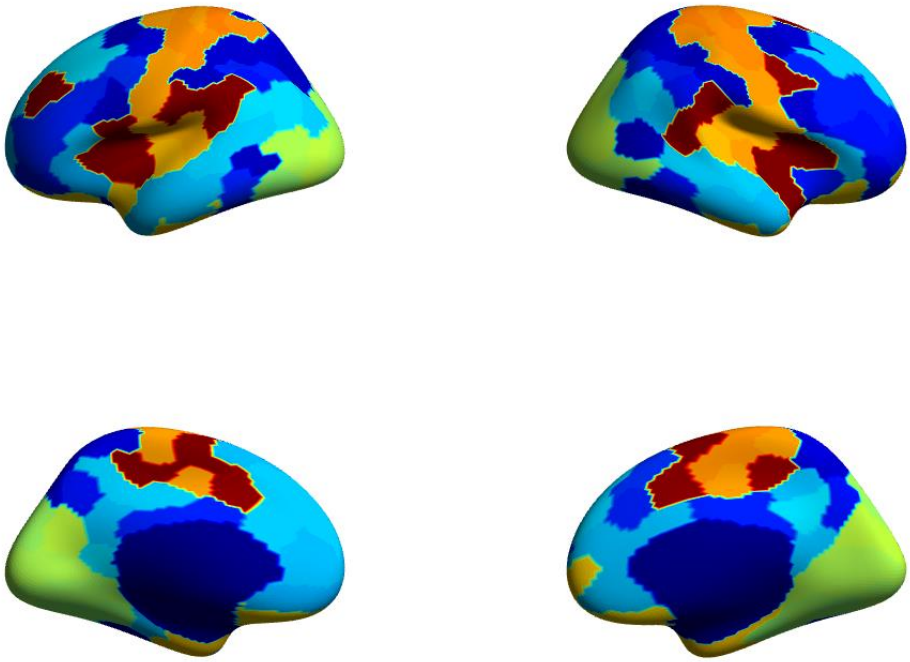


Figure 4. Illustration of an example parcellation derived from a single subject, initialized using the 200-parcel, 7-network Schaefer atlas (Schaefer et al., 2018). The parcel borders have been refined through the Gradient-based Parcellation Improvement Process (GPIP) to align more accurately with the subject's resting-state functional data, enhancing the functional correspondence of the segmented regions across the brain. This visualization showcases the detailed division of cortical areas, with each colour representing a distinct parcel tailored to the individual's neurofunctional profile.

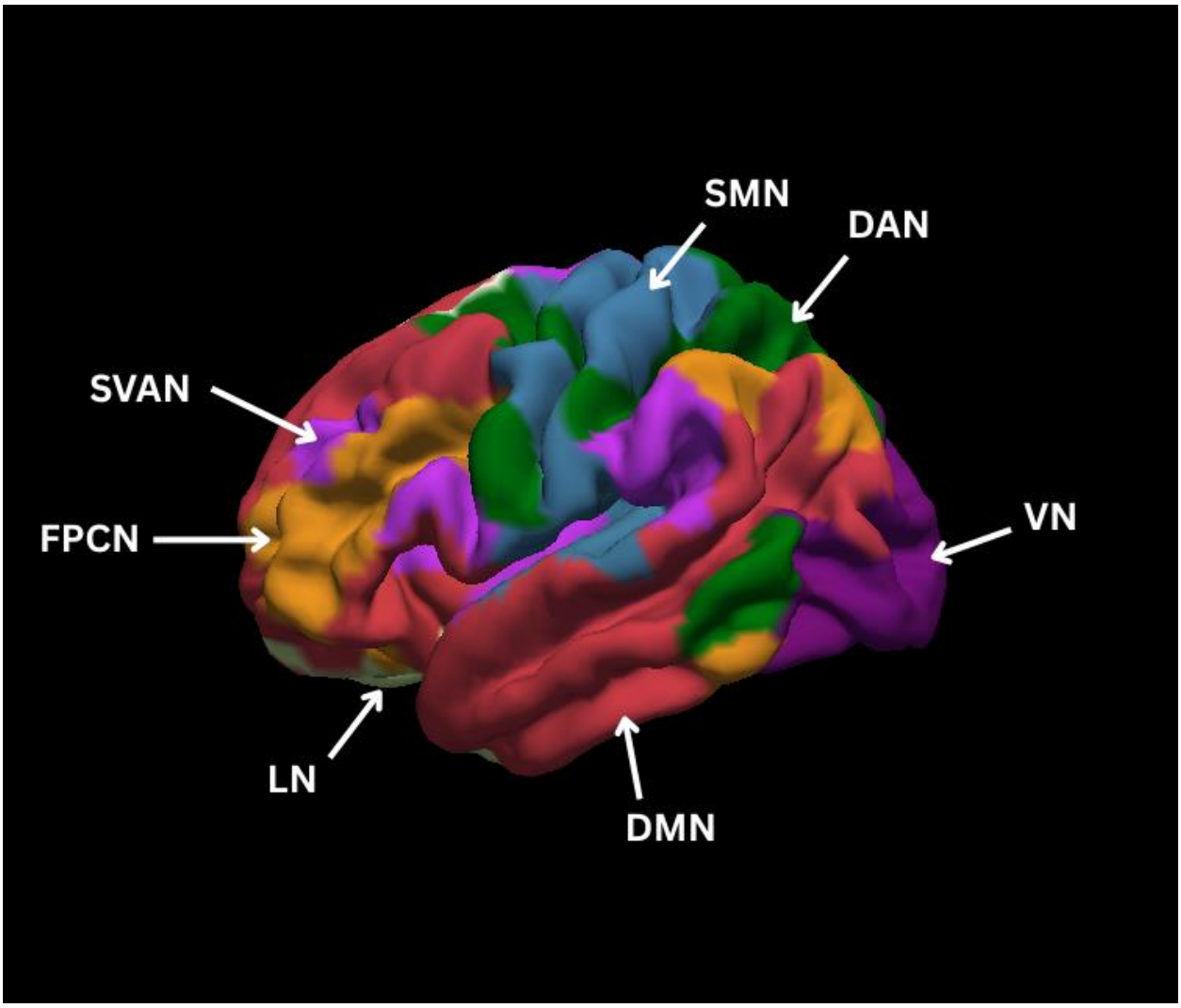


Figure 5. Representation of resting-state functional connectivity networks within the brain. This 3D visualization highlights key networks, including the Dorsal Attention Network (DAN), responsible for attentional control; the Default Mode Network (DMN), associated with internal thought processes; the Frontoparietal Network (FPCN), involved in executive functions; the Limbic Network (LN), linked to emotional regulation; the Sensorimotor Control Network (SMN), governing motor and sensory integration; the Salience Ventral Attention Network (SVAN), which detects and responds to salient stimuli; and the Visual Network (VN), dedicated to visual processing. Each network is distinctly coloured to illustrate its spatial distribution and functional role in the brain's intrinsic connectivity.

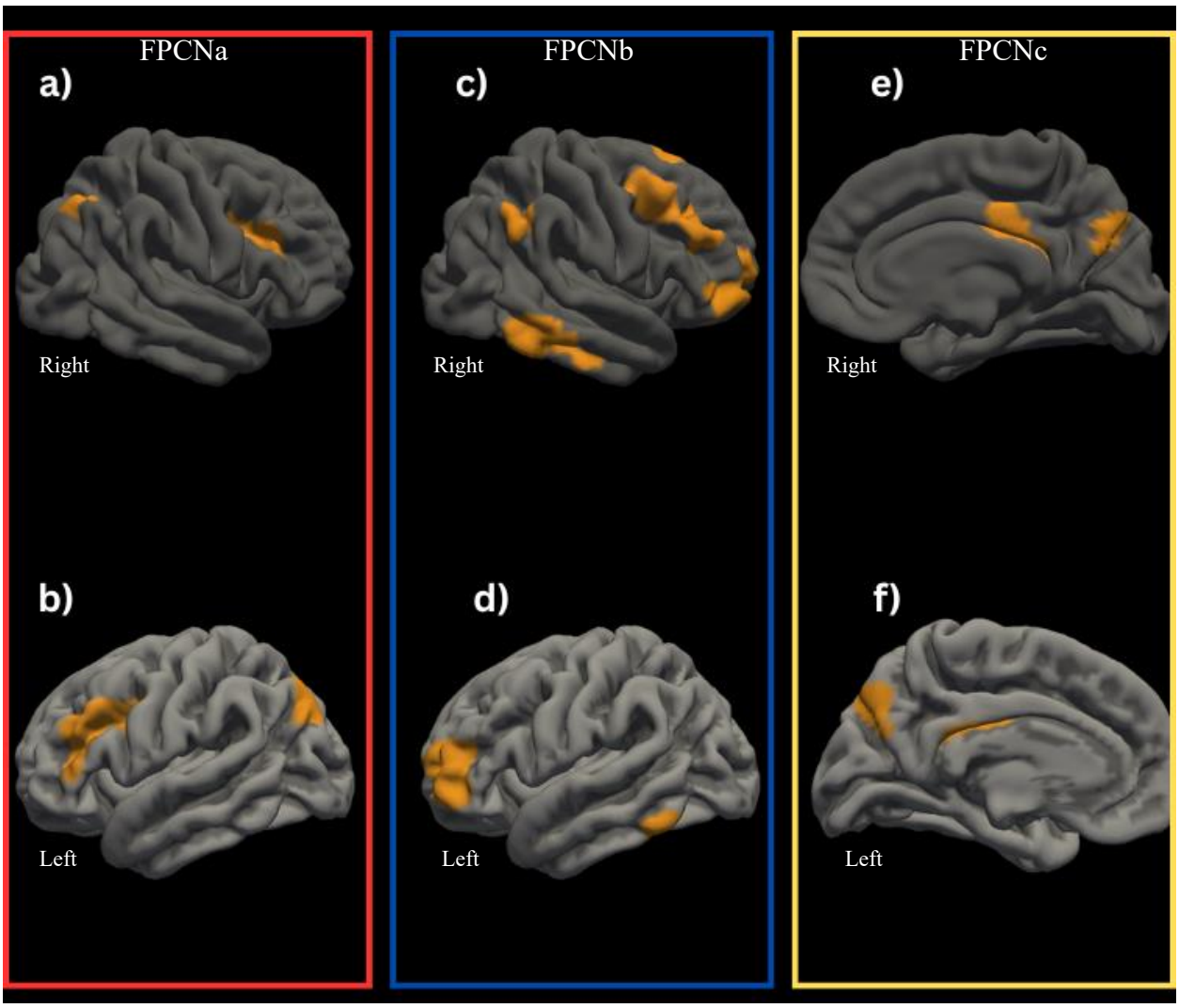


Figure 6. The 3 subnetworks of the frontoparietal control network (FPCN), **a)** right FPCNa; **b)** left FPCNa; **c)** right FPCNb; **d)** left FPCNb; **e)** right FPCNc; **f)** left FPCNc.

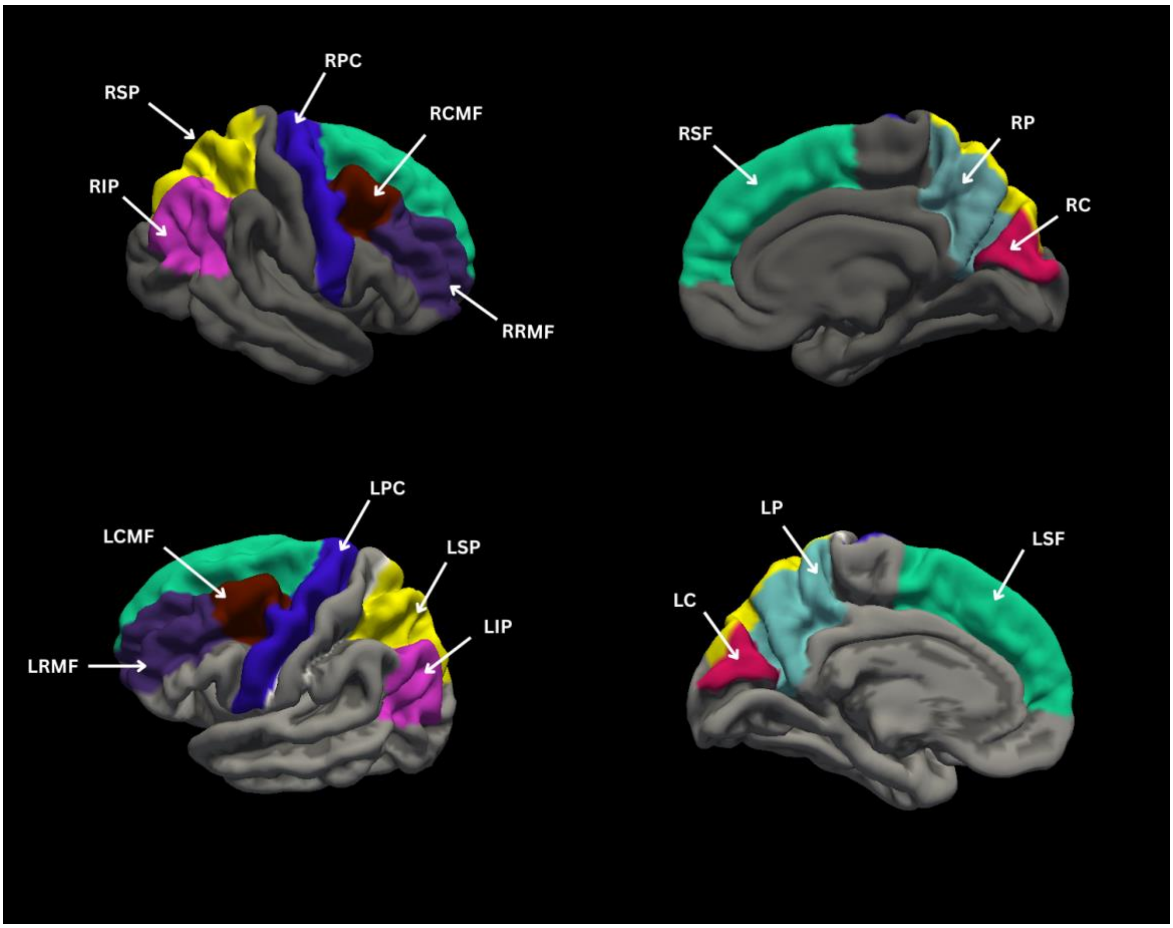


Figure 7. Cortical regions of interest. The **top panel** displays the right hemisphere, featuring the right superior parietal (RSP), involved in spatial orientation; right inferior parietal (RIP), associated with attention and sensory integration; right precentral (RPC), linked to motor control; right rostral middle frontal (RRMF), related to executive functions; right caudal middle frontal (RCMF), contributing to cognitive control; right superior frontal (RSF), involved in planning and decision-making; right precuneus (RP), associated with self-referential processing; and right cuneus (RC), dedicated to visual processing. The **bottom panel** illustrates the left hemisphere, including the left superior parietal (LSP), left inferior parietal (LIP), left precentral (LPC), left rostral middle frontal (LRMF), left caudal middle frontal (LCMF), left superior frontal (LSF), left precuneus (LP), and left cuneus (LC), mirroring their respective functions on the contralateral side. Each region is distinctly marked to facilitate the study of hemispheric specialization and functional connectivity.

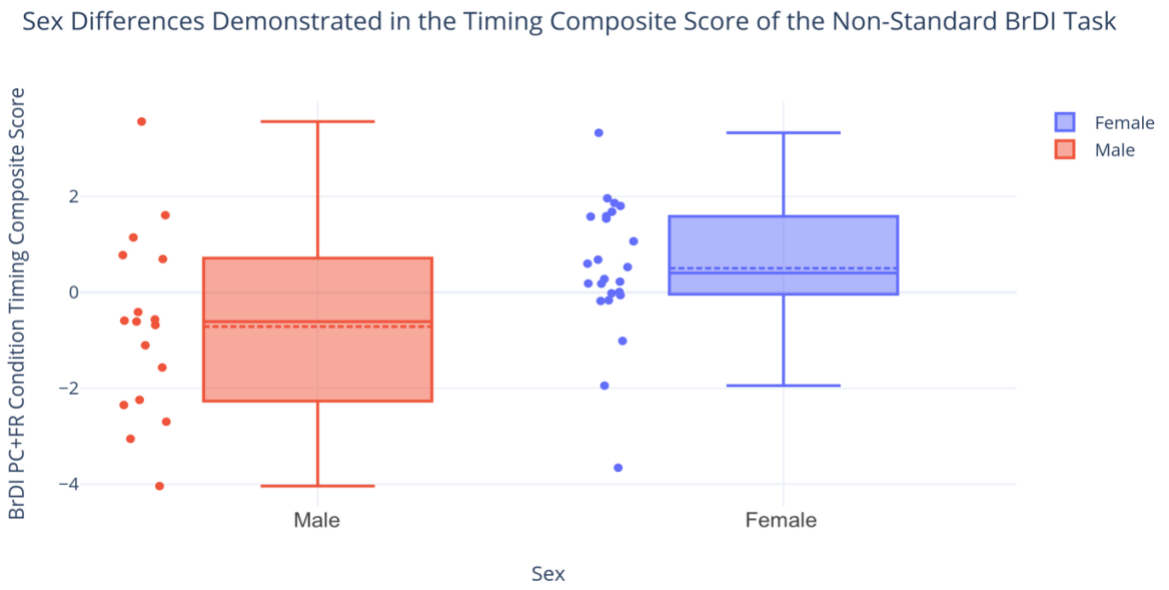


Figure 8. Boxplot illustrating sex differences in the timing composite score of the non-standard BrDI Task (PC+FR condition), with males (red) displaying a broader distribution and a median score less than 0 indicating faster performance, while females (blue) show a narrower distribution with a median score slightly above 0 demonstrating slower performance, highlighted by individual data points and interquartile ranges.

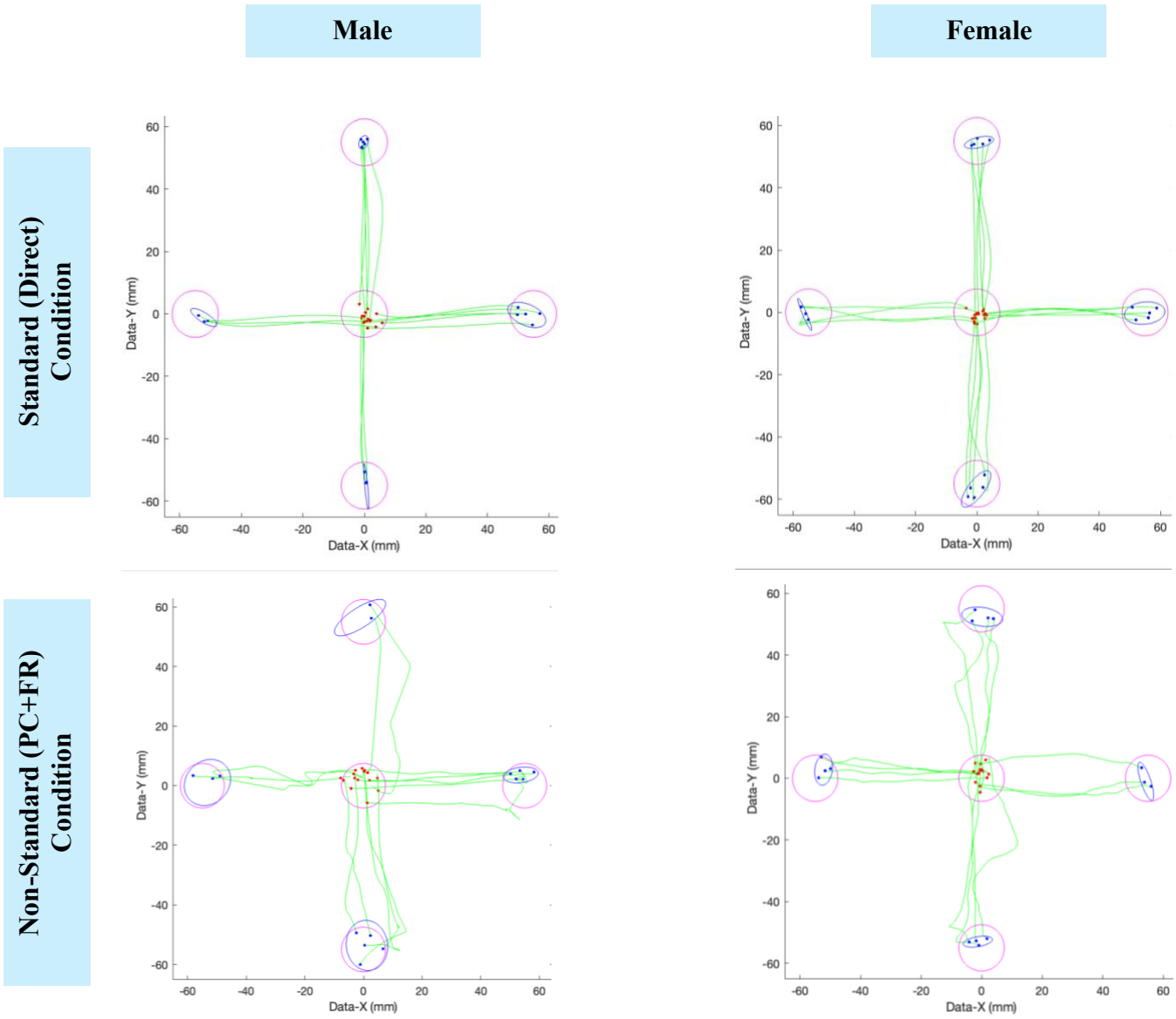


Figure 9. A typical example of male and female visuomotor performance in standard and non-standard conditions. Hand trajectories begin at the central target (red dots) and move towards one of four peripheral targets, where each green line represents a single movement trajectory. Blue ellipses denote the 95% C.I. for the final endpoint of the finger movements (blue dots).

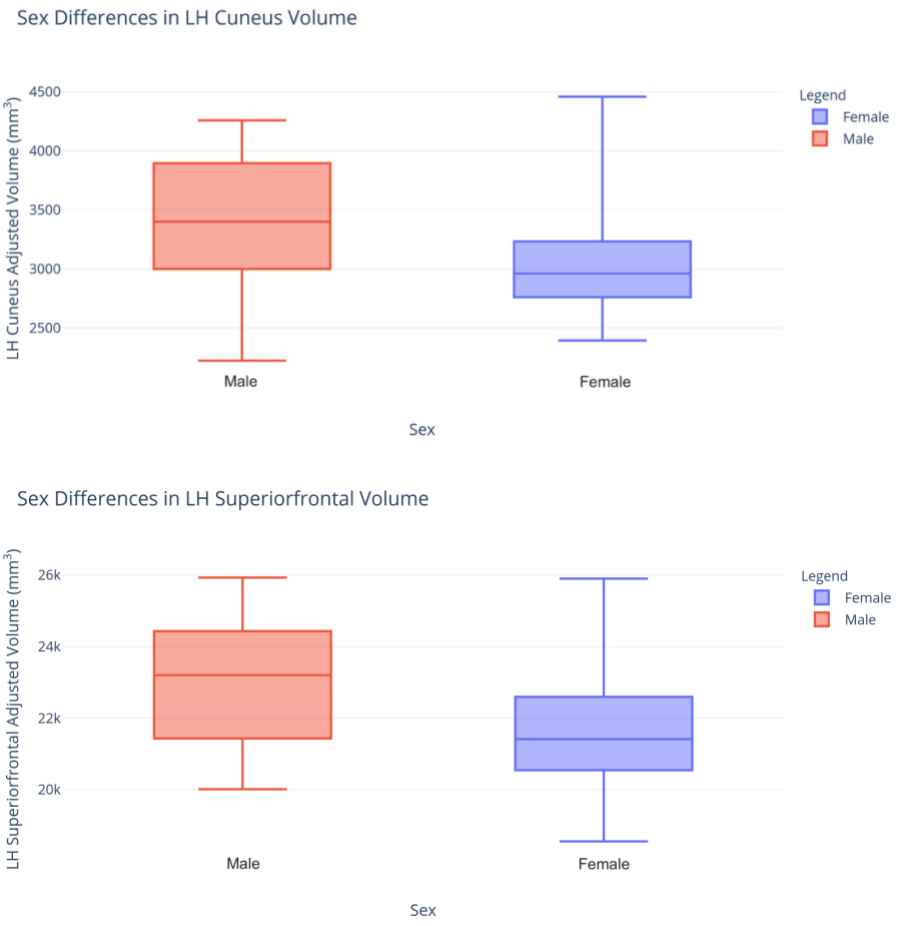


Figure 10. Boxplots depicting sex differences in adjusted cortical volumes (in mm^3) for the left hemisphere cuneus and left hemisphere superiorfrontal region, with males (red) exhibiting a broader distribution and higher median volumes compared to females (blue), who show narrower distributions and lower median volumes, highlighting potential sex-specific variations in brain structure.

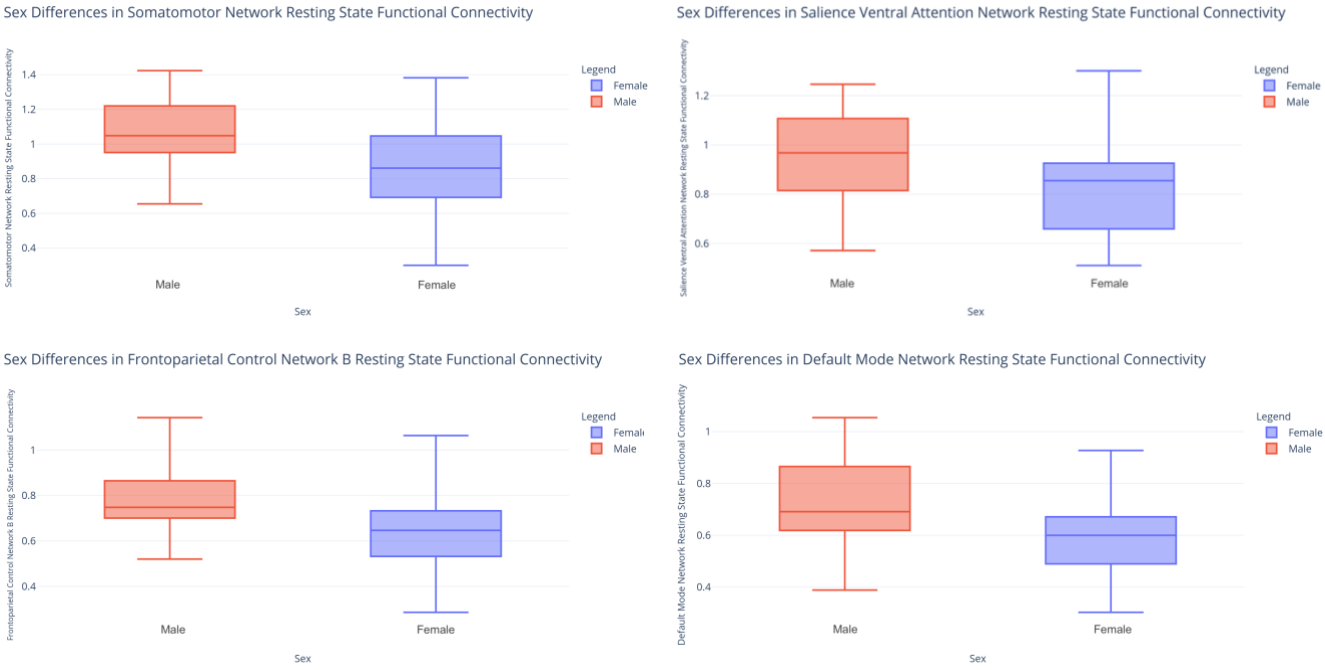


Figure 11. Boxplots illustrating sex differences in resting state functional connectivity across six networks – Somatomotor Network, Salience Ventral Attention Network, Frontoparietal Control Subnetwork B, and Default Mode Network – with males (red) and females (blue) showing distinct median connectivity levels and distribution patterns, highlighting potential sex-specific variations in network interactions.

Appendix

A: 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, or stand on a firm surface while leaning in different directions in response to displayed targets. 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.

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

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

Signature _____ **Date** _____

Principal Investigator

B: Dizziness Handicap Inventory – DHI

REHABILITATION Medicine Clinic

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
P1	Does looking up increase your problem?	☐	☐	☐
E2	Because of your problem, do you feel frustrated?	☐	☐	☐
F3	Because of your problem, do you restrict your travel for business or pleasure?	☐	☐	☐
P4	Does walking down the aisle of a supermarket increase your problem?	☐	☐	☐
F5	Because of your problem, do you have difficulty getting into or out of bed?	☐	☐	☐
F6	Does your problem significantly restrict your participation in social activities, such as going out to dinner, going to movies, dancing or to parties?	☐	☐	☐
F7	Because of your problem, do you have difficulty reading?	☐	☐	☐
F8	Does performing more ambitious activities like sports, dancing, and household chores, such as sweeping or putting dishes away; increase your problem?	☐	☐	☐
E9	Because of your problem, are you afraid to leave your home without having someone accompany you?	☐	☐	☐
E10	Because of your problem, have you been embarrassed in front of others?	☐	☐	☐
P11	Do quick movements of your head increase your problem?	☐	☐	☐
F12	Because of your problem, do you avoid heights?	☐	☐	☐
P13	Does turning over in bed increase your problem?	☐	☐	☐
F14	Because of your problem, is it difficult for you to do strenuous housework or yard work?	☐	☐	☐
E15	Because of your problem, are you afraid people may think that you are intoxicated?	☐	☐	☐
F16	Because of your problem, is it difficult for you to go for a walk by yourself?	☐	☐	☐
P17	Does walking down a sidewalk increase your problem?	☐	☐	☐
E18	Because of your problem, is it difficult for you to concentrate?	☐	☐	☐
F19	Because of your problem, is it difficult for you to walk around your house in the dark?	☐	☐	☐
E20	Because of your problem, are you afraid to stay home alone?	☐	☐	☐
E21	Because of your problem, do you feel handicapped?	☐	☐	☐
E22	Has your problem placed stress on your relationship with members of your family or friends?	☐	☐	☐
E23	Because of your problem, are you depressed?	☐	☐	☐
F24	Does your problem interfere with your job or household responsibilities?	☐	☐	☐
P25	Does bending over increase your problem?	☐	☐	☐

Scoring for Dizziness Handicap Inventory

Eval	Total Functional	Total Emotional	Total Physical	TOTAL SCORE
Reassess #1				
Reassess #2				
Reassess #3				
Reassess #4				

Always = 4

Sometimes = 2

No = 0

P = physical

E = emotional

F = functional

Subscales

Notes:

1. **Subjective measure of the patient's perception of handicap due to the dizziness**
2. **Top score is 100 (maximum perceived disability)**
3. **Bottom score is 0 (no perceived disability)**
4. **The following 5 items can be useful in predicting BPPV**
   - **Does looking up increase your problem?**
   - **Because of your problem, do you have difficulty getting into or out of bed?**
   - **Do quick movements of your head increase your problem?**
   - **Does bending over increase your problem?**
5. **Can use subscale scores to track change as well**

C: Health Questionnaire

Questionnaire
Pretest Intake Questionnaire – Brain Health and Skilled Performance
(The information received will remain confidential)

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

Questionnaire

Pretest Intake Questionnaire – Brain Health and Skilled Performance

(The information received will remain confidential)

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

Questionnaire

Pretest Intake Questionnaire – Brain Health and Skilled Performance

(The information received will remain confidential)

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

Questionnaire

Pretest Intake Questionnaire – Brain Health and Skilled Performance

(The information received will remain confidential)

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 ☐

Questionnaire

Pretest Intake Questionnaire – Brain Health and Skilled Performance

(The information received will remain confidential)

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 ☐

Questionnaire

Pretest Intake Questionnaire – Brain Health and Skilled Performance

(The information received will remain confidential)

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.

_____

_____

_____

_____

Questionnaire

Pretest Intake Questionnaire – Brain Health and Skilled Performance

(The information received will remain confidential)

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.

D: Rivermead Post-Concussion Symptoms Questionnaire – RPQ

The Rivermead Post-Concussion Symptoms Questionnaire*

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 at all
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

06/23/08

E: MRI Screening Form

York MRI Facility

Magnetic Resonance (MR) Safety Screening Form

Name _____ **Height** _____
Last *First* *Middle* **Weight** _____

Date of Birth ___/___/___
Month *Day* *Year*

☐ Male ☐ Female ☐ Other

Do you have a **Cardiac Pacemaker** or **Implantable Cardioverter Defibrillator** (ICD)?	☐ Yes	☐ No
Do you have an **Aneurysm Clip**?	☐ Yes	☐ No
Are you Claustrophobic?	☐ Yes	☐ No
Are you currently taking any medications? List: _____		
Have you ever had an injury involving a metallic object or fragment?	☐ Yes	☐ No
Have you ever worked in a metal shop?	☐ Yes	☐ No
Possibility of pregnancy? ☐ Not Applicable	☐ Yes	☐ No

Surgery

Brain/Head Surgery? *Type/Date*: _____	☐ Yes	☐ No	Heart/Chest Surgery? *Type/Date*: _____	☐ Yes	☐ No
Eye/Ear Surgery? *Type/Date*: _____	☐ Yes	☐ No	Other Surgery? *Type/Date*: _____	☐ Yes	☐ No
Artificial Implants/Mechanical Devices? *Type/Date*:				☐ Yes	☐ No

Please Indicate if you have any of the following

Piercings (ear or body)	☐ Yes	☐ No	Medication Patch	☐ Yes	☐ No
Hearing Aid or Cochlear Implant	☐ Yes	☐ No	Tattoo or Permanent Makeup	☐ Yes	☐ No
Permanent Retainer/Braces	☐ Yes	☐ No	Stent or Filter	☐ Yes	☐ No
Dentures or Partials	☐ Yes	☐ No	Antimicrobial Clothing	☐ Yes	☐ No
History of Bullets/Shrapnel/BBs	☐ Yes	☐ No	Intrauterine device (IUD)	☐ Yes	☐ No
History of Seizures	☐ Yes	☐ No	Underwire bra	☐ Yes	☐ No
Hair piece/wig/hair extensions	☐ Yes	☐ No	Magnetic Eyelash Extensions	☐ Yes	☐ No

WARNING: Certain implants, devices, or objects may be hazardous to you and/or may interfere with the MR procedure (i.e., MRI, MR angiography, functional MRI, MR spectroscopy). **Do not enter** the MR magnet room or MR environment if you have any questions or concerns regarding an implant, device, or object. Consult the MRI Technologist or Researcher BEFORE entering the MR system room. **The MR system magnet is ALWAYS on.**

I attest that the above information is correct to the best of my knowledge. I have read and understood the contents of this form and had the opportunity to ask questions regarding the information on this form and regarding the MRI procedure that I am about to undergo.

Signature of person completing form: _____ **Date** ___/___/___
M *D* *Y*

Form completed by: ☐MRI Participant ☐Other (specify) _____

Reviewed By: _____ **PI of study** _____